Papers and Originals

Hodgkin's Disease*—I

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[WITH SPECIAL PLATE]

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I must thank you, Mr. President, and your predecessor, for the great privilege of being invited to deliver this centenary Bradshaw lecture. William Wood Augustus Fitz-Milton Bradshaw died 100 years ago last August. Dr. Bradshaw, a member of this College, was clearly a man of intelligence, culture, and charm, but not a great deal seems to be known about his work beyond the conduct of a busy practice in Reading. In life, so far as I am aware, he had no outstanding professional claim to fame; in death his name has become well known to medicine in this country. His widow bequeathed £1,000 to the College in her will dated 6 September 1875 to found this annual lecture in honour of her husband. He is thus chiefly remembered here each year because he inspired his wife with pride and with affection. Men have been commemorated for lesser achievements. Many more would be famous if their work received the acknowledgement which their wives thought to be its due. Mrs. Bradshaw wrote on her husband's tombstone: "Such as he will never fade." Each time we remember him on this occasion we make her faith a little more secure.

In the same year that William Bradshaw died, at the age of 66, another more famous doctor ended his life at 68, for this year is also the hundredth anniversary of the death of Thomas Hodgkin. Such a concurrence of centenaries encouraged me to select Hodgkin's disease as the subject for this Bradshaw lecture.

Thomas Hodgkin was a man of parts: he could have addressed you in Greek, Latin, French, German, or Italian. As a young man he became curator of Guy's hospital museum, and later went for a short time to reorganize the medical school at St. Thomas's when appointed there as lecturer in the practice of physic. He is best known today for a paper which appeared in the *Transactions* of the Medical and Chirurgical Society of London in 1832, entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen." He is rightly remembered for that particular work because it was the first clear account we have of disease originating in the lymphoreticular system. He there reported his findings in six postmortem examinations of his own, and in one made by his friend Dr. Carswell. They had examined two boys and five men who had died with remarkable enlargement of their cervical, axillary, para-aortic, and inguinal nodes and spleen. Hodgkin related this post-mortem study to clinical observations which he had made, and concluded that here was no inflammatory reaction but a primary affection of the spleen and lymph nodes resulting in "interstitial enlargement" and "hypertrophied structure."

Both clinically and histologically Hodgkin's disease is now recognized as a progressive lymphoreticular neoplasm. It is a recognizable entity within this group, despite considerable varia-

tion in its histological components and in the range of its clinical manifestations, because there is a progressive change in its characteristic morphology and a recognizable set of peculiarities in its clinical behaviour. Hodgkin's disease develops the accepted characteristics of an aggressive neoplasm—proliferation, invasion, and dissemination—but it also presents unusual features to fascinate inquiring minds and disturb the tidy classifiers. It has been a point of controversy in and out of the field of neoplastic disorder for a hundred years.

In this lecture I will discuss a few selected manifestations of this disease which seem to me to have significance, and which must be accounted for by anyone attempting to explain its origins and its behaviour patterns. I shall then suggest how some of these same manifestations, through clinical observation and the test of animal experiment, may be fitted into a newly developing, if still rather blurred, pattern of understanding.

Incidence, Sex, and Age

Hodgkin's disease is not a very common disorder. It is about as frequent in men as tumours of the testicle, and in women as tumours of the salivary glands. It has a male preponderance, with a small shift in males towards earlier development and slightly worse prognosis. It occurs at any age, with a tendency towards a bimodal curve. In the Royal Marsden Hospital series the main age peak is in the twenties, with a minor peak in the late forties in men and early fifties in women.

Table I sets out the total number of patients with Hodgkin's disease seen at the Royal Marsden Hospital during 1935–64.

TABLE I.—Patients with Hodgkin's Disease Seen at the Royal Marsden Hospital During 1935–64

Years	No. of Patients Seen	Staging
1935–44	66	Not staged 66
1945–9	48	{ Stage I 67
1950–4	63	{ " II 104
1955–9	117	{ " III 39
1960–4	122	{ " IV 61
		{ Unstaged 1
		{ Recurrent 78
	416	416

Family History

There is a good deal of evidence for a familial tendency in Hodgkin's disease, and the literature on this aspect was well reviewed by Razis, Diamond, and Craver (1959). They found 63 instances of familial Hodgkin's disease in the literature and presented 13 examples. They found that the probability that a near relative of a patient with Hodgkin's disease would develop this disorder was three times that of near relatives of patients

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without the disease. In some cases the dates of onset were separated by a number of years, but a father and son and a brother and sister developed the disease at the same time, and nine pairs of relatives did so within three years of each other. As examples: Smith (1934) reported Hodgkin's disease in two sisters and in one of their female cousins; Uddströmer (1934) also reported Hodgkin's disease in two sisters and their cousin; Jackson and Parker (1947) reported it in a sister and three brothers; Craver (personal communication to Schier, 1954) reported it in two sisters and a brother, with the possibility that a third sister also had the disease. Rigby, Rosenlof, Pratt, and Lemon (1966) reported that in Nebraska the occurrence of leukaemia and lymphoma was two and a half times more frequent in the family members of a leukaemia-lymphoma proband group (92 families) than in a control group (62 families).

In our Hodgkin's disease series (Table II), one patient said that her brother had died of the same disease 10 years previously, and there were five instances of two brothers being affected. Small groups of cases from individual hospitals, while not in themselves of great significance, provide useful additions to the mounting evidence.

TABLE II.—*Hodgkin's Disease in Siblings in the Royal Marsden Hospital Series, 1935-64*

Patients with Histologically Confirmed Hodgkin's Disease				Siblings
Case	Sex	Age	Onset	
1	F	36	1937	Patient said her brother had died of Hodgkin's disease in 1927
2	M	24	1947	Histologically proved Hodgkin's disease in brother aged 29 in 1951
3	M	43	1951	Patient said brother had died of Hodgkin's disease aged 44
4	M	61	1952	Patient said brother had died of Hodgkin's disease in 1944
5	M	54	1961	Patient's brother died of Hodgkin's disease aged 40 in 1963 (postmortem findings at another hospital)
6	M	21	1964 (Jan.)	Histological diagnosis of Hodgkin's disease in brother aged 17 in March 1964

Accounts of chromosome abnormalities in Hodgkin's disease are quite recent (Ricci, Punturieri, Bosi, and Castoldi, 1962; Spriggs and Boddington, 1962; Miles, Geller, and O'Neill, 1966), and so far show only gross irregularities commonly found in the cells of many malignant tumours. The long intervals between times of onset in some families may make a common infective source seem unlikely, but most pairs occur within two to three years of each other, and in a slowly developing disease an infective origin must still be regarded as a possibility. One of our pairs of brothers developed their first symptoms within three months of each other. Gilmore and Zelesnick (1962) reported the occurrence of three cases of leukaemia and three of Hodgkin's disease in four families who occupied adjoining houses for 13 years in a town of 2,500 persons; these families had no previous history of these diseases, and during the period of observation there was only one other such case in the whole of the rest of the town. The work of Dowsett (1966) in the Kingston area south of London, and of Lundin, Fraumeni, Lloyd, and Smith (1966) in Pennsylvania, has added interest to this aspect of the study of this group of diseases. In the Pennsylvania report deaths from leukaemia and lymphoma grouped in pairs by spatial proximity showed an excessive number occurring as long as six to eight years apart. The pattern emerging in this aspect of Hodgkin's disease, though still indefinite, would seem to support an infective rather than an inherited source. Further work in this field is clearly needed.

Progression

Histologically there is a gradation of change in differentiation from Hodgkin's paraganuloma through Hodgkin's granuloma

to Hodgkin's sarcoma—to use the terms of Jackson and Parker (1947). This classification was most valuable in its day in stressing the wide variation in malignant characteristics to be found in this disease, but Lukes, Butler, and Hicks's (1966) classification seems preferable, with divisions into nodular or diffuse types of lymphocytic and/or histiocytic proliferation, then into nodular sclerotic, mixed, diffuse fibrotic, and reticular types. The evolution of the histological process according to Lukes *et al.* is from a stage of predominantly lymphocytic proliferation with a variable histiocytic component, usually associated with stage I of the disease, through to a stage of general depletion of cellular components, especially lymphoid, associated with a particular increase in Sternberg-Reed cells, in the diffuse fibrotic and reticular types which are commonly associated with a progressive systemic disease of brief duration. Variation in collagen band formation, in fibrosis, and in eosinophil and plasma-cell infiltration may represent reactions to the disease process or the scars of immunological battle. An important feature is that lymphocytic proliferation goes with long survival, and lymphocytic depletion, fibrosis, and reticular pattern with short survival. Hodgkin's disease provides another example of progression in malignant characters. Histologically, it also points, within the lymph node, to the serious significance of progressive lymphoid depletion which is to be observed clinically.

Primary Origin

Lymph Nodes

Hodgkin's disease is predominantly a tumour of lymph nodes, and though it may spread in the later stages to many parts of the body, particularly the spleen, liver, lungs, and bones, the nodes are the structures where the process constantly arises and has its being. The most common form of onset is enlargement of the lymph nodes of the neck (Table III). The more localized the disease when the patient first comes to hospital the more likely is it that enlargement of the neck nodes was the first sign detected (71% in stage I (a), down to 26% in stage IV (b)).

TABLE III.—*First Detected Lymph-node Enlargement, Being the Presenting Sign Among 326 Cases of Hodgkin's Disease Seen at the Royal Marsden Hospital, 1945-64*

Cervical ..	167 (51%)	Inguinal ..	27	Preauricular ..	1
Mediastinal ..	40	Abdominal ..	15	Parasternal ..	2
Axillary ..	30	Submental ..	1	Multiple sites ..	43

If such symptoms as cough, dyspnoea, dysphagia, mediastinal compression, and pain in the chest or abdomen are very properly counted as being due to mediastinal or abdominal node enlargement, then no more than 11 patients in our series of 350 first became aware of their illness through local symptoms other than those clearly due to node involvement. Three of these 11 patients had bone pain, three had thymic tumours, two had skin ulcers, two had spinal compression, and one had a thyroid tumour. The patients with bone pain and skin ulceration already had undetected lymph-node involvement. Spinal compression in Hodgkin's disease may occur after infiltration of the epidural space by extension from adjacent lymph nodes via the intervertebral foramina, and may also occur after metastatic vertebral involvement. It is probable, then, that the only primary tumours outside the lymph nodes to call attention to the disease in our series of patients were three in the thymus and one in the thyroid.

There have been 95 postmortem examinations in our 1945-64 group. For most of these we have detailed reports from our own pathology department, some equally thorough from other hospitals, but there are also a few rather brief statements of the more obvious spread. From these I have merely extracted information as given; no pathologist has yet made a detailed

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FIG. 1.—Lymphogram showing involvement of left iliac and inguinal nodes in a patient with left neck node enlargement and no other clinically or radiologically detected evidence of Hodgkin's disease.

FIG. 2.—Spleen scan in a patient with Hodgkin's disease.

FIG. 3.—Thymidine-labelled mononuclear cells from the peripheral blood in a patient with Hodgkin's disease.

FIG. 4.—A large node showing the pattern of oil distribution in lymphography in Hodgkin's disease.

correlation. Of the 95 patients, 91 had lymph-node involvement at death, widespread in 69 and more limited in 22. Of the four patients without node involvement one had lung infiltration persisting after treatment and three died with an acute terminal illness. Of these three, two had involvement of liver and spleen, but in one no sign of any tumour manifestation of Hodgkin's disease was left, and virtually no lymphatic tissue, the patient having been overwhelmed by infection (Smithers, 1959). This is the most nearly complete example of lymphoid depletion seen in our group.

Thymus

In any study of tumours involving what Medawar has called "immunologically competent cells," the thymus must be of special interest. Our three most likely cases of primary Hodgkin's disease of the thymus occurred in two women aged 23 and 33 and a man aged 24. All three had a thymectomy performed as their first treatment, one had a chain of nodes running up into the neck, but there was no sign of extension beyond the thymus in the other two. Thymic involvement was mentioned only rarely in our postmortem reports. Many

of the patients on whom necropsy was performed had mediastinal tumours, however, and it may have been difficult in some to know if the thymus was involved. Intrathoracic involvement outside the lungs was reported radiologically before treatment in 38% of our staged cases in the period 1945-64 (Table IV). Thymic involvement, primary or perhaps secondary, was confirmed in three patients, was suspected in another eight during life, was found at necropsy in two, and may well have been present in others. A few patients in whom a diagnosis of granulomatous thymoma (thymoma of Lowenhaupt) was made have not been included in this series owing to the dispute about its possible relation to Hodgkin's disease, which is not yet resolved.

TABLE IV.—*Pretreatment Radiological Evidence of Intrathoracic Tumour Outside the Lungs in 271 Patients with Staged Hodgkin's Disease Seen at the Royal Marsden Hospital, 1945-64*

Stage	No. of Patients	Patients with Intrathoracic Tumour Outside Lungs	Patients with Thymic Involvement	
			Suspected	Confirmed
I	67	7 (10%)	4	2
II	104	47 (46%)	3	1
III	39	20 (51%)	0	0
IV	61	28 (46%)	1	2*
	271	102 (38%)	8	5

* Confirmed at postmortem examination.

A higher incidence of thymic involvement than has been found in our series has been reported by others—for example, Marshall and Wood (1957) and Hoffbrand (1965). Nevertheless, experience refutes Thomson's (1955, 1956) idea that Hodgkin's disease is to be regarded as a primary tumour of the thymus. I opposed this suggestion at the time (Smithers, 1956), while listing some of the evidence for other connexions between the thymus and lymphoid tumours. It is interesting that our group of patients treated by thymectomy (3) or strongly suspected of thymic involvement during life (8)—all 11 of whom were irradiated—seems to have done well so far. The three patients operated on are all alive without having had any recurrence 2½, 3½, and 10½ years after their treatment. Of the eight patients who had radiological evidence strongly suggesting a thymic tumour during life and histological evidence of Hodgkin's disease on biopsy of a lymph node, one was not treated by us and has been lost sight of; six are alive 2½, 3½, 4, 5½, 10, and 15½ years after treatment; only one of these six living patients has had any recurrence—in an unirradiated axilla 10 years after treatment to the mediastinum. The eighth patient has died; he had no neck irradiation initially, had a recurrence in the neck nodes within nine months of treatment to the mediastinum, and died after repeated treatments nearly nine years later.

The relation between the thymus and radiation-induced lymphoma has long been established in laboratory animals (Kaplan, 1948, 1949). Whole-body irradiation can induce lymphomas transmissible to non-irradiated animals by thymic transplant after whole-body irradiation (Kaplan, 1950). Lymphomas can develop in non-irradiated thymic grafts placed in thymectomized irradiated mice (Kaplan and Brown, 1954; Law and Potter, 1958). Agents increasing thymic weight promote the induction of lymphoid tumours, and those reducing it prevent their occurrence or assist in their regression. The establishment in recent years of the thymus as a controlling influence in the development of immunological mechanisms—particularly through Miller's (1961, 1962) work on thymectomy in newborn mice—has added a new interest to the study of connexions between the thymus and lymphoreticular tumours.

Liver

Hodgkin's disease affecting the liver alone is rare; the liver is much more frequently involved as a terminal event than as a primary focus. Involvement of the liver by itself was reported

M. A. EPSTEIN *ET AL.* VIRUS IN LYMPHOBLASTS FROM BURKITT LYMPHOMA (p. 290)

All the figures are electron micrographs of thin sections of cultured lymphoblasts from a New Guinea Burkitt lymphoma. The cells were fixed in glutaraldehyde followed by osmium, embedded in epoxy resin, and contrast stained in the section with uranyl acetate.

FIG. 1.—Part of a nucleus bounded by its envelope (e) composed of the usual two membranes with perinuclear space between; some juxtanuclear cytoplasm with rough endoplasmic reticulum (er) lies on the extreme right. The nucleoplasm is of low electron opacity and contains immature virus particles (arrows) either empty or with dense central nucleoids. ($\times 34,000$.)

FIG. 2.—Detail of cytoplasm with altered mitochondria above, Golgi elements (g), and two immature virus particles about 75 m μ in diameter below and to the left; one of the particles lies close beside a membrane-bounded cytoplasmic space. ($\times 55,000$.)

FIG. 3.—Juxtanuclear cytoplasm with the double envelope of the nucleus just crossing the upper left corner of the field; free ribosomes are present throughout the cytoplasm together with some rough endoplasmic reticulum (er). On the right two immature virus particles can be seen in the process of budding into membrane-bounded cytoplasmic spaces. The particle above is close to a cytoplasmic membrane, causing it to bulge slightly, while the lower particle protrudes right into a cytoplasmic space whose limiting membrane now surrounds most of the particle's surface. ($\times 55,000$.)

FIG. 4.—Detail of cytoplasm between the nucleus on the left and the cell surface on the right. A mature virus particle (arrow) 115 m μ in diameter lies within a membrane-bounded cytoplasmic space; the particle is surrounded by its final additional outer membrane acquired from the cellular membrane as it matured by budding into the space from the cytoplasmic matrix (cf. Fig. 3). An altered mitochondrion (m) is also present. ($\times 55,000$.)

FIG. 5.—Part of a nucleus (on the left) and adjacent cytoplasm. In the centre of the field an immature virus particle is budding, in this case, through the inner nuclear membrane into the perinuclear space. At this stage the particle is partially enveloped by the inner nuclear membrane. ($\times 55,000$.)

FIG. 6.—Similar field to Fig. 5 with the nucleus again on the left. A virus particle lies in the perinuclear space. It is nearly mature, being almost fully surrounded by its final additional outer membrane derived from the nuclear membrane, but still remains attached at one point by a fine pedicle. On the right an altered mitochondrion can be seen. ($\times 55,000$.)

FIG. 7.—Similar field to Figs. 5 and 6. A mature virus particle enveloped by its final additional outer membrane, derived from nuclear membrane (cf. Figs. 5 and 6), lies free in the perinuclear space. There is abnormal reduplication of the nuclear envelope, and the mitochondria in the cytoplasm on the right are altered. ($\times 55,000$.)

FIG. 8.—Part of a degenerated lymphoblast. Mature virus particles (arrows) lie within membrane-bounded spaces in cytoplasmic debris. A large lipid body is present in the upper left corner of the field. ($\times 48,000$.)

by Goia (1935) and by Symmers (1944); in a case reported by Loehry (1964) liver involvement alone was detected at laparotomy, but at necropsy two months later abdominal nodes were also found to be infiltrated. Of the 95 postmortem examinations in our series the liver was involved in 73%, but always with deposits elsewhere as well.

Spleen

Splenic involvement is a classical part of Hodgkin's disease, but it is still most difficult to determine how often the spleen is the primary site. In only one of our 350 cases was splenomegaly the first sign of the disease, and lymph-node involvement was already detectable in this patient. In none of the 291 cases reported by Peters and Middlemiss (1958) did splenomegaly first call attention to the disease. Splenic enlargement is occasionally present for many years, but obvious clinical involvement—as with the liver—is more often a terminal than an early manifestation. Interest lies in the frequency with which the spleen is secondarily involved during the course of the disease in comparison with other metastasizing neoplasms, as well as in its role as a primary focus. At death such involvement is clear enough: in our 95 postmortem examinations the spleen was involved in 77%, and both spleen and liver were involved together in 59%. While enlargement of the spleen in Hodgkin's disease seems to be a serious and, more often than not, a late development, improved scanning methods may yet lead us to revise this opinion as earlier detection of splenic involvement and tests of splenic function become possible.

Multicentric Origin and Lymph-node Spread

Without going further here into the interesting question of other primary site origins in Hodgkin's disease, it is evident that it is a disease arising predominantly in lymph nodes, and, further, that it spreads predominantly to other nodes. A number of explanations have been offered to account for this pattern, from multicentric origin occurring in one group of nodes after another, to a spread entirely confined to lymphatic pathways. If multiple node involvement is indeed due to metastatic spread from one primary focus, then the disseminating tumour cells may behave in one or other of the following ways: they may travel exclusively or principally along the lymphatics; they may travel by the blood stream and be randomly distributed but capable of growth only in a lymph-node environment in the earlier stages; or they may travel by the blood stream but be filtered off into the most active lymph nodes.

Lymphography

Patients are often seen with multiple node involvement in non-adjacent regions (Special Plate, Fig. 1). This fact has been more clearly brought out since the introduction of lymphography, which we first used in 1961 but did not apply systematically in the lymphomas until 1963. Table V shows that out of 44 cases of Hodgkin's disease in which a lymphogram was done before treatment abdominal or pelvic node involvement

TABLE V.—*Reports on Lymphogram Examinations Made Before Treatment for Hodgkin's Disease in 44 Patients at the Royal Marsden Hospital from May 1963 to September 1966*

Clinical Stage	No. of Patients Examined	Lymphogram Report		
		Positive	Doubtful	Negative
I	10	5	0	5
II	17	7	2	8
III	8	7	0	1
IV	9	8	0	1
	44	27	2	15

was clearly shown in 27. Five out of 10 cases in stage I (all with neck nodes) were found to have nodes involved below the diaphragm. None of these patients showed any radiological evidence of mediastinal node enlargement.

Cook, Jelliffe, Kendall, and McLoughlin (1966) found 27 patients out of 67 with Hodgkin's disease to have positive lymphograms, but did not relate these to stage of disease. Schwarz, Lee, and Nelson (1965) studied 61 cases, and reported their findings by stage; they gave the figures for the effect of lymphography on staging; in their group the staging was changed after lymphography in stages I, II, and III from 9.30, and 22 to 6, 12, and 40—with three inconclusive results. Much more work has now been done, the publication of which will soon help to clarify the extent of spread in the clinically early cases. Lymphography of the intrathoracic nodes would be of great value, but apart from the occasional filling of a few mediastinal nodes after the abdominal under abnormal circumstances and a view from time to time of the thoracic duct, this has not yet been possible.

Scanning

The technique of scanning nodes in the mediastinum is not yet satisfactory though developing well. We are still studying the patterns and trying to decide if what we see is due to uptake in normal nodes and if failure to demonstrate uptake is itself significant. Liver and spleen scanning are now routine procedures. For the spleen we use 200 μ Ci of radioactive chromium incubated for 20 minutes with the patient's own red cells in a water-bath at 49° C. This shows the normal spleen, its size and position, and any enlargement due to disease (Special Plate, Fig. 2). Attempts are made to assess splenic function by estimating the blood-clearance time for these denatured red cells and also by measuring their rate of uptake in the spleen. Poor scans due to failure of denatured red cells to localize in the spleen may be seen in Hodgkin's disease and in other lymphomas. Liver scans with 150 μ Ci of radioactive gold colloid or, better, with 3 to 6 mCi of technetium-99 sulphur colloid give clear pictures. Enlargement is well demonstrated, but involvement by Hodgkin's disease is still not satisfactorily shown unless it is gross.

Lymphography has already to a large extent, and scanning of nodes, liver, and spleen to a less extent, made possible a far more valuable assessment of degree of involvement in this disease than was once possible. When intrathoracic nodes can be demonstrated as satisfactorily as abdominal, we shall be in an even better position, not only in treatment planning but also in providing better evidence on the question of continuous or discontinuous lymph-node spread.

Site of First Detected Node Enlargement

For the moment we must still rely a good deal on the less reliable evidence of gross, clinically detectable involvement for our information. Spread of Hodgkin's disease is obviously not of the same pattern as that seen with most carcinomas, where strictly regional node involvement is often followed by blood-borne metastases, nor like most sarcomas, where nodes are neglected and a predominantly blood-stream spread occurs. In Hodgkin's disease one lymph-node region after another, not necessarily in anatomical sequence and sometimes simultaneously, may be involved, so that at times the whole lymphatic system seems to be invaded before lung or bone metastases appear. Scheer (1963) recorded the sites of first detection of new node enlargement after treatment in stage I cases. He concluded that, though there might be a tendency in Hodgkin's disease for the first recurrence to occur in a contiguous lymph-node-bearing area, the pattern was quite possibly random. Our own records of the site of first recurrence (or of the second

manifestation of the disease in the stage I cases) tend to support this view. However, since node involvement in the early stages occurs most often in the neck, axillae, and mediastinum, later involvement might still appear in regions adjacent to the first rather more frequently than not even if they were new foci of origin. There is no doubt that primary node involvement is not randomly distributed; the questions at issue are ones of multicentric origin and of random spread on the one hand, and of unifocal origin and concentric lymphatic spread on the other. I shall be offering support for a modified version of the first of these alternatives.

Kaplan (1962) holds that Hodgkin's disease is unifocal in origin, basing this view on those stage I cases with early disease clinically confined to one site which show no recurrence for many years after treatment to that site alone. He also says that only one of his "radically treated cases in which the disease was not controlled relapsed with a clinical manifestation obviously remote from the site of initial involvement." In all other cases the first manifestation after remission was either in the treated group of nodes (a "recurrence") or in the next group of adjacent nodes outside the treatment field (an "extension"). Rosenberg and Kaplan (1966) have offered further evidence for this view that Hodgkin's disease arises in a single focus and spreads in a predictable manner along adjacent lymphatics. This is not the place to examine their evidence in detail, but their findings are not borne out by ours. Table VI shows no second manifestation in 11 of our 34 stage I cases; the primary persisted in two cases, it recurred in the primary site in three patients, in an adjacent area in three, and distantly or generally in 17. It is more difficult to make such an assessment in stage II cases, where more than one lymph-node region is involved from the start, but even here (Table VII) our experience does not support the theory of regular predictable spread by contiguity. The case for a simple pattern of concentric lymphatic spread to account for the multiple node involvement seen in Hodgkin's disease is not so firmly established—even on the data presented by Rosenberg and Kaplan—that alternative suggestions should be neglected.

Blood-stream Spread

I find it hard to accept the view that tumour cells in Hodgkin's disease always follow the long and tortuous path they

TABLE VI.—First Recurrence of Hodgkin's Disease After Treatment in 34 Stage I Cases (Royal Marsden Hospital, 1945–64)

Site of First Detected Node Enlargement	No. of Patients	First Recurrence Detected			
		At "Primary" Site	In an Unirradiated "Adjacent" Site	Distant or General	None
Cervical	24	3	2	10	9
Mediastinal . . .	2	—	—	1	1
Axillary	3	—	1	1	1
Inguinal	3	—	—	3*	—
Iliac	2	—	—	2*	—
	34	3	3	17	11

* Persistent primary disease in one case.

TABLE VII.—First Recurrence of Hodgkin's Disease After Treatment in 57 Stage II Cases (Royal Marsden Hospital, 1945–64)

Sites of First Detected Node Enlargement	No. of Patients	First Recurrence Detected			
		At One of "Primary" Sites	In an "Adjacent" Site	Distant or General*	None
Above diaphragm:					
2 "adjacent" . . .	32	3	5†	15	9
2 not adjacent . .	4	—	—	2	2
More than 2 . . .	15	3	—	11	1
Below diaphragm .	6	—	—	6	—
	57	6	5	34	12

* A number of patients with distant or general recurrence also had recurrence at a "primary" site.
† One in an irradiated region.

would have to take along the lymphatics if this was their regular route of spread. Since the neck is by far the commonest site of origin, cells would usually have to travel outside the regional group of nodes against the direction of lymph flow in a system which admittedly has a low pressure but which is liberally supplied with valves. Even if cells did take long journeys by this improbable route, it would be even harder to believe that they never found their way into the thoracic duct or through one of the numerous lymphaticovenous connexions which tend to show up even more prominently in the lymphomas.

The evidence that Hodgkin's disease spreads by the blood stream, whatever other route it may take, seems formidable to me. The first demonstration of tritiated-thymidine uptake by tumour cells in peripheral blood (Kuper and Bignall, 1964)—that is, confirmation of their ability to synthesize D.N.A.—included three cases of Hodgkin's disease. When I showed a slide of Dr. S. W. A. Kuper's at a meeting recently I was afterwards taken to task by a pathologist for encouraging non-pathologists to go away believing that they had indeed seen Hodgkin's disease tumour cells capable of division circulating in the blood stream. Since I had hoped to suggest to them that this was precisely what they might be seeing, a further word is clearly needed. Fig. 3 (Special Plate) is from the blood of a patient with Hodgkin's disease filtered through a Millipore membrane with no red cells or polymorphs remaining, in which a proportion of mononuclear cells have been labelled with radioactive thymidine where the tell-tale film marking which reveals the presence of the thymidine also makes single-cell identification difficult.

The proportion of such labelled mononuclear cells in normal controls and in controls with lung infections and leucocytosis is between 0.2 and 0.4%; in the case of Hodgkin's disease shown in Fig. 3 it was over 5%, or more than 10 times the normal level. One patient with reticulum-cell sarcoma had a count of 21.6%. It may be wise to be sceptical, but the evidence that tumour cells circulate in the blood in Hodgkin's disease is mounting. The most recent paper on this subject (Bouroncle, 1966) reported a study of the blood of 135 patients with Hodgkin's disease, 37% of whom had abnormal cells in the leucocyte concentrates. Typical Sternberg-Reed cells were found in 18.5% of Bouroncle's patients, all these being in an advanced stage of the disease.

Lymphography has brought out another point of interest in this connexion (Special Plate, Fig. 4). The pattern formed by the oily contrast medium in most nodes involved by Hodgkin's disease is quite different from that seen with metastatic involvement of regional nodes draining the site of a primary carcinoma. Instead of localized well-marked peripheral filling-defects resulting from tumours arising from cells brought in by the afferent lymphatics, the whole node appears to be involved by a diffuse process, represented by sinusoidal distortion, often detectable before any gross enlargement can be seen but associated with general expansion of the whole node in time. Node after node can be seen to be involved in this way. In the later stages some more definite filling defects resembling carcinomatous deposits may appear, but, in general, the pattern is distinctive and quite unlike that seen with the usual lymph-borne metastases.

Metastases in Central Nervous System

In its later stages Hodgkin's disease spreads widely. I shall not discuss the common sites of extralymphnodal spread to such structures as the lungs and bones, because they contribute little to any new understanding. These patterns of spread are of interest, but they differ in only minor ways from those of accepted blood-borne metastases from other primary tumours which they closely resemble. The rarity of metastases in the central nervous system does, however, call for comment.

Epidural spinal Hodgkin's disease with compression sometimes producing the first symptom is well known. In Bhagwati and McKissock's (1961) series of 519 spinal tumours there were 10 cases of Hodgkin's disease, eight of which presented primarily with symptoms and signs of spinal involvement. Eight of the 10 tumours were extradural and at operation were easily stripped from the dura. Richards and McKissock (1963) recorded no instance of primary Hodgkin's disease to account for any of the 389 intracerebral metastases they analysed. Not a single brain metastasis was found in our series of 95 post-mortem examinations in patients with Hodgkin's disease.

Winkelman and Moore (1941) reported one intracranial deposit without apparent direct continuity with other tumour in a patient who had extensive dural infiltration. Sparling, Adams, and Parker (1947) reviewed the subject of involvement of the nervous system by malignant lymphoma, and said that in their necropsy and surgical biopsy material they had not found Hodgkin's granuloma arising in the brain or spinal cord or involving the brain as a metastasis. The year before, however, Sparling and Adams (1946) had reported what they claimed to be the first proved example of a primary Hodgkin's sarcoma of the brain. Berkman, Netsky, and Zimmerman (1951) reported three cases of Hodgkin's sarcoma in the brain, one of which they thought must be primary, as no extracranial tumour was found at a complete necropsy. Schricker and Smith (1955) reported a case of Hodgkin's granuloma of the right temporal lobe with no recognizable involvement of any other organ, the patient being alive without recurrence three years after operation; and Vogel and Richland (1955) reported a case of primary involvement of the spinal cord which was followed five years later by a similar involvement of the brain. Other reports have appeared at intervals—for example, Storniello and Salvati (1963), Litvak, Leder, and Kauvar (1964), Ljungdahl, Strang, and Tovi (1965), and Kaufman (1965).

Hodgkin's disease primary in the central nervous system is undoubtedly rare, secondary involvement (in the more malignant cases) only rather less so. This rarity is of interest in view of the brain's lack of lymphoid tissue and lymphatic drainage. If lymphatic spread were all, a complete absence of brain involvement would be expected, but even on the basis of blood-stream spread this rarity has to be accounted for.

Non-metastatic neurological syndromes, which are sometimes associated with Hodgkin's disease, may give rise to some diagnostic confusion, though these neoplastic neuropathies are commonest with primary carcinoma of the bronchus, stomach, and ovary (Brain and Henson, 1958; Brain, 1963). The presence of complement-fixing antibodies against brain has been shown in a few cases of carcinomatous neuropathy (Wilkinson, 1964).

Theory of Dissemination

The pattern of origin and of spread in Hodgkin's disease is beginning to emerge from the shadows, though it is still not completely clear. My present theory follows a path which appears at least to be consistent with the known facts. This theory may be briefly stated as follows. There is no reason to believe that Hodgkin's disease cannot arise multicentrically at times, as many other malignant tumours do; in fact there are reasons for thinking that it may certainly do so. The system affected is widely spread through the body, and may be sub-

jected to the same tumour-initiating influences or may contain particularly susceptible cell lines at any point. Hodgkin's disease does in fact arise at many sites with a strong preference for some of them. Multicentric origin, however, could hardly account for all the lymph node and spleen involvement that we see. The frequency distribution of the site of first detected involvement suggests that the initiating influences are not evenly distributed, and that the regions drained by the neck nodes provide the main source of the disorder.

Secondary spread occurring more often than chance would allow in regions "adjacent" to the first manifestation (if this is true) could be accounted for in several ways other than by direct spread, and there are far too many examples of distant second developments to give solid support to the idea of a constant, continuous, concentric, contracirculatory lymphatic spread in this disease. The pattern might be accounted for on the basis of occasional multicentric origin, particularly at higher-risk sites, associated with progressively wider dissemination with each step in advancing malignancy, first by selective localization of tumour cells in lymph nodes (on a pattern modified by a variable chance that an individual node will become involved according to its size or other factors) with a variation in the distribution and number of the more susceptible nodes with age, and, second, by spread to many tissues.

The wide range of degree of malignancy and of speed of progression in this disease can account for the success of local treatment to solitary nodes in some cases of low malignancy, and also for the variation in the chance of success diminishing to vanishing-point in those cases where the course of the disease from first symptom to death covers only a month or two. The pattern of development in the more usual run of cases, however, strongly suggests the "homing" of specialized tumour cells in the blood to specialized sites of function. Gowans and Knight (1964) and Marchesi and Gowans (1964) have shown how normal lymphocytes in the rat recirculate from blood to lymph, and have pointed out that the main channel of communication lies within the lymph nodes. There seems to be an affinity of lymphocytes for the endothelium of a specialized set of blood vessels, the postcapillary venules, which are the site of a large-scale migration of lymphocytes from the blood into the lymph nodes. What lymphocytes can do may also be possible for the cells of lymphoid tumours—and they may even be especially well equipped for this migration.

The pattern of involvement within the nodes seen histologically and lymphographically certainly suggests a more diffuse distribution than would be expected with the more usual type of tumour-cell embolism. The frequency of involvement of the spleen and the infrequency of secondary involvement of the thymus would fit such a theory, since lymphocytes in the blood "home" to the spleen as well as to lymph nodes, but not to the thymus. The rarity of involvement of the brain perhaps remains a problem: Hodgkin's disease tumour cells may seldom reach it, which seems unlikely, or may be extracted from the blood stream with difficulty in the brain; or the fact that the brain is unable to mount a homograft reaction may have some bearing on its relative unacceptability as a place for this particular type of circulating tumour cell to grow—at least until a high degree of malignancy has been acquired.

[Part II, with a list of references, will appear in our next issue.]