Hodgkin's Disease: Challenges for the Future

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The successful treatment of patients with Hodgkin's disease has been a major accomplishment of research in clinical oncology. The advances in diagnosis and therapy, initiated by radiotherapists in the 1950s and 1960s, were accelerated by chemotherapists in the 1960s and 1970s. Today, approximately three of every four patients who develop Hodgkin's disease will be cured of their neoplasm at many major centers throughout the world (1–5). This is a major accomplishment in control of a disease which often affects young individuals, which had been uniformly fatal at the turn of the century, and of which the cause and pathogenesis have not been clarified.

It is timely to review these accomplishments, along with the costs of successful therapy in terms of morbidities and complications of management, and refocus the clinical and basic research which represents the challenge of Hodgkin's disease as we enter the 1990s.

Advances and Accomplishments

It is useful to describe each of the major advances and accomplishments which have led to the more successful management of Hodgkin's disease separately. However, clarification of the pathology of the disease, appreciation of clinical patterns at presentation and at progression, improved diagnostic methods, more successful radiotherapy techniques, and successful chemotherapy all influenced and contributed to each other leading to the improved cure and survival results of the past 25 years.

The pathological criteria, classification of subtypes, and clinicopathological correlations of Hodgkin's disease were clarified by the studies of Lukes and Butler (6) and by consensus reports of pathologists at the Rye, Paris, and Ann Arbor Conferences (7, 8). Worldwide acceptance and utilization of these recommendations have resulted in better separation of Hodgkin's disease from closely related inflammatory and other neoplastic conditions involving the lymphoid system. It was of importance to recognize that noncaseating granulomas associated with Hodgkin's disease did not indicate neoplastic involvement of the tissues containing these granulomas. The diagnostic Reed-Sternberg giant cell was shown to have several variants, such as the lacunar cells found in formalin-fixed sections of the nodular sclerosis subtype and the multilobated, or “popcorn,” cell found in the lymphocyte predominance subtypes. On the other hand, Reed-Sternberg-like giant cells were shown to be present in benign conditions such as infectious mononucleosis. Criteria were agreed upon to indicate involvement by Hodgkin's disease of extranodal sites, such as the liver and bone marrow, even without diagnostic Reed-Sternberg giant cells, in the presence of an established diagnosis of Hodgkin's disease from some other site. The importance of establishing the diagnosis and extent of Hodgkin's disease, prior to embarking on therapy and at the time of subsequent relapse, should it occur, became established principles and accomplishments of the pathologists, which have led to the better control of the disease.

Coincident with the availability of more potent and successful therapies for Hodgkin's disease was the need for and availability of better diagnostic methods to indicate the extent of the disease. These have included bipedal lymphography, diagnostic laparotomy with splenectomy, bone marrow biopsy, and thoracic computerized tomography. Less important advances included improved radioisotope scintography of the skeletal system with technetium and of soft tissues with gallium. Greater attention was focused on relatively nonspecific laboratory indicators of the disease, such as the erythrocyte sedimentation rate and the serum copper and alkaline phosphatase levels.

The lymphogram was a particularly important advance and remains an essential diagnostic test in the management of patients with Hodgkin's disease. Early lymph node involvement, as determined by enlargement and architectural abnormalities, in the paraaortic and iliaca regions could be demonstrated for the first time. The ethiodol dye, remaining in the lymph nodes for 6–36 months, allowed simplified follow-up of these important regions. The lymphogram is not replaced by abdominal computerized tomography for this purpose, although the latter study is an important procedure to study lymph nodes in the thorax and other abdominal locations such as the celiac and mesenteric regions and to study the abdominal viscera (9). The lymphogram studies and data of the 1960s provided considerable insight into patterns of Hodgkin's disease at presentation and progression, to be described subsequently.

In the context of clinical trials for the treatment of Hodgkin's disease, the Stanford group first used exploratory staging laparotomy and splenectomy as a diagnostic method (10). It became apparent, and was confirmed by numerous studies elsewhere, that Hodgkin's disease frequently involved the spleen, and splenic involvement could not be accurately determined by any method other than its total removal and careful examination by the pathologist. In addition, lymph node involvement by Hodgkin's disease was found in the splenic hilum and, more rarely in the celiac, porta hepatis, and mesenteric lymph nodes without other clinical or radiological evidence. Involvement by Hodgkin's disease of the liver and bone marrow were found to be uncommon at presentation and very poorly predicted by laboratory or radiological tests. Furthermore, Hodgkin's disease involvement of liver and bone marrow were virtually uniformly associated with coincident involvement of the spleen (11, 12).

The improvements in diagnostic methods for discovering sites and patterns of Hodgkin's disease at presentation led to revisions and worldwide acceptance of a relatively simple staging system for the disease. A consensus report following the Ann Arbor conference in 1971 resulted in the current staging system and recommended criteria of site involvement for the disease (13).

The studies and data of the 1960s led to the acceptance of the important concept of the orderly progression of the disease. Clarified by the frequent involvement of the upper paraaortic...
lymph nodes and the spleen and correlations of certain sites with each other, the proposals and concepts of Gilbert, Peters, Kaplan, and Musshof were substantiated with good observations and data. Hodgkin’s disease was not usually a systemic disease at onset but arose in a single or limited lymph node region and, for a variable but usually significant period of time, spread by contiguity, involving adjacent lymphoid regions, including the spleen. Spread by contiguity could involve nonlymphoid tissues, often in the chest adjacent to mediastinal and/or hilar lymphoid sites, and involve the lung, pericardium, pleura, chest wall, and bones such as the sternum, ribs, and vertebrae. To be sure, for many patients with uncontrollable disease usually later in their course, and for a minority of patients at onset, the disease could be widespread and behave as a systemic disorder with unpredictable sites of involvement. This appeared to be the case, however, in no more than 10% of patients at presentation (3, 14).

It is not the purpose of this review to detail the advances in the control of Hodgkin’s disease by modern radiotherapy and chemotherapy. These are well presented elsewhere (3–5, 15). These advances and accomplishments were made possible by technical and conceptual developments. Supervoltage X-ray therapy machines, primarily the linear accelerator, made possible the delivery of tumoricidal doses of irradiation to relatively large single fields, with relative skin sparing and improved colurnation allowing better protection of surrounding, uninvolved radiosensitive structures. The mantle, inverted-Y, and total nodal or total lymphoid fields became standards used by experienced radiotherapists with excellent clinical results throughout the world.

During this same period following World War II, the field of cancer chemotherapy evolved with the availability of an increased number of potent effective drugs, and the experience and knowledge of how to use them in the treatment of Hodgkin’s disease. The MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy regimen developed at the National Cancer Institute in Bethesda, and the doxorubicin regimens, such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), developed at the National Cancer Institute in Milan were standards in the field (4, 5). For the first time Hodgkin’s disease could be cured, in approximately one-half of the patients treated, with systemic chemotherapy. Of importance, this could be accomplished even for patients who developed a relapse of their disease after initial treatment with irradiation.

These overlapping developments in pathology, diagnostic methodologies, radiotherapy, and chemotherapy began in the 1960s and continued into the 1970s and early 1980s. During the past decade, studies have helped to refine prognostic criteria; to clarify the situations in which combined modality therapy (i.e., irradiation and combination chemotherapy) should be used as initial treatment; and to identify and, when possible, to reduce the acute and long term morbidities and complications of the treatment of the disease. Of particular importance has been the recognition of secondary neoplasms such as acute nonlymphocytic leukemia following certain types of chemotherapy and radiation-associated carcinomas and sarcomas in long term survivors (16–18). Local radiation effects on bone and muscle development in children and on the lungs, heart, and gonads have received the attention of radiotherapists with modifications of their treatment plans (3, 19, 20). Chemotherapy-induced sterility has received increased attention inasmuch as young people are surviving, otherwise well, for long periods after treatment (21, 22).

**Future Clinical Research**

Such is the state of the treatment and clinical research of Hodgkin’s disease. There are debate and controversy as to which chemotherapy regimen is the most successful and/or least toxic, or if a less toxic chemotherapy can be utilized earlier in the course of the disease, or if standard chemotherapy can be utilized instead of irradiation for even the most prognostically favorable patients, or if and when to utilize autologous bone marrow transplantation in secondary or “salvage” treatment approaches.

As important as these questions may be, and surely they will occupy investigators of the disease for the next decade or more, their solution is unlikely to make a very significant impact on a disease, in which approximately 75% of patients, treated appropriately at onset, can be cured of the disease, and a significant number of the remainder can be treated effectively with prolonged palliation and even cure, after initial relapse of the disease.

It seems remarkable and significant that the clinical research of Hodgkin’s disease has reached this state of apparent “success,” without a better understanding of the cause and pathogenesis of the disease. There has been no advance in an understanding of the immune deficit of patients with Hodgkin’s disease, before and after therapy (23). There have been observations and clues to understanding the disease from epidemiologists in recent years, but these remain unexplained and unexploited (24–26). There are tantalizing observations of familial Hodgkin’s disease, and a minimum of data on genetic associations, which surely have great potential in understanding the disease (27–30). Even the identification of the malignant cell in Hodgkin’s disease and its origin remain obscure (23).

Any student of Hodgkin’s disease must be impressed, both by the heterogeneity of the disease, pathologically and clinically, and by the threads of common features which tie the spectrum of the illness together. Why are there so many “inflammatory” features of the disease? The bulk of the tumor so often is, or appears to be, made up of benign reactive cells and tissues. The diagnostic giant cell, although obvious in its classic form, is more often extremely variable in its appearance among patients, among different histological subtypes, and over the course of the illness. The malignant cell or cells are extremely difficult, if not impossible, to culture in the laboratory. What “spreads” in Hodgkin’s disease? Do malignant cells metastasize via the lymphatics or the blood stream or by direct invasion as with other neoplasms? It is a remarkable, still unexplained observation to have Hodgkin’s disease develop months or even years after initial irradiation in lymph nodes just at the margins of irradiation fields. Why should iliac lymph node develop the disease after paraaortic irradiation has been given in laparotomy-staged negative individuals? It seems possible, even likely, that so-called prophylactic irradiation increased the curability of Hodgkin’s disease, not only by eradicating malignant cells but also by eliminating fertile lymphoid ground which interacts with a still unidentified promoter in the development of the neoplasm. Yet it is unlikely that radical irradiation or chemotherapy would eliminate such a causative agent or reverse a defective immune system or genetic susceptibility.

It may be of value to list areas of research which seem opportune at this time. They are not listed in any priority.

1. Chemotherapy regimens must be refined. It is probable that drug regimens which have less acute toxicity and little or no long term morbidity can be utilized for occult disease in combined modality management with irradiation.
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Patients with established very poor prognostic factors will require even more aggressive chemotherapy and radiotherapy programs, probably administered over relatively brief periods of time (i.e., 12 weeks) combined with hematopoietic growth factors.

2. Radiation therapy remains as the single most potent treatment for Hodgkin's disease, but its use should be limited in volume (to major bulky sites of disease) in combined modality management schemes.

3. The immune deficit of untreated patients and their families should be studied carefully with current techniques and understanding. It should be documented and clarified which immune abnormalities of patients are improved by curative therapy and which are induced or aggravated by the various treatments utilized.

4. Efforts should be made to reverse the specific immune deficit of the disease with immune modulators and/or lymphokines as these become better understood and manipulated.

5. The epidemiology and familial occurrences of Hodgkin's disease should be studied intensively preferably within homogeneous histological subtypes such as the nodular sclerosis and mixed cellularity groups. The lymphocyte predominance and lymphocyte depletion subtypes should be excluded from these analyses, because of difficulty in recognizing these rarer types and the possibility that they result from different pathogenetic and etiological mechanisms.

6. The genetics of patients and their families with Hodgkin's disease should be studied carefully using all of the newer tools and understanding of molecular genetics. Herein lies the greatest hope and probability that the nature of the disease can be discovered and then prevented or reversed.

Summary

Clinical investigators of Hodgkin's disease of the recent past have reason to be proud. Tens of thousands of individuals, many of them young, fertile, and productive, have been cured of their life-threatening disease. There are few better examples of the success and rewards of clinical oncology than in the control of Hodgkin's disease by improved diagnostic methods and the appropriate use of radiation and chemotherapy.

Yet the clinical investigator of today cannot be satisfied with these successes. The treatment required for high cure rates remains empirical, difficult, and costly. The goal must be to prevent or reverse this fascinating disease, utilizing specific therapy designed from a knowledge of the cause and pathogenesis of the disease. There are sufficient biological clues and methodologies to predict that this will be possible, and in the decade of the 1990s!

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