Hodgkin Disease

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**Hodgkin Disease**

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**DR. SHOHET:** *Significant advances have been made in the management of hematologic malignancies in the past ten years. We have asked Dr. Samuel R. Newcom to discuss Hodgkin disease this morning at Medical Grand Rounds.*

**DR. NEWCOM:** Hodgkin disease is an uncommon disease representing about 1 percent of all cancers. However, it has created significant interest and excitement in the medical community because of its complex management and its very responsive nature to chemotherapy and radiation therapy.

Although all ages are affected, the patient is usually a young adult, 20 to 40 years old. The patient most frequently presents with an asymptomatic enlarged lymph node. Most often the cervical lymph nodes are involved first, the left somewhat more frequently than the right. Axillary nodes are involved on initial presentation less often and inguinal presentation is quite rare. There is a propensity for mediastinal involvement particularly in the nodular sclerosing variety.

**Clinicopathologic Correlations**

The histopathologic classification and clinicopathologic correlations of Hodgkin disease are shown in Table 1.

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1Samuel R. Newcom, MD, Assistant Clinical Professor, Associate Chief, Hematology and Oncology Clinics.

The most important physician in the initial evaluation is the hematopathologist utilizing the diagnostic criteria developed by Lukes and coworkers and modified at the Rye symposium in 1966. This is a four-part classification scheme which has significant prognostic implications.

Lymphocyte predominant Hodgkin disease is one of the rarer histologies representing 10 to 15 percent of the total in most series. Of these patients 80 to 90 percent have early-stage disease confined to one side of the diaphragm, stage I or II, and they rarely have symptoms. The five-year survival is very good (85 percent).

The largest group of patients are those with nodular sclerosing Hodgkin disease, usually representing 40 to 50 percent of the total, but at some institutions representing as much as 75 percent of the Hodgkin disease population. More than two thirds of these patients have stage I or II disease, only a third of the patients have symptoms and the five-year survival is quite good (70 percent).

The other large group of patients with Hodgkin disease are those with mixed cellularity. This group represents 30 to 40 percent in most series and tends to be an older group. Only half of these patients have stage I and II disease. Also, half have symptoms and the five-year survival is significantly worse than for patients whose tumors have the preceding two histologies (38 percent).

The rarest category is lymphocyte depletion. This histology represents 5 to 10 percent of the...
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TABLE 1.—Histopathologic Classification and Clinicopathologic Correlations of Hodgkin Disease

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total Percent</th>
<th>Stage I or II Patients</th>
<th>B Symptoms*</th>
<th>5-Year Survival Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph predominance</td>
<td>10-15</td>
<td>8/9</td>
<td>9/9</td>
<td>0/9</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>40-50</td>
<td>63/92</td>
<td>68</td>
<td>32/92</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>30-40</td>
<td>37/65</td>
<td>55</td>
<td>30/65</td>
</tr>
<tr>
<td>Lymph depletion</td>
<td>5-10</td>
<td>3/10</td>
<td>30</td>
<td>7/10</td>
</tr>
</tbody>
</table>

*Fever, weight loss, night sweats.

**TABLE 2.—Staging Classification of Hodgkin Disease**

**Stage**

I Single lymph node region (I) or a single extralymphatic site (II)

II Two or more lymph node regions on the same side of the diaphragm (II) or a localized site of extralymphatic involvement plus one or more node regions on the same side of the diaphragm (III)

III Lymph node regions on both sides of the diaphragm (III) which may include the spleen (III) or a single extralymphatic site (III) or both (III)

IV Diffuse or disseminated involvement of one or more extralymphatic organs:

- marrow = M+
- lung = L+
- liver = H+
- pleura = P+
- bone = O+
- skin = D+

The classification is labeled A if the patient has none of the three B symptoms: (1) fever, (2) night sweats, or (3) unexplained loss of 10 percent or more of the body weight in the six months preceding admission.

Histopathology

Figure 1 shows specimens of tissue in Hodgkin disease.

In lymphocyte predominant tissue one sees occasional, classical Reed-Sternberg cells which are binucleate with inclusion-like eosinophilic nuclei. The Reed-Sternberg cells are large, measuring 30 to 50 microns in diameter. Mononuclear Reed-Sternberg variants may also be seen but are not diagnostic. These cells appear in a sea of well-differentiated nonmalignant lymphocytes.

Nodular sclerosis is characterized by two findings: (1) thick bands of collagen fibers and (2) lacunar cells. During formalin fixation these rather atypical Reed-Sternberg cells undergo shrinkage of the cytoplasm leaving lacunae. The cellular infiltrate is variable and tends to be pleomorphic.

Mixed cellularity Hodgkin disease is generally seen with abundant Reed-Sternberg cells and a pleomorphic cellular infiltrate characterized by multiple eosinophils, as well as histiocytes, lymphocytes and plasma cells.

The rarest histology, that of lymphocyte depletion, is characterized by the presence of multiple bizarre, highly malignant Reed-Sternberg cells and mononuclear variants with little in the way of normal cellular reaction.

Clinical Evaluation

The staging classification of Hodgkin disease is shown in Table 2.

Initial clinical evaluation should include a few specific studies that have been established as being useful. The history provides information regarding B symptoms. Three statements classify a patient as having B symptoms: (1) loss of 10 percent of the body weight in the preceding six months, (2) fever and (3) night sweats, particularly when volunteered in the history.

Physical examination will provide information
about the clinical stage (for example, lymph nodes above or below the diaphragm, palpable spleen, liver).

Routine laboratory studies should always be made. Anemia, if seen, correlates well with B symptoms and is generally that of chronic inflammation;\(^7\) it may occasionally be microcytic in spite of adequate iron stores. A rare patient will present with Coombs positive hemolytic anemia.\(^9\) Thrombocytosis may be present and correlates with B symptoms and poor prognosis.\(^10\) Liver function tests are very unreliable. The alkaline phosphatase tends to be the most sensitive indicator of liver involvement but is associated with many false positives.\(^11\) The nonspecific acute phase reactants, as measured by the sedimentation rate and the serum copper value, are useful tests primarily for monitoring relapse but should be measured during the initial evaluation to be followed during remission induction. Because of the likelihood of mediastinal involvement, an x-ray study of the chest is mandatory and whole lung tomograms are quite useful, particularly if the diagnosis is nodular sclerosis or if there is hilar or mediastinal involvement. Bipedal lymphangiography is mandatory in the initial evaluation and useful for documenting para-aortic lymph node enlargement as high as L-2. With the Jamshidi bone marrow biopsy needle, one can now discover most of the 8 to 10 percent of patients who have bone marrow involvement provided bilateral iliac crest biopsy studies are done. Computerized axial tomography, ultrasonography and isotope scanning have not been helpful, in our hands, for routine initial evaluation.

Following these studies, a decision must be made regarding further evaluation of the abdomen. A multidisciplinary group representing medical oncology, hematology, hematopathology, radiation therapy, diagnostic radiology, peritoneoscopy and surgery is helpful at this juncture.

Peritoneoscopy

Peritoneoscopy (see Table 3) is a method that has been used at our institution for staging and restaging. A 2 cm incision is placed, utilizing local anesthesia, immediately below the umbilicus. The peritoneoscope is introduced into the abdomen after the peritoneal cavity has been filled with air. Tumor nodules on the liver can be visualized directly and, through a separate locally anesthetized area, a biopsy needle can be inserted and directed at the nodule (Figure 2). Randomly taken biopsy specimens of the normal appearing liver can also be obtained. Following the biopsies, hemorrhage can be visualized, tamponade can be applied from above and, if the bleeding does not stop, surgical procedures can be undertaken. In addition, some investigators roll the patient into the right decubitus position, the omentum falls away and the spleen can be visualized for evidence of tumor nodules. Splenic punctures have been carried out in more than 100 patients.\(^15\) Using a probe, the undersurface of the liver can be visualized as well and other structures can be manipulated as necessary to obtain adequate visualization (Figure 3).

The advantage of peritoneoscopy over laparotomy is, of course, the decrease in morbidity and mortality; 2 to 4 percent of cases have morbidity, as compared with about a third in staging laparotomy.

![Figure 2.—Hodgkin disease tumor nodule as visualized with the peritoneoscope. Biopsy needle is directed at the nodule percutaneously. (Courtesy of M. Lieberman, MD, Dept. of Medicine, University of California, San Francisco.)](image)
No deaths have been reported. The sensitivity is quite good, although occasionally liver disease is missed by peritoneoscopy.

**Indications for Staging Laparotomy**

Indications for laparotomy following sequential evaluation including bone marrow biopsy studies, lymphangiogram and negative peritoneoscopy are shown in Table 4.

Beretta and co-workers suggest that one can safely avoid laparotomy when the peritoneoscopy, lymphangiography, and bone marrow biopsy studies are negative, if there is disease involving only high cervical lymph nodes with very little chance of intra-abdominal involvement. In addition, laparotomy can be avoided if there is disease confined to the mediastinum which also has little chance of intra-abdominal involvement. If the patient has B symptoms, and the institution consulted would deliver radiation therapy plus chemotherapy, then the risk of laparotomy is also not warranted; and certainly, if the patient is at high risk for surgical operation, laparotomy should be avoided.

Therefore, laparotomy becomes most useful in those patients that have low cervical nodes, particularly left supraclavicular nodes. If one plans to deliver just radiation therapy to more advanced stages and desires assurance that there is no liver involvement, laparotomy is indicated. If the lymphangiogram is equivocal, surgical operation is necessary to determine if there is involvement of retroperitoneal lymph nodes. If there is a large spleen, the radiation therapist usually asks that the spleen be removed, not only to document involvement, but to reduce the port-size and spare the left kidney and left lower lung field from radiation damage. If an oophoropexy is to be done, a complete staging laparotomy should be carried out as well.

**Laparotomy**

If a staging laparotomy (see Table 5) is indicated, the radiation therapist should accompany the patient to the operating room to assure that the following are carried out: (1) Abnormal lymph nodes noted on a lymphangiogram should be excised and the excision should be documented by a kidney, ureter and bladder study before closure of the abdomen. (2) Because 10 to 15 percent of patients with normal lymphangiograms will have positive para-aortic nodes, random

**TABLE 5.—Staging Laparotomy**

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excisional biopsy of abnormal nodes</td>
</tr>
<tr>
<td>Random excision of normal nodes</td>
</tr>
<tr>
<td>Splenectomy</td>
</tr>
<tr>
<td>Liver biopsies</td>
</tr>
<tr>
<td>Open marrow biopsy</td>
</tr>
<tr>
<td>Oophoropexy</td>
</tr>
<tr>
<td>Radioopaque clips</td>
</tr>
</tbody>
</table>

**TABLE 4.—Indications for Laparotomy Following Sequential Evaluation Including Bone Marrow Biopsies, Lymphangiogram and Negative Peritoneoscopy**

<table>
<thead>
<tr>
<th>Laparotomy Most Useful If:</th>
<th>Laparotomy Unnecessary If:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IA with low C-nodes or IIA, IIIA if radiotherapy alone planned</td>
<td>1. IA with high C-nodes and —LAG</td>
</tr>
<tr>
<td>2. Suspicious LAG, and RT alone planned</td>
<td>2. IA or IIA with mediastinal disease only</td>
</tr>
<tr>
<td>3. Splenomegaly</td>
<td>3. IB, IIB, IIIB or IIIA if chemotherapy planned</td>
</tr>
<tr>
<td>4. Fertile women requesting oophoropexy</td>
<td>4. High-risk patients</td>
</tr>
</tbody>
</table>

*Adapted from Beretta et al.*

LAG = lymphangiogram
RT = radiation therapy

Figure 3.—Tumor nodule on the undersurface of the liver visualized through the peritoneoscope with the aid of a probe inserted percutaneously. (Courtesy of M. Lieberman, MD, Dept. of Medicine, University of California, San Francisco.)
lymph node excisions must be carried out in at least three different locations when there are no abnormalities noted on lymphangiography. (3) Splenectomy should be done; an enlarged spleen is involved half of the time, a normal sized spleen a third of the time. The pathologist should serially slice the spleen using a large knife and looking for the white tumor nodules of Hodgkin disease. (4) Similarly, the surgeon should examine the liver closely for the presence of the surface nodules of Hodgkin disease, as well as take a large wedge biopsy specimen from the right lobe and two or three needle biopsy specimens from each lobe. (5) If four Jamshidi bone marrow biopsy specimens have been obtained before laparotomy, the open marrow biopsy is considered optional; it is currently carried out through a separate incision over the right anterior iliac crest. (6) Oophoropexy in women who are menstruating is useful in salvaging ovarian function, and (7) at the completion of the procedure, radiopaque clips should be applied to the splenic hilum, to any enlarged lymph node masses, and to the lateral borders of the ovaries so that the radiation therapist can identify these structures.

Oophoropexy

The ovaries lie in close proximity to the iliac lymph nodes and will be included in the inverted-Y radiation therapy field. Therefore, the patient will be sterilized if the ovaries are left in their usual location. To attempt to salvage ovarian function, the ovaries and fallopian tubes can be dissected free and the ovaries moved into the midline and sutured to the uterus with radiopaque material.

At Stanford University 97 women have undergone this procedure followed by total nodal radiation therapy. Some of these women have also received MOPP (nitrogen mustard, vincristine [Oncovin®], prednisone and procarbazine) chemotherapy. In spite of using a 10 cm lead shield, the ovaries receive about 350 to 400 rads by scatter when the usual 4,000 to 4,400 rads is delivered to the inverted-Y field. Many of these women are amenorrheic for a short time, but about 60 percent of them recover normal menses following therapy. At this time there are seven women who have become pregnant, one with twins, one with two sequential births, and one who underwent therapeutic abortion. All of the term babies have been normal in appearance and there has been no evidence of acute leukemia.

It is too early to estimate the risk of acute leukemia to the child or the risk of recessive chromosomal damage to the succeeding generations.

Radiotherapy

Johnson has had significant criticism of this aggressive approach to staging utilizing laparotomy and, for many years, has proposed that patients be treated without doing invasive abdominal studies. He uses his own data to support that concept with respect to patients who are staged with lymphangiograms and bone marrows alone, and have clinical stage IA, IIA, IB, or IIB disease. Johnson has shown excellent survival treating such patients with total nodal radiation therapy yielding six-year survival rates of 98 percent for asymptomatic patients and 76 percent for patients with B symptoms.

On the other hand, Glatstein, who first proposed doing staging laparotomies, has shown that if all sites of disease are documented, patients can be treated with a smaller radiation therapy field, and the survival rates will be identical to the results obtained with total nodal radiation therapy. However, the relapse rate and the necessity for repeated courses of therapy is greater for those patients treated with small fields.

We have selected a compromise of these approaches making use of the staging evaluation as recommended by Beretta and co-workers and selecting radiation therapy fields that yield extended field irradiation, good survival and the least damage to normal tissues.

For good risk stage IA patients (nodular sclerosis and lymphocyte predominant) mantle field irradiation giving 4,000 rads in four to five weeks appears to be adequate therapy. For poor risk histologies (mixed cellularity and lymphocyte depletion) as well as all stage II patients, we use subtotal nodal radiation utilizing the mantle field followed by para-aortic nodal and splenic hilar irradiation to the same dosage. For stage IIIA patients total nodal radiation remains our standard approach although we are carefully evaluating studies utilizing less aggressive radiotherapy for abdominal disease confined to the spleen as well as subtotal nodal radiotherapy followed by chemotherapy for disease confined to the upper abdomen.

Chemotherapy

For those patients with stage IIIB and IV disease, there is little question that radiation therapy
is not adequate therapy. There is now a ten-year experience with the combination chemotherapy regimen of MOPP, developed at the National Cancer Institute. At this time 194 patients have been treated. Of these, 94 percent were stage III or IV. The complete response rate was 81 percent and this has been duplicated by many others, including workers at our own institution. Only 22 of these patients did not have B symptoms. Within this asymptomatic group the response rate was 100 percent and there have been no relapses at the ten-year mark. For patients with B symptoms, the response rate is significantly lower (77 percent), but good. Overall, two thirds of those patients with complete remission appear free of disease at both the five- and ten-year evaluations. The nodular sclerosing histology has a significantly worse disease-free interval but similar survival.

Maintenance chemotherapy is not of any benefit provided complete remission is well-documented by rigorous restaging. In general, studies of maintenance chemotherapy have shown no improvement in survival and increased morbidity and mortality because of drug toxicity and bone marrow damage with resulting infectious complications.

For those patients in whom a complete remission is achieved with MOPP and in whom remission is sustained for more than one year, the chance of responding to MOPP again and sustaining remission is greater than 50 percent and this is the therapy of choice. However, if the patient relapses while receiving MOPP, or within one year after complete remission is achieved with MOPP, the chance of inducing remission with MOPP is less than 20 percent and alternative therapy is indicated.

There are now alternative combination chemotherapy regimens which are useful for treating MOPP-resistant patients. The most widely used is that of Bonadonna which includes doxorubicin hydrochloride (Adriamycin®), bleomycin, vinblastine sulfate (Velban®) and imidazole carboxamide (ABVD). These are all agents with activity as single agents in Hodgkin disease. In MOPP failures a complete remission rate approaching that of MOPP is obtained. A variation of the Bonadonna regimen, B-DOPA, also gives complete remission rates which are quite satisfactory in patients failing MOPP chemotherapy.

A less aggressive regimen, not associated with as severe nausea and vomiting, is that employing 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), doxorubicin hydrochloride and vinblastine sulfate with and without bleomycin. Here, the complete remission rate is roughly 50 to 60 percent. Another regimen, combining bleomycin, vinblastine sulfate, doxorubicin hydrochloride and streptozotocin (a nitrosourea with bone marrow sparing properties) has also yielded a 50 percent complete remission rate in a small group of patients resistant to MOPP chemotherapy.

In addition to these studies with alternative chemotherapy, several studies are being carried out comparing radiation therapy alone with radiation therapy plus chemotherapy. The longest follow-up is available from the data generated at Stanford. This study compares extended field radiation therapy alone to extended field radiation therapy followed by six cycles of MOPP or nitrogen mustard, vincristine (Oncovin®) and procarbazine (MOP). The study is now eight years old. There is no significant difference in survival between the two regimens even when analyzed by stage and histologic category. However, there continues to be significant improvement in the disease-free interval in those patients receiving radiation therapy followed by chemotherapy as compared with those treated with radiation therapy alone. O'Connell and associates have essentially repeated this study using total nodal radiation for all stages with and without six cycles of MOPP. They have also achieved similar results—that is, no difference in survival but improvement in disease-free interval with the addition of chemotherapy.

The ability to give effective therapy to patients who relapse after receiving radiation therapy alone is obviously good, as pointed out by the survival figures from these two studies. In addition, there are increasing reports of second malignancies, particularly acute leukemia, in patients treated for Hodgkin disease. The incidence of leukemia appears to correlate with the amount of therapy delivered and seems to be highest in those receiving combination radiotherapy and chemotherapy. With these points in mind our recommendation is to use radiation therapy alone for stages IA through IIIA regardless of histology. Chemotherapy can then be used selectively for the minority of patients in whom there develops extranodal disease not identified initially, or who relapse, or in whom there is persistence of disease in an irradiated field.

Because of the striking results achieved in pa-
patients without symptoms in the MOPP chemotherapy regimen, the British National Lymphoma Investigation has compared the results of total nodal radiation with MOPP chemotherapy in stage IIIA patients. The study is a well designed prospective randomized trial. Preliminary reports would suggest that MOPP is inferior to radiotherapy in inducing a complete remission and sustaining that complete remission. Chemotherapists have criticized this study because the MOPP de-escalation doses are significantly more conservative than in the original study where 25 percent of the dose of nitrogen mustard and procarbazine was given even when the leukocyte count was 1,000 to 2,000 per cu mm.

There are also studies being done for more advanced stages, IIIB and IV, comparing chemotherapy and chemotherapy followed by radiation therapy to areas of previous bulky disease, as well as MOPP plus radiotherapy versus ABVD plus radiotherapy. Although there are no significant differences at this time, these studies are only two to three years old, and there is a suggestion that adjuvant radiation therapy may have some merit and that there is no significant difference between the results obtained with MOPP or ABVD when coupled with radiation therapy.

In conclusion, then, it can be said that with our current approach to therapy, one could expect to duplicate the results reported by Kaplan and Rosenberg in more than 500 patients. They used total nodal radiation therapy for all stages I through IIIA, total nodal radiation therapy with either hepatic irradiation or six cycles of MOPP for stage IIIB, and MOPP with and without adjuvant radiation therapy as felt to be necessary for stage IV. An 81 percent five-year survival and a 61 percent relapse-free survival was obtained overall. The survival in stage I through III disease was very good. The survival in late stage patients was inferior to that reported with MOPP alone. In our own institution, 131 patients have been treated in the past ten years; the 10-year survival is 55 percent and the five-year survival is 65 percent; formerly more conservative staging techniques and smaller radiation therapy fields were used.

Characterization of the Hodgkin Cell

Physicians have known for many years that patients with Hodgkin disease have an increased susceptibility to herpes zoster-varicella infections. More recently, it has been shown that these same patients have decreased levels of measurable T-cells by E-rosette measurement, and that they have normal levels of T-cells by cytoxicity assay. In addition, skin test reactivity and E-rosetting can be restored toward normal by giving levamisol. Another observation, pointed out by Kadin, has been the occurrence of Hodgkin disease in T-cell dependent areas of some patients' lymph nodes with residual intact normal follicular areas, the B-cell area (Figure 4). For these reasons Order and Hellman have hypothesized that Hodgkin disease arises as a T-cell defect associated with virally infected T-lymphocytes.

On the other hand, Lukes and co-workers have observed Reed-Sternberg-like cells in infectious mononucleosis and similar cells have also been reported in angioimmunoblastic lymphadenopathy, two disorders which are B-lymphocytoid in nature. In addition, Leech has shown intracytoplasmic immunoglobulin in Reed-Sternberg cells, a characteristic of the B-lymphocyte. Recently, from Lukes' laboratory, composite transmission electronmicrographs of normal B-lymphocytes, pokeweed mitogen-stimulated B-lymphocytes, atypical mononuclear cells from nodular sclerosing Hodgkin disease, and classifiable lacunar cells from nodular sclerosing Hodgkin disease have been used to support the hypothesis of a B-lymphocyte transformation as the origin of the Hodgkin cell.

However, for many years morphologists such as Rappaport have stated that the Reed-Sternberg cell is a malignant histiocyte based on morphologic grounds alone. The multinuclearity is
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atypical but the size, nuclear/cytoplasmic ratio, and hematoxylin and eosin staining characteristics are quite reminiscent.

The study of this cell has been extremely difficult because of its sparse occurrence within involved tissues and the necessity for working with sterile, viable tissue. In addition, the occurrence of the cell in the presence of a pleomorphic infiltrate has made its concentration and selection for study difficult. Kadin, Gold, Stites and I undertook this project beginning in 1974. We made use of a velocity sedimentation technique to eliminate the small lymphocytes and concentrate the large, mononuclear and binuclear Hodgkin cells.\textsuperscript{56} We found that they were always surrounded by normal-appearing small lymphocytes which were closely adherent.

We had previously been able to characterize malignant cells using the E-rosette test in acute lymphoblastic leukemia and applied this technique to Reed-Sternberg cells. We saw no evidence of T-lymphocyte properties on the cells themselves. However, about 95 percent of the small lymphocytes surrounding the cell were T-lymphocytes by this criterion (Figure 5). Stites confirmed this observation using rabbit anti-human thymocyte serum and indirect immunofluorescence. Fluorescence of the small, adherent lymphocytes was shown. No fluorescence was shown on the membrane or within the cytoplasm of the Reed-Sternberg cells.\textsuperscript{51}

Scanning electron microscopy showed that the surrounding T-cells were closely adherent and that there were cytoplasmic bridges between the surrounding lymphocytes and the Hodgkin cells (Figure 6).\textsuperscript{52} We have speculated that perhaps this is a manifestation of a good immunologic response although normal histiocytes and lymphocytes have shown similar interaction.\textsuperscript{53,54}

Kadin had also been able to show monoclonal immunoglobulin within the cytoplasm of malignant B-lymphocytes such as multiple myeloma cells, and that the immunoglobulin was similar in nature to the monoclonal protein spike in the serum electrophoresis. As with Leech,\textsuperscript{57} we were able to show intracytoplasmic immunoglobulin within the Hodgkin cells. However, we were unable to show any Hodgkin cells with definable surface immunoglobulin. This study also confirmed our initial conclusion that the cell was surrounded by T-lymphocytes and not by B-lymphocytes (Figure 7).

Recently Reed-Sternberg cells in frozen section have been proved to have complement receptors.\textsuperscript{55} This study utilized sheep red blood cells coated with immunoglobulin (IgM) and complement. This observation has been substantiated by Kaplan who has also documented that the complement receptor on this cell is specific for C\textsubscript{3b} and that when C\textsubscript{3b} is inactivated to C\textsubscript{3d} there is no rosetting.\textsuperscript{56} This specificity for C\textsubscript{3b} has been shown to be characteristic of the receptor on the monocyte-histiocyte.\textsuperscript{57} The B-lymphocyte has a complement receptor for both C\textsubscript{3b} and C\textsubscript{3d}.

Billing has recently prepared an antiserum that is apparently similar to the anti-leukemia serum of Halterman and co-workers.\textsuperscript{58,59} This antiserum labels the myeloblasts and lymphoblasts of acute leukemia,\textsuperscript{60} the B-lymphocytes of lymphocytic lymphoma, and normal monocytes and histio-
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cytes. It does not label normal or malignant plasma cells, the mesenchymal cells seen in pleural effusions, or solid tumor cell suspensions (lung cancer, colon carcinoma, breast cancer, for example). Positive labeling of the binucleate Reed-Sternberg cell further confirms the histiocye-macrophage or B-lymphocyte origin of this cell.

Preparations of Reed-Sternberg cells in our laboratory confirm previous observations that the Hodgkin cell does not contain nonspecific esterase.\textsuperscript{61,62} Positive nonspecific esterase staining is characteristic of monocytes and histiocytes.\textsuperscript{63}

Phagocytosis studies with staphylococci and zymosan particles have always been negative in our laboratory. However, Kaplan has recently reported the slow phagocytosis of India ink by Hodgkin cells in short-term tissue culture suggesting a macrophage-histiocyte property.\textsuperscript{56}

Scanning electron microscopy has also added confusion to the evaluation of the Hodgkin cell. In the preparations from our laboratory, one can appreciate the ruffles on the Hodgkin cell surrounded by the smooth T-lymphocytes and the similar surface characteristics seen on a normal histiocyte-macrophage (Figure 8). In addition, Figure 9 shows a binucleate Reed-Sternberg cell containing a phagocytosed lymphocyte.

In summary, then, one can state that conclusions regarding the origin of the Hodgkin cell are still not possible. The surface properties and lethargic phagocytosis are most reminiscent of the monocyte-histiocyte cell series. On the other hand, intracytoplasmic immunoglobulin is not characteristic of this cell series but more consistent with a B-lymphocyte origin. Experiments have been completed to determine the origin of the cytoplasmic immunoglobulin—that is, exogenous or endogenous to the Hodgkin cell—and findings will be published shortly. This observation should clarify the true nature of the cell and provide new approaches to the identification of unsuspected, residual, microscopic disease and, perhaps, new therapeutic tools.

Figure 7.—Reed-Sternberg cell showing intracellular immunoglobulin identified by fluorescein-labeled rabbit anti-human IgG antiserum (Meloy). Surrounding T-lymphocytes are not labeled. Labeled B-lymphocytes can be identified in the surrounding cellular matrix (×1000). (Courtesy of M. Kadin, MD, Dept. of Path. and Lab. Med., University of Washington.)

Figure 8.—Left, Hodgkin cell showing surface ruffles (lamellae) and surrounding smooth T-lymphocytes (reduced from ×3770), and Right, normal peritoneal macrophage (reduced from ×4330). (Reproduced by permission from The Lancet.\textsuperscript{12})

Figure 9.—Binucleate Reed-Sternberg cell seen by phase-contrast microscopy with phagocytosed lymphocyte appearing on the same focal plane as Reed-Sternberg nuclei (magnified from ×1000). (Reproduced by permission from The Lancet.\textsuperscript{12})