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Anatomic Patterns by Histologic Type of Localized Hodgkin's Disease of the Upper Torso*

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Summary

A series of 160 consecutively enrolled patients in a clinical trial of radiotherapy for localized Hodgkin's disease of the upper torso has been analysed with respect to anatomic patterns of disease and histologic type. The distribution of 55 patients with stage 1 disease involving a single nodal region was used to predict distribution patterns for the remaining 105 patients of more advanced stage.

It was found that deviations from the expected anatomic patterns were more common than agreements. These deviations often favored a pattern of spread to anatomically adjacent regions, but this was not true in the case of spread from one side of neck to the other. Rather, extension to the contralateral neck was seen to depend on functionally contiguous pathways through mediastinum.

Nodular sclerosing and mixed cell types differed strikingly in patterns of spread, with nodular sclerosing cases rarely deviating from a pattern of contiguous regional spread. The regions involved were commonly first mediastinum, then neck, either left or right. In contrast, mixed cell type disease deviated only in minor ways from spread independent of site of origin. Bilateral axillary involvement was predicted to occur rarely on an independent spread basis, but with mixed cell disease this special anatomic pattern was reported significantly in excess.

The anatomic distribution of Hodgkin's disease has been the subject of a number of investigations (1–7), and these observations have been interpreted in relation to various theories as to the nature of spread of the disease. *Rosenberg* and *Kaplan* (1) have spoken of an "orderly progression", and from the text this appears to refer to a step-wise progression from a given region to anatomically adjacent regions. *Smithers* (2) has described a "pattern of susceptibility", in which both the initial site of disease in an individual and the sites of subsequent spread are determined by characteristics of the lymphnodes of the various anatomic regions. This pattern is described as "non-random", though it is not specified what the concept of randomness implies in this context.

Several investigators have called attention to differences in stage or anatomic pattern associated with different histologies (8–10), and these differences have been interpreted in terms of variations in nature of spread for different histologic types. *Bonnadonna, Banfi,* et al. (3, 4) have given a similar interpretation to differences between Hodgkin's disease and other lymphomas.

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In the present paper we have presented a scheme for categorizing all possible anatomic patterns of localized Hodgkin's disease of the upper torso and have shown the distribution of a newly reported series in terms of this scheme. Distributions have been shown separately for the two common histologies, nodular sclerosing and mixed cell types.

Two general theories of the method of spread of disease have been considered, the one postulating that extension to new anatomic regions is dependent on the initial site, while the alternative theory supposes that spread is determined by characteristics of the new site and is independent of the site of origin. Within these two general theories some more specific modes of spread have been considered. If extension is dependent on the site of origin, one specific pattern of spread might be to the next anatomically adjacent regions. A second possibility would be for spread to occur along major lymphatic channels to functionally contiguous areas, and in some instances these routes would give low priority to certain anatomically adjacent regions. Within the general theory of spread independent of site of origin several factors might determine vulnerability of a region. The simplest concept would be that of random spread, whereby the probability of spread to a region would be determined solely by the number of available sites for a daughter cell to settle in the region. Another possibility is the susceptibility concept of *Smithers* (2), whereby the lymphoid tissue of various anatomic regions is more or less susceptible as a site for new growth, depending on its local immune status.

The present analysis is primarily concerned with determining whether the pattern of spread is consistent with extension independent of the site of origin. It will be shown that for some categories of Hodgkin's disease the independent theory must be discarded, and the discrepancies have been investigated to see whether they are explained either by a theory of adjacent spread or a theory of contiguous spread.

Materials and Methods

A collaborative clinical trial to evaluate the relative effects of two techniques of radiotherapy for management of localized Hodgkin's disease was undertaken in 1967. The present study includes initial data from the first 160 patients with upper torso disease enrolled in this trial.

Patients have been submitted from 22 radiotherapy centers in the United States and Canada. Enrollment is accomplished by telephone or telegram to the coordinating center after initial evaluation of a patient for diagnosis and stage. Histologic slides supporting the diagnosis of Hodgkin's disease are submitted to one pathologist of record for all collaborating groups, and patients are accepted for enrollment only if the diagnosis is confirmed. Only localized Hodgkin's disease is under study, and staging requires the presentation of a satisfactory lymphangiogram. Lymphangiogram films are read centrally by one radiologist of record. In addition to routine investigations an intravenous pyelogram and specified liver function studies are required. When hilar nodes are considered to be involved, chest tomograms are required to investigate the possibility of parenchymal lung disease.

Extent of recognized disease is reported to the collaborating center by submission of a standard diagram and an accompanying check list. The diagram and check list identify some 37 specific nodal sites above the diaphragm. Disease distributions described in this paper are determined by the sites checked on these diagrams and lists. While histologic confirmation in each patient is required, it is not required to present histologic confirmation for each site considered clinically positive, and for the most part biopsy has not been done at sites other than the diagnostic site.

A. Patterns of disease

For convenience of analysis of the limited case material the 37 nodal sites above the diaphragm are grouped into 5 regions, namely, left neck, right neck, left axilla, right axilla, and mediastinum. It will be recalled that localized disease refers to disease limited to nodes on one side of the

diaphragm, so that the 160 cases exhibit upper torso disease patterns only. Each case may be described in terms of presence or absence of disease in each of the 5 upper torso regions. A given case may have involvement of all 5 regions, or of any 4, 3, 2, or 1 region. Table 1 indicates all possible combinations, comprising 31 anatomic distributions. The relative frequencies of occurence of these 31 distributions at initial enrollment in this study have been tested for conformity with the theories of spread of disease described above.

B. Spread independent of site of origin

If spread is independent of site of origin, it should be possible to assign a probability value to each anatomic region which would be proportional to the likelihood that that region would become next involved, irrespective of what region was first affected. These regional probabilities could be used to compute the probabilities that any two anatomic regions would become the next two involved, and the procedure could be extended to more complex patterns of spread.

Smithers has suggested that the same characteristics of regional nodes may determine both initial susceptibility to Hodgkin's disease and susceptibility as a site for secondary spread. It may similarly be supposed that under a random spread theory the number of sites available for a metastasis in a region is closely related to the number of sites available for initiation of new disease. We have therefore used the anatomic distribution of stage 1 disease, involving single anatomic sites, to determine the probability values for spread to the 5 upper torso regions.

The following stage 1 frequencies have been observed in our material and are shown in comparison with corresponding values given by *Smithers* (2).

	Present Study	*Smithers*
Left neck	0.34	0.35
Right neck	0.40	0.35
Left axilla	0.07	0.06
Right axilla	0.09	0.06
Mediastinum	0.09	0.18
Total	0.99	1.00

The values given by *Smithers* are determined from his own and other studies. The only important difference between the two distributions is the frequency of observed primary mediastinal cases. It is possible that our sample is by chance unrepresentative in primary mediastinal cases and that our excepted pattern frequencies in later tables in this paper should show somewhat higher values for all patterns in which mediastinum is involved. The pattern frequencies do not vary greatly with small changes in the primary regional frequencies, and small increases in frequencies of mediastinal patterns do not alter any of the conclusions importantly.

The following numerical example illustrates the process of computing expected frequencies of two-region involvement under the theory of spread independent of site of origin.

$p_1 = 0.34$, the initial likelihood of disease in the left neck

$p_2 = 0.40$, the initial likelihood of disease in the right neck

$p_3 = 0.26$, the initial likelihood of disease in any other upper torso nodal group (either axilla or mediastinum)

If we suppose that disease detection is equally good and duration of localized disease equally long in all regions, patients diagnosed after involvement of one region and before involvement of a second will have the relative frequencies shown above. When precisely two regions are involved, ten possible combinations of the 5 upper torso regions are possible, for example bilateral neck, ipsilateral neck and axilla, etc. The pattern of bilateral neck involvement can

result from the sequence of left neck followed by right neck, sequence 12, or from the sequence right neck followed by left, sequence 21, and these two sequences will not in general be equally likely. The probability of sequence 12 is given by

$$0.34\left(\frac{0.40}{0.40+0.26}\right)=0.21$$

where the term in parentheses is the probability of secondary involvement of area 2 after area 1 is already involved. Similarly the probability of sequence 21 is

$$0.40\left(\frac{0.34}{0.34+0.26}\right)=0.23$$

The total probability of bilateral neck involvement, achieved in either sequence, is .21 + .23 = .44. Thus a little less than half of all patients with exactly two regions involved would have bilateral neck involvement, while the eight other combinations of two regions would be represented in total in somewhat more than half of patients. The probabilities for all combinations are shown in Table 2 as proportions expected.

A similar process can be followed to determine the probabilities of patterns involving 3 or 4 regions.

Findings

A. Observed numbers, all cases

Table 1 shows the frequencies of appearance of all 31 possible patterns in our 160 cases. It is seen that almost all possible patterns have appeared. Only 4 patterns are shown with frequency 0. In every case these 4 involve one axilla without apparent disease in the ipsilateral neck. These are all patterns designated in the tables as involving non-adjacent regions. The total number of patients with patterns of non-adjacent sites in Table 1 is 14, while 79 patients exhibit adjacent patterns. Clearly patients with a single site (55) or with all 5 sites (12) involved are not relevant to this question of adjacency. The high proportion of adjacent sites may seem to support a theory of preferable spread to adjacent regions, but it will be seen that the concept of spread independent of site of origin predicts a very similar number of adjacent and non-adjacent patterns.

Table 2 shows observed and expected patterns for disease involving exactly 2 regions. In this table bilaterally symmetrical groups are combined. Thus the pattern of ipsilateral neck and axilla actually involves a right and a left pattern, and contralateral neck and axilla involves the two patterns of left neck-right axilla and right neck-left axilla. No significant differences in the two sides have appeared in any of the symmetrical patterns in this study, though with more voluminous material it may still be useful to consider the sides separately.

The observed distribution in Table 2 differs strikingly from prediction. Bilateral neck disease is clearly deficient, while patterns of neck and adjacent axilla or mediastinum are clearly excessive. Perhaps the most telling argument against the theory of spread independent of origin is the finding of 13 ipsilateral neck-axilla cases and only a single contralateral neck-axilla case. These two patterns would be predicted to be equally likely if the two sides of neck were equally likely and the two axillae equally likely in initial probabilities. The deficiency of bilateral neck disease agrees with the known lack of lymphatic communication across the mid-line of the neck. The finding of 2 cases of bilateral axillary disease is surprising and will be considered later in relation with the more complex patterns.

Table 1 Distribution of Patients by Anatomic Region Groups.

Group Number	Regions	Regions Adjacent	Number of Patients
1.1	Left neck	–	19
1.2	Right neck	–	22
1.3	Left axilla	–	4
1.4	Right axilla		5
1.5	Mediastinum		5
2.1	Bilateral neck	Yes	7
2.2	Ipsilateral neck, axilla, left	Yes	6
2.3	Ipsilateral neck, axilla, right	Yes	7
2.4	Contralateral left neck, right axilla	No	0
2.5	Contralateral right neck, left axilla	No	1
2.6	Left neck, mediastinum	Yes	13
2.7	Right neck, mediastinum	Yes	8
2.8	Bilateral axillae	No	2
2.9	Left axilla, mediastinum	No	0
2.10	Right axilla, mediastium	No	0
3.1	Bilateral neck, left axilla	Yes	1
3.2	Bilateral neck, right axilla	Yes	1
3.3	Bilateral neck, mediastinum	Yes	22
3.4	Left neck, bilateral axillae	No	2
3.5	Right neck, bilateral axillae	No	2
3.6	Ipsilateral neck, axilla, left, mediastinum	Yes	3
3.7	Ipsilateral neck, axilla, right, mediastinum	Yes	1
3.8	Contralateral left neck, right axilla, mediastinum	No	1
3.9	Contralateral right neck, left axilla, mediastinum	No	0
3.10	Bilateral axillae, mediastinum	No	1
4.1	Bilateral neck, axillae	Yes	3
4.2	Bilateral neck, left axilla, mediastinum	Yes	3
4.3	Bilateral neck, right axilla, mediastinum	Yes	4
4.4	Left neck, bilateral axillae, mediastinum	No	2
4.5	Right neck, bilateral axillae, mediastinum	No	3
5	Bilateral neck, axillae, mediastinum	–	12
	Total		160

Table 2 Groups of Two Anatomic Regions.

Group Number	Regions	Number of Patients Observed	Number of Patients Expected	Proportion Observed	Proportion Expected
2.1	Bilateral neck	7	19.4	.16	.441
2.2, 2.3	Ipsilateral neck, axilla	13	7.3	.30	.166
2.4, 2.5	Contralateral neck, axilla	1	7.2	.02	.163
2.6, 2.7	Neck, mediastinum	21	8.1	.48	.183
2.8	Bilateral axillae	2	0.6	.05	.014
2.9, 2.10	Axilla, mediastinum	0	1.4	.00	.032
Total		44	44.0	1.01	.999

Group Numbers	Regions	Number of Patients Observed	Number of Patients Expected
2.1, 2.2, 2.3, 2.6, 2.7	Adjacent	41	34.8
2.4, 2.5, 2.8, 2.9, 2.10	Non-adjacent	3	9.2
Total		44	44.0

If the several patterns involving adjacent regions are grouped together, they are found significantly in excess.

	Observed	Expected
Adjacent	41	34.8
Non-adjacent	3	9.2

Table 3 Groups of Three and Four Anatomic Regions.

Group Number	Regions	Number of Patients Observed	Number of Patients Expected
3.1, 3.2	Bilateral neck, axilla	2	17.2
3.3	Bilateral neck, mediastinum	22	9.6
3.4, 3.5	Neck, bilateral axillae	4	2.1
3.6, 3.7	Ipsilateral neck, axilla, mediastinum	4	2.5
3.8, 3.9	Contralateral neck, axilla, mediastinum	1	2.4
3.10	Bilateral axillae, mediastinum	1	0.2
Total	Groups of three regions	34	34.0
4.1	Bilateral neck, axillae	3	4.3
4.2, 4.3	Bilateral neck, axilla, mediastinum	7	10.0
4.4, 4.5	Neck, bilateral axillae, mediastinum	5	0.7
Total	Groups of four regions	15	15.0

When adjacent site patterns are grouped together for Table 3 they are actually found to be significantly deficient in number.

	Observed	Expected
Adjacent 3-regions	28	29.3
Adjacent 4-regions	10	14.3
Total Adjacent	38	43.6
Non-adjacent 3-regions	6	4.7
Non-adjacent 4-regions	5	0.7
Total Non-Adjacent	11	5.4

Nevertheless both the bilateral neck pattern and the bilateral axilla pattern contradict a theory of preferable spread to adjacent regions.

Table 3 presents similar data for patterns involving 3 regions and patterns involving 4 regions.

Again striking differences from prediction are seen, and again these are not regularly accounted for by adjacency. Thus bilateral neck with one axilla is greatly deficient and bilateral neck with both axillae is slightly deficient. Bilateral neck and mediastinum, however, is clearly in excess. Thus spread from one side of neck to the other may be supposed to occur almost exclusively by way of the mediastinum.

As with patterns of 2 regions, the distributions of 3 region patterns favors ipsilateral neck-axilla over contralateral neck-axilla, though with the smaller numbers in Table 3 the finding is less striking. Again patterns involving bilateral axillae with unilateral neck or no neck disease occur in excess of expectation.

When all sites from Tables 2 and 3 are combined with respect to adjacency, the resulting total is in striking agreement with expectation.

	Observed	Expected
Adjacent	79	78.4
Non-adjacent	14	14.6
Total	93	93.0

If these totals were considered without attention to the component groups, it would appear that the theory of spread independent of site of origin was well supported. The components, however, indicate that this theory is not acceptable, and much of the deviation is in the direction of preferred spread to anatomically adjacent regions between neck and ipsilateral axilla or mediastinum. The concept of anatomically adjacent spread, however, must also be rejected in view of the deficiency of cases with bilateral neck disease in the absence of mediastinal involvement.

An alternative theory that envisions spread dependent on the site of origin has been referred to as functional contiguity. This concept is defined by the sequence

right axilla – right neck – mediastinum – left neck – left axilla

Contiguous patterns are almost routinely in excess of expectation and discontiguous patterns deficient. Totals observed and expected by contiguity are:

	Observed	Expected
Contiguous	67	37.5
Discontiguous	26	55.5
Total	93	93.0

When individual patterns in Tables 2 and 3 are reviewed there remain 5 exceptions to the rule favoring contiguous patterns, namely.

	Observed	Expected
1. Discontiguous		
a) Bilateral axillae	2	0.6
b) Neck, bilateral axillae	4	2.1
c) Bilateral axillae, mediastinum	1	0.2
d) Neck, bilateral axillae, mediastinum	5	0.7
2. Contiguous		
Bilateral neck, axilla, mediastinum	7	10.0

For the first 4, discontiguous, patterns above, observed cases exceed expectation. In total 12 such patients are shown, while only 3.6 are expected. All 4 patterns involve bilateral axillae. This observation will be considered later in relation to histologic type. The fifth pattern listed above is a contiguous pattern and would be expected to appear in excess of prediction. It actually appears to be deficient, though not significantly so, and this is acceptable as a chance deviation in this small series.

While it seems clear that bilateral neck regions are not commonly simultaneously involved with disease in the absence of mediastinal involvement, it seemed useful to determine whether *lower* neck and supraclavicular regions show bilateral disease. To investigate this possibility we excluded 16 patients in whom neck involvement was confined to mid-and upper neck. Table 4 shows the pattern of the remaining 77 cases. This limitation makes no important difference in the interpretation of patterns, and it appears that even in the lower neck, bilateral spread is chiefly by way of the mediastinum.

B. Observed Numbers by Histologic Type

Table 5 indicates the distribution of these cases by histologic type. The method of analysis of regional distribution patterns as discussed in the previous section requires a breakdown of groups of patients with 2 regions, 3 regions, or 4 regions involved into their specific anatomic patterns. The table shows that such an analysis within histologic type will be possible only for the two more common morphologies, nodular sclerosing and mixed cell type.

It may be noted in Table 5 that the 4 histologic types differ significantly in number of regions involved. Among 12 upper torso cases with lymphocytic predominance there are 7, or 55%, confined to a single region. The mixed cell cases are similar in this respect, with 26 of 55, or 47%, confined to one region. Nodular sclerosing histology, on the other hand rarely appears as stage 1 disease of a single region (16 or 73 cases, 22%), and the small group of 3 cases with lymphocytic depletion includes no instance of disease limited to one region.

Table 6 shows the distribution by region of the cases confined to a single region for the two common histologies, and these numbers are compared with expected values determined from cases of all morphologies. There is a suggestion of a concentration of nodular sclerosing disease in right neck and mediastinum and of mixed cell disease in the left neck. Unfortunately the numbers of cases confined to a single region are too small to establish with significance any tendency of initial disease to have different anatomic distributions for the two morphologies. Consequently the expected distribution by anatomic pattern in Table 7 are derived from the initial likelihood percentages used for the total material.

Table 4 Observed and Expected Numbers. Excluding Patients with Neck Involvement Confined to Upper Neck.

	Number of Patients Observed	Expected
Groups of 2 regions		
Bilateral neck	6	13.1
Ipsilateral neck, axilla	11	7.0
Contralateral neck, axilla	0	7.0
Neck, mediastinum	20	8.9
Bilateral axillae	2	0.9
Axilla, mediastinum	0	2.2
Groups of 3 regions		
Bilateral neck, axilla	1	10.8
Bilateral neck, mediastinum	17	7.0
Neck, bilateral axillae	2	2.2
Ipsilateral neck, axilla, mediastinum	4	2.9
Contralateral neck, axilla, mediastinum	1	2.9
Bilateral axillae, mediastinum	1	0.3
Groups of 4 regions		
Bilateral neck, axillae	2	3.0
Bilateral neck, axilla, mediastinum	6	8.0
Neck, bilateral axillae, mediastinum	4	1.0
Total	77	77.2

Table 5 Distribution of Patients by Histologic Type and by Number of Regions Affected.

Number of Regions	Hystologic Type L. P.*	N. S.*	M. C.*	L. D.*	Unclassificable	Unknown	Total
1	7	16	26	0	1	5	55
2	3	23	12	2	0	4	44
3	0	20	10	1	1	2	34
4	2	6	4	0	1	2	15
5	0	8	3	0	0	1	12
Total	12	73	55	3	3	14	160

* L. P. = Lymphocytic predominance; N. S. = Nodular sclerosing; M. C. = Mixed cell; L. D. = Lymphocytic depletion.

Table 6 Observed and Expected Numbers. By Histologic Type. One Region Involved.

	Nodular Sclerosing Observed Number	Nodular Sclerosing Observed %	Nodular Sclerosing Expected Number	Mixed Cell Observed Number	Mixed Cell Observed %	Mixed Cell Expected Number
Left neck	4	.25	5.5	12	.46	9.0
Right neck	8	.50	6.4	10	.38	10.4
Left axilla	0	.00	1.2	1	.04	1.4
Right axilla	1	.06	1.5	2	.08	2.4
Mediastinum	3	.19	1.5	1	.04	2.4

Table 7 Observed and Expected Numbers. By Histologic Type. Multiple Regions Involved.

	Number of Patients			
	Nodular Sclerosing		Mixed Cell	
	Observed	Expected	Observed	Expected
Groups of 2 regions				
Bilateral neck	2	10.1	3	5.3
Ipsilateral neck, axilla	7	3.8	4	2.0
Contralateral neck, axilla	1	3.8	0	2.0
Neck, mediastinum	13	4.2	4	2.2
Bilateral axillae	0	0.3	1	0.2
Axilla, mediastinum	0	0.7	0	0.4
Groups of 3 regions				
Bilateral neck, axilla	0	10.2	1	5.0
Bilateral neck, mediastinum	17	5.7	4	2.8
Neck, bilateral axillae	0	1.2	4	0.7
Ipsilateral neck, axilla, mediastinum	3	1.4	0	0.7
Contralateral neck, axilla, mediastinum	0	1.4	0	0.7
Bilateral axillae, mediastinum	0	0.1	1	0.06
Groups of 4 regions				
Bilateral neck, axillae	0	1.7	1	1.1
Bilateral neck, axilla, mediastinum	5	4.0	0	2.6
Neck, bilateral axillae, mediastinum	1	0.3	3	0.2
Total	49	48.9	26	25.96
Adjacent Regions	47	41.1	17	21.7
Non-adjacent Regions	2	7.8	9	4.3
Total	49	48.9	26	26.0
Contiguous Regions	45	19.1	12	10.3
Discontiguous Regions	4	29.8	14	15.7
Total	49	48.9	26	26.0

In Table 7 some of the characteristics seen in Tables 2 and 3 are found to appear in both nodular sclerosing and mixed cell type cases. Thus for both types the ipsilateral neck-axilla combination is more common than expected while the contralateral pattern is less common.

There are, however, differences between the two types. For nodular sclerosing disease the association between neck and mediastinum and the failure of association between the two sides of the neck is striking and significant. While the tendency is also present in mixed cell disease, it is slight and may be a purely chance finding.

The association between the two axillae is seen only once in the 49 nodular sclerosing cases, and in this patient the mediastinum and one side of the neck were also involved. In the smaller mixed cell series, 26 cases in total, there are 10 instances of bilateral axillary involvement.

When patterns are designated as adjacent or non-adjacent, it is found that nodular sclerosing almost uniformly fits the pattern of adjacent area involvement. In contrast, mixed cell disease shows fewer adjacent patterns than expected on a basis of spread independent of site of origin.

The concept of contiguity is even more satisfactory than that of adjacency in describing patterns of nodular sclerosing disease. Only 4 discontigous patterns are reported, as compared with 29.8 expected. One may wonder whether so few exceptions do not represent failure in observation or clerical errors in recording observed disease. With mixed cell disease the finding is quite different. Fourteen discontiguous patterns are reported among 26 cases. This number is almost equal to the number 15.7 expected.

In general then mixed cell disease confined to the upper torso shows no more than a chance tendency to spread to contiguous regions, and it shows a significant tendency to spread preferentially to non-adjacent regions, particularly to both axillae. Since no theory has been proposed that predicts a preference for non-adjacent spread over random spread, one may question the basic likelihood values used in computing expected numbers. These likelihood values were derived from the stage 1 cases of all morphologic types taken together, and the frequencies of axillary disease as the initial site were

Left axilla	0.07
Right axilla	0.09

If mixed cell disease appears initially in axillae more commonly than other histologic types do, we should use larger values for generating the expected frequencies of bilateral axillary disease. Our stage 1 mixed cell cases, however, give no support to this argument, since for mixed cell disease Table 6 indicates frequencies of 0.04 and 0.08 for initial axillary involvement. Smithers' overall figures similarly give no support to the suggestion that our axillary frequencies are too low, since his figures of 0.06 and 0.08 are even lower. There remains then the phenomenon of mixed cell disease having no apparent initial predisposition for the axillae but of its spreading preferentially to axillae.

Discussion

The data described here were not collected primarily for the purpose for which they have been used, and any conclusions must be considered suggestive rather than definitive. It has been mentioned that the reported disease patterns are based on clinical

reports, and microscopic confirmation has not been obtained, except for the fact that at least one involved region must be confirmed in each accepted patient. It is entirely possible that in doubtful cases observers have reported the patterns they expected to find. Such a bias would not, we believe, affect one histologic type differently from another, since the clinical description of disease is commonly recorded before the specific histologic type is known.

The sequence in which disease is detected may differ strikingly from the sequence in which it occurs, since detection by physical examination is much easier in cervical regions, for example, than in mediastinum. This effect would tend to decrease the reported frequency of mediastinal disease in stage 1 more than in stage 2 and could account in part for the observed excess of disease involving neck and mediastinum. Some of the most striking findings in our data, however, are the preferences for ipsilateral patterns over contralateral patterns, and these findings are not explainable in terms of difficulty of detection.

We have used distribution of disease at the time of initial diagnosis as a clue to a sequence leading to this distribution. Clearly these sequences would be better studied by observations over time. A particular difficulty in using observations at one point in time, as we have done here, is that any observed pattern may be frequent either because it occurs commonly in the time course of events or because it persists for an extended time. Thus ipsilateral neck-axilla disease may occur with the same frequency over time as does contralateral disease. Ipsilateral disease, however, may be a very stable pattern, slow to progress to other areas, while contralateral neck-axilla may advance rapidly to involve the "skip" areas. We will ultimately have some data relevant to longitudinal observations, though at present our sequences of extension are too few for more than anectodal comment. *Fuller,* et al. (12) have given a detailed analysis of patterns of extension in a series of patients observed from 6 to 22 years.

Even recognizing these reservations, we feel that these data give support to the impression of a rather marked difference in behavior between nodular sclerosing and mixed cell disease. Nodular sclerosing may be thought of as a form of Hodgkin's disease rising very commonly in mediastinal nodes. Since disease confined to the mediastinum will be recognized only by chance chest X-Ray or by symptoms, nodular sclerosing disease is, in fact, rarely discovered in stage 1 confined to one region. Its commonest route of extension is to the neck with little preference to side, and by the time this extension is clinically detected it is very likely to have extended to both sides.

By contrast mixed cell disease may be though of as arising commonly in one side of the neck, with little preference to side. It commonly becomes palpable before extending beyond its region of origin. Its extension is unlikely to be to the contralateral neck and is likely to be to contiguous areas, though this effect is slight and in our small series does not differ significantly from a pattern of spread independent of site of origin. Our series suggests a tendency to extend preferentially to bilateral axillae, even without involvement of intermediate contiguous regions.

A somewhat larger series of upper torso cases studied by *Kaplan* (11) shows similar deviations from expected distributions for cases with disease confined to two or to three regions. In particular, bilateral neck disease in the absence of mediastinal involvement is significantly less common than expected, and ipsilateral neck-axilla

patterns are greatly in excess of contralateral patterns. Furthermore these deviations are strikingly apparent in nodular sclerosing disease, while mixed cell disease does not differ significantly from expectation in its anatomic distribution. There are, however, certain interesting differences between the present series and Kaplan's data. First, the ratio of mixed cell cases to nodular sclerosing cases is greater in the present series than among Kaplan's patients (.53 in present series, .40 in Kaplan's series). Second, the proportions of localized cases diagnosed while still confined to a single nodal region is greater in the present series (0.33 present series, 0.22 Kaplan's series). Third, for the group of patients with four anatomic regions involved the distribution of disease patterns is significantly different between the two series. The excess of patients with bilateral axillary disease in this group is seen only in the present series. These findings suggest that there may be some important differences in case material, in diagnostic evaluation, or both between the two series. Nevertheless the two series support one another in the principal conclusions.

Bonnadonna, Banfi, et al. (3, 4) have compared Hodgkin's disease and other lymphomas with respect to frequency of adjacent patterns of initial involvement. They find that 66% of initial Hodgkin's disease involves adjacent regions as contrasted with 35% for other lymphomas. The initial likelihood proportions for the two diseases are given by these authors as follows

	Hodgkin's disease	Other lymphomas
Neck	41%	27%
Axillae	10%	16%
Mediastinum	20%	6%
Paraaortic	20%	9%
Spleen	2%	2%
Iliac	6%	23%
Inguinal	1%	17%

It is immediately apparent that the common regions for Hodgkin's tend to be adjacent to one another, while the other lymphomas appear chiefly in two widely separated regional groups, namely neck-axilla and iliac-inguinal. Clearly adjacent regions would be much more common in Hodgkin's disease than in the other diseases, if spread were independent of site of origin. Assuming bilateral symmetry for the neck, axilla, iliac, and inguinal regions it can be shown that patterns involving precisely two regions would be expected to involve adjacent regions in 50% of Hodgkin's patients and in 26% of cases of other lymphomas.

	Hodgkin's	Other lymphomas
Proportion Adjacent.		
Observed	66%	35%
Expected	50%	26%
Observed/Expected	1.32	1.35

It would then appear that both diseases may have somewhat more frequent adjacent patterns than expected but that the proportion excess adjacent cases over expected is essentially the same. The major difference between the two diseases is in the relative susceptibility of the various nodal regions rather than in the effect of the initial region of involvement in determining the next affected region.

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