# CLINICAL ASPECTS AND DIAGNOSIS OF HODGKIN'S DISEASE

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Hodgkin's disease is a complex pathologic entity involving one or more lymph nodes and, often, other organs with a wide variety of clinical manifestations. Even though it has been 135 years since Hodgkin first described this disorder, the etiology of the disease has not yet been elucidated. In 1865, Wilks further delineated the syndrome and named the disease with Hodgkin's name. In 1870, Murchison described the first patient with fever and Hodgkin's disease, but it was not until 1900 that Pell and Epstein delineated the fever characteristic of this illness. The credit for separating Hodgkin's disease histologically from the other lymphomata must go to Sternberg and Reed who, in 1898 and 1902, respectively, described the histologic picture which characterizes Hodgkin's disease.

The current interest in Hodgkin's disease stems first from the fact that clinical observations together with recently developed laboratory techniques now permit greater understanding of the pathophysiology than was previously possible and, second, that new therapeutic approaches are now available which promise to extend useful life in many patients and to cure some.

**Incidence**

In the United States of America, each year approximately 3200 deaths are due to Hodgkin's disease. Incidence rates are somewhat higher than mortality rates; the difference is probably due to the substantial portion of persons with Hodgkin's disease who live long enough to have their deaths attributed to other causes. The incidence of the lymphomata appears to be rising in Europe and in the Americas. In contrast to the experience in Western countries, the Chinese of Hong Kong, the Koreans and the Japonese have a distinct absence of lymphomata in general and of Hodgkin's disease in particular. Although rare, the most common lymphoma in the Orient is reticulum cell sarcoma.

Unlike lymphosarcoma and reticulum cell sarcoma, Hodgkin's disease has a characteristically bi-modal curve, with the first mode between 15 and the second mode at over 50 years of age. Fifty-eight to sixty-six per cent of Hodgkin's disease patients are male. The bi-modality by age is exhibited in both sexes. Mortality data show fewer females in the 15 to 34 year age group than is apparent in the incidence data. The explanation for this appears to be the fact

that women have their disease diagnosed earlier than males, have a higher proportion of localized disease when diagnosed, and have a better survival than males in comparable stages. This difference in mortality rates does not exist over age 50.

**Initial Clinical Findings**

Characteristically, the patient gives a history of excellent health until the onset of his disease. This 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 to 80%, the axillary, 6 to 20%, and the inguinal, 6 to 12%. The mediastinal and/or retroperitoneal lymph nodes may be involved initially in as many as 40% of patients. The liver and the spleen are less commonly clinically involved in the early phases of the disorder.

**Biopsy**

Therapy for Hodgkin's disease should not be undertaken without histologic confirmation of the diagnosis. After ruling out local causes for lymph node enlargement, such as tonsilitis, infections of the hands and feet, dermatitis or pediculosis capitis, and after eliminating systemic causes, such as infectious mononucleosis, tuberculosis, syphilis, sarcoid, systemic lupus erythematosus or reactions to diphenylhydantoin and related compounds, biopsy of an enlarged lymph node should be performed. If the disease is confined to deep lymph nodes in the thoracic or retro--peritoneal regions, a scalene lymph node biopsy, thoracotomy, or laparotomy may have to be considered. Certainly, no more than 3 to 4 weeks should elapse between the recognition of an unexplained lymph node enlargement and the performance of a biopsy. It is advisable to remove large lymph nodes rather than superficial or small ones. The disease process is more likely to be evident in the former. At times, the pathologist may be unable to give a definite answer. It is a disservice to the patient to start therapy when the diagnosis is in doubt. A second biopsy of another lymph node often gives the answer. As a rule, the pathologic features are most easily recognized in biopsies from the cervical lymph node chains. Biopsy of inguinal lymph nodes is to be avoided if possible, particularly in men, because the interpretation may be made difficult by previous chronic infectious processes. If a biopsy of a femoral, iliac, or retroperitoneal lymph node is contemplated, it is advisable to perform it prior to lymphangiography as a non-specific inflammatory reaction to the Ethiodol[R] may in part obscure the histology of the lymph node.

**Histologic Stages**

Biopsy serves not only to arrive at a definitive pathologic diagnosis of Hodgkin's disease but allows consideration of the differences in natural history of the disease as related to its pathologic picture. The histologic classification of the lymphomata generally consists of the lymphosarcoma group subdivided as giant follicular lymphosarcoma, small cell lymphosarcoma, and larg cell lymphosarcoma, and of Hodgkin's disease generally now subdivided into the stage of lymphocytic predominance, of nodular sclerosis, of mixed cellularity, and of the lymphocytic depletion, the latter again subdivided into the stage of diffuse fibrosis and reticular type. A third histologic classification is generally reserved for malignant lymphomas which cannot be classified fully.

**Clinical Stages**

Hodgkin's disease is specifically staged at the time of diagnosis in order to plan the appropriate therapeutic program. The need for an acceptable staging classification for Hodgkin's disease has been emphasized at recent conferences in the United States of

America, in France, and in other countries. The current staging definitions represent modifications of the widely used classification of Peter's which divided the disease into three groups: 1) the local, which consisted of a single organ site or a single lymphatic region; 2) the regional, which consisted of two or more adjacent lymphatic lesions, or a single organ and regional lymph nodes; and 3) disseminated disease, which consisted of many groups of lymph nodes or of other organ involvement. Any of these three groups could be with or without symptoms. Kaplan proposed an additional grouping. The American Cancer Society and the National Institutes of Health in the U.S.A. have adopted a modified classification of Hodgkin's disease. In this group, Stage I-1 is lymph node involvement limited to one anatomical region. Stage I-2 is lymph node involvement limited to two contiguous anatomical regions on the **same** side of the diaphragm. Stage II is disease in more than two non-contiguous regions on the **same** side of the diaphragm. Stage III is disease on **both** sides of the diaphragm, but limited to lymph nodes, spleen, and Waldeyer's ring. Finally, Stage IV consists of those patients who have involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract or any tissue or organ **other** than lymph node, spleen, or Waldeyer's ring. All stages are subclassified "A" or "B" to indicate the absence or presence, respectively, of systemic symptoms. Any of the following symptoms will be considered as significant: documented, otherwise unexplained fever, night sweats, pruritus, or weight loss of more than 10% of normal body weight. Other signs or symptoms of Hodgkin's disease are important to document but are not considered sufficient in themselves to relegate a patient to the "B" subgroup. These include malaise, weakness, fatigue, anemia, leukocytosis, leukopenia, lymphopenia, elevated sedimentation rate, cutaneous anergy, or alcohol pain.

The following studies are considered desirable for accurate staging: 1) careful history with special attention to the systemic symptoms described above; 2) complete physical examination; 3) complete blood count including a white blood cell count, differential count, hematocrit or hemoglobin, platelet count, and erythrocyte sedimentation rate; 4) "PA" and lateral chest film, whole lung tomograms in presence of hilar adenopathy; 5) skeletal survey to include at least the thoraco-lumbar spine and pelvis; 6) retroperitoneal studies to include lower extremity lymphangiography if possible and an exploratory urogram; 7) bone marrow examination with an histologic section of the marrow clot or, if possible, a needle biopsy or open marrow biopsy; 8) liver function test to include a serum alkaline phosphatase; 9) renal function tests to include a urinalysis; and 10) documentation of cutaneous anergy.

From the list above it is obvious that the clinical findings with radiologic studies is extremely important and useful. Lung tomography, intravenous pyelography, and gastrointestinal studies have been employed for many years. More recently, employment of radio-opaque iodized oil, Ethiodo-R, for lymphangiography; radioactive gold, $Au^{198}$, for liver scanning and bone marrow scanning; heat-damaged $Cr^{51}$-labeled red cells for spleen scanning; and $I^{131}$ aggregated albumin for lung scanning has added new dimensions to the meaning and limitations of "clinical local disease".

The usefulness of the liver scan is shown on the next slide. In this particular patient, there are seen two areas in which the $gold^{198}$ has not been taken up by the Kupfer cells of the liver. At post-mortem examination, it was shown that there was a large, single metastasis in the left lobe of the liver and that, in addition, a large, bulky mass of lymphoid tissue in the porta hepatis was enlarging this particular area making the uptake appear to be decreased in the area of the porta hepatis. Liver scans are often difficult to interpret, however, in examples such as the one shown they may be extremely helpful in pointing to areas grossly involved by Hodgkin's disease. The second tchnique is the spleen scan performed with heat-damaged $Cr^{51}$-labeled autologous red cells. As shown in this particular slide, one can detect enlargement of a spleen which may have been missed on physical examination and on flat plate of the abdomen. Detection of isolated masses in the spleen is considerably more difficult than in the liver, and such findings must be interpreted with great caution.

Lymphangiography is probably the most useful of the techniques which were mentioned. The next slide shows an intravenous pyelogram; it can be readily seen that on the left there is displacement of the ureter in the upper one-third by a mass. In most instances, this would be sufficient to alert the clinician to the presence of retroperitoneal nodes. In this particular patient, however, it was desirable for other reasons to perform lymphangiography. The next slide indicates that the deviation of the ureter is due to an enlargement of a lymph node by involvement with Hodgkin's disease. The next slide shows the usefulness of a lymphangiogram in a patient who had established Hodgkin's disease and recurrence of symptoms including fever, weight loss, and itching. Physical examination and routine tests failed to reveal the location of the recurrent disease; however, by lymphangiography, shown on this and subsequent slides, involvement of the retroperitoneal lymph node chain by Hodgkin's disease could be readily demonstrated. The second slide in this series points out the usefulness of an oblique film and the third slide, the usefulness of a lateral film in the analysis of lymphangiographic studies.

Lymphangiography appears to be indicated in Stage I and II-A patients with disease above the diaphragm to rule out the presence of retroperitoneal involvement before administering radical radiation therapy to the diseased nodes and to the contiguous areas. If retroperitoneal disease is discovered, as it is in about 10% of cases with cervical Stage I disease and in one-third of patients with cervical Stage II-A disease, this occult disease can be treated with radiation therapy in an attempt to eradicate all known foci of disease. It is in these groups, old Stage I and old Stage II-A, in whom the most interesting observations relative to the usefulness of lymphangiography and prophylactic radiation therapy will evolve. Namely, how much does the discovery of asymptomatic retroperitoneal Hodgkin's disease and its subsequent treatment with current modes of therapy prolong survival?

Lymphangiography is usually not indicated in patients with the old Stages II-B and III disease. Ninety per cent of these patients have retroperitoneal disease. A lymphangiogram would seem necessary only if it is planned to cure patients with generalized Hodgkin's disease with irradiation of all involved lymph node-bearing areas. This program is under investigation in a number of radiotherapy centers.

The complications of lymphangiography should be kept in mind when performing these studies. They include: symptomatic pulmonary oil embolism; oil embolism to other organs, including kidney, brain, and liver; cellulitis at the site of injection; allergy to iodine-containing dye or to the blue dye used for tracing the lymphatic vessels; occasional fever lasting 12 to 36 hours after injection of the contrast material (this may be associated with excessive pulmonary oil embolism); and transient pain usually at the site of involved nodal masses within the abdomen or pelvis.

The contra-indications to this diagnostic test, therefore, are: parenchymal pulmonary disease whether it is symptomatic or not; patent foramen ovale; renal vascular disease; or other underlying conditions predisposing to excessive deposition of Ethiodol[R] in a vital organ; excessive intra-abdominal disease, especially with palpable nodal involvement below the diaphragm; and a history of allergy to the iodine-containing or blue dyes.

Whereas the staging classification just discussed is of great practical value, a number of additional factors of prognostic significance should also be considered. These might be particularly important in patients classified as Stage III or Stage IV. These factors to be discussed in greater detail in a later portion of this Symposium include the age of the patient, the sex of the patient, the duration and number of signs and symptoms, the exact location of presenting lymph nodes, and the completeness and duration of response to initial therapeutic procedures. Although these factors and the stating are of general value in predicting the clinical course, it must be remembered that there is no single, reliable prognostic sign for an individual case.

**Course of Disease**

The clinical course of Hodgkin's disease is characterized by great variability. Progression is by successive exacerbations which occur at intervals of weeks, months,

or years. Fever occur eventually in over 50% of cases and is cyclic, continuous, intermittent, or more rarely, the Murchison--Pell-Epstein type. The pulse is rapid. Drenching sweats are common in presence of fever but occur also in its absence. Weakness, fatigue, weight loss, and cachexia eventually occur in all patients. Up to 85% of the cases have pruritus at some time.

Intrathoracic involvement is frequent. In a study of 50 cases coming to post--mortem examination, the centrally located lymph nodes (the mediastinal and hilar lymph nodes) were involved in 49 out of 50 cases. The involvement of other structures was also frequent, particularly the lungs, the bony thorax, and the pleura. In addition, the diaphragm, the heart, the pericardium, the thymus, and the esophagus may be involved. Pulmonary involvement may appear in 15 to 50% of cases. Hodgkin's disease may be primary in the lung, but more often there are direct infiltrations from the mediastinum or multicentric lesions, originating presumably by hematogenous spread. A few patients are asymptomatic; the majority complain of dry, hacking cough, chest pain, and of those signs and symptoms which are commonly associated with active Hodgkin's disease. In addition, a few have hemoptysis, dyspnea, and the signs of pneumonitis. The involvement of the pulmonary area may be subpleural, bronchial, or endobronchial, the latter often leading to atelectasis, parenchymal which may be isolated or massive and occasionally may terminate in cavitary lesions, and non-specific, including fibrosis. Most frequetly the lesions are located in the upper lobes.

The next slide shows the chest film of a patient who has a cavitary lesion, proven at autopsy to be due to Hodgkin's disease alone. The next slide shows an even more complex picture of a patient with Hodgkin's disease treated eight years earlier with extensive radiotherapy who, at the time this radiologic examination was done, had pulmonary fibrosis secondary to the radiation. In addition, he had infiltrations due to Hodgkin's disease and one of these, in the right middle lobe, had a cavity. In addition to these lesions, one may encounter pleural effusions; radiation fibrosis and penumonia; pneumonitis due to bacterial and fungal infections; and pulmonary edema due to congestive heart failure secondary to anemia. Pulmonary fibrosis with severe restriction of ventriculatory capacity may appear in the course of the disease or as a result of radiotherapy to the lung. The next slide shows a patient who had **no** intrathoracic disease and had a normal maximal breathing capacity before radiation therapy to her breast, axilla, and internal mammary chain for cancer. Two hundred days following her radiation treatment, her maximum breathing capacity was severely diminished and, as shown on the next slide, the work of breathing was markedly increased, that is, a greater pressure was necessary to inhale a given volume of air folowing therapy than during the control period. It is believed that these changes are due to the fact that radiation makes the expansion of the thoracic cage more difficult and stiffens the underlying pulmonary tissue.

Abdominal and retroperitoneal involvement is extremely frequent in the course of Hodgkin's disease. The gastrointestinal tract appears to be involved in about 15% of patients coming to autopsy. Most frequently the disease occurs in the stomach and in the small bowel. The symptoms are due to infiltration of the gastrointestinal tract, or due to pressure from large retroperitoneal masses, or from enlargement from the spleen and liver. The spleen, initially affected in up to 30% of patients, eventually is involved in 80% of cases. In the presence of enlargement of spleen, hypersplenism may occur; this will be discussed later.

Hepatomegaly is an early finding in about one-third of cases. Liver involvement, determined microscopically, occurs in over half of patients. However, in two large series the incidence of clinical jaundice was only 10 to 15%. In addition, in a series of 101 patients with jaundice and proven Hodgkin's disease accumulated at the Memorial Hospital, involvement of the liver with Hodgkin's disease occurred in only 16% of the cases. Other liver disease accounted for the jaundice in these patients, including serum hepatitis, toxic hepatitis, cholelithiasis, passive congestion, viral hepatitis, a liver carcinoma, and in 49% other

causes which could not be clearly delineated. The pathologic findings in the liver of 15 jaundiced patients with Hodgkin's disease who did not have tumor involvement in the liver or extrahepatic bile ducts revealed that the majority had passive congestion or fatty metamorphosis and others, hemosiderosis and non-specific atrophy of the liver cells. Various types of extrahepatic bile duct involvement were seen in 14 jaundiced patients with Hodgkin's disease and included pressure on the common duct by lymph nodes, infiltration of the common duct, and occasionally pressure on the hepatic duct.

Bone involvement as manifested by pain, radiologic evidence of destruction, or frank fractures are found in 15 to 30% of cases. The thoracolumbar vertebrae are most frequently involved; the pelvis and sacrum less frequently; the ribs, sternum, and skull the least. One-third of the lesions appear to be sclerotic; less than one-third, lytic; and the remainder, mixed. Hypercalcemia occurs in 10 to 20% of cases; usually, hypophosphatemia is also present and the serum alkaline phosphatase is elevated. Radiologic examination may be negative for bone involvement but bone involvement appears to occur in 60% of patients coming to autopsy and having a thorough study of the skeletal system. However, there are occasional cases in whom hypercalcemia may occur without any bone involvement by Hodgkin's disease.

Abnormalities of the central nervous system are noted in over 10% of patients. The brain or spinal cord may be invaded directly; however, more commonly, symptoms are due to compression of the spinal cord. Peripheral neuropathy and cranial nerve palsies may occur. Toxic encephalitis, without manifest lesions of Hodgkin's disease in the brain, particularly involving the cerebellum (cerebellar leukoencephalopathy) has been reported. Alcohol intolerance has been described in 17 to 20% of cases but does not appear to be specific for Hodgkin's disease. The most important neurologic complication of Hodgkin's disease is cord compression occurring in approximately 25% of patients who have some neurologic abnormality. It is characterized by weakness, paresthesias, back pain, and leg pain, and, in later stages, by difficulties with urinary and bowel control. The thoracic spine appears to be involved in 62% of cases; the lumbar spine in 24%. Physical examination may reveal abnormalities suggesting cord involvement. Radiologic examination of the spine and particularly myelography may more accurately localize the lesion. This complication constitutes a medical emergency and decompression by neurosurgery, nitrogen mustard treatment followed by radiotherapy, or radiotherapy alone or after surgical decompression, is the treatment of choice. Herpes zoster will be discussed in conjunction with the other infections encountered in Hodgkin's disease.

Skin involvement may be due to direct invasion by Hodgkin's disease, an "id" reaction, or excoriations produced in response to pruritus. Almost any other organ may be involved initially or in late stages by Hodgkin's disease. Thus, reports of Hodgkin's disease of the thyroid, breast, ovary, cervix, vulva, bladder and other genitourinary areas, nasopharyns, and the larynx have appeared in the literature.

Most studies indicate that pregnancy can be well tolerated particularly in patients who have the chronic form of the disease. It has been suggested that pregnancy should be avoided until 2 to 5 symptom--free years have passed.

**Laboratory Findings**

Anemia may occur with localized disease but it is almost uniformly present in the late stages of Hodgkin's disease. Except for a few cases of hypochromic anemia, secondary to blood loss, the majority of patients have normochromic, normocytic anemia. The direct Coombs test is usually negative. The next slide summarizes the results of a red cell life span study in a patient with severe anemia and splenic enlargement. A marked decreased in the $Cr^{51}$ red blood cell life span and significant sequestration of red blood cells in the spleen are seen. Klein and Berlin and others have reported similar findings. In addition, hypoferremia and abnormalities in iron metabolism, as measure by $Fe^{59}$, and consisting of excess uptake of iron by liver and spleen, impaired incorporation of iron into erythrocytes, and for re-utilization of hemoglobin iron have been noted. The anemia becomes progressively worse as the disease advances and

correlation with disease activty is often possible.

The changes in the white blood cells are not constant and not diagnostic. Leukocytosis with neutrophilia is often present. Monocytosis or lymphocytosis occurs occasionally early in the disease. Leukopenia and, in particular, lymphopenia are seen in advanced disease and will be discussed later in this Symposium. Eosinophilia is frequently found and occasionally may be marked. The platelets are normal or increased in the beginning of the illness, but usually diminished in the course of the disease. The leukocyte alkaline phosphatase value is often elevated during the active phases of the disease and falls during remissions. In about 5% of cases of Hodgkin's disease, myeloid metaplasia associated with hypoplastic marrow or tumor infiltration of bone marrow may be seen. Bone marrow aspiration is usually not helpful in ruling out bone marrow involvement, and formal biopsy may be necessary. When present, Reed-Sternberg cells are readily recognizable. On very rare occasions these cells have been found in the blood. The erythrocyte sedimentation rate is elevated in the presence of active disease and falls after effective therapy or during spontaneous remission.

Hypercalcemia may occur and is usually associated with hypophosphatemia and elevated serum alkaline phosphatase. As already mentioned, roentgnographic evidence of skeletal involvement by tumor may be absent although autopsy usually reveals osseous involvement. Hyperglycemia may be seen in association with steroid therapy or during exacerbations of the disease. Gout and decreased renal function following persistent hyperuricemia have been reported. Uremia may occur as a terminal event. Serum abnormalities occur regularly. Albumin is often reduced, mainly due to a decrease in synthesis. Alpha-1, alpha-2, and beta-2 globulins are usually increased; the alpha-2 globulin may be increased in up to 77% of the cases. The increase in the alpha-2 globulins is largely due to an increase in haptaglobin and ceruloplasmin. An increase in hexose bound to alpha-2 globulin has been noted by Whitmore in lymphomata including Hodgkin's disease. Although some authors feel that hypogammaglobulinemia is seen only rarely in patients with Hodgkin's disease, we have found that significant hypogammaglobulinemia (i.e., less than 0.9 gm% gamma globulin) occurs in almost half (48%) of the cases, particularly in advanced disease.

**Complications and Cause of Death**

The clinical condition or conditions apparently responsible for the patient's death in 115 cases studied at our hospital included: severe infection, failure of pulmonary function, central nervous system involvement or malfunction, gastrointestinal bleeding, and liver failure. In 30 patients, anemia, leukopenia, thrombocytopenia, or a combination of these, mainly attributable to antecedent therapy contributed to the death of the patient.

The frequency of infections merits further examination. A number of investigators have described the characteristics of the immune defect found in Hodgkin's disease. As Aisenberg will summarize later, anergy to tuberculin, tricophiton, candida, streptokinase, and diphtheria toxin as well as delayed homograft rejection have been demonstrated in some of the patients with Hodgkin's disease. Response to vaccination with typhoid, mumps, pneumococcal polysaccharides, and other antingens has been inconcluisve. Properidin levels are low; serum complement normal. Cellular defense mechanisms measured by skin-window technique appear to be normal. Lymphopenia and low gamma globulin levels have already been mentioned.

The next slide summarizes the various types of infections which were encountered at the National Institutes of Health in Bethesda, Maryland, by Carbone **et al.** Of 86 patients, 36 had bacterial infections, 17 viral infections, 10 fungal infection, and 3 miscellaneous infection. The number of episodes of infection per patient was 1.7; the number of episodes of infection per patient with infection was actually 2.3. As regards the bacterial infections in the U. S. National Institutes of Health series, 36 cases were encountered: 29 with septicemia, 14 with pneumonia, and 13 with enteritis, urinary tract, skin infections, and miscellaneous infections. Common organisms observed were **Staphylococcus aureus, Escherichia coli,** and **Pneumococcus pneumonii. Salmonella typhimurium** and **Kleb-**

**siella pneumoniae** were also encountered. **Pneumocystis carinii, Listeria monocytogenes,** and others have been reported. In our own series, we have examined the frequency, distribution, and types of bacterial infection in 141 patients with Hodgkin's disease seen between 1951 and 1965. We were able to demonstrate that leukopenia and neutropenia predispose only rarely to bacterial infection; that lymphopenia and hypogammaglobulinemia progress as the disease advances; and that this appears to predispose patients to infections. Antecedent radio—or chemotherapy and corticosteroids may increase further the risk of infection. The fact that the 5-year survival probability for the entire group, for the patients with bacterial infections, and for those without bacterial infections was the same, 27.4%, permitted analysis of our data by quarters, i.e., dividing the course of each patient living more than six months into four equal parts. Fifty-four patients had 82 episodes of bacterial infection; 17 patients had 19 episodes of herpes zoster; and 16 patients had severe fungus infection, mainly moniliasis. Although some of the infection occurred in the first, second, and third quarters, the majority of infections and the majority of recurrences of infections occurred in the fourth quarter of the patient's illness. Some of the patients were afflicted not only with bacterial infections but had concurrent infections with herpes zoster and superinfections with monilia.

Neither the leukocyte count nor the absolute neutrophilic granulocyte count appeared to correlate with the incidence of infections. The data for the neutrophilia actually emphasize the point that particularly in the first three quarters it was more often due to the underlying Hodgkin's disease than to bacterial infections. The findings regarding the absolute lymphocyte count in patients with and without bacterial infection have been analyzed. The normal lymphocyte level ranges from 1500 to 3000 per cubic mm. There appears to be a progressive, statistically singnificant. fall in the lymphocyte count in all the patients as the disease advances. By the fourth quarter, 111 out of 126, or 88% of patients, had lymphopenia. This supports data previously published by Aisenberg and by others. Whereas in the first 3 quarters, only 10 of 18 (56%) patients with infection had lymphopenia, in the final quarter, 37 of 44 (34%) patients with infection had lymphopenia. The risk for a patient with lymphopenia of developing bacterial infection in the fourth quarter is 33% (37 out of 111). The serum gamma globulin level, plotted in grams per cent, in patients with and without infection was also examined. In the third and fourth quarters there was a significant decrease in the mean gamma globulin level compared to the first two quarters. In the fourth quarter, 31 out of 84 patients (37%) had a gamma globulin below 0.95 gram%. The risk for a hypogammaglobulinemic patient developing a bacterial infection in the fourth quarter is 54% (17 out of 31).

The occurrence of bacterial infections following administration of radiotherapy, chemotherapy, or corticosteroids was examined next. Of the 141 patients, the 87 who never developed infection had 130 courses of radiotherapy, 156 courses of chemotherapy, and 50 courses of corticosteroids. The 54 cases with eventual bacterial infections also had many courses of radiotherapy (97), chemotherapy (60), or steroids (15) with no subsequent infection. Especially in the fourth quarter, however, this group of patients experienced bacterial infections often related to antecedent chemotherapy (41) or treatment with corticosteroids (25). The risk of bacterial infection following therapy increased greatly from the first three quarters to the fourth quarter. Thus, following radiotherapy, it increased from 0.5 to 19%, following chemotherapy from 5 to 34%, and following steroids from 4 to 38%.

Regarding the therapy of bacterial infections, none of the patients was on prophylactic antibiotics or gamma globulin; each infection was treated with appropriate local measures where applicable and with specific antibiotics as determined from sensitivity studies on the isolated bacteria.

The clinical importance of these bacterial infections is emphasized by the following findings. In 26 of the 54 patients, meningitis, septicemia, pneumonia, severe urinary tract infection, or a combination of these, contributed to the death of the patient; however, all patients died with

active Hodgkin's disease and none from infection alone. These data appear to indicate that leukopenia and granulocytopenia are not important in determining the occurrence of bacterial infections in patients with Hodgkin's disease. The presence of lymphopenia occurring in 88% and of hypogammaglobulinemia in 37% of cases in the fourth quarter predisposes a significant number of individuals to infection. The administration of radiotherapy and, particularly, of chemotherapy and steroids aggravates the tendency to contract bacterial infections.

There were several patients with severe monilial infection; two-thirds of these had hypogammaglobulinemia. Some patients had central nervous system tolurosis. Other types of fungi, including aspergillosis, mucormycosis, and nocardiosis have been encountered.

The occurrence of viral infections has been documented in a number of series. At the U. S. National Institute of Health, herpes zoster, varicella, cytomegallovirus, and herpes simplex have been described. In our own series, 17 patients had 19 episodes of herpes zoster. Generalized zoster occurred in six cases. Hypogammaglobulinemia was present in 8 of 10 cases, and leukopenia in 6 of 19. In 9 of the 19 episodes, chemotherapy proceded the appearance of the herpes zoster. During steroid administration, 6 patients developed herpes zoster and 4 of these had generalized herpes zoster involvement.

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 their infection. It is difficult to assign responsibility to the various factors involved in the high rate of infection. They include: 1) deficit in antibody formation, hypogammaglobulinemia, and lymphopenia; 2) failure of cell-bound antibody mechanisms; 3) possibly leukopenia and neutropenia secondary to replacement of bone marrow, hypersplenism, and drug or radiation toxicity; 4) glucocorticoid administration; 5) prior administration of antibiotics; 6) debility and poor nutritional state; and, finally, 7) local predisposing factors such as tumor involvement or radiotherapy.

Others in this Symposium will discuss in detail the immunologic aspects, staging and prognosis, pathologic features, radiotherapy, and chemotherapy of Hodgkin's disease. Knowledge of the natural history of Hodgkin's disease, of the complications which might be expected, and of the therapeutic modalities available helps the physician plan for the total care of the patient.