Hodgkin’s Disease: Biology, Treatment, Prognosis

By Henry S. Kaplan

This lecture presents a review of recent advances in Hodgkin’s disease, with particular reference to the identity and origin of its neoplastic cell population, their mode of spread in the body, the mechanisms underlying the selective deficit of cell-mediated immunity, and the remarkable impact of modern megavoltage radiotherapy and/or combination chemotherapy on the prognosis and curability of this once inexorably fatal disorder.

HODGKIN’S DISEASE has long defied classification because it presents, in varying degree, a curious amalgam of the features of a malignant lymphoid neoplasm, a chronic granulomatous infection, and an immunologic disorder. Debate has centered not only on the fundamental nature of the disease but on the identity of its putative tumor cell population and its pattern of spread within the body. It is only in the last two decades that definitive evidence of the malignant neoplastic nature of Hodgkin’s disease has finally emerged from cytogenetic and cell culture studies demonstrating that the giant cells of Hodgkin’s disease satisfy two of the most fundamental attributes of neoplasia: aneuploidy and clonal derivation. During the same 2 decades, impressive progress has also been made in charting the patterns of dissemination of the disease, in defining staging classifications and procedures, and in developing improved radiotherapeutic and chemotherapeutic regimens that have dramatically altered its once inexorably fatal prognosis. This lecture presents a brief summary of these advances. A much more detailed treatment of these and other subjects relevant to Hodgkin’s disease has recently been presented elsewhere.¹

THE GIANT CELLS OF HODGKIN’S DISEASE

The distinctive binucleate or multinucleate giant cells of Hodgkin’s disease are usually associated with the names of Dorothy Reed and Sternberg despite the fact that they were first described by several other investigators 2–3 decades earlier.² Their large size and certain features of their morphology suggested that they probably originated from the histiocyte. However, this interpretation was called into question when histochemical studies failed to reveal the presence of nonspecific esterase,³ an enzyme characteristically present in cells of the monocyte-histiocyte-macrophage lineage. At about the same time, it became clear that small lymphocytes may undergo remarkable changes in size and morphology during the process of lymphoblastoid transformation in response to mitogenic lectins and specific antigens, leading to the alternative hypothesis that Reed-Sternberg cells might be binucleate or multinucleate transformed lymphocytes.⁴

It was once widely presumed by those who considered Hodgkin’s disease to be a malignant neoplasm that the Reed-Sternberg cells comprise the tumor cell population. This view came under serious challenge when studies of fresh biopsy material from patients treated with vinblastine revealed that the cells arrested in mitosis were apparently limited to a mononuclear cell population. This view came under serious challenge when studies of fresh biopsy material from patients treated with vinblastine revealed that the cells arrested in mitosis were apparently limited to a mononuclear cell population. Moreover, after short-term incubation of cell suspensions from lymph node biopsies,
tritiated thymidine was incorporated into the DNA of mononuclear but not of binucleate or multinucleate cells, suggesting that the mononuclear Hodgkin's cells are the actively proliferating neoplastic population, and that Reed-Sternberg cells are end-stage degenerative forms.

Unambiguous evidence that Hodgkin's disease is indeed a malignant neoplasm has now emerged from cytogenetic studies. Such studies have been performed in at least 100 cases from 1962 through 1978. In addition to normal lymphoid cells with a modal chromosome number of 46, cell populations with aneuploid numbers of chromosomes, often in the near triploid or hypotetraploid range, have been observed in at least two-thirds of all cases. In one such study involving 4 cases of Hodgkin's disease, near-tetraploids were observed in 31 (16%) of 193 scorable mitoses. Although no single characteristic structural abnormality has been consistently encountered, marker chromosomes have been observed in at least 40% of the cases studied to date and have in some instances provided compelling evidence of the clonal derivation of the aneuploid cell population. In a remarkable case described by Seif and Spriggs, 18 of 63 cells had chromosome numbers between 77 and 86. Two unusually long marker chromosomes ($M_1, M_2$) were both present in 10 of these hypotetraploid cells, and $M_2$ alone in an eleventh cell.

The notion that Reed-Sternberg cells are end-stage degenerative forms incapable of DNA synthesis or mitosis has now been refuted. Labeling of these cells with tritiated thymidine has been successfully demonstrated in short-term incubations of fresh biopsy material, as well as in long-term cell cultures. Kaplan and Gartner observed that 17 (20.7%) of 82 binucleate or multinucleate giant cells in their long-term cell cultures were labeled (Fig. 1); this proportion was only moderately less than the 36.5% labeling index of the mononuclear cell population in the same culture. The observation of binucleate mitotic figures in fixed tissues and in cell cultures indicates that Reed-Sternberg cells are also capable of mitotic division.

The type of cell from which the Reed-Sternberg cell arises has been a subject of intense controversy, which has not been resolved by morphological or cytochemical studies. Some investigators have been impressed

![Fig. 1. Autoradiograph of cells from a long-term culture of involved spleen tissue from a patient with Hodgkin's disease. Both nuclei of a binucleate Reed-Sternberg cell are labeled with tritiated thymidine.](image_url)
by the electron micrographic resemblance of the nuclei of Hodgkin's cells to those of transformed lymphocytes. Others have called attention to the presence of elaborate cytoplasmic processes, actin-like cytoplasmic microfibrils, and small lysosomes, suggesting an origin from the macrophage. Nonspecific esterase activity, a distinctive feature of cells of the monocyte-macrophage lineage, has been absent or only very weakly positive in the giant cells of Hodgkin's disease in some studies, whereas distinct granular activity has been observed by others. Using fluoresceinated antisera to human immunoglobulins, some investigators have detected surface and/or cytoplasmic IgG in a varying proportion of Hodgkin's giant cells, leading to the suggestion that these cells might be derived from B lymphocytes. However, immunohistochemical staining procedures have revealed both \( \lambda \) and \( \kappa \) light chains in the cytoplasm of many of these cells. Since an individual B lymphocyte is not capable of synthesizing both types of light chains, the presence of both \( \lambda \) and \( \kappa \) suggests that cytoplasmic immunoglobulin is not an endogenous product of these cells.

Long-term cultures of the giant cells of Hodgkin's disease have been derived from involved lymphoid tissues and from cytologically positive pleural effusions, and the establishment of a small number of permanent cell lines has been reported. It has been difficult to prove unambiguously that the giant cells observed in such cultures, despite their morphological similarity to Reed-Sternberg cells, are indeed the progeny of the giant cell neoplastic population. In long-term cultures the giant cells from involved spleens exhibited a strong tendency to adhere not only to the surface of the culture vessel, but also to each other, leading to the formation of irregular clusters (Fig. 2). This observation immediately cast doubt on the notion that they are derived from transformed lymphocytes, since it is well established that lymphocyte populations transformed by lectins, antigens, or Epstein-Barr virus form nonadherent clusters of cells suspended in the liquid phase of the culture. The

*A recent reinvestigation of the 4 permanent cell lines reported by Long et al. has revealed unambiguously that 3 are of owl monkey rather than human origin; the fourth is of human origin, but the spleen from which this cell line was purportedly derived did not contain grossly or microscopically identifiable tumor (N. L. Harris et al., Nature 289: 228, 1980).
adherent giant cells in one such study possessed both Fc and complement receptors as revealed by their capacity for the formation of IgG-EA and IgM-EAC

rosettes, respectively.11 In contrast, they lacked such distinctive T- and B-lymphocyte markers as the capacity to form E-rosettes and the presence of surface membrane immunoglobulin. Although their phagocytic activity was sluggish relative to that of normal spleen macrophages, the cultured giant cells did phagocytize India ink, heat-killed _Candida_, and antibody-coated sheep erythrocytes. In several instances, positive staining reactions for nonspecific esterase were observed, and culture supernatants revealed significantly elevated lysozyme concentrations.11

Suspensions of viable Reed-Sternberg cells from 12 patients with Hodgkin's disease were examined by Kadin et al.21 using immunofluorescent reagents for surface and intracellular heavy and light immunoglobulin chains. IgG was often detected on the cell surface, whereas IgM and IgA were absent. Whenever surface IgG was detected, cytoplasmic IgG was also present within the same cell, though the converse was not necessarily the case. Every giant cell bearing cytoplasmic IgG contained both κ and λ light chains. When viable cells were incubated in medium containing fluorescein-conjugated aggregated human IgG, both cell surface binding and intracellular uptake of fluorescein aggregates was observed. It was concluded that the immunoglobulin observed in Reed-Sternberg cells is not endogenously synthesized within these cells; instead, it appears to be ingested from the extracellular environment.

Collectively, these studies may have partially resolved the controversy concerning the origin and nature of the Reed-Sternberg and Hodgkin's giant cells. Their neoplastic character is documented by their aneuploidy and heterotransplantability, whereas their adherent growth pattern in culture, cell surface markers, phagocytic activity, nonspecific esterase activity, and capacity to excrete lysozyme suggests that they may be derived from cells related to the mononuclear phagocyte system, rather than from the lymphocyte.

NATURAL HISTORY AND MODE OF SPREAD

The introduction of two diagnostic procedures, lower extremity lymphangiography22,23 and staging laparotomy with splenectomy,24,25 opened the way to the systematic mapping of sites of involvement in patients with Hodgkin's disease. In a study of 100 consecutive, previously untreated patients, Rosenberg and Kaplan26 found that involvement of various chains of lymph nodes was distinctly nonrandom; when a given chain of lymph nodes was affected, other chains known to be directly connected with it via lymphatic channels were likely also to be involved, either concurrently or at the time of first relapse. Even extralymphatic sites such as the lung, liver, and bone marrow were more likely to be involved in association with certain lymph node chains and/or with spleen involvement. These studies were subsequently extended to significantly larger numbers of patients with essentially similar results.12,27 Other groups of investigators have also provided confirmatory evidence.28,29

Two quite different theories, the "contiguity" theory of Rosenberg and Kaplan26 and the "susceptibility" theory of Smithers,30,31 have been proposed to account for the patterns of spread in Hodgkin's disease. The contiguity theory postulates that Hodgkin's disease is a monoclonal neoplasm of unifocal origin that spreads secondarily by metastasis of preexisting tumor cells, much like other neoplasms, except that its spread is predominantly via lymphatic rather than blood vascular channels. The term _contiguity_ refers to the existence of direct lymphatic channels connecting pairs of lymph node chains.

Smithers31 suggested that the giant cells of Hodgkin's disease may move in and out of lymph nodes from the blood stream following a traffic pattern similar to that known to occur with normal lymphocytes. In his view, Hodgkin's disease is a systemic disorder of the entire lymphatic system. He suggested the possibility that the disease may have a multifocal origin, perhaps by spread of a causative agent with de novo reinduction in different sites, rather than the spread of preexisting tumor cells. His theory predicted that, after the involvement of an initial site, other lymph node chains would have independent probabilities of next becoming involved, which would be proportional to their respective probabilities of initial involvement in patients with stage I disease.

Careful mapping of the initial sites of involvement in consecutive, previously untreated patients revealed the occurrence of noncontiguous patterns in only 4 (2%) of 185 patients with stage II disease.27 Hutchinson32 compared the observed distributions in 158 Rye stage II cases with expectation based on random association of two or more sites with the probabilities given by their respective frequencies in 53 observed stage I cases. The observed patterns for two or three involved sites departed significantly from random expectation. For example, there was a marked deficiency of bilateral cervical node involvement in the absence of associated mediastinal lymphadenopathy, an excess frequency of association between cervical and mediastinal node involvement, and a striking deficiency of all noncontiguous contralateral distributions.
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Lillicrap\textsuperscript{33} compared the predictions of the Smithers susceptibility hypothesis with observed patterns of spread in three different series of patients with Hodgkin's disease. He found involvement of bilateral cervical lymph node chains significantly less often than would have been predicted by the Smithers theory, whereas involvement of the neck and mediastinum was more frequent than predicted. There were 46 instances of homolateral cervical-axillary involvement, and only two contralateral cases, whereas the susceptibility theory would have predicted equal numbers of each. It was of interest that the observed patterns in his study were consistent with the contiguity theory in all but 4\% of 212 cases. Modifications of the susceptibility theory have subsequently been proposed by Smithers et al.\textsuperscript{34} in an attempt to make the theory more consistent with observed distribution frequency; however, these modifications accept the concept of spread of tumor cells via lymphatic channels, and are thus no longer very different in concept from the contiguity theory.

The most controversial remaining issue is the mechanism of spread between the lower cervical-supraclavicular lymph nodes and the upper lumbar paraaortic nodes. Among 80 patients presenting with clinical involvement of the lower cervical-supraclavicular lymph nodes and a negative lymphangiogram, Kaplan\textsuperscript{27} observed subsequent paraaortic lymph node extensions in 29 (36\%). Transdiaphragmatic extension was also observed in 33 (40\%) of 83 patients with clinical stage I and II disease studied by Rubin et al.\textsuperscript{35} Many of these paraaortic lymph node relapses occurred several years after initial treatment and frequently involved lymph nodes that were well visualized and appeared entirely normal on the original lymphangiogram. It was therefore suggested that spread in such instances may have occurred in the retrograde direction, from the supraclavicular fossa downward along the thoracic duct into the upper lumbar paraaortic nodes.

The occasional presence of Reed-Sternberg and Hodgkin's giant cells in the thoracic duct lymph has been documented by Engeset et al.\textsuperscript{36} There is no controversy concerning the possibility that these cells may enter the thoracic duct and travel in the antegrade direction from involved lymph nodes below the diaphragm, but the concept of retrograde spread along the thoracic duct has been much more controversial because the duct is equipped with valves. However, the pressure in the duct is only a few millimeters of water, and reversal of flow was readily observed following chronic ligation of the thoracic duct in dogs.\textsuperscript{37} Yet, other investigators were able to demonstrate retrograde flow in only 1 of 16 dogs after ligation and cannulation of the thoracic duct and injection of opaque contrast material in the retrograde direction.\textsuperscript{39} It is of course possible that retrograde flow might well occur more often in the thoracic duct of man, which is usually vertical, than in that of dogs, which is horizontal. Rouvière\textsuperscript{40} noted that anatomical variations affecting the competence of the valves near the upper end of the thoracic duct are not uncommon. It is thus conceivable that prolonged compression and partial occlusion of the duct by enlarged lymph nodes near its insertion into the subclavian vein may cause dilatation of the duct with secondary valvular incompetence and reversal of flow.

The role of vascular invasion in the spread of Hodgkin's disease is not well understood. In one study,\textsuperscript{41} there was no clear correlation between the occurrence of extranodal dissemination following primary radiotherapy and the presence of vascular invasion in the original lymph node biopsy material. Kirschner et al.\textsuperscript{42} noted that vascular invasion was present in 7 (16\%) of 44 spleens involved by Hodgkin's disease and was associated with hepatic and bone marrow metastases, early relapse, and decreased survival. In contrast, vascular invasion detected in 4 of 91 lymph node biopsies was not attended by an increased frequency of extranodal dissemination or an impaired prognosis. Yet, Naeim et al.\textsuperscript{43} observed an average survival time of only 21.8 mo in a group of patients whose lymph node biopsies showed vascular invasion, as contrasted with a 65.8 mo mean survival of patients in whom vascular invasion was not demonstrable.

**NATURE OF THE IMMUNOLOGIC DEFECT**

The existence of an impairment of cell-mediated immune reactivity in patients with Hodgkin's disease has been firmly documented by an extensive series of investigations.\textsuperscript{1} The impairment is not an all-or-none phenomenon, but a more subtle continuous gradient of immunologic deficit that is present in some degree even in patients with the earliest manifestations of the disease. In recent years, efforts have been directed toward elucidation of the underlying mechanisms of these immunologic abnormalities through the analysis of in vitro tests that are considered analogs of the cell-mediated immune response in vivo. Among the responses measured by such in vitro tests are the capacity of lymphocytes to undergo lymphoblastoid transformation after stimulation by lectins or antigens and to respond in the mixed lymphocyte reaction; to bind sheep erythrocytes to their surface membranes (E-rosette formation); and to bind and become agglu-
tinated by certain lectins and to mediate the polar migration (capping) and shedding of the bound lectins from the cell membrane.

Peripheral blood lymphocytes (PBL) from previously untreated patients with Hodgkin's disease have a distinctly impaired capacity to undergo lymphoblastoid transformation in response to lectins such as phytohemagglutinin (PHA) and to a number of antigens, including tetanus toxoid, Toxoplasma, tuberculin and streptokinase-streptodornase. Refinements of technique have revealed abnormalities of the PHA stimulation response even in patients with stage I disease. In a kinetic study of the daily uptake of tritiated thymidine by limiting concentrations of cells, Matchett et al. observed striking impairment of response in all of 26 patients studied, including those with localized disease and no symptoms. Levy and Kaplan measured the uptake of tritiated leucine in PBL stimulated with a range of PHA concentrations. This assay requires only 20 hr; thus, cell viability can be preserved in the absence of serum, enhancing precision and reproducibility. The peak response of PBL from 37 normal subjects was noted at a PHA concentration of 1 μg/ml. The response of PBL from 44 consecutive untreated patients with Hodgkin's disease was very significantly below normal and was observed both in patients with limited (stage I and II) as well as those with advanced (stage III and IV) disease. Similar results were encountered when this study was extended to include 132 patients with untreated Hodgkin's disease (Fig. 3). Concentration-dependent defects in PBL response to PHA have also been reported by Ziegler et al. and by Faguet. In contrast, another in vitro test, the allogeneic mixed lymphocyte reaction (MLR) has yielded conflicting results. Some investigators have observed impaired MLR responses in a significantly increased proportion of patients with Hodgkin's disease, whereas others have found essentially normal responses. In a recent study employing the autologous mixed lymphocyte reaction, the capacity of peripheral blood T lymphocytes of patients with untreated Hodgkin's disease, as well as those in long-term remission following prior radiotherapy, to respond in this test was found to be profoundly impaired. Finally, the capacity of PBL from patients with Hodgkin's disease to form spontaneous E-rosettes with uncoated sheep erythrocytes, a specific property of human T lymphocytes, was impaired in 13 of 15 untreated patients with Hodgkin's disease, whereas the percentage of T lymphocytes in the peripheral blood as detected by a cytotoxic antibody assay was normal.

It is now well established that cells capable of specific suppression of immune responses exist in the lymphoid system. Several investigations have yielded evidence suggesting that suppressor cells may play a role in inhibiting cell-mediated immune responses in Hodgkin's disease. However, the specificity of these suppressor effects remains to be established.

Tests of binding affinity, agglutinability, and capacity for cap formation with lectins such as concanavalin A (Con-A) have provided another approach to the study of lymphocyte surface membranes. Three groups of investigators have now reported that the percentage of PBL capable of cap formation is significantly reduced, and that the agglutinability of PBL by Con-A is significantly increased, in patients with Hodgkin's disease. Thus, a subpopulation of T lymphocytes in these patients appears to have under-
gone membrane alterations that are reflected in enhanced lectin agglutinability and diminished capacity for cap formation.

Humoral factors in the serum may alter the T-lymphocyte surface membrane, perhaps by masking specific receptors, and thus inhibit or abrogate cell-mediated immune functions. The presence of cytotoxic antilymphocyte antibodies in the sera of patients with Hodgkin’s disease has been reported by one group.64 Other investigators65 found that impaired E-rosette formation and PHA responses by PBL from patients with Hodgkin’s disease could be readily restored to normal levels by short-term incubation in fetal calf serum. Further studies66 revealed the presence of an E-rosette inhibitor in the sera of such patients; a similar or perhaps identical inhibitor was extracted from the involved spleens of patients with Hodgkin’s disease.67 After sequential fractionation of Hodgkin’s disease sera on sucrose gradients and then on potassium bromide isopyknic gradients, followed by thin-layer chromatography, the active material appears to be a glycolipid, the further chemical characterization of which is still in progress (Bieber et al., submitted for publication). Similarly fractionated normal sera were devoid of detectable amounts of this inhibitory substance. Moroz et al.68 demonstrated the presence of a blocking protein that could be released from the surface of PBL from four patients with Hodgkin’s disease by incubation with levamisole, an antihelminthic drug. The blocking protein reacted with antibody to human spleen ferritin, but contained no detectable iron, and could be dissociated into 18,000 dalton subunits, suggesting that it is an apoferritin rather than ferritin. After release of the blocking protein with levamisole, E-rosette responses of PBL from patients with Hodgkin’s disease returned to normal levels. It is of course possible that apoferritin acts as a carrier for a low molecular weight E-rosette inhibitory substance; if so, this would reconcile the glycolipid and apoferritin observations.

Thus, there is abundant evidence that virtually all patients with Hodgkin’s disease, including those with localized involvement, suffer from a selective, often subtle, impairment of cell-mediated immunity. In vivo, this deficit is expressed by an increased susceptibility to certain types of bacterial, fungal, and viral infections and by a decreased capacity for delayed hypersensitivity reactions to recall antigens or chemical allergens. A spectrum of in vitro test responses, including lymphoblastoid transformation by lectins and specific antigens, the capacity to form E-rosettes, and the capacity for cap formation after lectin binding, are also impaired. These alterations appear to be due to functional abnormalities of one or more T-lymphocyte subpopulations rather than to quantitative depletion of either T or B lymphocytes. Humoral inhibitors in the sera of patients with Hodgkin’s disease and suppressor cell effects have been implicated in these abnormalities.

TREATMENT AND PROGNOSIS

The development of linear electron accelerators69 and other megavoltage radiotherapy apparatus about 25 yr ago released radiotherapists from the severe constraints of the earlier kilovoltage era and permitted exploration of progressively higher tumor doses and of novel field shapes designed to encompass multiple lymph node chains in patients with Hodgkin’s disease. It was demonstrated that megavoltage radiotherapy could safely be carried to dose levels of approximately 4400 rad, delivered at the rate of 1100 rad/wk, and that such doses were capable of eradicating disease in involved lymph nodes with >95% probability.70 These high-dose, shaped-field techniques were first applied to patients with regionally localized (stage I and II) disease, in whom a striking improvement in prognosis was observed.71 In 1962, the first randomized clinical trial aimed at extending high-dose megavoltage radiotherapy to patients with stage III disease was initiated. The treatment of essentially all lymph node chains and other lymphatic tissues within the body, a technique designated total lymphoid radiotherapy, though initially undertaken with considerable apprehension, proved to be remarkably well tolerated72 and led ultimately to what were probably the first recorded cures of patients with stage III disease, almost 40% of whom remain relapse-free more than 18 yr after the initiation of that clinical trial.1 Complications such as radiation pneumonitis, radiation pericarditis, and radiation hepatitis have all been reduced to essentially negligible levels by progressive refinements in radiotherapeutic technique. Details of radiotherapy technique, the delineation of treatment fields, beam alignment, and dosimetry are beyond the scope of this presentation and are fully detailed elsewhere.1

Modern cancer chemotherapy began nearly 40 yr ago with the introduction of the first alkylating agents and antifolates. A broadening spectrum of drugs active against Hodgkin’s disease has been introduced in the intervening years. Initially, the role of these drugs was confined to palliation; there is no well documented evidence of the cure of any patient with Hodgkin’s disease treated with a single chemotherapeutic agent alone. The first major breakthrough came when De Vita and his colleagues73 initiated a study in patients with advanced (stage III and IV) Hodgkin’s disease using a cyclically administered combination of
nitrogen mustard, oncovin (vincristine), procarbazine, and prednisone (MOPP). Subsequently, many other multidrug combinations have been investigated and found to yield similar complete remission rates in the 70%-80% range. MOPP and other multidrug combinations also appear to have a very significant role in salvage therapy of patients who relapse following initial radiotherapy, approximately 50% of whom may achieve long-term relapse-free survival following retreatment with MOPP.74

In the last decade, clinical investigations have focused on the use of combined modality therapy, employing both radiotherapy and multidrug chemotherapy under varying conditions. The Stanford group,75,76 which initiated the first such study, was soon able to report a highly significant decrease in relapse rates in patients with advanced disease, as compared to those in patients treated with radiotherapy alone, but long-term survival was not significantly altered, in large part due to the efficacy of MOPP salvage in the patients relapsing following radiotherapy alone. Alternating schedules of drug and radiation treatment introduced more recently have improved hematologic tolerance and yielded improved survival and freedom from relapse in patients with stage III-B disease.77 The use of low-dose radiotherapy followed by six cycles of MOPP chemotherapy has permitted the preservation of normal bone growth in young children with Hodgkin’s disease, in whom actuarial survival at 10 yr is 94%, and relapse-free survival is 90%. Low-dose radiotherapy plus combination chemotherapy has also been used in adult patients with stage III and IV disease with diminished late complication rates, improved hematologic tolerance, and encouraging survival rates.78 Radiotherapy combined with another multidrug combination, ABVD, has also yielded impressive long-term results in adult patients with advanced disease.79 Most recently, the sequential cyclic use of two different multidrug combinations, MOPP and ABVD, has reportedly yielded impressive results. However, enthusiasm for these advances has been tempered by the occurrence of azoospermia, which is usually irreversible, in essentially all males treated with MOPP80 and by the observation of a significantly increased incidence of acute leukemias81,82 and secondary non-Hodgkin’s lymphomas83 in patients treated with both radiotherapy and MOPP combination chemotherapy. Accordingly, combined modality therapy should be reserved for patients presenting well defined indications for its use, and multidrug chemotherapy should not be given indiscriminately to patients with regionally localized, asymptomatic Hodgkin’s disease, whose prognosis with properly administered megavoltage radiotherapy alone is excellent.1

Collectively, advances in histopathologic diagnosis and classification, diagnostic assessment of sites of involvement, clinical staging, intensive megavoltage radiotherapy, and combination chemotherapy have achieved a dramatic improvement in the prognosis of this once inexorably fatal disease. The curves in Fig. 4 compare survival data from the era in which no specific therapy was available with those of the high-dose kilovoltage x-ray therapy era and with recent Stanford University Medical Center data in patients staged by modern techniques and treated with megavoltage radiotherapy, combination chemotherapy, or combined modality therapy. Analysis of survival and relapse rates in patients with previously untreated Hodgkin’s disease of all stages admitted to Stanford University Medical Center during three successive 5-yr accession periods has yielded clear evidence of a continuing progressive improvement in prognosis during the past decade.1 Moreover, analyses of several series of patients staged and treated at Stanford University Medical Center have indicated that the time course of relapses in Hodgkin’s disease is a highly skewed function, with approximately 80% of all relapses occurring within the first 2 yr after the completion of treatment and 95% or more occurring within the first 5 yr.84 For example, among 1225 consecutive patients first treated at Stanford University Medical Center between 1961 and 1977, the ultimate cumulative relapse rate was 39.1%, with the last recorded relapse occurring at 10.3 yr. Only 6 (3.3%) of 184 patients who had remained relapse-free for the first 5 yr developed primary relapses thereafter.1 It is apparent that more than 95% of patients who
remain relapse-free for 5 yr or more following treat-
ment are in fact cured, since they are never again
destined to develop a relapse of Hodgkin's disease. There is thus no longer any justification for the view
that Hodgkin's disease is an inexcusably fatal condi-
tion. In the years ahead, we must address the remain-
ing challenges of advanced clinical stage, unfavorable
histopathologic type, constitutional symptoms, and
advanced age in an attempt to make the total therapeu-
tic conquest of Hodgkin's disease a reality.

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