Hodgkin’s lymphoma was once a uniformly fatal disease. However, today at least 80% to 85% of all patients are cured. No stage of disease is beyond cure. Patients may even be cured after they have relapsed. Indeed, anecdotal data make it difficult to ever throw in the towel in managing patients with Hodgkin’s lymphoma. When one sees a patient who has been in her fifth complete remission for 26 years, it makes one reluctant to ever say “never.” Even when the physician has exhausted the conventional curative approaches, palliative therapy may also produce long periods of symptom-free survival. The paradoxical outcome from this success is that it makes the death of a patient with Hodgkin’s lymphoma much more difficult to bear. For many advanced cancers, death is the expected outcome and when it comes, it is painful to be sure, but the physician has been preparing himself or herself, the patient, and the patient’s family for the event. When a patient with Hodgkin’s lymphoma dies, it is often an even more devastating blow because the course of treatment was embarked upon with such high hopes.

Despite the enormous progress that has been made in successfully treating patients with Hodgkin’s lymphoma, our knowledge about the disease is far from comprehensive. Furthermore, even the information we know about Hodgkin’s lymphoma and its treatment is not agreed upon. Controversy surrounds the decision on the best treatment approach. In this issue of *The Cancer Journal*, I have been fortunate to collect the thoughts of many of the leading figures in Hodgkin’s lymphoma in the world. Their contributions here will bring the reader up to date on the facts and opinions of many experienced thought leaders.

What causes Hodgkin’s lymphoma? We don’t know. However, in these pages, Neil Caporaso and his colleagues from the National Cancer Institute (NCI) discuss what has been revealed from studies of the epidemiology of the disease. Genetic factors contribute to the disease, but we do not know precisely what genes are involved or how they lead to the tumor. A higher incidence occurs in westernized populations including those who emigrate from low-incidence sites to the United States. Efforts to find an infectious etiologic agent have been largely unsuccessful, though a role for Epstein-Barr virus has been implicated in some cases.

How does Hodgkin’s lymphoma present and progress? Fortunately, we have Joseph Connors, a master clinician and clinical researcher at the British Columbia Cancer Agency, to draw on his own vast experience and the world literature on the clinical manifestations and natural history of Hodgkin’s lymphoma. The disease has a predilection for lymph nodes. If only a single site is involved, it is usually the left supraclavicular node region. The disease marches progressively from one lymph node-bearing group to the next. When it spreads to the abdomen, usually the spleen is the first site involved. Because the spleen lacks afferent lymphatics, this may argue for hematogenous spread with selective growth in the fertile soil of the spleen. Fever, weight loss, and night sweats reflect systemic effects from tumor-induced cytokines. The disease may also be associated with important alterations in other organs including nephrotic syndrome and neurologic symptoms.

What is Hodgkin’s lymphoma? As discussed in detail by the NCI’s Franziska Eberle, Haresh Mani, and Elaine Jaffe, Hodgkin’s lymphoma currently seems to be at least 2 diseases, as reflected in the World Health Organisation classification of lymphoid malignancies: the more common classic Hodgkin’s lymphoma and the much less common nodular lymphocyte predominant Hodgkin’s lymphoma. However, more recent evidence suggests that classic Hodgkin’s lymphoma may be a heterogeneous category with at least 2 diseases, nodular sclerosis representing 1 subset and mixed cellularity and lymphocyte depleted types forming a continuum on the other. Reliably distinguishing these entities is the first step toward sorting out their pathogenesis and perhaps defining new therapeutic targets for the subset of patients not cured by existing approaches.

The staging of the extent of disease has undergone changes through the years as therapy has produced better results and nearly all patients receive some systemic therapy. Thus, removed from
the evaluation is the exploratory laparotomy that was formerly an essential component of treatment decision making. However, novel evaluation methods, particularly positron emission tomography scanning, have taken on new significance in patient management. We are fortunate to have Mary Gospodorowicz from Princess Margaret Hospital in Toronto to summarize the current state of the art of patient evaluation. As she explains, the notion of adapting therapeutic strategy to risk factors is complicated by the fact that the factors were defined as affecting outcome at an earlier time when treatment was not so successful. As treatment improves, fewer factors influence outcome. We must modify old habits in light of new information to assure that our patients have the best chance of achieving cure with a minimized risk of late complications.

The next 4 articles in this volume deal with treatment. Beate Klimm and Andreas Eggert of the German Hodgkin Study Group based at the University of Koln summarize data from studies of combined modality therapy. Pamela Seam, John Janik, Vincent DeVita, and I (all current or former NCI researchers) discussed combination chemotherapy as a sole modality of therapy. Joachim Yahalom from Memorial Sloan-Kettering Cancer Center makes a case for radiation therapy. Fahd Quddus and James Armitage from the University of Nebraska discuss treatment options for patients whose initial treatment has failed to cure the disease.

Finally, Andrea Ng and Peter Mauch from Harvard review what is known about the late complications of Hodgkin’s lymphoma treatment. It was these careful investigators who first noted that more people died of treatment complications (especially second cancers and fatal cardiovascular disease) than from Hodgkin’s lymphoma. The documentation of late effects in people cured of Hodgkin’s lymphoma has received too little attention. The late effects of mechlorethamine, vincristine, prednisone, procarbazine chemotherapy and radiation therapy have been well defined, but little has been published on late effects of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy. This could be because ABVD is not associated with serious late complications or that ABVD-treated patients have not yet been followed sufficiently to have the effects documented.

Now embracing my role as editor, it is difficult for me to understand the current widespread use of combined modality therapy to treat nearly every patient with Hodgkin’s lymphoma. It has been amply demonstrated that subtotal nodal radiation therapy produces an unacceptable rate of late toxicity and fatality. Similar data do not exist for ABVD chemotherapy. Perhaps there are late effects from ABVD, but those effects could not possibly be of the magnitude seen with radiation therapy and have gone unnoticed. Therefore, the approach has been the creation of treatment programs that administer less than curative chemotherapy (either lower doses or fewer cycles or both) plus lower doses and smaller fields of radiation therapy. The reasoning seems to be that radiation therapy will have fewer late effects if it is delivered to smaller fields at lower doses. However, long-term follow-up data documenting that hope are not widely available. It remains unclear why it is thought that the late effects of ABVD require amelioration. The chemotherapy is being reduced because of a phantom; fear of not-yet-documented late effects. Does it make sense to use less than curative doses of 2 modalities rather than curative doses of 1 modality?

To their credit, these combined modality approaches achieve excellent short-term results, but no data have been published with follow-up into the second decade, when the effects of radiation begin to emerge with a vengeance. Will second malignancies be reduced? Will the combination of radiation and an anthracycline have less serious effects on the heart and vasculature? No one knows. Regardless of one’s feelings (because there are no data), the safest dose of radiation therapy is zero. Thus, the onus should be on those who want to use radiation therapy to justify its use at all. Does it produce better long-term survival when added to chemotherapy than does chemotherapy alone? The available data suggest not. I wish there were more data. More studies should directly assess long-term survival of patients treated with chemotherapy alone versus combined modality therapy. But several studies that have addressed the question have found no value in adding radiation therapy to curative combination chemotherapy.

It would be my preference that we acknowledge that not all the bad effects of radiation therapy can be eliminated by reducing the field and giving 2400 rather than 4400 cGy. I would prefer that we acknowledge that chemotherapy alone is highly effective treatment in all stages of Hodgkin’s lymphoma. And finally, I would prefer that we acknowledge that the best approach would be to cure as many people as possible with chemotherapy alone and reserve radiation therapy (and its late effects) for the subset that actually need it to be cured. This would include those, whose best chemotherapy response is a partial response and possibly those with slow clearance of positron emission tomography-positive disease. We do not need to expose every single patient to radiation therapy to cure him/her.

Although a substantial amount of territory is covered here, we have not been comprehensive. Important work has been omitted. A substantial amount of information is now available on the malignant cell of Hodgkin’s lymphoma, the Reed-Sternberg cell. For example, it is known that the cell is of B-cell origin based on the rearrangement of its immunoglobulin genes. However, unlike any other malignancy of B cells, the rearranged genes are not transcribed into mRNA and immunoglobulin proteins are not synthesized. The essential transcription factors for immunoglobulin transcription are not expressed. This is similar to a phenomenon observed in the laboratory many years ago by investigators working with somatic cell fusion. A phenomenon called extinction made any cell fusion between a B cell and another type of somatic cell unable to transcribe the immunoglobulin genes. Although we know the missing transcription factor in Reed-Sternberg cells, we do not know why it is not expressed or whether its downregulation is an integral part of the neoplastic process. Much remains to be learned about the molecular pathogenesis of the disease.

Similarly, we devote little to no attention here to important aspects of the host-tumor relationship in Hodgkin’s lymphoma. It has long been noted that patients with Hodgkin’s lymphoma have defects in cellular immunity that are not fully characterized. Indeed, some evidence suggests that the immune defect may precede the development of overt Hodgkin’s lymphoma. We do not understand the basis for this immune dysfunction and have not defined the degree to which it contributes to later problems in patients cured of the disease. These and other fascinating aspects of Hodgkin’s lymphoma will likely be further elucidated over the coming years.

I would like to make one final comment about fads. Two fads have made an impact on Hodgkin’s lymphoma in the past decade. It has been 177 years since the original report of the disease by Thomas Hodgkin. It has been 144 years since Samuel Wilks proposed naming the disorder Hodgkin’s disease in the year before Hodgkin’s death. Throughout that time, the condition has been known to affect lymph nodes primarily, even though the fundamental nature of the malignant cells was not defined with precision until more recently. The disease has always been taught along with the other lymphomas. I am unhappy with the fad of changing Hodgkin’s disease to Hodgkin’s lymphoma. I would argue that Hodgkin’s lymphoma is not better than Hodgkin’s disease as a descriptor. Everyone recognizes that at least 3 distinct entities currently comprise Hodgkin’s lymphoma and it is expected that further research will better define the discrete illnesses currently lumped together as...
well as their relationship to one another and to other lymphomas. In other areas of medicine, it has not been the standard practice to rename the disease as one gets closer to its pathogenesis. Pernicious anemia is still pernicious anemia, not intrinsic factor deficiency anemia. Peptic ulcer disease is still peptic ulcer disease, not *Heli-cobacter pylori*-induced duodenal erosion. Alzheimer’s disease is still Alzheimer’s disease, not β-amyloid deposition neurodegenerative disease. In the grand scheme of things, knowing that Hodgkin’s disease is a malignancy of lymphoid cells is not particularly insightful and certainly does not represent a grand leap forward in our understanding that would justify changing 144 years of tradition. Furthermore, it is confusing. I have had trainees who asked me how Hodgkin’s lymphoma is different from Hodgkin’s disease. When I explain that they are the same, I can’t answer the next question: why the change? It isn’t to distinguish this from some other disease that Hodgkin described. It isn’t because some revolutionary new insight taught us that the disease is not a sarcoma or a carcinoma. The change is just because. To follow suit, we should expect Cushing’s syndrome to become Cushing’s endocrinopathy and Alzheimer’s disease to become Alzheimer’s neurodegenerative cognitive decline. I suppose that is one way to stamp out “disease.”

Although I resent this particular fad, I have acquiesced to it in this volume. The second fad I shall not follow; the omission of apostrophe “s” as an indicator of the possessive form of a proper noun. It has become all the rage to list eponym-associated tests, signs, and diseases in medicine without the apostrophe s. Thus, it has become Alzheimer disease, Cushing disease (not to be confused with Cushing syndrome), and, alas, Hodgkin lymphoma. I won’t do it. I won’t go along with this fad. It seems to me to be a form of intellectual laziness to try to eliminate apostrophe s. Is there some sort of war on apostrophes? Will we soon omit them from contractions? That would be confusing. Some words have different meaning without an apostrophe (won’t versus wont; can’t versus cant). It is my understanding from my former colleague, Jean Wilson, a paragon of scholarship, that the practice of omitting possessive apostrophes originated innocently with Victor McKusick when he began using a computer to revise his great work, *Mendelian Inheritance in Man*. Apparently, his first computer was primitive and the keyboard did not have an apostrophe key. Therefore, he left apostrophe s off when he designated eponym-associated disease. From there, medical journal editors got a hold of the idea (it saves space) and apostrophe s became history; but their use was eliminated selectively. Some medical journals retain them even in their name (eg, Bailliere’s family of publications). Classic medical texts continue to use them (eg, *Braunwald’s Heart Disease*, *Harrison’s Principles of Internal Medicine*). People continue to use possessive eponyms when they speak to each other and in talks at scientific and medical meetings. It is my hope that the effort to eliminate apostrophe s goes the way of certain other suggestions through the years such as adopting the metric system and SI units.