The Clinical Picture of Hodgkin’s Disease

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Summary

The clinical manifestations and laboratory findings in patients with Hodgkin’s disease have been reviewed. Variability of the course makes prognostication for any 1 patient difficult. Extent of disease; histologic appearance; age and sex; involvement of specific organs, such as liver or bone; and response to initial therapy all affect prognosis. The cause of death of patients with Hodgkin’s disease may be due to tumor involvement or due to complications, in particular, infections and bleeding. During the past 50 years, improvement in survival of patients has been due largely to identification of patients with local or regional disease and their treatment with aggressive radiotherapy. Current modes of chemotherapy combined with improvements in supportive care have had only modest effects on survival rates. The major obstacle to a rational approach to the problem of Hodgkin’s disease is the identification of the etiology of this disorder.

Introduction

In a recent review of 19th century foundations of cancer research, Triolo (229, 230) reported that the 1st cooperative venture in oncology was promoted by a group of English clinicians who in 1802 organized themselves into a professional society. In 1806, they circulated a questionnaire among practitioners in which they inquired regarding current opinions on etiology, heredity, diagnosis, and treatment of cancer. This English cancer society thrived under the aegis of Hunter, and his tradition was continued by the work of Home and others (230). Among this group of investigators was a pathologist named Thomas Hodgkin, who, in 1832, reported 7 cases of generalized lymphadenopathy and splenomegaly and noted that “as far as could be ascertained... this enlargement of the glands appears to be a primitive affection of those bodies” (58, 87). In 1865, Wilks clarified the clinical entity by describing 15 cases, 13 of which “resembled in all particulars the first four which Dr. Hodgkin first brought unto the notice of the profession,” and he suggested the name “Hodgkin’s disease” (245, 246).

Now, 1½ centuries have passed since the original description and it might be asked: “What have we learned since then? Has our clinical knowledge increased since microscopy, bacteriology, virology, immunology, and other medical disciplines have begun to flourish? How have the developments of radiotherapy, chemotherapy, antibiotics, and blood transfusion affected the natural history and prognosis of the disease?”

The present conference affords us the opportunity to examine those features of the clinical picture of Hodgkin’s disease which might present obstacles to its control. A review of the recent literature (1, 27, 34, 94, 102, 131, 147, 154, 238) and of the 135 cases seen at Francis Delafield Hospital during the past 14 years confirms a number of previous observations and raises some additional questions.

Clinical Findings

Characteristically, the patient gives a history of excellent health until the onset of his disease which usually is manifested by adenopathy with or without systemic manifestations. Occasionally a brief antecedent history of upper respiratory infection, or of infections about the head and neck is given. The duration of symptoms and of physical findings before biopsy is variable. Delay by the patient or by his physician prior to the recognition of the disease may be considerable.

The presenting symptoms most commonly are those of painless, progressive enlargement of a superficial lymph node or a group of lymph nodes, especially in the neck, and various systemic manifestations, including malaise, anorexia, weight loss, nausea, vomiting, fever, or pruritus. The order of frequency of involvement of the superficial lymph nodes is the cervical (60-80%), the axillary (6-20%), and the inguinal (6-12%) (34, 81). The mediastinal lymph nodes are involved initially in 6 to 11 per cent of cases (34, 81). The retroperitoneal lymph nodes, the liver, and the spleen are less commonly clinically involved in the early phases of the disorder.

Fever occurs eventually in 30-50% of cases, is cyclic, continuous, intermittent, or more rarely the Murchison-Pet-Ebstein type (34, 48, 87, 94, 135, 158, 167, 168). During fever, the pulse is rapid and drenching sweats are common. Occasionally patients complain of diaphoresis even in the absence of fever. Weakness, fatigue, anorexia, weight loss, and cachexia eventually occur in all patients. In 10-15% of cases, pruritus is an early symptom but up to 85% of the cases have pruritus some time during their illness (94).

Intrathoracic involvement is frequent (146) and mediastinal nodes are involved in over 60% of the patients in the course of the disease (34). Symptoms of involvement of thoracic structures — such as dyspnea due to mediastinal node pressure, a brassy
cough, and dysphagia—all may mimic other tumors and infections of the chest. Obstruction of the superior vena cava may occur. Clinical involvement of the lungs is seen eventually in up to 40% of cases (34, 116, 155, 156, 186, 217) and may simulate other tumors and pulmonary infections. Pulmonary fibrosis with severe restriction of ventilatory capacity may appear in the course of the disease or as a result of radiotherapy to the lungs (50, 217, 218). Cavitation has been reported (44, 214). Endobronchial lesions may occur (72). Cytologic study of sputum and of bronchial washings may show tumor cells, which, with experience, are recognizable as Hodgkin's cells (221). One-third of the patients show pleural effusion (217); however, at autopsy up to 60% of cases have this finding (248). Although positive identification of the lymphomas can be made in over ½ the cases of pleural effusion, malignant cells are seldom found in Hodgkin's disease (149). Other thoracic structures, including thymus (141), heart (24, 103, 185) or pericardium (77, 103), may be affected.

Abdominal and retroperitoneal disease is extremely frequent in the course of Hodgkin's disease (34). Symptoms of abdominal disease may be those of bleeding; obstruction; or nausea, vomiting, and diarrhea secondary to infiltration of the mucosa of the gastrointestinal tract (28, 34, 109, 115, 174, 216). Bleeding from esophageal varices as a result of portal hypertension from extensive involvement of the liver has been reported (126). Pressure symptoms from a large mass in the retroperitoneum or from the enlargement of spleen and liver are common.

The spleen is involved initially in up to 30% of patients; eventually, in 80% of cases (34, 81, 102). Primary splenic Hodgkin's, however, is rare (34, 194). In the presence of enlargement of the spleen, hypersplenism may occur with anemia, leukopenia, thrombocytopenia, or a combination of these. Hepatomegaly is an early finding in ¾ of cases; liver involvement, determined microscopically, occurs in over ¼ of patients (34, 128); however, in 2 large series the incidence of clinical jaundice was only 10–15% (16, 127, 128).

Bone involvement is found in 60% of autopsied cases; however, during the course of illness, the number of patients with bone pain or X-ray evidence of destruction of osseous structures is less than 30% of total (34, 53, 94, 102, 220).

Abnormalities of the central nervous system are noted in over 10% of the patients (43, 80, 94, 102, 227). The brain or spinal cord may be invaded directly (43). However, more commonly, symptoms are due to compression from tumor outside the spinal cord (43). Toxic encephalitis without manifest lesions of Hodgkin's disease in the brain, particularly in the cerebellum (cerebellar leukencephalopathy), has been reported (34, 39, 45, 180). Alcohol intolerance has been described in 17–20% of cases but does not appear to be specific for Hodgkin's disease (13, 17, 29, 104, 105). Peripheral neuropathies and cranial nerve palsies may occur (43). Involvement of the eye with invasion of lacrimal gland, uveal tract, optic nerve, or retroorbital region has been recorded (172).

Skin involvement may be due to direct invasion, an "id reaction" or excoriations produced in response to pruritus (34, 51, 94, 102, 139, 184, 222). Ichthyosis and severe anhidrosis are seen occasionally (51).

Almost any organ may be involved initially or in late stages by Hodgkin's disease, including: thyroid (182, 190), breast (118, 145, 152), ovary (9), cervix (161), vulva, bladder (138), and other portions of the urinary tract. Reed-Sternberg cells may be recognized by cytologic examination of urine sediment (193). Involvement of the tonsil or Waldeyer ring may occur as an initial manifestation (163); other portions of the nasopharynx and the larynx may also be affected.

Most studies appear to indicate that pregnancy can be well tolerated, particularly in patients who have the "chronic form" of the disease. It has been suggested that pregnancy be avoided until 2 symptom-free years have passed (10, 34, 59, 83, 84, 97, 112, 210, 211).

**Laboratory Findings**

Anemia is a frequent complication. A few patients (10%) have a hypochromic microcytic anemia, usually secondary to blood loss. Hemolytic anemia (101, 233) may occur with localized disease, but is present in 80% of cases with late Hodgkin's disease. This anemia is characterized by normochromic, normocytic erythrocytes; anisocytosis; spherocytosis with increased osmotic fragility of red cells; reticulocytosis; and minimal icterus. The direct Coombs test is usually negative. In instances where Coombs-positive hemolytic anemia is present, quantitative studies of the effect of red blood cell sensitization on red cell survival have been performed implicating the protein coating in the erythroclasia (31). Hoffbrand has reported 2 patients with Hodgkin's disease and severe hypo-γ-globulinemia who had...
anemia, reticulocytosis, shortened red cell life-spans, and marked hyperplasia of reticuloendothelial cells (88). The anemia appears to be related to the proliferation of histiocytes in the spleen and other reticuloendothelial sites capable of phagocytosing red cells (18). Chart 1 summarizes the results of a red blood cell (RBC) life-span study in a patient with severe anemia and splenic enlargement. A marked decrease in $\text{^{51}Cr}$ RBC life-span and significant sequestration of red blood cells in the spleen are seen. Cline and Berlin (26) and others (40, 60, 64, 95, 124, 176, 244) have reported similar findings. In addition, hypoferrremia and abnormalities in iron ($^{56}$Fe) metabolism consisting of excessive uptake of iron by liver and spleen and impaired incorporation of iron into erythrocytes have been noted (26). It has also been demonstrated that labeled hemoglobin-iron (Hb-$^{56}$Fe) is re-utilized poorly (79). A relative decrease in erythropoiesis may, in part, be due to a deficiency of folic acid ([175] Kipstein and Ullmann, unpublished observations, 1965). The anemia becomes progressively worse as the disease advances and correlation with disease activity is often possible (176).

The changes in the white blood cells are not constant and not diagnostic (34, 56, 94, 102, 234). Leukocytosis with neutrophilia is present in over 50% of patients. Monocytosis and lymphocytosis have been noted in a few. Leukopenia as well as lymphopenia often occur in advanced disease. Eosinophilia, occasionally marked, may be seen. The leukocyte alkaline phosphatase (LAP) value is often elevated during the active phase of disease and falls during remissions. When leukopenia occurs, increased LAP activity can be used as an index of active disease (57, 120, 142, 150). The platelets are normal or increased (9% of cases) in the beginning of the illness, in the course of the disease, they usually diminish in number because of the cumulative toxic effects of radiation and chemotherapy and, more rarely, because of bone marrow replacement by Hodgkin's disease. About 5% of cases show myeloid metaplasia associated with hypoplastic bone marrow or tumor infiltration of bone marrow (125). Bone marrow aspiration is usually not helpful in ruling out bone marrow involvement and formal biopsy may be necessary (94, 130, 234, 251). When present, Reed-Sternberg cells are readily recognizable (251). On rare occasion, these cells appear in the blood (137, 195).

The erythrocyte sedimentation rate (ESR) is elevated in the presence of active disease and falls after effective therapy or during spontaneous remission. Thus, in patients who have elevation of the ESR at an early stage of their disease, this test becomes a good index of the activity (34, 94).

Hypercalcemia may occur (up to 30% of cases) and is usually associated with hypophosphatemia and elevated serum alkaline phosphatase. Roentgenographic evidence of skeletal involvement by tumor may be absent, although autopsy usually reveals osseous involvement (157). Hyperglycemia may be seen in association with steroid therapy and during exacerbations of the disease (140). Gout as well as decreased renal function following steroid therapy and during exacerbations of other lymphomas and leukemias—have been observed. There have been reported no differences in the incidence of major blood types in patients with Hodgkin's disease as compared to various control groups (129).

### Roentgenologic and Isotope-scanning Studies

The evaluation of the extent of initial involvement is of immeasurable help in prognosis and in planning of therapy for each patient. The correlation of the clinical findings with radiologic studies is extremely important and useful. Tomography, intravenous pyelography, gastrointestinal studies, and splenopancreatography have been employed for many years. More recently, employment of radioopaque iodized oil (Ethiodol) for lymphangiography (11, 117, 196, 197), radioactive gold ($^{198}$Au) for liver scanning and for bone marrow scanning (49), heat-damaged $^{51}$Cr-labeled red cells for spleen scanning, and $^{131}$I-aggregated albumin for lung scanning (225) have all added new dimensions to the meaning and limitations of "clinical local disease." A major by-product of these diagnostic studies is the possibility of delivering therapeutic agents to local areas. Therapy with radioactive colloidal or iodized oil substances by these routes is already under investigation.

### Prognosis

Prognosis has always been difficult to evaluate, as the clinical course of Hodgkin's disease is characterized by great variability. Progression is by successive exacerbations which may occur at intervals of weeks, months, or years. Shlimkin (201) as well as Osgood (165) have stressed the difficulty of comparing results of treatment in Hodgkin's disease between various centers. This occurs because of: (a) differing methods of reporting survival (from onset, from accession to hospital, from biopsy, from therapy; some divide their series into living and dead patients, others consider all patients "dead" at time of tabulation, whereas still others examine their data by life-table (actuarial) approaches, etc.); (b) variability of patient material (i.e., age, sex, economic background, etc.); and (c) differences in approach to patients over a long period of years, yet all patients being included in a single series.

The actuarial method measuring probability of survival from...
date of biopsy probably reflects results most accurately. A comparison (Table 1) of a selected number of recent reports shows a range of 5-year survival for all patients with Hodgkin's disease from 22 to 38% and of 10-year survival from 5 to 24% (32, 34, 63, 85, 148, 164, 171, 208, 240).

Chart 2 summarizes the age and sex distribution in our group of patients. Sixty % of our patients were males. Table 2 (34, 55, 102, 124, 147, 232, 235) compares our series with others regarding age distribution. In our series, a larger proportion of patients were over 40 years of age compared to other reported series. The effect of age on survival is shown in Chart 3. A comparison of survival data according to sex in our patients and in selected reports is shown in Table 3 (124, 202). It is readily apparent that young patients or females will show longer survival than older patients or men regardless of differences in other parameters or in therapy.

Chart 4 emphasizes the not unexpected finding that survival of patients with localized disease is better than that of the other cases. In our patient material, the therapy of the Class I and II cases was often carried out in nonspecialty hospitals and the majority of these patients did not receive intensive radiotherapy. Table 4 stresses the further improvement which can be achieved by intensive radiation to localized disease. The table also indicates that the prognosis of cases with disseminated disease (Stage III) is poor in all reported series (34, 85, 164, 171, 198, 240).

The data show an impressive difference in survival between the patients presenting initially with local or regional disease and those presenting initially with disseminated disease. Since, by history, the patients with Stage III disease have not apparently all gone through Stages I or II, the possibility exists that we are dealing with variants of Hodgkin's disease rather than a single disease entity. Our lack of understanding of this issue appears to be an obstacle to the effective control of Hodgkin's disease.

The effect on survival of histologic type has been clearly established since Jackson and Parker's studies (102). Patients with paragranuloma show over-all survival results superior to the other groups (37, 208, 250). Recently, Lukes (131, 132) and Hanson (78) have shown that nodular sclerosing Hodgkin's disease has a prognosis as favorable as paragranuloma.

Cohen et al. (27) have attempted to prognosticate regarding survival in the presence or absence of certain clinical and laboratory findings. They found that as the number of initial physical findings and laboratory abnormalities increased, the survival dep-

### Table 1

**Comparison of Survival Data in Patients with Hodgkin's Disease**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of Patients</th>
<th>50% Survival (mo.)</th>
<th>5-yr Survival (%)</th>
<th>10-yr Survival (%)</th>
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<tr>
<td>Nice and Stenstrom (164)</td>
<td>1954</td>
<td>208</td>
<td>25</td>
<td>10</td>
<td></td>
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<tr>
<td>Smetana and Cohen (208)</td>
<td>1956</td>
<td>388</td>
<td>33</td>
<td>17</td>
<td></td>
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<tr>
<td>Gelhorn (63)</td>
<td>1957</td>
<td>121</td>
<td>27</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Peters and Middlemiss (171)</td>
<td>1958</td>
<td>221</td>
<td>38</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Cook et al. (32)</td>
<td>1959</td>
<td>347</td>
<td>35</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Warwick and Sellers (240)</td>
<td>1959</td>
<td>411</td>
<td>24</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Craver (34)</td>
<td>1964</td>
<td>514</td>
<td>38</td>
<td>10</td>
<td></td>
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<tr>
<td>Hilton and Sutton (85)</td>
<td>1962</td>
<td>107</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meighan and Ramsey (140)</td>
<td>1963</td>
<td>150</td>
<td>28</td>
<td>32</td>
<td></td>
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<tr>
<td>Ultmann et al. (survival method)</td>
<td>1965</td>
<td>135</td>
<td>23</td>
<td>22</td>
<td>5</td>
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<td>Ultmann et al. (life table method)</td>
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<td>135</td>
<td>25</td>
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### Table 2

**Distribution by Age in Hodgkin's Disease**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Year</th>
<th>No. of Patients</th>
</tr>
</thead>
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<tr>
<td>Uddströmer (232)</td>
<td>Sweden</td>
<td>1915-1931</td>
<td>536</td>
</tr>
<tr>
<td>Videbaek (235)</td>
<td>Denmark</td>
<td>1930-1945</td>
<td>172</td>
</tr>
<tr>
<td>Jackson and Parker (102)</td>
<td>Boston</td>
<td>1902-1946</td>
<td>329</td>
</tr>
<tr>
<td>Fayos et al. (55)</td>
<td>Michigan</td>
<td>1940-1955</td>
<td>175</td>
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<tr>
<td>Levinson et al. (124)</td>
<td>Utah</td>
<td>1945-1955</td>
<td>91</td>
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<td>Meighan (148)</td>
<td>Saskatchewan</td>
<td>1946-1959</td>
<td>186</td>
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<tr>
<td>Craver (34)</td>
<td>New York City</td>
<td>1949-1955</td>
<td>490</td>
</tr>
<tr>
<td>Ultmann et al.</td>
<td>New York City</td>
<td>1951-1965</td>
<td>135</td>
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**Chart 2.** Age at onset and sex of 135 patients with Hodgkin's disease seen at the Francis Delafield Hospital from 1951 to 1964.
creased. Using an analogous approach, we have calculated survival from date of biopsy in symptomatic Stage III patients with hepatomegaly (Chart 5). The poor prognosis of a finding of hepatomegaly is striking.

It has been stated by Stuhlbarg and Ellis (220) that "unlike other forms of malignant disease involving bone, that seen in Hodgkin's disease occurs in patients who have a longer survival than patients without such clinical manifestations." In their study, survival was measured from date of 1st biopsy and not from occurrence of the 1st bone lesion. Examination of our own patient material (Chart 6) indicates that evidence of involvement of bone by Hodgkin's disease is an ominous sign. Patients who had this type of involvement at the time the diagnosis of Hodgkin's disease was proven had a short survival. Those patients who developed bone involvement at a later date in the course of their disease were indeed patients who had lived longer—an average of 35 months (range 1–140 months, median 22 months); however, whenever bone involvement became symptomatic or was discovered roentgenologically, it appeared to be a serious complication and ½ the patients succumbed within 6 months.

Complications and Cause of Death

It has been stated in the literature that the most common causes of death of patients with Hodgkin's disease are a "toxic state" associated with extensive visceral involvement or a terminal state associated with secondary infection. The nature of the toxic state has never been defined (34, 94, 102). In our own group of 135 patients, 115 have died. The following clinical conditions were apparently responsible for the patient's death (often more than 1 condition was present): severe infection (21% of cases), failure of pulmonary function (20% of cases), central nervous system involvement or malfunction (11% of cases), gastrointestinal bleeding (10% of cases), and liver failure (7% of cases). In 30 patients, anemia, leukopenia, thrombocytopenia, or a com-

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**TABLE 3**

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>YR</th>
<th>CHRONOLOGIC PERIOD</th>
<th>MALE</th>
<th>FEMALE</th>
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<td>Levinson et al.</td>
<td>1957</td>
<td>1940–44</td>
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<td>29</td>
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<td>Shimkin (201)</td>
<td>1964</td>
<td>1945–49</td>
<td>157</td>
<td>112</td>
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<td>Ulmann et al.</td>
<td>1900–54</td>
<td>1950–54</td>
<td>609</td>
<td>419</td>
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**CHART 3.** Survival from date of biopsy according to age in 135 patients with Hodgkin's disease. The calculations of survival were performed according to the life table method (63).

**CHART 4.** Survival from date of biopsy according to regional classification in 135 patients with Hodgkin's disease. The calculations of survival were performed according to the life table method.
TABLE 4

Comparison of Survival Data in Patients with Hodgkin's Disease According to Regional Classification

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Stage I 5-yr Survival (%)</th>
<th>Stage I 10-yr Survival (%)</th>
<th>Stage II 5-yr Survival (%)</th>
<th>Stage II 10-yr Survival (%)</th>
<th>Stage III 5-yr Survival (%)</th>
<th>Stage III 10-yr Survival (%)</th>
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<td>Nice and Stenstrom (164)</td>
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<td>77</td>
<td>90</td>
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<td>2</td>
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<td>Sellers (198)</td>
<td>1957</td>
<td>57</td>
<td>35</td>
<td>35</td>
<td>35</td>
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<td>1958</td>
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<td>58</td>
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<td>Warwick and Sellers (240)</td>
<td>1959</td>
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<td>38</td>
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<td>15</td>
<td>11</td>
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<td>Hilton and Sutton (185)</td>
<td>1962</td>
<td>79</td>
<td>55</td>
<td>55</td>
<td>38</td>
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<td>3</td>
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<td>Craver (34)</td>
<td>1964</td>
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<td>19</td>
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<td>17</td>
<td>3</td>
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<tr>
<td>Ullmann et al.</td>
<td></td>
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**Chart 5:** Survival from date of biopsy in 28 patients with hepatomegaly compared with all patients with systemic manifestations but without hepatomegaly.

combination of these, directly attributable to antecedent radiotherapy or chemotherapy, contributed to the death of the patient.

The frequency of infections merits further examination. Others in this conference will speak in greater detail on the characteristics of the immune defect (1-3, 46, 91). Anergy to tuberculin, Trichophyton, Candida, streptokinase, and diphtheria toxoid as well as delayed homograft rejection have been demonstrated (1, 203). Response to vaccination with typhoid, mumps, and pneumococcal polysaccharides has been inconclusive (203). Properdin levels are low (188) but serum complement is normal (187). Cellular defense mechanisms as measured by the skin-window technic appear to be normal (203, 241). Serum γ-globulin changes have been mentioned earlier.

Various types of infections were encountered. Episodes of bacterial septicemia as well as pulmonary, skin, and urinary tract infections occurred in many patients. Common organisms were Staphylococcus aureus, Escherichia coli, and Pneumococcus pneumoniae. Salmonella typhimurium (82) and Klebsiella pneumoniae also were encountered. Pneumocystis carinii pneumonia (98) and listeriosis (189) have been reported. Serum γ-globulin abnormalities were frequent; leukopenia, however, was not a constant feature. Active tuberculosis occurs in approximately 2% of cases (178).

There were 16 patients with severe monilial infection; 10 of these had hypo-γ-globulinemia. An additional patient had central nervous system tuberculosis (Cryptococcus neoformans) (15, 69, 153). Other types of fungus infections, including aspergillosis (23, 100), mucormycosis (52, 99), and nocardiosis (93) have been encountered. The occurrence of toxoplasmosis has been recorded (25, 30, 114).

Seventeen patients had 19 episodes of herpes zoster. γ-Globulins were reduced in 5 the cases. Six patients progressed to generalized herpes zoster; 4 of these were receiving prednisone.
Similar experiences have been reported by many investigators (35, 38, 199, 242).

Unquestionably, infections contribute in a major way to morbidity and mortality in Hodgkin's disease. In many instances the patients were already in the advanced phase of their disease when they contracted the infection. It is difficult to assign responsibility to the various factors which may be involved in the high rate of infection. They include: (a) deficit in antibody formation, hypo-γ-globulinemia, and lymphopenia; (b) failure of cell-bound antibody mechanisms; (c) leukopenia and neutropenia secondary to replacement of bone marrow, hypersplenism, and drug or radiation toxicity; (d) glucocorticoid administration; (e) prior administration of antibiotics; (f) debility and poor nutritional state; and (g) local predisposing factors, such as tumor involvement or radiotherapy.

Effects on Survival of Changes in Management: 1900–1965

One might conveniently examine the natural history of the disease in various time periods defined in terms of the therapeutic modalities available. During the earliest period no therapy at all was given. The number of cases recognized was too small to come to any conclusions regarding the prognosis of untreated disease (68, 166, 179, 204, 215).

Beginning in 1908 and to the end of the 1930's was the period of radiotherapy prior to the advent of antibiotics and of efficient blood-banking. Five-year survival from onset in most series was from 10 to 25% of the cases (33, 41, 55, 102, 106, 124, 133, 207, 219, 232, 235).

The next era is that in which radiotherapy was retained as the prime agent of treatment but in which sulfa drugs and penicillin were available to combat infections (Chart 7) (12, 14, 32-34, 41, 55, 66, 81, 85, 92, 102, 106, 110, 124, 133, 151, 164, 169, 198, 207, 219, 232, 235). During this time, further improvement in 5-year survival from biopsy is apparent.

Finally, one would like to look for alterations in the management of disseminated disease with our present chemotherapeutic armamentarium together with the tremendous changes brought about in the management of infectious diseases by broad spectrum antibiotics and of anemia by modern transfusion technic. In the last 15 years there appears to have been only slight improvement in the over-all survival statistics and this is due mainly to recognition and intensive therapy of the localized disease (47, 110, 170). The survival of patients with disseminated disease (Class III) remains at between 5 and 20% (5-year survival) (12, 14, 32, 34, 66, 81, 85, 92, 110, 133, 151, 164, 169, 198). Let us now turn to a consideration of the obstacles to effective therapy. If the phenomenon of progression of Hodgkin's disease exists, that is, if there is a unicentric origin and a subsequent spreading from that region, the medical profession does not seem to be in a position to identify it early. Examination of our protocols indicates that patient delay, together with delay by physicians from onset of symptoms to 1st biopsy, averaged 7 months.
in each 5-year period from 1940 to 1965. The effect of the educational process of stressing the importance of early recognition and early biopsy seems to have been negligible. However, if further education could achieve a decrease in patient or doctor delay, would this necessarily improve the patient's prognosis? Peters and Middlemiss (171) have pointed out that the patients who have adenopathy of more than 6 months' duration prior to seeking medical attention have a longer survival than those seeking treatment under 6 months from the onset of disease. This was particularly true for Stages I and II. Our own data regarding the Stage III cases suggest a similar relationship but lack statistical significance. It is likely that Hodgkin's disease which is slowly progressive and comes to the attention of the patient and doctor only gradually has a better prognosis than the early symptomatic or early recognizable disease—an intrinsic property of the tumor alluded to previously. If the patient were to seek medical attention promptly, can we identify the individuals subject to early progression or those who have already progressed when we still think they have localized disease? Dr. Lee in discussing lymphangiography will indicate to us how we have extended our capability of identifying individuals who have already extended their disease. Do these individuals have a particular histologic characteristic which would allow us to identify them early in their disease? Dr. Lukes will speak on this subject.

Comparison of cases who died early with those who lived over 5 years (Table 5) indicates that widespread disease, histology of sarcoma, and initial systemic manifestations and fever do not preclude a long survival. It is readily apparent, however, that these features together with early hepatomegaly or splenomegaly predispose to an unfavorable course in many cases. Most striking, however, is the difference in response to the modalities of therapy available at present. The "long" survivors have uniformly responsive disease; the "short" survivors generally fail to respond to anything available at present. Other investigators have made similar observations (56).

Comparison (Chart 8) of the Stage III patients, who never responded to any chemotherapeutic agent, with those who had at least 1 significant response to chemotherapy indicates that the responders had their disease process significantly longer prior to 1st administration of chemotherapy and eventually lived considerably longer than the nonresponders. Reference to previous or later experience with radiotherapy in these patients indicates the appearance of new classes of chemotherapeutic agents may change the survival statistics for Class III patients. The results obtained with vinblastine (Velban) by others (6, 61, 119) and ourselves suggest that this alkaloid may suppress disease in patients who have failed to respond to radiation and the alkylating agents from the start or have become resistant to these modalities of therapy. The experience with the methylhydrazine derivatives (Natulan) (19, 54, 144, 228) also indicates that previously resistant disease may be amenable to chemotherapeutic control. Some of the patients resistant to the alkylating agents and vinblastine have shown significant remissions following administration of methylhydrazine. The attempt to treat Class III cases with extensive high voltage radiotherapy as advocated by Kaplan and by others may further improve the prognosis for these patients. Storage of autologous bone marrow to be administered after intensive chemotherapy or radiotherapy has been advocated but has not been proved to be of real value (143).

If the rationale of intensive radiotherapy and intensive chemotherapy is based upon the hypothesis of Skipper (206), which suggests that one must eliminate the last neoplastic cell, we have not been successful in patients with disseminated disease. After 1, 2, or many significant responses to radiotherapy or to chemotherapeutic agents, the disease becomes refractory. It has recently been pointed out by Gross et al. (76) that the virus of murine leukemia persists even after all neoplastic cells are wiped out by γ-irradiation because it is particularly resistant to radiation. Thus, if a virus is found to be the causal agent of Hodgkin's

### Table 5

<table>
<thead>
<tr>
<th>Characteristics of Long-Term and Short-Term Survivors</th>
<th>Long-term (&gt;5 yr)</th>
<th>Short-term (&lt;6 mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>Median age at onset (yr)</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>Males (%)</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>Class III (%)</td>
<td>62</td>
<td>100</td>
</tr>
<tr>
<td>Sarcoma (%)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Presenting with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic symptoms (%)</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>Benefit from:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (%)</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Nitrogen mustard (%)</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td>All other agents (%)</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

### Chart 8

Survival from date of 1st chemotherapy as related to response in patients with Stage III Hodgkin's disease.
disease, even if we were able to eradicate the last Hodgkin cell, the virus might reinfect new cells and the disease would continue. The characterization of the etiologic agent responsible for Hodgkin's disease and identification of modes of anti-viral therapy must be a prime goal of research in this area.

Etiologic Considerations

Kassel (113), Aisenberg (1), and others have reviewed recent reports regarding the etiology of Hodgkin's disease. Any current hypothesis must take the following into consideration: (a) the developments in tumor virology (73, 75); (b) the findings gathered in connection with the African lymphoma; (c) the epidemiologic data collected by MacMahon (134) and others; (d) the increased incidence of Hodgkin's disease in individuals who have a close relative with the disease (42, 108, 177); (e) the finding of the Atomic Bomb Casualty Commission that the incidence of Hodgkin's disease is 4 times greater in exposed than non-exposed individuals (4); (f) the possible interrelationship between Hodgkin's disease and other lymphomata, Kaposi's disease, and leukemia (20, 121); (g) the finding of Hodgkin's-like lymphomata in other species, particularly the rat (74) and the dog (205, 209, 213); and (h) the finding of Hodgkin's-like lesions in the adenopathy induced by anticonvulsants, in which the lesions regress when the offending drug is removed (191, 192).

We have already alluded to the fact that some histologic features point to a neoplastic nature in this disorder, others resemble more those of a granuloma. Murray and Stout (159, 160), employing tissue culture technics, found that "the behavior of the Hodgkin's node in vitro distinguishes it sharply from neoplastic tissues in general and tends to align it with granulomatous lesions." The resemblance to tissue cultures of lymph nodes from Boeck's sarcoid or infectious lymphadenitis may be great, whereas no Hodgkin's disease cells behave autonomously as would be expected of a cancer. Rottino has made similar observations (183). In contrast, chromosome analyses of Reed-Sternberg cells show hyperdiploid forms compatible with a neoplastic disorder (8, 62, 212).

In connection with this question, the previously mentioned report of LeRoy (123) regarding the levels of hydroxyproline-containing protein in human plasma is of interest. They suggest that hydroxyproline peptides reflect collagen degradation. In a survey study, elevated values were found in connective tissue disorders, inflammatory and febrile diseases, and afebrile Hodgkin's disease but not in the other lymphomas or other tumors.

In addition to the abnormalities in immune response, altered hypersensitivity, delayed homograft rejection, autoimmune hemolytic anemia, and lack of response of lymphocytes in vitro cultures to various stimuli (86), the occasional finding of amyloidosis (65, 200, 226, 237, 247), and the appearance of rheumatic diseases (22, 122), Sjögren's syndrome (21) and L. E. phenomena (96) should be considered not only as complications of Hodgkin's disease but also as possible clues to the pathogenesis of the disease (70, 71, 111, 231).

Conclusion

The influence on the course of age and sex, of localization of disease, and of histologic type was noted. The question was raised whether all patients start with unicentric disease or whether some have variants of Hodgkin's disease which are multicentric from the start. The rate of progression of the disease and its response to radiotherapy or chemotherapy are unpredictable and the mechanisms responsible for these differences remain unknown. Certain histologic features, tissue culture experiments, and biochemical observations suggest differences from rather than similarities to cancer in general. The etiology of Hodgkin's disease remains unknown and this presents the major obstacle to a rational approach to the problem.

The studies of the clinical and laboratory features, investigations of laboratory models which might shed light on pathogenetic mechanisms, development of new chemotherapeutic and roentgenologic technics, and the broad investigations into viral carcinogenesis and antiviral therapy will be required to unravel the mysteries which still surround Hodgkin's disease.

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