Hodgkin's Disease in Children

Cancer Treatment and Research

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Hodgkin's Disease in Children: Controversies and Current Practice

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1989 **KLUWER ACADEMIC PUBLISHERS**
Boston / Dordrecht / London

Distributors

for the United States and Canada: Kluwer Academic Publishers, 101 Philip Drive, Assinippi Park, Norwell, MA 02061

for the UK and Ireland: Kluwer Academic Publishers, MTP Press Limited, Falcon House, Queen Square, Lancaster LA1 1RN, UK

for all other countries: Kluwer Academic Publishers Group, Distribution Centre, P.O. Box 322, 3300 AH Dordrecht, The Netherlands

Library of Congress Cataloging in Publication Data

Hodgkin's disease in children.

(Cancer treatment and research)
Includes bibliographies and index.
1. Hodgkin's disease in children—Treatment—
Evaluation. 2. Clinical trials. I. Kamps, W.A.
(Willem A.) II. Humphrey, G. Bennett (George Bennett),
1934– . III. Poppema, Siebrandes. IV. Series.
(DNLM: 1. Hodgkin's Disease—in infancy & childhood.
2. Hodgkin's Disease—therapy. W1 CA693/WH 500 H6896]
RJ416.H63H63 1988 618.92'99446 88–1672
ISBN-13: 978-1-4612-8978-4 e-ISBN-13:978-1-4613-1739-5
DOI: 10.1007/978-1-4613-1739-5

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Cancer Treatment and Research

Foreword

Where do you begin to look for a recent, authoritative article on the diagnosis or management of particular malignancy? The few general oncology textbooks are generally out of date. Single papers in specialized journals are informative but seldom comprehensive; these are more often preliminary reports on a very limited number of patients. Certain general journals frequently publish good in-depth reviews of cancer topics, and published symposium lectures are often the best overviews available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes that aim to meet this need. It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

We have approached the problem in the following fashion. First, by dividing the oncology literature into specific subdivisions such as lung cancer, genitourinary cancer, pediatric oncology, etc. Second, by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis. Each topic and tumor type is covered in a volume appearing frequently and predictably, discussing current diagnosis, staging, markers, all forms of treatment modalities, basic biology, and more.

In Cancer Treatment and Research, we have an outstanding group of editors, each having made a major commitment to bring to this new series the very best literature in his or her field. Martinus Nijhoff Publishers has made an equally major commitment to the rapid publication of high-quality books, and world-wide distribution.

Where can you go to find quickly a recent authoritative article on any major oncology problem? We hope that Cancer Treatment and Research provides an answer.

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Preface

Hodgkin's Disease: Current Practice and Controversies is the fourth volume in the series *Cancer Treatment and Research* devoted to pediatric oncology. Like its predecessors, it is organized into two sections. The first section deals with preclinical and clinical issues that relate to controversies on the current status of our knowledge of Hodgkin's Disease.

In the second part, major pediatric oncology centers, institutions, and cooperative groups have reviewed the status of their clinical research. Contributors to this section were asked to limit their review to the current status of the management of Hodgkin's disease. Independent reviews of Hodgkin's disease, its epidemiology, its past controversy, *etc.*, have already been published.

We appreciate the willingness of the authors of both sections not only to review the current status of Hodgkin's disease, but also to speculate on the direction the future research in Hodgkin's disease should take.

Hodgkin's Disease in Children

I

Selected Topics

1. Introduction

G. Bennett Humphrey, Sibrand Poppema, and Willem A. Kamps

Is Hodgkin's disease an enigma?

Certainly much of what we have learned about this disease (or maybe we should say, this condition) is hard to understand. The very nature of Hodgkin's disease is obscure. For example, one can occasionally still read a discussion that concerns whether Hodgkin's disease is a malignancy. Is it one disease? Does it have more than one etiology? Is it a monoclonal or polyclonal proliferation of cells?

Despite advances in molecular and cellular biology, the cell of origin of Hodgkin's disease has not been defined—or the normal counterpart of the Reed-Sternberg cell remains a mystery. Each new advance in immunology or genetics adds what we hope are valuable data to our fund of knowledge—but the cell of origin has become to a certain extent more obscure: for example, is it a T cell, a B cell, a monocyte?

Despite these fundamental problems, we had developed very effective curative treatment regimens—one might say, overdeveloped treatment schedules. The scientific basis or rationale for these schedules does not exist—these schedules are based on cancer chemotherapy's trial-and-error approach combined with 'more is better' philosophy.

Current research is still trying to unravel the mystery. Recent work in growth factor and oncogenes may indicate that there is hope for a rational explanation of what Hodgkin's disease is. If activation of oncogenes is a consistent pattern in Hodgkin's disease cells, if these genes increase production of growth factor(s), if the growth factor can recruit large numbers of lymphocytes, monocytes, granulocytes, and fibroblasts into the adjacent area of the Hodgkin's disease cell, and if these factors can be produced in sufficient quantity, then a very convincing story can be presented to explain the low percentage of malignant cells within the Hodgkin's disease tissue, the altered immunity, and the systemic constitutional symptoms that may accompany Hodgkin's disease.

At the intellectual level, our encounter with Hodgkin's disease may be considered a humiliating enigma. But success is success. There are not very many cancers in which the clinical research goals are to eliminate unnecessary components of therapy while maintaining high cure rates, or to be preoccupied with reducing such effect, secondary malignancies, *etc.*

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2. Evidence for a B-cell origin of the proliferating cells

Sibrand Poppema, Marja G.L. Brinker, and Lydia Visser

Hodgkin's disease differs from the non-Hodgkin's lymphomas by the presence of reactive lymphocytes, histiocytes, plasma cells, fibroblasts and eosinophils in addition to the abnormal so-called Reed-Sternberg cells and their variants (Figure 1). Usually, Reed-Sternberg cells constitute only a minor population, whereas there is a majority of reactive small lymphocytes. During the disease, there is a general tendency to an increase in the number of Reed-Sternberg cells and a decrease in the lymphocyte admixture. The non-Hodgkin's lymphomas have been demonstrated to be monoclonal proliferations of B- or T-lymphocytes, but in Hodgkin's disease neither the cell of origin nor the monoclonal origin of the Reed-Sternberg cells has been established with certainty.

In this chapter, we summarize data derived from immunohistochemical, cell culture, and gene rearrangement studies indicating that Reed-Sternberg cells quite frequently are of B-cell origin. In addition, we present an hypothesis on the pathogenesis of Hodgkin's disease.

1. Immunophenotype of Reed-Sternberg cells

With respect to the origin of Reed-Sternberg cells, several conflicting notions have been published during the past few years. Garvin *et al.* [1], Leech [2], and Taylor [3] described the presence of immunoglobulin G (IgG) in the cytoplasm of Reed-Sternberg cells in suspensions and in paraffin tissue sections in 1974. The findings suggested a B-cell origin of Reed-Sternberg cells. Subsequent studies confirmed the presence of IgG in Reed-Sternberg cells, but also demonstrated the presence of kappa as well as lambda light chains in individual cells, whereas α-1-antitrypsin and albumin also was demonstrated in the same cells [4, 5]. Therefore, it was concluded that the presence of IgG did not prove the B-cell origin of Reed-Sternberg cells. *In vitro* studies suggested phagocytosis of Ig by the Reed-Sternberg cells *via* Fc receptors [6], and tissue culture studies indicated a macrophage origin of the neoplastic cells of Hodgkin's disease [7]. The presence of α-1-antitrypsin was also taken as an argument for a macrophage origin [8]. However, in subse-

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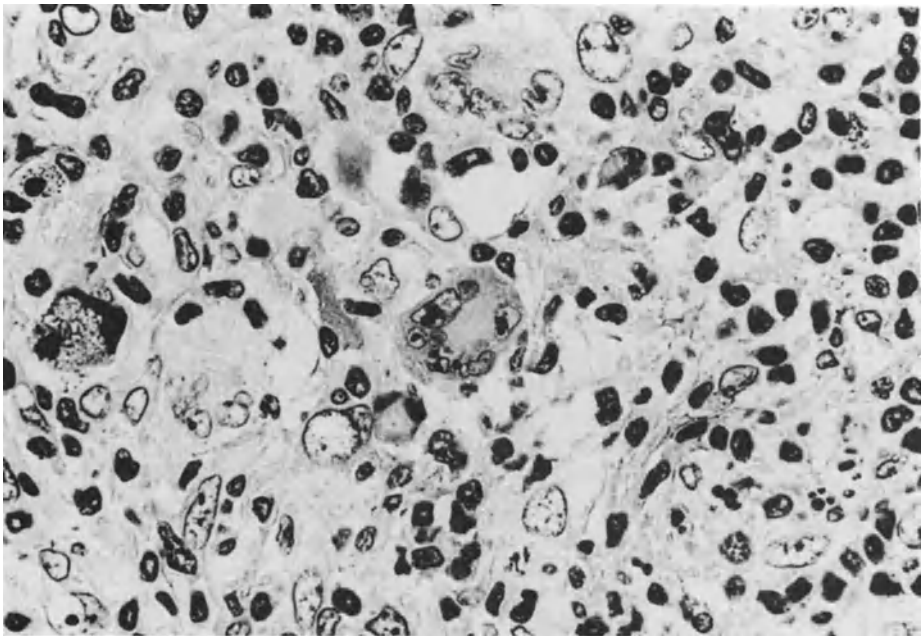

Figure 1. Hematoxylin–eosin-stained tissue section of lymph node involved by nodular-sclerosis type of Hodgkin's disease. Characteristic mixture of Reed-Sternberg cells and reactive cells.

quent studies, Fc receptors could not be demonstrated on Reed-Sternberg cells in fresh suspensions, whereas the IgG as well as the α-1-antitrypsin disappeared from Reed-Sternberg cells after 2 days of *in vitro* culturing in the absence of human serum [9].

The availability of monoclonal antibodies has enabled the analysis of Reed-Sternberg cells with antibodies against lymphocyte subset-specific antigens [10]. Such studies have shown the absence of T-cell-specific antigens (CD1, CD2, CD3, CD4, CD5, CD6, CD7, and CD8) on the Reed-Sternberg cells in a vast majority of cases of Hodgkin's disease [10, 11]. In few cases, T-cell antigens were identified on Reed-Sternberg cells [12]. In addition, a number of anti-monocyte-macrophage antibodies (OKM1, monocyte 1, Leu M5, My7) were found not to react with these cells. However, Leu M1 and Leu M3 were reported to stain Reed-Sternberg cells [13, 14], and recently some antibodies developed against a true histiocytic lymphoma cell line were reported to also react with Reed-Sternberg cells [15]. Anti-B-cell monoclonal antibodies were demonstrated to be reactive in some, but not all, cases of Hodgkin's disease [16–18]. In particular, all cases of lymphocyte-predominant type of Hodgkin's disease were found to be B1 positive [19], but also ~40% of mixed-cellularity, nodular-sclerosis, and lymphocyte-depleted cases exhibit B1 reactivity, in particular when studied on cytospins of lymph node suspensions [16]. Uniform strong reactivity can

be observed with anti-HLA-DR antibodies, antitransferrin receptor antibodies, and anti-interleukin-2 receptor antibodies. In addition, cytoplasmic staining of Reed-Sternberg cells with polyclonal antibodies directed against interleukin 1 has been described by Hsu and Zhao [20].

However, using the same polyclonal reagent, we found reactivity of a minority of Reed-Sternberg cells in a diffuse pattern, similar to that of IgG staining. This staining was completely inhibited by the addition of 1% human serum to the antibody dilution, indicating that the staining of Reed-Sternberg cells by this anti-interleukin-1 antiserum is probably not due to specific staining of interleukin 1 (S. Poppema, unpublished, 1987).

A separate category is formed by antibodies with predominant Reed-Sternberg cell reactivity. Ki-1, prepared against Hodgkin's disease-derived cell line L428, reacts with Reed-Sternberg cells and variants [21], but also with PHA-stimulated T cells and with Epstein-Barr virus (EBV)-transformed B-lymphoblastoid cell lines *in vitro* [22]. In normal lymphoid tissues, a small population of perifollicular cells was reported to be reactive. In addition, Ki-1 reacts with some T-cell lymphomas, some B-cell lymphomas, and also with the atypical cells of lymphomatoid papulosis [23, 24]. We have prepared antibody SR7 against Hodgkin's disease-derived cell line DEV and found it to react with Reed-Sternberg cells, macrophages, and interdigitating reticulum cells, but also with several large cell B-cell and T-cell lymphomas [25]. Leu M1 and Clonab Tu1 are antibodies that react with granulocytes, but also with Reed-Sternberg cells and their variants [13, 26]. These antibodies recognize lacto-N-fucopentaose (III), a carbohydrate also present on several epithelial cell types [27]. Virtually all EBV-transformed lymphoblastoid cell lines and several B-cell non-Hodgkin's lymphoma cell lines react with Leu M1 (W. Timens and S. Poppema, in preparation). Finally, all Reed-Sternberg cells appear to react with Ki-67 antibody, recognizing a proliferation-associated nuclear antigen.

Examples of the immunohistologic staining patterns of Reed-Sternberg cells are shown in Figure 2. The findings indicate that Reed-Sternberg cells and their variants are activated lymphocytes with an immunophenotype that is very similar to that of transformed lymphoblastoid B-cell lines. It can not be excluded that, in some cases, the Reed-Sternberg cells are of T-cell origin. In the lymphocyte-predominant type of Hodgkin's disease, the so-called L&H-type Reed-Sternberg cells can be demonstrated to be clearly of B-cell origin, since these cells do contain J-chain in their cytoplasm, indicating the production of Ig in these cells [28, 29], and recently we also demonstrated the presence of cytoplasmic IgD in the L&H-type cells in some cases. The L&H Reed-Sternberg cells invariably react with anti-B-cell monoclonal antibodies B1, B4, and Leu 14 [19]. In contrast to Reed-Sternberg cells in the other types of Hodgkin's disease, the L&H-type cells show only small amounts or absence of α-N-fucopentaose [30]. When paraffin tissue sections are preincubated with neuraminidase, the L&H-type Reed-Sternberg cells also clearly stain with Leu M1. Since neuraminidase

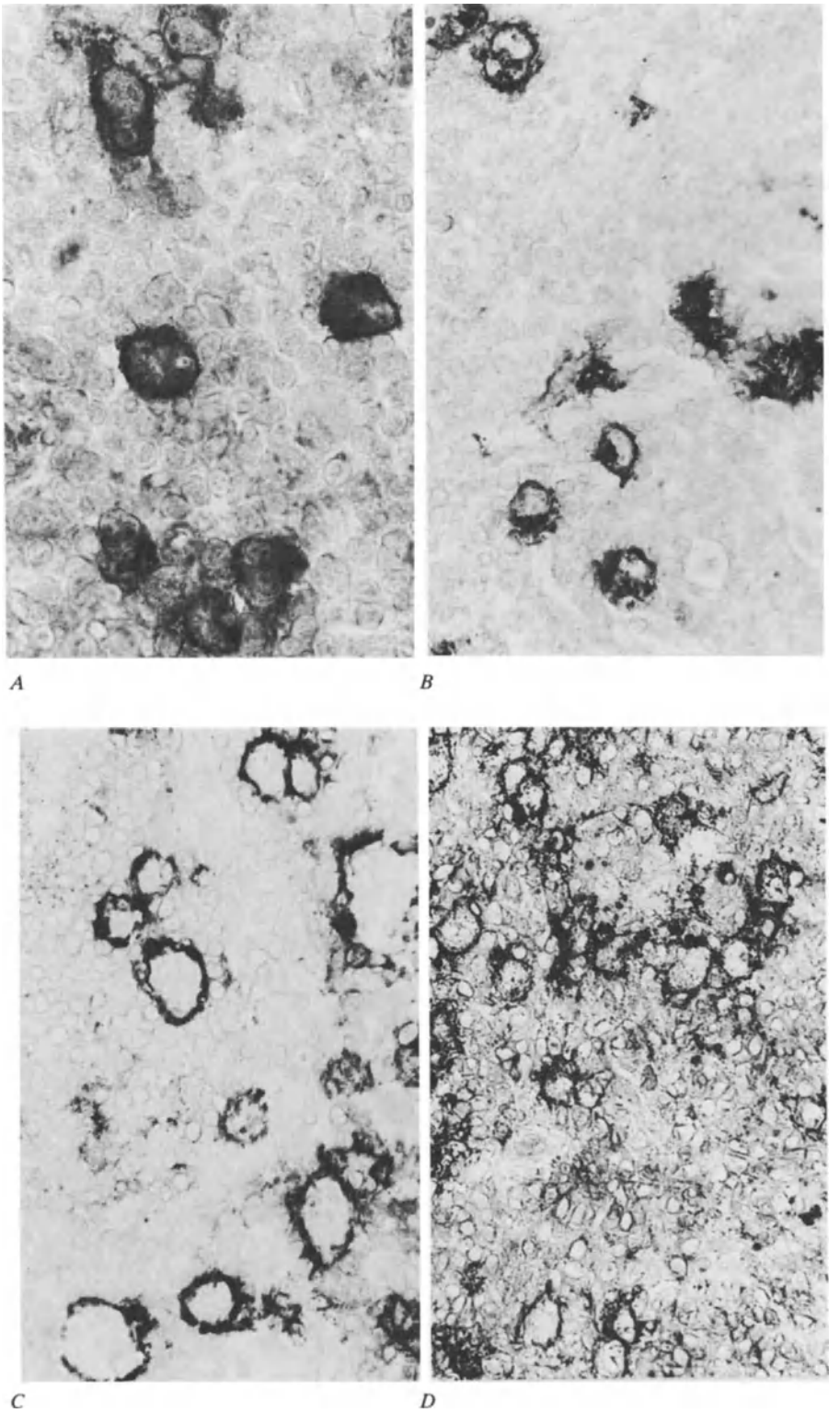

Figure 2. Indirect immunoperoxidase staining of Reed-Sternberg cells in tissue sections of lymph nodes with Hodgkin's disease: (*A*) anti-interleukin–2 receptor, (*B*) anti-α-N-fucopentaose III, (*C*) anti-SR7, and (*D*) anti-B1 (CD20).

Table 1. Immunophenotype of Reed-Sternberg cells.

	Typical and lacunar	L&H type
Ki-1	+	+
Leu M1	+	+ or −
Leu M3	+ or −	+ or −
SR-7	+	+
Ig	?	+
J chain	−	+
HLA-DR	+	+
Transferrin rec.	+	+
Pan-B-cell (CD20)	+ or −	+
Interleukin-2 rec.	+	+
Conclusion	Possibly B cell	B cell

treatment also leads to Leu M1 staining of interdigitating reticulum cells, Hsu *et al.* concluded that L&H-type Reed-Sternberg cells are derived from interdigitating cells [31].

However, not only interdigitating reticulum cells, but also interfollicular immunoblasts and some centroblasts located at the outer margin of the germinal center, become Leu M1 positive after neuraminidase pretreatment of the sections (S. Poppema, unpublished observations, 1986). In the Ig-positive cases, always kappa- as well as lambda-positive L&H cells can be demonstrated, indicating a polyclonal origin of this cell population. Since Reed-Sternberg cells in the other subtypes of Hodgkin's disease do not produce detectable amounts of Ig, also reflected by the finding that they are J-chain negative, no information on the clonal origin of these cells can be gained by this method. The immunophenotypes of Reed-Sternberg cells in the different subtypes of Hodgkin's disease are summarized in Table 1.

In conclusion, Reed-Sternberg cells in lymphocyte-predominance type of Hodgkin's disease are transformed B cells of polyclonal origin, whereas the Reed-Sternberg cells in the other types of Hodgkin's disease also have many similarities to transformed B-lymphocytes, but can not be identified as such with certainty by immunohistochemical procedures.

2. Immunophenotype of the reactive lymphocytes

Several studies have demonstrated that tissues involved by Hodgkin's disease contain a majority of small lymphocytes (Figure 3). These cells were shown to exhibit stable E-rosette formation, natural attachment, and increased glucocorticoid sensitivity, similar to immunoactivated T cells [32]. Immunophenotype analysis of the lymphocytes surrounding the Reed-Sternberg cells in tissue sections demonstrated that these were T-lymphocytes [33]. With the help of monoclonal anti-T-cell antibodies, the lymphocytes were found to be not reactive with CD8 antibodies and anti-natural-killer cell antibodies (*leu7* and *leu11*). In several studies [10, 34, 35],

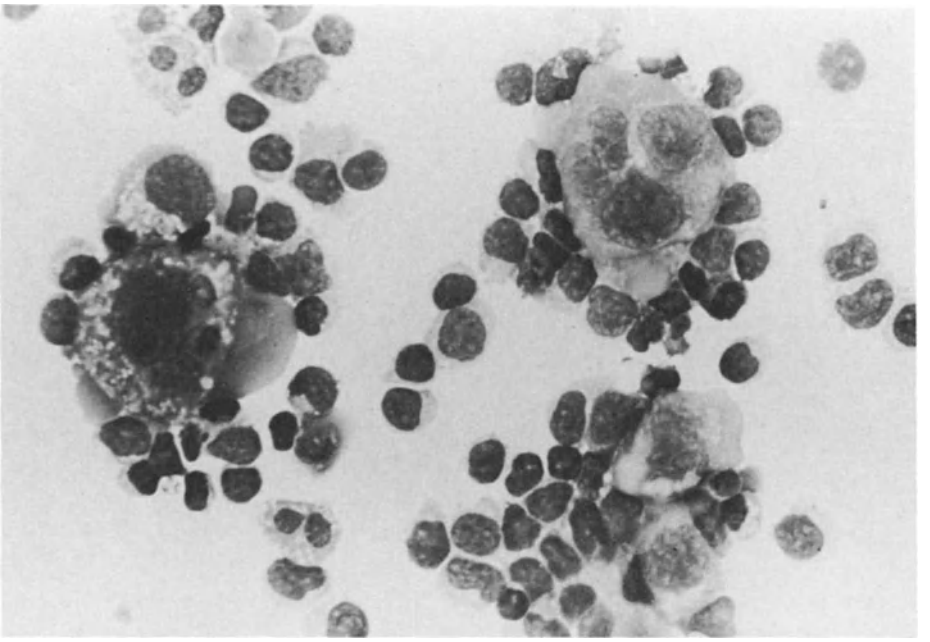

Figure 3. MGG-stained cytocentrifuge preparation of a cell suspension of a lymph node involved by Hodgkin's disease. Lymphocytes cluster around Reed-Sternberg cells.

the lymphocytes were reactive with CD4, CD2, CD3, CD5, CD6, and CD7. In addition, the lymphocytes also reacted with T10 [10] and, to a lesser degree, with anti-interleukin-2 receptor, antitransferrin receptor, and anti-HLA-class-II antigen antibodies. No reactivity was found with anti-CD1 antibodies, which argues against an immature thymocyte origin of these cells. This phenotype seems to indicate that the lymphocytes in Hodgkin's disease are of the helper/inducer subset and exhibit several features of lymphocyte activation.

However, immunophenotype studies do not necessarily indicate the functional activity of *in vivo* cells. In a recent study, Romagnani *et al.* [36] demonstrated the presence of a higher percentage of CD4-positive clones from spleens involved by Hodgkin's disease that had cytolytic activity and produced high amounts of interleukin 2. Therefore, it can not be excluded that the CD4-positive cell population in Hodgkin's disease tissues contains a significant HLA-class-II-restricted cytotoxic cell population. On the other hand, in the system used, the T-lymphocytes were transformed cells in contrast to the small nontransformed T cells characteristically found in Hodgkin's disease-involved tissues.

In the lymphocyte-predominant type of Hodgkin's disease, a different lymphocyte population is found. First, it was demonstrated that the majority of the cells were IgM-positive B-lymphocytes of polyclonal origin [33].

Table 2. Immunophenotype of T-lymphocytes in Hodgkin's disease.

	Mixed type and nodular sclerosis	Lymphocyte predominance
CD1 (OKT6)	−	−
CD2 (OKT11)	+	+
CD3 (WT31 and WT32)	+	+
CD4 (Leu3)	+	+
CD5 (Leu1)	+	+
CD6 (Clonab T)	+	+
CD7 (WT1)	+	+
CD8 (OKT8)	−	−
Leu7	−	+
Leu8	+	+/−
Transferrin rec.	+/−	+/−
Interleukin-2 rec.	+/−	+/−
OKT10	+	+
HLA class II	−/+	−/+
Conclusion	Activated HLA class II restricted T cell	Germinal center T-cell subset

Subsequently, these cells were shown to be also IgD positive, but expressed diminished amounts of *leu8* antigen when compared with mantle-zone B-lymphocytes, indicating an activated state of these cells. Second, a particular T-lymphocyte population is present in the lymphocyte-predominant type. These are CD4-positive T-lymphocytes (indicated by CD2, CD3, and CD5 positivity) that also express *leu7* antigen [30]. This T-cell subpopulation is extremely scarce in peripheral blood, but is the predominant type of T-lymphocyte in germinal centers, in particular in the light zone in later stages of the germinal center reaction [37]. Recently, these cells were cloned and cultured *in vitro* and exhibited no natural killer cell activity [38].

We suggest that these cells are a regulating T-cell population probably driving B cells to memory cells and inhibiting differentiation toward plasma cells. That this cell population is expanded in the lymphocyte-predominant type of Hodgkin's disease, which is characterized by the absence of plasma cells and the presence of so-called progressively transformed germinal centers that consist predominantly of small nontransformed B-lymphocytes, may explain these features. Another feature distinguishing the nodular lymphocyte-predominant type from other subtypes of Hodgkin's disease is the presence of nodular aggregats of dendritic reticulum cells, the type of reticulum cell reactive with anti-C3b and anti-C3d receptor antibodies, and virtually restricted to normal and neoplastic B-cell follicles [19].

The immunophenotype of the lymphocytes in different subtypes of Hodgkin's disease is summarized in Table 2. The findings indicate that the nodules of the nodular lymphocyte-predominant type of Hodgkin's disease are abnormal B-cell follicles containing all cell types also present in normal follicles. In this sense, the nodular lymphocyte-predominant subtype can be considered a germinal center type of Hodgkin's disease, in contrast to the

Table 3. Immunophenotype of Hodgkin's cell lines.

	428	ZO	KM-H2	540	CO	DEV	DUS	CAT
Immunoglobulin	−	−	−	−	−	+	+	+
Ki-1	+	+	+	+	−	+	+	+
Leu M1	+	+	+	−	−	+	+	+
SR-7	+	+		−	+	+	+	+
HLA-Dr	+	+	+	+	−	−	+	+
HLA-ABC	−	−		+	+	−	+	+
aIL2r	+	+		+	+	+	+	+
CLA (200kD)	+	−		+	+	+	+	+
MB1 (200kD)	+	−		+	+	+	+	+
MT1 (190kD)	−	−		+	+	−	−	−
B1 (CD20)	−	−	−	−	−	+	+	+
Leu14 (CD22)	−	−		−	−	+	+	+
B2 (CD21)	−	−	−	−	−	−	+	+
aC3br	−	−	−	−	−	−	−	−
aCALLA	−	−	−	−	−	−	−	−
LeuM5	−	−	−	−	−	−	−	−
Fc rec.	−	−	−	−	−	−	−	−
Leu1 (CD5)	−	−	−	+	+	−	−	−
Leu5 (CD2)	−	−	−	+	−	−	−	−
WT32 (CD3)	−	−	−	+	+	−	−	−
WT31 (CD3)	−	−	−	+	+	−	−	−
Leu3a (CD4)	−	−	−	−	−	−	−	−
OKT6 (CD1)	−	−	−	−	−	−	−	−
Tu1 (CD6)	−	−	−	−	−	−	−	−
WT1 (CD7)	−	−	−	−	−	−	−	−
OKT8 (CD8)	−	−	−	−	−	−	−	−
p19 (HTLV1)	−	−	−	−	−	−	−	−
EBNA	−	−	−	−	−	−	+	+
Receptor for T cells	+	+	+	+	−	−	−	−

other types that are localized in the perifollicular region and do not contain dendritic reticulum cells and *leu7*-positive T-lymphocytes.

3. Hodgkin's disease-derived cell lines

Over the years, a number of authors have reported cell lines derived from tissues or body fluids involved by Hodgkin's disease. Several of these lines were later shown to be unrelated to Hodgkin's disease [39]. Ideally, one should be able to demonstrate identical membrane markers, chromosomal abnormalities, and gene rearrangements in the tissue Reed-Sternberg cells and in their *in vitro* culture counterparts. Cell lines meeting at least some of these requirements have been described by Schaadt *et al.* [40], Poppema *et al.* [16], Jones *et al.* [41], and Kamesaki *et al.* [42]. Here we summarize the immunocytologic findings and the results of gene rearrangement studies in some of these lines (Table 3). In addition, we describe a new cell line, denominated ZO, which was recently established from involved pleural fluid in a patient with Hodgkin's disease.

The histology of an excised cervical lymph node was diagnostic of a nodular-sclerosis (NS) subtype of Hodgkin's disease. Most nodules con-

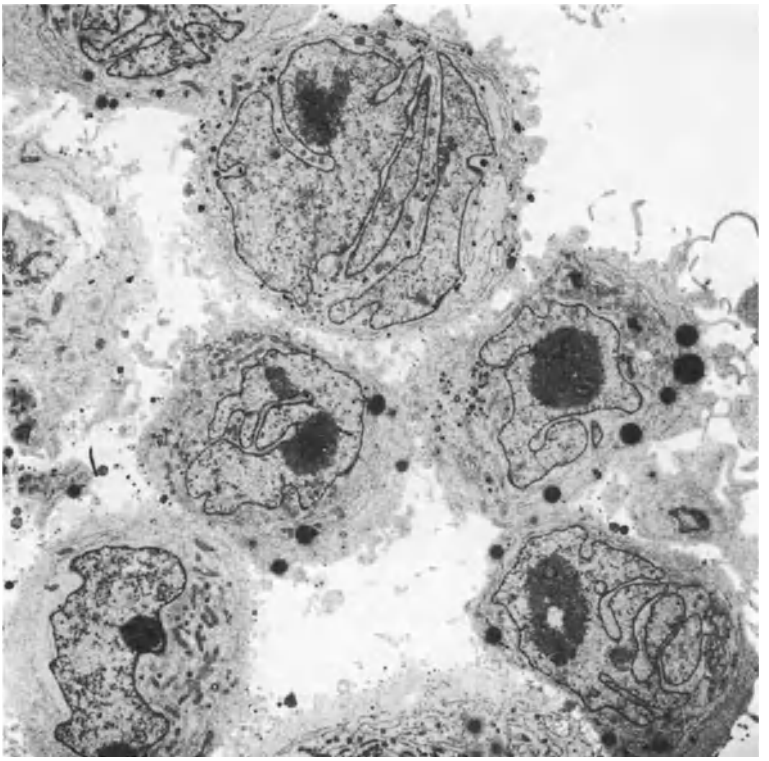

Figure 4. Transmission electron microscopy of cell line ZO. Multilobated nuclei with large nucleoli and a cytoplasm containing many polyribosomes, some strands of rough endoplasmic reticulum, several fat inclusions, and few dense bodies.

tained a majority of lacunar-type Reed-Sternberg cells, in agreement with the poor-prognosis subgroup NS II, as distinguished by the British Lymphoma Group [43].

The patient was treated with MOPP-C (nitrogen mustard, Oncovin [vincristine], procarbazine, and prednisone + cyclophosphamide) and relapsed 1 year later with massive pleural and pericardial effusions containing high numbers of Reed-Sternberg cells in addition to lymphocytes, mesothelial cells, and reactive macrophages. These cells were cultured in RPMI-1640 supplemented with 20% fetal calf serum, and began growing within 1 week with doubling times of 48 h. At passage 8, when the admixed reactive cells had gradually disappeared, the cell proliferation stopped. This was overcome by adding an interleukin-2-containing medium (Lymphocult, Biotest). The need to add interleukin 2 may result from the loss of other reactive cell populations, such as macrophages and mesothelial cells.

The morphology of the cells is shown in Figure 4, demonstrating large multilobated nuclei, with giant nucleoli, and a moderately basophilic cytoplasm. At the ultrastructural level, these cells contain many polyribosomes,

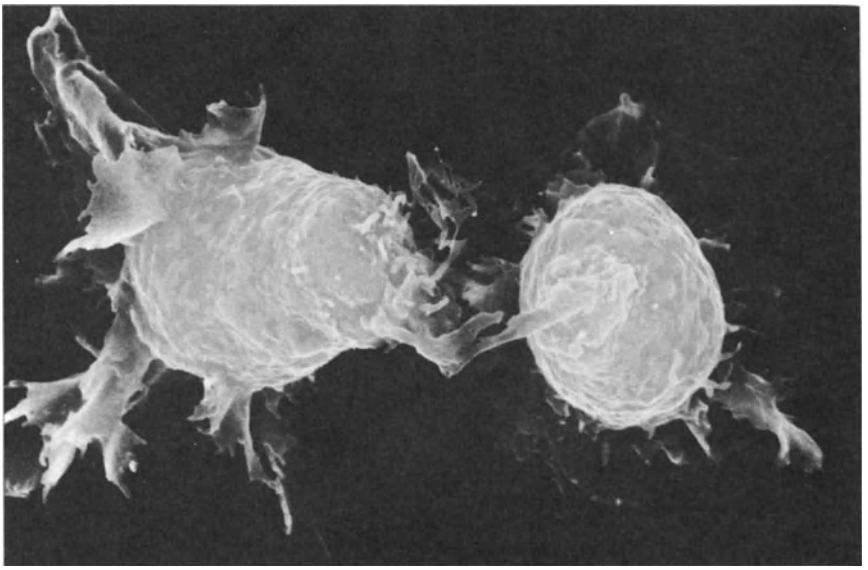

Figure 5. Scanning electron microscopy of cell line DEV. Cells with extensive villi and veils at the cell surfaces.

strands of nondilated endoplasmic reticulum, and a small Golgi area. There are few dense bodies, several large lipid droplets, and strands of microfilaments. This ultrastructure is similar to that of Reed-Sternberg cells in tissue sections.

Scanning electron microscopy reveals short villi and blebs. This is clearly different from cell line DEV, which has extensive cytoplasmic villi and veils (Figure 5). The immunocytology of the cultured ZO cells and that of the original pleural fluid cells are identical. The cells are Ki-1, Leu M1, SR7, HLA-Dr, and IL2r positive. No reactivity is found with anti-Ig antibodies or with B-cell- or T-cell-specific antibodies. This is the immunophenotype of Reed-Sternberg cells most frequently present in the nodular-sclerosis type of Hodgkin's disease.

Chromosomal analysis of the original pleural fluid indicated 54 chromosomes with several structural abnormalities in a small percentage of the metaphases, whereas all cells of the cell line have similar abnormalities. The Ig gene and T-cell receptor gene analyses of the original pleural fluid showed germ-line patterns only, whereas the cell line clearly has JH as well as Ck gene rearrangements, and germ-line patterns for C lambda, and the alpha and beta chains of the T-cell receptor. These findings indicate that this cell line with its typical Reed-Sternberg cell immunophenotype and the absence of Ig production and other B-cell markers is clearly of B-cell origin.

The other cell lines reported in the literature can be grouped according to the immunophenotype and gene rearrangement findings. Lines 428 and

KM-H2 exhibit the same typical Reed-Sternberg cell phenotype as ZO and both have Ig heavy-chain gene rearrangements. Cell lines 540 and CO lack some of the Reed-Sternberg cell markers and do express some T-cell markers, which is a very unusual phenotype of the Reed-Sternberg cells in tissue sections. In accordance with their T-cell membrane phenotype, 540 and CO have beta-chain T-cell receptor gene rearrangements and no Ig gene rearrangements.

Finally, the DEV cell line expresses B-cell membrane markers such as B1 (CD20) and *leu14* (CD22), and produces α-2-Ig heavy chains, in addition to the Reed-Sternberg cell markers. This immunophenotype is infrequent in nodular-sclerosis and mixed-cellularity, subtypes but is a regular finding in the lymphocyte-predominant subtype of Hodgkin's disease. The B-cell origin of this line is further confirmed by the presence of JH rearrangement and Ck deletion.

The status of the Epstein-Barr nuclear antigen (EBNA)-positive lines 591, DUS, and CAT is not clear. In all three cases, the cells have chromosomal abnormalities from the beginning, which is highly unusual in EB-virus-transformed lymphoblastoid cell lines [44]. The immunophenotype of these lines is similar to that of Reed-Sternberg cells (Ki-1, Leu M1, RS-7, and IL2r positive), but they are also reactive with B2 (CD21), indicating a C3d-EB-virus receptor [45]. In addition, DUS and CAT react with anti-B-cell monoclonal antibodies B1 and Leu 14. In both cases, the Reed-Sternberg cells in the tissue sections also react with these anti-B-cell reagents. DUS was derived from a lymph node with the nodular lymphocyte-predominant type and CAT from a lymph node with the nodular-sclerosis subtype of Hodgkin's disease with B1-positive Reed-Sternberg cells.

In general, Reed-Sternberg cells do not react with anti-EBNA antibodies, although we have observed one case of chronic mononucleosis not distinguishable from Hodgkin's disease with EBNA-positive Reed-Sternberg cells [46]. With respect to the EBNA-positive Hodgkin's disease-derived cell lines, it is not clear whether these lines are derived from a seldom occurring *in vivo* EB-virus-transformed Reed-Sternberg cell or from an *in vitro* transformation of a B-lymphocyte with subsequent chromosomal changes.

In conclusion, three types of Hodgkin's cell lines can be distinguished: those with typical phenotype and Ig gene rearrangements, those with T-cell markers and T-cell receptor rearrangements, and those with B-cell markers (EBNA positive or negative) and Ig gene rearrangements.

4. Chromosomal findings in Hodgkin's disease

There are only a limited number of chromosome studies on lymph nodes of patients with Hodgkin's disease. This is mainly due to the low yield of dividing cells in these preparations. Frequently, no mitotic cells are found

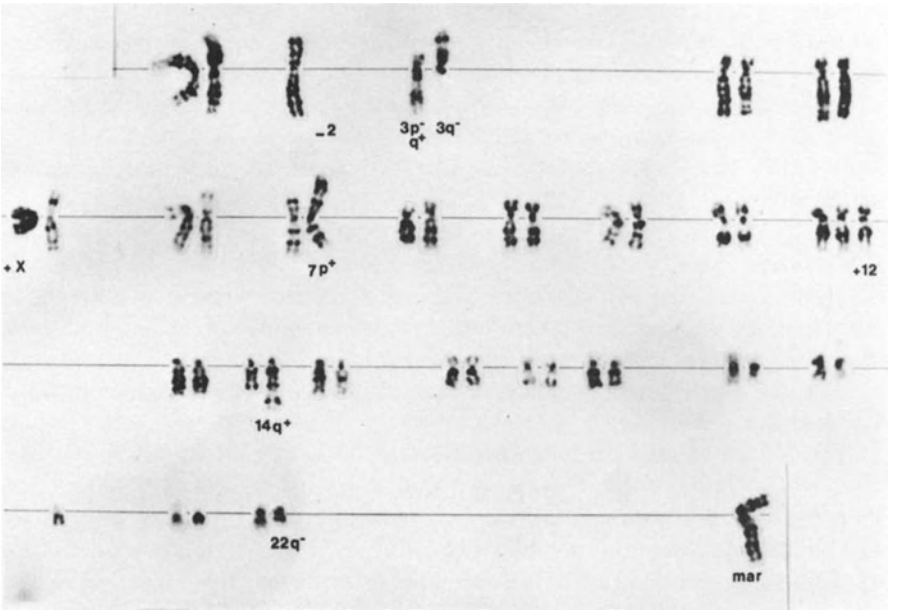

Figure 6. G-banded karyotype of DEV cell showing the 48,XXY,−2,+12,+mar,t(3;14)(3;22),t(3;7), del3 karyotype.

and, in other instances, only normal mitoses are present. Aneuploid numbers of chromosomes have frequently been described.

In a study by Rowley, only four of 25 lymph nodes studied had clonal chromosomal abnormalities [47] and, in another study, four of 22 cases had specific clones [48]. In this latter study, it was noted that the abnormalities all occurred in relapses. Pleural effusions of patients with Hodgkin's disease were also found to contain several chromosomal abnormalities, including 6q− and 14q+ markers and structural rearrangements of chromosomes 3 and 5 [49].

The cell lines derived from Hodgkin's disease also had several chromosomal abnormalities, including 14q+ markers in DEV and L428, and several abnormalities of chromosomes 6 and 12. It is noteworthy that essentially all of these clonal abnormalities were found in patients with relapsed Hodgkin's disease. Therefore, it can not be excluded that this is a selection of unfavorable cases or a selection of cells as a result of therapy. Nevertheless, the chromosomes involved appear to be similar to those reported in large cell non-Hodgkin's lymphomas of B-cell origin (Figure 6).

5. Growth factors in Hodgkin's disease

Few studies have dealt with the production of growth factors by Hodgkin's disease-involved tissues or Hodgkin's cell lines. Tissue studies have involved the culturing of cell suspensions derived from lymph nodes or spleens involved by the nodular-sclerosis type of Hodgkin's disease. In one study, the supernatant of cells from lymph nodes was found to have fibroblast growth-potentiating activity, especially when the suspension had been enriched with Hodgkin's giant cells [50]. In another study, fragment cultures of Hodgkin's tumor nodules from spleen were found to produce interleukin 1 and fibroblast stimulatory factors [51]. Interleukin 1 stimulates T cells to secrete interleukin 2, but also has fibroblast-activating activity and endogenous pyrogen activity. Hodgkin's cell line L428 was also demonstrated to produce factors with interleukin-1-like activity [52]. In addition, the supernatant of L428 cells was shown to have colony-stimulating activity [53], whereas the supernatant of DEV cells has fibroblast growth-stimulating activity (S. Poppema, unpublished, 1987).

All of these findings were originally interpreted as providing support for a macrophage origin of Reed-Sternberg cells, but more recently it has been shown that transformed B cells may also produce factors with interleukin-1-like activity [54]. Whatever the origin of these biologically active factors may be, their activities match well with some of the features of Hodgkin's disease, such as the presence of sclerosis, fever, night sweats, and myeloid hyperplasia.

6. Role of HLA class II antigens

There are two different lines of research indicating a role of human leukocyte antigens (HLA) in the pathogenesis of Hodgkin's disease. The first one is the finding that Hodgkin's disease is one of the very few malignancies that is HLA related. Although there is no clear relation with one particular HLA type, a number of investigators have found some HLA classes more frequently than others in patients with Hodgkin's disease [55, 56], and some HLA classes apparently influence the prognosis of Hodgkin's disease [57]. There are a few striking case reports on the occurrence of Hodgkin's disease in siblings with the same HLA type, whereas other siblings with different HLA types were not affected [58]. Another approach has been the demonstration of anti-HLA-class-II antibodies in the sera of patients with untreated Hodgkin's disease [59].

The last finding indicates similarity to the spontaneous lymphomas in SJL/J mice, which sometimes exhibit some morphologic similarity to Hodgkin's disease. It has been demonstrated that the transformed cells in these lymphomas express HLA class II antigens not present on the normal cells in this mouse strain, and that they have antibodies against these so-called alien

HLA as well as a reaction of L3T4-positive T-lymphocytes, the mouse equivalent of the human CD4-positive T-cell population [60]. Moreover, this T-cell reaction is essential for the development of the SJL/J lymphomas, since these tumors can not be passaged in neonatally thymectomized mice [61].

7. Immunoglobulin gene rearrangements in Hodgkin's disease tissues

During the past few years, developments in molecular biology have provided new tools for the identification of B and T cells by examination of changes in the cellular DNA. B cells undergo rearrangements of the Ig genes early in their differentiation preceding the production of cytoplasmic or membrane Ig in an orderly fashion. Heavy-chain gene rearrangement is followed by kappa light-chain and, if unsuccessful, by lambda light-chain rearrangement [62]. Clonal populations of B cells can be detected by the presence of clonal Ig gene rearrangements [63, 64]. In a similar way, T cells undergo rearrangements of the T-cell receptor genes and, consequently, clonal T-cell populations can be detected by the demonstration of clonal rearrangements of the T-cell receptor genes [65, 66].

Surprisingly, it was found that some T-cell proliferations also had clonal rearrangements of the Ig heavy-chain genes and some B-cell lymphomas had clonal rearrangements of T-cell receptor genes [67, 68]. Further, rearrangements of the Ig heavy-chain gene were found in some cases of myelogenous leukemia [69]. Nevertheless, rearrangements of the Ig light-chain genes have been found exclusively in B-cell lymphomas. By employing these techniques, it was shown that most so-called O-cell lymphomas in fact are of B-cell origin, and most so-called histiocytic tumors also have rearrangements of Ig genes or of T-cell receptor genes [70, 71].

Application of gene analysis techniques to Hodgkin's disease-involved tissues is therefore a logical step. It should be kept in mind that Reed-Sternberg cells and their variants generally constitute only a minority of the cell population in tissues involved by Hodgkin's disease, the majority being T-lymphocytes, macrophages, and eosinophils. Therefore, possible gene rearrangements in minor clonal populations of Reed-Sternberg cells may stay below the threshold of sensitivity of the technique.

Generally, it is accepted that clonal populations that are 5% can be demonstrated consistently. A number of groups have applied gene analysis to tissues involved by Hodgkin's disease. By this approach, two questions can be answered: first, whether there is a clonal population of cells in these tissues and, second, whether this clonal population is B-cell or T-cell related. To answer the first question, a clonal rearrangement with any of the probes would suffice, whereas light-chain Ig gene rearrangement is needed to demonstrate a B-cell origin. Rearrangement of T-cell receptor genes

Table 4. Immunoglobulin gene rearrangements in Hodgkin's disease.

	JH	C kappa	C lambda	TCR beta
Weiss *et al.* [73]				
Case 1	R(G)	G	(R)	G(G)
Case 3	G(R)	R	(G)	G(G)
Case 4	G(G)	G	(R)	G(G)
Case 5	G(G)	R	(G)	G(G)
Case 6	G(R)	G	(G)	G(G)
Case 7	G(G)	G	(R)	G(G)
Case 8	R(G)	G	(G)	G(G)
Brinker *et al.* [75]				
Case 1	R(R)	R	(G)	G(G)
Case 2	G(G)	R	(G)	G(G)
Case 3	G(R)	R	(G)	G(G)
Case 4	R(R)	D	(R)	G(G)
Case 5	R(R)	R	(G)	G(G)
O'Connor *et al.* [74]				
Case 1	R	R	(G)	G(G)
Case 2	R	R	(G)	G(G)

JH, heavy-chain gene; C kappa, kappa light-chain gene; C lambda, lambda light-chain gene; TCR beta, beta-T-cell receptor gene; G, germ-line bands only; R, rearranged bands; D, deletion of germ-line bands; G or R, Bam HI restriction enzyme; and (G) or (R), Eco RI restriction enzyme.

without rearrangement of Ig genes is a strong argument for a T-cell origin. The results of gene analysis in the cases studied by the different groups are the same with the exception of some cases reported by the Kiel group, which found clonal rearrangements of T-cell receptor genes in four cases [72]. In Stanford [73], Oxford [74], and Groningen [75], Ig gene rearrangements were regularly detected in cases of recurrent Hodgkin's disease, but seldom in primary lesions. The results of these studies are compiled in Table 4.

The immunophenotype of the Reed-Sternberg cells in the recurrent lesions was compared with that of the primary lesions and found not to differ. The finding of clonal Ig gene rearrangements in the tissues is also in agreement with the results in a number of Hodgkin's cell lines [42, 76, 77] (Figure 7).

The presence of clonal Ig gene rearrangements in tissues involved by Hodgkin's disease indicates the presence of a clonal population of B-cell origin in these tissues. To prove that Reed-Sternberg cells constitute this clonal B-cell population, it would be necessary to isolate the Reed-Sternberg cells and find the same rearrangements. However, the finding of clonal rearrangements in cases with a predominance of Reed-Sternberg cells and the absence of significant numbers of B-lymphocytes and of monoclonal Ig staining of the lymphocytes in these cases makes it very likely that the Reed-Sternberg cells contain the clonal Ig gene rearrangements and thus

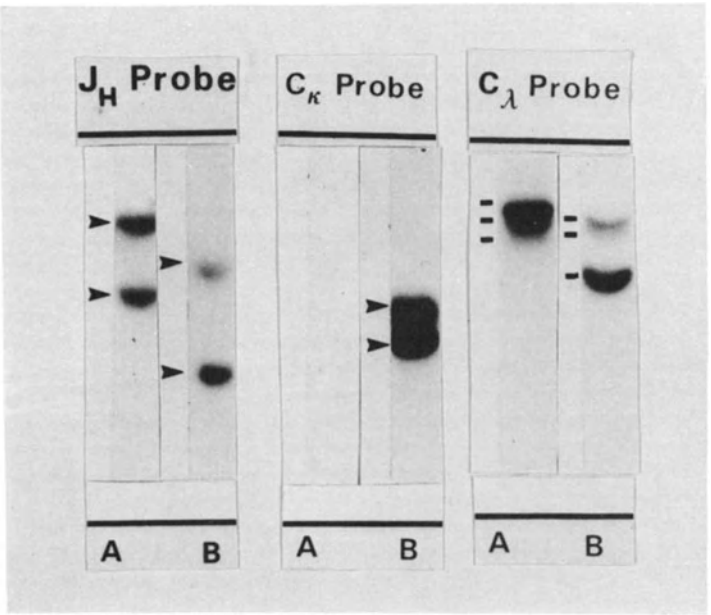

Figure 7. Autoradiographs of hybridizations with JH, C kappa, and C lambda probes. The results are shown for cell line DEV in the *A* lanes and for cell line ZO in the *B* lanes. Both lines have rearranged heavy-chain genes; the DEV kappa-chain gene is deleted and the ZO kappa-chain gene is rearranged. Both lines show a lambda-chain gene germ-line pattern. The results support a B-ceil origin of both Hodgkin's cell lines.

may be of B-cell origin. Final proof can only be provided by further isolation of the Reed-Sternberg cells and by the induction of Ig synthesis in these cells.

Even more important is the question of why no clonal rearrangements were found in most primary lesions despite the fact that several of them appeared to contain >5% of Reed-Sternberg cells and variants. First, the Reed-Sternberg cells in these cases may not be of B- or T-cell origin. However, the immunophenotypes of positive and negative cases are the same, arguing against such a difference. Second, the Reed-Sternberg cells in these cases may not be clonal. This would imply that Reed-Sternberg cells during that stage of the disease are not a malignant cell population, but the result of transformation of several different B-lymphocytes and also some T-lymphocytes.

To evaluate this possibility, we have chosen the following approach. A suspension of a lymph node from a patient with the nodular-sclerosis type of Hodgkin's disease with numerous Reed-Sternberg cells, but without clonal gene rearrangements, was prepared. The cells were hybridized with mouse myeloma cell line X63 according to standard procedures to obtain human-

Table 5. Immunophenotype and genotype analysis of R-S cell mouse myeloma cell hybrids

	Ki-1	Leu M1	Human HLA class I	SR7	CD20	Jh	Ck	C-Lambda
X63 Myeloma	–	–	–	–	–	–	–	*
Clone 3A4	+	–	+	+	+/–	R	–	G
Clone 3A6	+	–	+	–	–	R	–	G
Clone 3F4	+	–	+	–	–	R	R	R
Clone 3G5	+	–	+	+/–	–	R	–	–

* one cross reacting band
\+ positive
– negative
+/– some positive
R rearranged
G germ line

mouse hybrids. These were cloned and allowed to grow in selective medium in 96-well tissue culture plates. From a total of 192 wells, 80 growing hybrids were obtained. These were cultured in tissue culture flasks, tested for the presence of human and mouse chromosomes, and immunophenotyped. All hybrids expressed human class I HLA and human transferrin receptors. To determine which clones were of Reed-Sternberg cell origin, they were immunophenotyped to detect Ki-1 or Leu M1 positivity. The results are summarized in Table 5.

Positive clones were subsequently analyzed for the presence of Ig gene and T-cell receptor gene rearrangements. The rationale of this approach is that, when the Reed-Sternberg cells are of clonal origin, this should result in identical rearranged bands in the hybrid clones, whereas a polyclonal origin leads to different rearranged bands. Our first results indicated that all clones with detectable rearrangements had different bands, suggesting a polyclonal origin of the Reed-Sternberg cells in this case (M.G.L. Brinker *et al.*, in preparation).

In conclusion, gene rearrangement studies in tissues involved by Hodgkin's disease show absence of clonal rearrangements in early stages and presence of clonal Ig gene rearrangements in recurrent, late stages of the disease. These findings suggest a polyclonal origin of the Reed-Sternberg cells of most cases in the early stages of the disease, and a development to a monoclonal Reed-Sternberg cell population of B-cell origin in the late stages.

8. Summary and hypothesis

The problem of the origin of Reed-Sternberg cells has not yet been solved. However, it is clear now that, at least in some cases—in particular in the

lymphocyte-predominant type, but also in other subtypes—an abnormal, proliferating cell population of B-cell origin can be found. This is supported by immunohistologic, cell culture, chromosomal, and gene rearrangement studies. It can not be excluded that other cells may also transform into cells morphologically defined as Reed-Sternberg cells, although we have found no data to support this.

The lymphocytes surrounding the Reed-Sternberg cells generally are CD4-positive T-lymphocytes with several features indicating some degree of activation. No firm data on the functional activity of these lymphocytes are available although *in vitro* they do not appear to be actively cytotoxic toward the Reed-Sternberg cells.

Another important question is whether the Reed-Sternberg cells are a malignant, monoclonal cell population or a nonmalignantly transformed, polyclonal cell population. Clonal chromosomal abnormalities and clonal Ig gene rearrangements so far have been demonstrated in several cases with relapsed disease, but only very seldom in primary lesions. Our preliminary cell fusion data and the presence of kappa- as well as lambda-positive cells in lymphocyte-predominant cases indicate that Reed-Sternberg cells in early cases of Hodgkin's disease may well be of polyclonal origin.

There are a number of features suggesting that, despite the absence of a clonal population, Hodgkin's disease could progress as an autonomous process. Hodgkin's disease-involved tissues and cell line L428 produce factors with interleukin-1-like activities. In addition, Reed-Sternberg cells apparently bear antigens recognized by autologous CD4-positive lymphocytes. The presence of antibodies with anti-HLA-class II specificities in some patients and the apparent HLA association of the disease in some families with multiple cases of Hodgkin's disease suggest that this antigen may be HLA-Dr related. These features create the conditions necessary for the activation of the CD4-positive T-lymphocyte population, which may lead to the production of factors like interleukin 2.

Reed-Sternberg cells strongly express structures reactive with anti-interleukin-2 receptor antibodies and Hodgkin's cell line ZO indeed depends on the presence of exogenous interleukin 2. This may create a situation in which the Reed-Sternberg cells proliferate as a result of the continuous influx and stimulation of CD4-positive T-lymphocytes. A major result of therapy in Hodgkin's disease may be the interruption of this loop by the effect on the activated T-lymphocytes. The players in this hypothetical model and their roles are illustrated in Figure 8. Therapy resistance may be the result of the occurrence of a malignant clone that is not dependent on the presence of the activated lymphocytes and their interleukins.

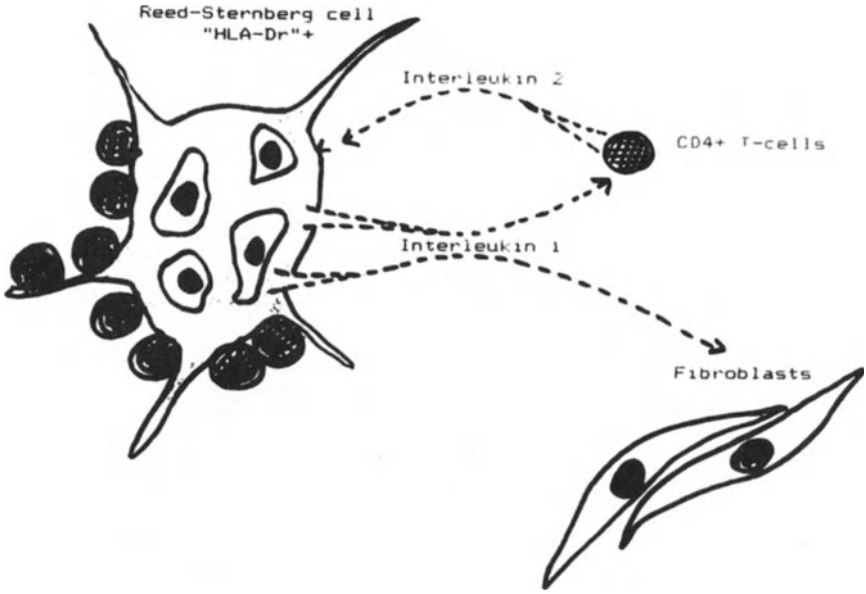

Figure 8. Model of interactions between transformed Reed-Sternberg cell and activated CD4-positive T-lymphocytes.

Acknowledgment

This work was supported by KWF grant GUKC 83/3 and the J.K. de Cock Foundation.

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3. Conclusions from Hodgkin-derived cell lines

H. Burrichter, M. Schaadt, and V. Diehl

The diagnosis of Hodgkin's disease is based on the identification of Hodgkin's (H) and Sternberg-Reed (RS) cells in tissue biopsies [1], but it should be noted that cells morphologically indistinguishable from H and SR cells have been described in a variety of malignant or nonmalignant disorders other than Hodgkin's disease [2–7]. Hodgkin's disease has been assigned to the malignant lymphomas, and this is true from the clinical point of view, since the early manifestation of this disease is strongly related to the lymphoid tissue. To clarify the origin of H and SR cells, ultrastructural, histochemical, and immunologic studies have been performed on histologic sections or after separation of H and SR cells from biopsy material. In spite of these efforts, the origin of H and SR cells is still uncertain and there is no cell lineage of the hematopoietic system that has not been suggested as a candidate for the nonmalignant precursor of the malignant H and SR cells: endothelial cell [8], transformed lymphoblast [9], reticulum cell [10, 11], myeloid cell [12], megakaryocyte [13], and histiocyte [1, 14]. During the last two decades, the discussion concerning the origin of H and SR cells has focused on the lymphatic and reticular–histiomonocytic system.

Faced with the difficulties of determining the derivation of H and SR cells from *in situ* material, many investigators have tried to establish *in vitro* cell lines derived from H and SR cells. There are several reports about short-term or long-term cultures, but these cultures could not be maintained *in vitro* over a long period, have not been sufficiently characterized, did not represent lymphoblastoid cell lines, or were not Hodgkin derived [15–28].

This chapter focuses on cell lines that have been claimed to be Hodgkin derived: L428 [29], L540 and L591 [30, 31], HDLM-2 [32], DEV [33], Cole [34], SU/H-HD-1 [35], and KM-H2 [36]. These cell lines are still in culture and are available for further investigations.

1. Characteristics of Hodgkin's and Sternberg-Reed cells *in vivo*

There is a principal problem defining a marker pattern of H and SR cells because many data are contradictory. So far, a marker that is specific for H

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and SR cells, exclusively, has not been defined. The monoclonal antibody Ki-1 [37], originally thought to be specific for H and SR cells, turned out to bind to an antigen expressed by activated cells. This antigen is not even lineage restricted, since it binds also to cells other than lymphocytes [35, 38]. The presence of activation markers raises the general question of whether the 'normal' pattern of differentiation antigens, demonstrated on resting cells, can be found on activated cells.

It is not known whether marker profiles of cultured cell lines are identical to that of H and SR cells *in vivo*, because there is evidence that the expression of certain markers on H and SR cells depends on environmental conditions [39, 40], but this is a general question not restricted to Hodgkin-derived cell lines.

Another difficulty in comparing the marker profile of H and SR cells *in vitro* in different studies results from the use of different techniques and/or the different materials by investigators in many cases, *e.g.*, monoclonal antibodies as markers for a certain cell lineage.

Probably the most logical way to define prerequisites for H and SR cells *in vitro* is to center on those characteristics of the *in vivo* counterpart that have been found by the majority of the investigators. These markers should also be present on Hodgkin-derived cell lines to accept a cell line as a *in vitro* representative of H and SR cells. The marker profile of H and SR cells *in vivo* (Table 1) is based on four recent studies [3, 39, 41, 42].

2. Characteristics of established cell lines (Tables 2 and 3)

2.1. L428 [29]

Cytochemistry. The cells are positive for acid α-naphthyl acetate esterase and acid phosphatase staining and negative for peroxidase, alkaline phosphatase, or naphthol chloroacetate.

Immunologic findings. Staining is negative for surface and cytoplasmic immunoglobulins (Ig). α_1-fetoprotein, or lysozyme. The cells do not bind complement, Ig, or mouse or sheep erythrocytes, but they form rosettes with human T cells. Cells are Epstein-Barr nuclear antigen (EBNA) negative.

Reactivity with monoclonal antibodies. Apart from LeuM1, L428 cells are negative with antimacrophage monoclonal antibodies (moabs). They are negative with six anti-T-cell antibodies and 16 anti-B-cell antibodies, but positive with B4. They do not bind anti-TdT (terminal deoxynucleotidyl transferase), anti-CALLA (common acute lymphoblastic leukemia antigen) moabs, or an antibody against dendritic reticulum cells. They are positive for Ki-1, Tac (T-activated cell), and Tü69 antigens, and HLA-DR (human leukocyte antigen).

Functional properties. The cells are able to present antigen [43] and to

Table 1. Properties of Hodgkin's and Sternberg-Reed cells *in vivo*.

Cytochemistry	
Peroxidase	neg
Acid phosphatase	neg/pos
Alkaline phosphatase	neg
α-NAE	neg/pos
Naphthol AS-D CAE	neg
Immunohistochemistry	
Lysozyme	+/−
Surface Ig	−
Cytopl Ig	(+)?
SRBC receptor	−
Fc-gamma	+/−
Fc-u	−
C3b	+/−
Receptor for human T	+
Reactivity with monoclonal antibodies	
HLA-DR	+
B1	+/−
OKT3	−
OKT4	−
OKT8	−
OKT9	+
Anti-Tac	+
OKM1	+
R4/23	−
Ki-1	+
Leu-M1	+
Tü9, 3C4, VIMD5	+
Anti-NK	−

α-NAE, α-naphthyl acetate esterase; CAE, chloroacetate esterase; Ig, immunoglobulin; SRBC, sheep red blood cell; Tac, T-activated cell; and NK, natural killer cell.

produce colony-stimulating factor (g-CSF), interleukin 1 (IL-1), a rosette-inhibiting factor, and migration-inhibitory factor [44, 45]. The cells do not incorporate latex beads.

Molecular genetic analysis. L428 cells show a deletion in the heavy-chain locus including the μ and part of the γ constant regions in both alleles and an unusual k rearrangement with deletion of Ck in one allelel. Cγ-specific transcripts can be demonstrated. Ig γ-chain expression can not be found.

Differentiation experiments. Attempts to induce differentiation in a subline (L428KS) of L428 with TPA and dimethyl sulfoxide leads to expression of certain myeloid markers (VIMD5) and to adherent growth after treatment with TPA. No phagocytosis, lysozyme, or expression of Fc receptors is observed [46].

Supposed origin. 'The genotype is compatible with the state of pre-B-cells....' [38]. This statement is based on data of genetic analysis of Ig and T-cell receptor rearrangements, since Ig rearrangements found in L428 so far have not been demonstrated in cells other than B cells. However, phenotypically the cells lack TdT, CALLA, and Ig heavy or light chains. The pre-B genotype is in contrast to markers, which are not expressed on

Table 2. Properties of Hodgkin-derived cell lines.

	L428	L540	L591	HDLM2	SU-H/HD1	KLM2	DEV	CO	H-SR *in vivo*
Patient									
Histology	NS	NS	NS	NS	NS	MC LD	NS	NS	
Stage	IV	IV	IV	IV	III	IV	IV	III	
Source	pe	bm	pe	pe	spleen	ln	ln	ln	
Culture									
Adherent growth	−	−	−	−	+	−	−	−	
Cytochemistry									
Acid ph	+	+	+	+		+	+	+	+
Alk ph	−	−	−			−	−		−
Nonspec esterase	+	+	+	+	+		−	+	+
ANAE	+	+	+			+	−	−	+
NASD ch ac est	−	−	−			−		+	−
Perox	−	−	−	−	−	−	−	−	−
Functional properties									
Phagoc	−	−	−	−	+	−	−	−	
Antigen pres	+				+				
IL-1, CSF, prod	+	+	+		+				
Lysoz	−	−	−		−	−	−	−	−
Other properties									
EBNA	−	−	+	−	−	−	−	−	−
sIg	−	−	−	−	−	−	−	−	−
cIg	−	−	(+)	−	−	−	(+)	−	+/−
SRBC ros	−	+	+	−	−	−	−	−	
EA ros	−	−	−	−	+	+	−	−	+/−
EAC ros	−	−	−	−	+	+	−	−	+/−
Human T	+	+	+			+		+	+

NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depleted; pe, pleural effusion; bm, bone marrow; ln, lymph node; Acid ph, acid phosphatase; Alk ph, alkaline phosphatase; ANAE, α-naphthyl acetate esterase; NASD chl ac est, naphthol AS-D chloroacetate esterase; Perox, peroxidase; Phagoc, phagocytosis; Antigen pres, antigen presentation; IL-1, CSF prod, interleukin 1, colony-stimulating factor production; Lysoz, lysozyme; EBNA, Epstein-Barr nuclear antigen; sIg, surface immunoglobulin; cIg, cytoplasmic immunoglobulin; SRBC ros, sheep red blood cell rosettes; EA ros, EA rosettes; EAC ros, EAC rosettes; and Human T, human T cells.

pre-B cells (Ki-1, HLA-DR, or IL-2 receptor); however, these markers are expressed on activated cells.

2.2. *L540* [30]

Cytochemistry. L540 cells are positive for nonspecific esterase and acid phosphatase, but negative for peroxidase staining.

Immunologic findings. Cytoplasmic or surface Ig can not be demonstrated. The cells are negative for lysozyme. They do not bind Ig or comple-

Table 3. Reactivity with monoclonal antibodies.

	L428	L540	L591	HDLM2	SU-H/HD1	KLM2	DEV	CO	H-SR *in vivo*
Ki-1	+	+	+	+	−	+		+	+
LeuM1	+	+	+	+	−	+		+	+
HLA-DR	+	+	+	+	+	+	1%	+	+
OKT3	−	−	−	−		−	−	+	−
OKT4	−	+	−	−	−	−	−	−	−
OKT8	−	−	−	−	−	−	−	−	−
OKT11	−	+	+	−	−	−	−	−	−
M1	−	+	+	−	+	−	−	−	−
R4/23	−	−	−			−		−	−
NA 1/34	−	−	−			−		−	−
VIMD5	(+)	(+)	−	+	+	+		+	+
B1	−	−	+	−		+		+	+
Anti-NK	−	−	−			−	−	−	−
Anti-Tac	+	+	+						+

ment, but form rosettles with sheep red blood cells (SRBC) and human T cells. Test for EBNA is negative.

Reactivity with monoclonal antibodies. There is no reactivity with 17 moabs defining antigens on B cells. The cells bind to OKT11, OKT4, and Leu3a, but not to OKT8, OKT1, Leu1, OKT2, OKT3, or UCHT1. Mo1 and Mo2, reacting with macrophages, stain 100% of L540 cells. All cells are positive for staining with Ki-1, anti-Tac, and anti-HLA-DR, but negative with R4/23 and anti-TdT.

Functional properties. IL-1-like activity, g-CSF, rosette inhibition factor, migration inhibitory factor, and a fibroblast-activating factor can be demonstrated in the culture supernatant. The cells do not phagocytize iron particles, latex beads, or Ig-coated erythrocytes.

Molecular genetic analysis. There is no evidence for heavy- or light-chain rearrangements or transcription of Ig genes. The α-chain, β-chain and γ-chain genes of the T-cell receptor (TCR) are rearranged. TCR, a specific RNA, can be demonstrated.

Supposed origin. The cells 'show some markers of a T-lymphocytic lineage' [38]. T-cell receptor genes are rearranged and TCR-a RNA can be demonstrated, but L540 does not express a functional T-cell receptor (OKT3−). They express some T-cell markers, as well as markers for the macrophage/monocyte lineage and for activation.

2.3. L591 [30]

Cytochemistry. The cells show nonspecific esterase and acid phosphatase activity. They are negative for peroxidase.

Immunologic findings. SRBC are bound to the surface, but not complement or Ig. Production of lysozyme cannot be demonstrated. The cells are EBNA positive.

Reactivity with monoclonal antibodies. The cells can be labeled with moabs against B cells (anti-IgA, lambda, To15, B1, and B4) and bind OKT11. There is a positive reaction with antimacrophage moabs Mo1, Mo2, S-HCL3, and Ki-M1. The cells are positive with Ki-1, anti-Tac, and anti-HLA-DR antibodies and negative with R4/23 and anti-TdT.

Functional properties. L591 cells secrete IL-1, low levels of g-CSF and rosette inhibition factor. The cells do not show phagocytic activity.

Molecular genetic analysis. A deletion in the heavy-chain locus including $C\mu$ and part of the γ constant regions can be demonstrated. Rearrangements are seen in the Ig-λ locus, but not in the Jk-Ck region. $C\alpha$-, Ck-, and $C\lambda$-specific RNA can be detected.

Supposed origin. 'The data suggest a B-cell origin....' [38].

2.4. HDLM-2 [32]

Cytochemical findings. The cells are positive for nonspecific esterase and acid phosphatase activity, but are negative for peroxidase.

Immunologic findings. The cells did not form E, EA, or EAC rosettes. They are negative for EBNA.

Reactivity with monoclonal antibodies. They were negative for anti-B-cell moabs (B1, B2, B4, BA1, and FMC7), anti-T-cell moabs (pan-T = OKT1, OKT3, Leu1, 3A1, 4H9, and T-101; helper/inducer subset = OKT4 and Leu3a; suppressor/cytotoxic subset = OKT8, OKT5, and Leu2a; thymocytes = OKT6 and Leu6; immature = OKT10; E receptor = OKT11 and Leu5; and natural killer [NK] cells = Leu 7). They react with myelomonocytic cell lineage-associated moabs MCS1, VIMD5, and LeuM1, but not with OKM1 or LeuM3. All of the cells are positive with anti-HLA-DR antibodies (OKI-1 and BA4) and with moabs reacting with the transferrin receptor (B3/25).

Functional properties. The cultured cells do not incorporate latex beads.

Differentiation experiments. Treatment with TPA induces distinct morphologic changes indicative of a partial differentiation along the myeloid cell lineage. Production and expellation of benzidine-positive, unnucleated particles are observed. The induced isoenzyme profiles resemble those found in myeloid (normal and leukemia) cells and in erythroleukemia cell lines.

Supposed origin. They 'are derived from cells of the myeloid or monocyte/macrophage or both lineages; some cells might originate from progenitor cells that might give rise to myeloid–monocyte/macrophage and erythroid cells' [32].

2.5. SU/H-HD-1 [35]

Cytochemical findings. The cultured cells are nonspecific esterase positive and negative for lysozyme and reverse transcriptase activity in culture supernatants.

Immunologic findings. Cells express Fc receptors and HLA-DR antigens, but do not form rosettes with SRBC. They are EBNA negative.

Reactivity with monoclonal antibodies. SU/H-HD-1 cells bind one monocyte/macrophage antibody (LeuM2), but are negative with LeuM1. They are unreactive with antibodies against antigens found on T cells, B cells, or myeloid cells.

Functional properties. Phagocytic activity can be demonstrated with ink and latex particles. The cells are able to present antigen, secrete IL-1, and produce colony-stimulating factor after TPA treatment.

Cytogenetic findings. Chromosome analyses demonstrate variable chromosome content, including a marker chromosome.

Supposed origin. They 'originate from cells of the mononuclear phagocyte/reticulum lineage' [35].

2.6. *KM-H2* [36]

Cytochemical findings. The authors could not demonstrate peroxidase, alkaline phosphatase, or naphthol-AS-D chloroacetate esterase activity in KM-H2 cells. A weak reaction for acid phosphatase and α-naphthyl acetate esterase was observed in most cells.

Reactivity with monoclonal antibodies. They express Ki-1, LeuM1, HLA-DR, receptors for T cells, transferrin, C3b, Fc receptors, and markers found on granulocytes (Tü9, 3C4, and VimD5), but lack markers characterizing B cells (surface or cytoplasmic Ig and B1), T cells (SRBC receptor, Leu1, OKT3, OKT4, OKT6, and OKT8), monocytes (OKM1, MCS2, My4, My7, lysozyme, and α_1-antitrypsin), dendritic reticulum cells (R4/23), IR cells (OKT6 and S100 protein), and NK cells (Leu7, Leu11, and OKM1). The cells are EBNA negative.

Functional properties. KM-H2 cells do not exhibit phagocytosis of C3b-coated zymosan beads or Ig-coated erythrocytes or India ink particles.

Heterotransplantation in nude mice. Subcutaneous inoculation of KM-H2 cells fails to induce tumors.

Cytogenetic findings. The clonal origin of the KM-H2 cell line is ascertained by identifying common marker chromosomes: 5p+, 6p+, and 14p+.

Molecular genetic analysis. The JH segment of BamH1-digested DNA from KM-H2 cells is observed as a single band at 10 Kb, indicating the presence of α heavy-chain rearrangement; the Jk segment digested by BamH1 was detected at 10 Kb, however, and was considered as a germ line of the K-chain gene. Gene rearrangement of the T-cell receptor β chain did not occur in the DNA (digested by EcoR1 and BamH1).

Supposed origin. 'Based on these properties of the KM-H2 cells, Hodgkin's disease may be derived from a cell lineage other than T-cell or B-cell' [36].

2.7. *DEV* [33]

Cytochemical findings. The DEV cells have weak paranuclear acid phosphatase activity, but appear to be negative for alkaline phosphatase, peroxidase, and α-naphthyl acetate esterase.

Immunologic findings. The cultured cells do not form E, EA, or EAC rosettes. EBNA can not be demonstrated.

Reactivity with monoclonal antibodies. Staining for membrane and cytoplasmic Ig shows cytoplasmic staining with anti-α_2 moabs. Staining is negative with anti-K and anti-L light-chain moabs. No reactivity is demonstrated with antilysozyme, anti-α_1 antitrypsin, and antialbumin antibodies. T-cell antibodies, anti-common-ALL antibodies (J5), anti-NK (Leu7), and antimonocyte moabs (OKM1 and OKM2) are negative. Anti-HLA-DR is positive on <1% of the cultured cells. Staining for transferrin receptors (OKT9) is positive. The cells react with the B-cell antibody B1, but not with BA1.

Heterotransplantation in nude mice. DEV cells form tumors after transplantation in C57B110 nu/nu mice.

Cytogenetic findings. The following karyotype is found: 48,XXY, t(3;14)(3;22),t(3;7),del3,−2,+12,+mar.

Supposed origin. 'Hodgkin's disease derived cell line exhibits morphologic, immunologic and chromosomal features consistent with a B-cell origin of these cells' [33].

2.8. *Co* [34]

Cytochemical findings. Co cells are positive for acid phosphatase, weakly for α–naphthyl acetate esterase, and ASD chloroacetate esterase.

Immunologic findings. The cells lack receptors for SRBC, complement, or Fc, but they bind human T cells. Staining for surface or cytoplasmic Ig is negative. No cytoplasmic lyzozyme, α_1-antitrypsin or α_1-antichymotrypsin is demonstrated. Cole cells are EBNA negative.

Reactivity with monoclonal antibodies. All markers of the monocyte lineage were negative on cell membrane and cytoplasm as was the DRC marker R4/23 and the anti-B-cell antibodies TO15 and RF4. A minority of the cells stained with the myeloid/granulocyte markers 3C4 and TG1. Positivity was noted in all cells with the Ki-1 antibody. HLA class II antigens were variably expressed. The cells were positive ith T-cell antibody UCH-T1, but negative with OKT11, OKT4, and OKT8.

Cytogenetic findings. The Co cell line is tetraploid with a chromosome number ranging from 86 to 90. Cells show variations in chromosomes 8, 18, 19, and 20. All of the number 9 chromosomes show abnormalities of the p arm and two of the x chromosomes present also have p arm abnormalities.

Molecular genetic analysis. Heavy- and light-chain genes are not rearranged.

Supposed origin. 'The precise origin of Co cells...cannot be determined.

It is possible that these cells represent a unique cell lineage, though an origin within the lymphocytic series cannot be excluded' [34].

2.9. Other characteristics

Unfortunately not all cell lines were characterized with the same methods, with the same antibodies, or to the same extent, probably because some of them were not in culture for a very long period of time.

There are some corresponding characteristics in all cell lines: they were derived from patients in stage III or IV and are negative for surface Ig, OKT8 antigen, acid phosphatase, and lysozyme.

Six out of seven cell lines are negative for EBNA (591 pos), OKT4 (L540 pos), OKT3 (Co pos), and phagocytosis (SU/H-HD-1 pos), and are positive for HLA-DR (DEV neg) and nonspecific esterase (DEV neg). Most cell lines grow in suspension (SU/H-HD-1 adherent) and were established from nodular-sclerosing subtype (KMH2 mixed cellularity).

There are three cell lines that obviously fit the marker pattern of H and SR cells *in vivo*: L428, HDLM2, and KLM2. The other cell lines more or less are different from the *in vivo* cells (see Table 1):

The *L540* reacts with OKT4, OKT11, and M1.

L591 reacts with OKT4 and OKT11 and is the only cell line that is positive for EBNA. Although there are no data about EBNA H and SR cells *in vivo*, one should keep in mind that sometimes lymphoblastoid cell lines, being in culture for a longer period of time, develop chromosomal aberrations as they were demonstrated in L591 so that the genetic aberrations in this cell line are not proof of a malignant origin.

The *SU/H-HD1* cell line does not react with Ki-1 or LeuM1, which react with almost all H and SR cells *in vivo*, and it is reactive with M1. It is the only cell line growing adherent.

DEV is negative for nonspecific esterase, for α-naphthyl acetate esterase, and only 1% of the cells react with anti-HLA-DR antibodies (normally 100% of H and SR cells stain strongly). Unfortunately there are no data about Ki-1 and LeuM1 reactivity in the literature.

Co differs in NASD–chloroacetate esterase reaction and in reactivity with OKT3.

The functional studies performed with some of the cell lines did not add evidence for derivation from a defined lineage, since antigen presentation or the proteins generated are not restricted to a certain cell type. Molecular genetic analyses helped to classify cell lines that could not be sorted into a certain lineage by conventional methods, but L428, L540, L591, and Co were classified as lymphocytic and KLM2 as nonlymphocytic. The cytogenetic studies did not define a Hodgkin-specific marker chromosome that could help to identify H and SR cells.

The results concerning the origin of the different Hodgkin-derived cell lines are inconsistent. The authors proved their Hodgkin's cell lines to be derived from a defined cell lineage, but obviously H and SR cells of different origins have been established: B cells (L428, L591, and DEV), T cells (L540 and Co), other than T cells or B cells (KM-H2), myeloid/macrophage lineage (HDLM-2), and phagocyte/reticulum cell lineage (SU/H-HD-1).

3. Discussion

A cell line must fulfill several conditions to be accepted as Hodgkin derived:

1. The diagnosis of Hodgkin's disease must be confirmed by at least two independent pathologists; the anatomic sites of involvement, the clinical presentation, and course must leave no doubt about the pathological diagnosis.
2. The markers of the cultured cells should resemble the markers of H and SR cells in *vivo*.

An important question is whether all described cell lines are derived from H and SR cells. Indeed, the derivation from H and SR cells of two of the described cell lines has been questioned [36, 38]. The SU/RH-HD-1 cell line does not react with the monoclonal antibodies Ki-1 and LeuM1, which reportedly stain H and SR cells in almost all cases of Hodgkin's disease. On the other hand, H and SR cells are not stained in any case. Moreover, malignant cells may express antigens that are not normally present on the nonneoplastic counterpart [35].

The DEV cell line was derived from a patient who had a popliteal lymph node for more than 10 years, an extremely uncommon site of involvement of Hodgkin's disease and extraordinary clinical course [38]. Besides, staining of the original H and SR cells with B1 and anti-α_2-chain antibody seemed to represent an atypical, immunologic phenotype [36].

The authors proved their cell lines to be derived from a certain cell lineage, but they did not prove the derivation from H and SR cells: the cell lines resemble more or less H and SR cells *in vivo*. Supposing that any of the described cell lines are derived from malignant H and SR cells, one must assume that the origin of H and SR cells is heterogeneous, or that H and SR cells *in vivo* represent undifferentiated cells at least in the beginning of the disease and are capable of differentiating in several directions. The same conclusion would be true even if both questioned cell lines are excluded.

To prove an undifferentiated cell as nonmalignant counterpart as postulated [3, 31], L428 and HDLM2 have undergone differentiation experiments and both cell lines express markers of the myeloid/monocyte or erythrocyte lineage after induction with TPA.

The concept of lineage heterogeneity of H and SR cells based on enzymohistologic, morphologic, or cell culture observations has been proposed by several authors who distinguished H and SR cells of lymphoid and reticulum

cell or histiocytic origin [36, 47, 48]. The data obtained from cell lines add evidence supporting this hypothesis.

The establishment of more Hodgkin-derived cell lines is desired, especially from different histologic subtypes of Hodgkin's disease. The methods for characterization should be standardized to make a comparison easier. Especially the DNA probes recognizing the Ig and T-cell receptor gene rearrangements should be applied to detect early stages of lymphoid differentiation. However, one should keep in mind that, in some T-cell lymphomas and in some cases of acute myeloid leukemia (AML), heavy-chain Ig rearrangements have been found and, in some B-cell lymphomas and in AML, T-cell receptor β-chain gene rearrangements have been demonstrated. A functional rearrangement with demonstration of m-RNA or protein is the only proof for derivation from T or B cells.

A characterization and isolation of H and SR cells from biopsies is needed to rule out culture artifacts.

Taken together, the discussion is still open, as it was before monoclonal antibodies and molecular genetic techniques had been developed. The establishment of Hodgkin-derived cell lines opens the possibility of performing reproducible and more extensive studies (*e.g.*, molecular genetic analysis), producing new monoclonal antibodies, and learning something about the functional properties of these cells.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Stiftung Deutsche Krebshilfe.

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4. The Sternberg-Reed cell
A Cell-fusion Product?

Peter P. Bucsky

Hodgkin's disease (HD), with its peculiar Sternberg-Reed (SR) cell, is in particular very contradictory. The controversies are most prominent regarding the SR cell origin. Among the cells composing the structure of a normal lymph node, there is almost no cell that has not been suspected as being the normal counterpart of the SR cell. In this chapter, the most relevant opinions are summarized in an attempt to resolve some conflicting evidence regarding the SR cell origin, and thus also explain some other pecularities of the disease.

1. B-lymphocyte origin

Evidence for a B-lymphocyte origin is based first of all upon the finding of intracytoplasmic immunoglobulin (Ig) in the SR cell, indicating that certain types of SR cells are B immunoblasts [1, 2]. Human B-lymphocyte antigens (HBLA) have also been detected on SR cells [3] and have been found positive by monoclonal antibodies specific for B cells [4–6]. Thus, SR cells have antigens in common with B-lymphocytes [6].

Circulating Hodgkin's cells were shown to be of B-cell origin by immunologic phenotyping and the demonstration of clonal Ig gene rearrangement [7]. On the basis of the characteristic cytoplasmic staining of HD cells with peanut lectin, HD cells may be closely related to the B-lymphoid lineage [8]. Histochemically, SR cells show a gamma-glutamyl transpeptidase (γGT) activity pattern like multiple myeloma cells. γGT is an enzyme related to the transport of amino acids into cells, and an intake of amino acids in these cells followed by synthesis of protein is assumed [9]. Ultrastructurally, Ig was found on the ribosomes in all types of SR cells. The ribosomal Ig synthesis is a major argument for the B-lymphocyte nature of SR cells [10, 11].

2. Macrophage/histiocyte and reticulum cell origin

Since one individual lymphocyte is thought to be able to synthesize only one type of light chain due to allelic exclusion, the strongest evidence against the

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B-lymphocyte origin is that both kappa and lambda light chains have been found in some of SR cells [12, 13]. SR and Hodgkin's cells were found to be positive for α_1-antitrypsin and lysozyme by immunoelectron optic investigations [14]. *In vitro* studies confirmed the internalization of exogenous IgG and phagocytosis of immunocomplexes, heat-killed *Candida*, and India-ink- and antibody-coated sheep erythrocytes by viable SR cells. The uptake of IgG seems to be an active process and supports an origin from cells of the monocyte/macrophage lineage [15–17]. Lectin binding studies and the abundant cytoplasmic fibronectin also suggest the macrophage origin of the neoplastic cells in HD [18, 19]. Ultrastructurally, tumor samples from HD patients yielded a population of atypical cells with the anatomic and functional attributes of macrophages supporting the concept of the derivation of SR cells from monocyte/macrophage [20, 21].

In comparative immunologic and cytochemical analyses, SR cells resemble interdigitating reticulum cells [22–24]. The dendritic reticulum cell of lymphoreticular tissue has also been proposed as the origin of Hodgkin's and SR cells on the basis of staining with metallic salts [25]. Cells of HD-derived cell cultures share many properties of dendritic cells [26, 27], and can function as antigen-presenting cells. Thus, HD may be classified as a tumor of antigen-presenting cells [28].

3. T-cell origin

Previously, reports suggested that, in HD, T-lymphocytes infected by a virus are modified and attacked by normal T cells or by reactive B cells. Membrane fluorescence with anti-IgG could not be detected on the SR cells, which supports the idea that these cells are of T-cell origin [29, 30]. On the basis of the first site of infiltration in a lymph node, a T-cell origin of HD has been favored [31]. In lymphomatoid papulosis, there is a spectrum of activated helper T cells, including cerebriform cells and large SR-like cells. It has been assumed that, as clonal expansion of cerebriform cells leads to mycosis fungoides, so expansion of SR-like cells results in HD. The SR cells have been proposed to be lymphoblasts arising from activated helper cells [32].

4. Granulopoietic origin

The concept that SR cells have their normal counterpart in the myeloid lineage is not a new one. A report from 1941 concluded from motion-picture studies that 'Dorothy Reed cells' were myeloid rather than lymphoid or monocytic in origin [33]. Recently, the profiles of Hodgkin's and SR cells

were studied in a large number of cases using monoclonal antibodies found to react with more mature granulocytic cells. Hodgkin's and SR cells consistently expressed antigens associated with the granulocytic cell lineage. The presence of granulocytic antigens suggests that Hodgkin's and SR cells may be more closely related to cells of granulocytic cell lineage than to any other type of the hematolymphoid system and are not heterogeneous but rather homogeneous in origin [34].

5. Ki-1 cell

A monoclonal antibody, the Ki-1, has been described reacting specifically with Hodgkin's and SR cells, but not with any other cells in biopsy material. A small subset of cells in normal lymphoid tissue and bone marrow has also been found to bind this antibody, but to lack markers for B cells, T cells, and monocytes. This newly characterized cell type, the Ki-1 cell, has been suggested to be the normal counterpart of Hodgkin's and SR cells [35, 36].

As can be seen, the findings and concepts concerning the origin of the SR cell are really rather controversial. One of the possible causes of the inconsistent results may be the variation of methods applied and their lack of standardization. Another reason is the fact that some of the investigations mentioned before were made on HD tissue suspensions or on HD-derived cell cultures. There is no solid evidence, however, identifying the cells investigated with the SR cells. Also, the deduction of the biologic features of the nonneoplastic counterpart of a malignant cell population by characterization with monoclonal antibodies has some pitfalls [37]. Monoclonal antibodies recognize only a single epitope with high specificity, but with low affinity, and most monoclonal antibodies have a large extent of cross reactivity [38]. Another pitfall is that malignant cells may express antigens not present on their normal counterpart [37] or they can lose one or more antigens as, *e.g.*, in the case of peripheral T-cell lymphomas [39]. Third, hemopoietic lineage promiscuity in tumor cells can also occur [40]. Now it is also well known that the Ki-1 antibody is not specific for Hodgkin's and/or SR cells. Activated B and T cells are also Ki-1 positive, and cells from several permanent cell lines of different hemopoietic origin, *e.g.*, K-562, MOLT-4, and HL-60, react with the Ki-1 antibody. The Ki-1 antibody is not lineage restricted and seems to be a gene product expressed on some activated cells or upon permanent *in vitro* culture of malignant cell lines [5, 41, 42].

However, most of the theories favor either a B-lymphocyte or a monocyte/macrophage origin. Further, none of the theories mentioned can explain the rarity, the 'loneliness,' and the almost complete lack of mitotic figures of SR cells. The relative low malignancy of the disease among the lymphomas is also awaiting an explanation.

6. A fusion product?

A fusion between lymphocytes and 'reticulum cells' [43], between B and T cells [44], and between Hodgkin's cells [45] has been proposed, so far.

In an attempt to resolve the contradiction between the two most favored hypotheses, *i.e.*, origin either from B-lymphocytes or from monocyte/macrophages, it may be assumed that, in a genetically predisposed person, SR cells originate from a fusion between B-lymphocyte(s) and monocyte/macrophage(s) induced by a (pathogen?) virus [46]. There is some evidence that seems to support this fusion theory:

a) Such a fusion, a 'heterokaryosis' induced by a virus, is a rare phenomenon. Indeed, in the typical HD tissue, SR cells are rare, alone, not in colony.

b) Human lymphomas, including HD, were found to contain viral-related RNA [47].

c) Mitotic forms of SR cells can scarcely be found. Indeed, 'heterokaryotic' cells in general are end-stage cells unable to multiply. A comprehensive study also stated that SR cells showed no evidence of DNA synthesis [48]. Only some SR cells showed weak labeling of tritiated thymidine. In this report, the fusion between Hodgkin's cells has been raised as one of the possibilities for the origin of SR cells [45]. In a contradictory report, SR cells showed evidence of DNA synthesis and nuclear division, but the cells investigated by autoradiography were not phenotypically characterized [49]. According to the morphology of the cell culture, the cells were most likely spontaneously immortalized lymphoblastoid cells possessing Epstein-Barr virus (EBV) genomes. Thus, the multinucleated cells could represent B-lymphoblasts.

d) The monoclonal pattern of staining favors *in situ* production of Ig in the SR cells; the double-staining pattern supports either phagocytosis by or passive transport of Ig into the SR cell. This conflicting evidence may have two possible resolutions: first, bizarre neoplastic lymphocytes and certain plasma cells with secretory abnormalities may synthesize components of both light chains, and certain B-cell neoplasms may not conform to the general thesis of restricted Ig synthesis [50, 51]. On the other hand, if fusion between B cells and monocyte/macrophages occurs, the different nuclei can originate from different individual B cells. Thus, they may represent two different patterns of DNA template activity. This may satisfactorily explain biclonality.

e) The effect of cell fusion on the malignant phenotype has been studied intensively by somatic cell hybridization. The results showed a partial or total loss of tumorigenicity [52]. One explanation of this phenomenon could be that expression of c-onc genes is controlled by negative regulatory genes called antioncogenes. Since <7% of cell DNA is transcribed, a negative control mechanism together with gene-specific positive controls would be likely. There is some evidence for specific negative regulation of eukaryotic

genes [53]. Supposing somatic cell hybridization events between neoplastic Hodgkin's cells as B-immunoblast-like cells and monocyte/macrophages, new neoplastic multinucleated cells (*i.e.*, the SR cells) are originated. Since in HD tissue suspension activated N-ras could be demonstrated [54], the mechanism mentioned before might also be responsible for the relative low malignancy of HD.

f) To investigate this fusion hypothesis, in a preliminary study mononuclear blood cells of normal donors obtained by Ficoll-Paque centrifugation were cultured in RPMI-1640 medium supplemented with 10% heat-inactivated fetal calf serum, 2 m*M* glutamine, streptomycin (100 μg/ml), and penicillin (100 μ/ml) at 37°C in air containing 5% CO_2. To induce fusion, the cells were infected at the beginning of cultures with EBV [55] that had been harvested from supernatants of B95–8 marmoset cell cultures at growth saturation [56]. The connection between HD and EBV has also been proposed [57–60]. At present, EBV is the only T-cell-independent B-cell stimulator. This close restriction is determined at the receptor level. The receptor of B cells for EBV is related [61], and perhaps identical [62], to the C3d receptor, which is specific for B-lymphocytes. Several days after infection, the typical cell aggregates appeared. After 3 months of culture, some cells were removed and mounted on bio-Merieux slides. Cell surface markers were determined with monoclonal antibodies specific for T cells (Leu4 + Leu 9), B cells (RFB4 and RFB6), granulocytes/monocytes (VIM-2), macrophages (KI-M6), and granulopoiesis/monocytes (OKM-1, VIM-D5, and S-HCL-3). The alkaline phosphatase–anti–alkaline–phosphatase method was used [63]. Cell suspensions were also analyzed biochemically for esterase isoenzymes as described [64]. Briefly, enzymes were extracted and analyzed by analytical isoelectric focusing on thin-layer polyacrylamide gels and subsequent staining using α-naphthyl-acetate as a substrate and Fast Blue RR as a coupling salt.

For cytochemical analysis, the naphthol-AS-acetate esterase reaction was tested [65].

The EBV-associated nuclear antigen (EBNA) was detected according to the method described by Reedman and Klein [66] using controls for both positive and negative reactions.

By light microscopy, among the lymphoblastoid cells, large, multinucleated cells were observed, some of which resembled SR cells with their large nuclei having a reticular chromatin pattern as well as prominent nucleoli.

The results of reactions performed with this panel of monoclonal antibodies were as follows: with pan-B, almost 100% of cells stained positively; with pan-T, the number of positive cells was <1%; and with the monoclonal antibodies VIM-2 and KI-M6, some large multinucleated cells stained positively, whereas VIM-D5, OKM-1, and S-HCL-3 were all negative.

Nearly all of the mononucleated and multinucleated cells were EBNA positive. Also, all of the nuclei in the multinucleated cells showed positive reaction for EBNA.

Cytochemically, some multinucleated cells reacted positively with the naphthol-AS-acetate esterase.

The biochemical characterization of cells in suspension provided evidence also for the presence of monocyte-specific isoenzymes. According to these results, the cell cultures represented B-lymphocyte populations, but some large multinucleated cells had markers also for monocytes/macrophages. These cells were EBNA positive (B-cell marker) and showed positive reactions for nonspecific esterase and/or with monoclonal antibodies specific for macrophages (VIM-2 and KI-M6). On the basis of these preliminary results, it may be supposed that an *in vitro* fusion between stimulated B-lymphocytes and monocytes can occur [67].

However, taking into consideration such a fusion for these 'biphenotypic' cells, one can assume that at least one of the nuclei of a fusioned cell (originating form a monocyte) should be negative for EBNA, but all of the nuclei of the multinucleated cells investigated were EBNA positive. On the other hand, it can be supposed that the nuclei originating from monocytes become EBNA positive following fusion with B cells that have receptors for EBV. This presumably is also the case in nasopharyngeal carcinoma. These neoplastic epithelial cells are also positive for EBNA, although they do not have EBV receptors. It is assumed that these cells obtain their EBNA positivity by *in vivo* fusion with EBNA-positive B-lymphocytes in the pharynx [68].

In summary, taking all of these data and concepts together, the origin of SR cells is still obscure despite intensive investigations. Cell culture studies have provided a lot of new information, but the mystery of SR cell has as yet remained unsolved. Assuming, however, an *in vivo* fusion between B cell(s) and monocyte/macrophage(s) induced by a virus as a possible origin of the SR cell, a number of peculiarities of this cell type and Hodgkin's disease can be explained.

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5. The immune derangement and strategies for immunotherapy

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The existence of an immune deficiency in patients with Hodgkin's disease (HD) has been widely proven by both clinical and laboratory findings. Although immune alterations can be demonstrated during the advanced stages of different tumors, including non-HD lymphomas, during the advanced stages, there is general agreement that the immune derangement in HD shows a peculiar pattern because of its complexity as well as its appearance at the earlier phases of the disease.

1. Clinical relevance of the immune alterations

The clinical relevance of immune alterations in HD has been recognized for many years:

- Patients with HD show increased susceptibility to bacterial, disseminated fungal, and viral infections.
- A less favorable prognosis has been demonstrated in older HD patients, who usually have more marked immune alterations.
- There is evidence of increased risk of second malignancies in long-term survivors of treated HD.

Before the introduction of modern radiotherapy and chemotherapy, untreated patients with HD usually died because of infectious diseases sustained by opportunistic agents [1, 2]. When tuberculosis was very frequent, it was often associated with HD. In addition, some rare infections, such as cryptococcosis, were found to affect HD patients with a prevalence (up to 10%) and a severity unknown in the general population. The prevalence of other fungal (*Aspergillus, Nocardia, Candida, Actinomyces,* and *Histoplasma*), protozoan (*Toxoplasma* and *Pneumocystis carinii*), viral (herpes zoster–varicella and cytomegalovirus), and bacterial (*Staphylococcus, Pseudomonas*, and *Escherichia coli*) infections was also markedly increased in HD [1, 2]. Different species of *Brucella* were often isolated from lymph nodes of rural people with HD. As already stated, these findings reflected a natural evolution of HD that has rarely been observed after the introduction of the modern therapeutic regimens. Nevertheless, the more recent data indicate

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that infections account for over half of all deaths of patients with HD [3].

Another finding suggesting the importance of immune alterations in influencing the clinical course of HD is derived from studies performed on aged patients. A less favorable prognosis has been demonstrated in older patients with HD, who usually have more severe immune alterations than do younger HD patients [4, 5].

Finally additional evidence suggesting the clinical relevance of immune alterations in HD patients is provided by findings showing an increased incidence of secondary malignancies, such as acute leukemias, in long-term survivors treated for HD [6–8]. It is very difficult, however, to establish whether these malignancies are secondary to disease-related immune deficiencies or, more likely, reflect treatment-induced immune depression. Several investigators believe that, since modern radiotherapy and multidrug chemotherapy have achieved a dramatic improvement in the prognosis of this once inexorably fatal disease, iatrogenic immune deficiency now represents more of a risk for patients than does disease-related immune deficiency.

2. Spectrum of the immune alterations

In the first half of century, when tuberculosis was very common, unresponsiveness to tuberculin was the first immunologic abnormality observed in patients with HD. As early as 1902, Dorothy Reed reported that 'tuberculin was given in five cases but without reaction' [9]. Later *in vivo* and *in vitro* studies clearly demonstrated that immune deficiency in patients with HD is not merely represented by reduction in reactivity against *Mycobacterium tuberculosis* antigens, but consists of a complex spectrum of alterations.

The main immunologic changes detected in patients with HD are summarized in Table 1. Only data obtained in patients who did not undergo any type of treatment at the time of testing have been considered, because many earlier studies on immune deficiency in HD are open to criticism on the grounds that some of the patients were undergoing treatment, which is itself immunosuppressive, thus making it impossible to discriminate immune alterations that are surely disease related from those that might be induced by diagnostic splenectomy, irradiation, or chemotherapy. For simplicity, T-cell alterations have been distinguished from B-cell alterations, even though such a dichotomy may be inappropriate because of the numerous interactions occurring between the two main lymphocyte subpopulations during the immune response.

2.1. T-cell alterations

The impairment of the delayed cutaneous hypersensitivity (DCH) response to either recall antigens or neoantigens, such as dinitrochlorobenzene

Table 1. Spectrum of the immune alterations in untreated patients with HD.[a]

T-cell responses	B-cell responses
Delayed cutaneous hypersensitivity (DCH) to Recall antigens Neoantigens (DNCB) ↓ Enumeration of peripheral blood T cells T-lymphocytes T helper/inducer ↓ *In vitro* lymphoproliferative response To mitogens (PHA, Con A, PWM) ↓ To recall antigens In autologous MLR ↓ Spontaneous ↑ Lymphokine production Induced by mitogens or antigens ↓ Spontaneous ↑	Primary antibody responses *in vivo* ↓ Serum levels of IgG, IgA, IgD, and IgE ↑ Serum titers of antiviral antibodies ↑ Circulating immune complexes ↑ Antilymphocyte antibodies ↑ *In vitro* immunoglobulin production Induced by antigens or mitogens ↓ Spontaneous ↑

[a]Decreased (↓) and Increased (↑).

(DNCB), has clearly been demonstrated by a number of studies [10, 11]. The impairment is not an all-or-none phenomenon, but a more subtle continuous gradient of an immunologic defect that is present to some degree even in the initial stages of the disease [11]. Passive transfer of DCH as well as the capacity to reject skin homografts are also impaired in patients with HD [12, 13].

A panlymphocytopenia occurs in ~30% of untreated patients and is usually associated with advanced disease [4]. The results concerning quantitation of T-lymphocytes by E rosetting in the peripheral blood (PB) of HD patients are confusing, some groups reporting reduced [14–16] and other groups reporting normal [17–20] values of E-rosette-forming cells. More clear-cut results were obtained by the use of monoclonal antibodies directed against cluster differentiation (CD) antigens. Mononuclear cells (MNC) in the PB from a group of 33 newly diagnosed, untreated patients with HD showed increased percentages of monocytic cells, as evaluated by three different antimonocyte reagents, and reduced percentages of T-lymphocytes, as revealed by the anti-CD3 (pan-T) reagent. The mean absolute number of T cells was also reduced, whereas the absolute number of cells recognized by antimonocyte reagents was the same as in healthy controls, suggesting that enhanced percentages of monocytes were relative to the depletion of circulating T cells [21]. Reduction of circulating T-lymphocytes mainly reflected the selective loss of cells showing the helper/inducer ($CD4^+$) phenotype, since a lower number of these cells was demonstrated in patients with both advanced and initial disease, whereas decreased values of T cells with the cytotoxic–suppressor ($CD8^+$) phenotype were found only in patients with advanced disease showing panlymphocytopenia (Figure 1) [21]. These data are consistent with our previous findings showing increased percentages of T cells equipped with Fc receptors for IgG (T_G)

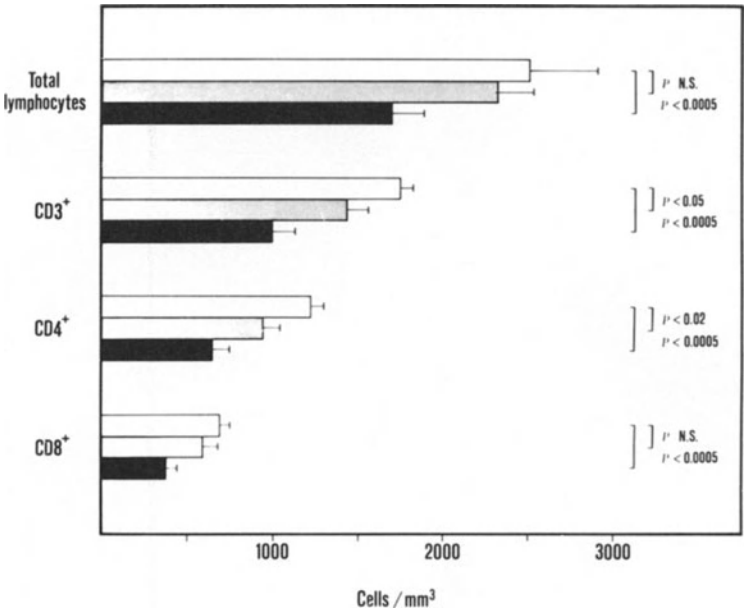


Figure 1. Absolute values of total, $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes in the PB from 16 normal subjects (□), 17 untreated HD patients with stage I–II disease (□), and 16 untreated HD patients with stage III–IV (■) disease. The results represent the mean values ±SE.

and reduced percentages of T cells with Fc receptors for IgM (T_M) in the PB of many untreated patients with HD [22, 23]. It has been shown that virtually all circulating T_M belong to the helper–inducer subset and show the $CD4^+$ phenotype. Unlike PB, lymph nodes and spleens involved by HD usually showed increased percentages of T-lymphocytes, especially of those possessing the $CD4^+$ phenotype, thus suggesting displacement of these cells from PB to lymphoid organs in HD patients [21, 24].

Studies *in vitro* of the proliferative responses of PB lymphocytes from patients with HD have revealed a depressed response to phytohemagglutinin (PHA) as well as to other T-cell mitogens, such as concanavalin A (Con A) and pokeweed mitogen (PWM) [16, 25, 26]. Technical refinements of the PHA-response assay, such as evaluation of response kinetics or analysis of dose–response curves, enabled the demonstration of unequivocal abnormalities in the great majority of untreated patients, including those with initial disease (Figure 2) [26–28]. The proliferative response *in vitro* of PB lymphocytes to recall antigens has also been found to be markedly depressed [4, 20, 29]. The study of the ability of PB lymphocytes from untreated patients with HD to respond in allogeneic mixed-lymphocyte reaction (MLR) has yielded conflicting results, but the preponderance of evidence suggests that the MLR to allogeneic cells is usually normal or only moderately impaired [20, 30, 31]. However, the capacity of T-lymphocytes to respond in auto-

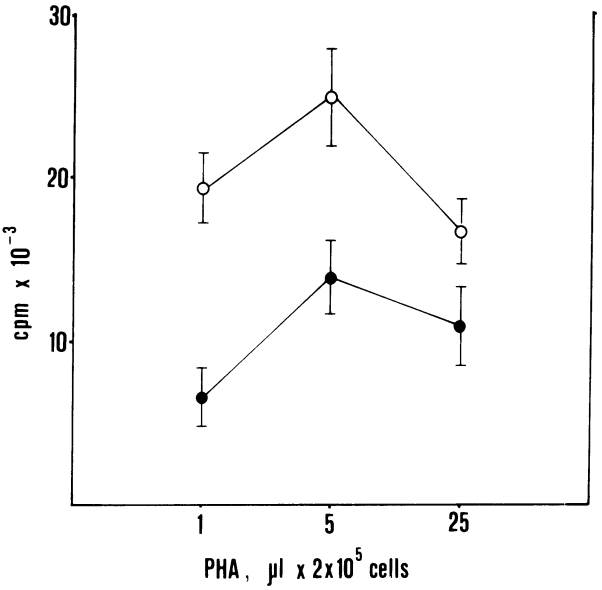


Figure 2. Dose–response curve to PHA of PB lymphocytes from 84 untreated patients with HD (•) and from 38 normal sex- and age-matched normal individuals (○). PB cells were cultured for 72 h with three different concentrations of PHA and ^{3}H-thymidine and uptake was measured. The results represent the mean cpm values ±SE.

logous or syngeneic MLR was found to be profoundly depressed [32]. In contrast to mitogen- or antigen-stimulated lymphoproliferative responses, which are usually impaired, there is evidence of spontaneous DNA synthesis by PB lymphocytes from a proportion of untreated patients with HD, which is independent of the presence of circulating neoplastic cells. Indeed, earlier studies with the use of labeling *in vitro* showed at least three populations of spontaneously proliferating cells, one characterized as Hodgkin's cells, which commonly showed evidence of aneuploidy, and another two consisting of large basophilic transformed lymphocytes and smaller lymphocytic cells [33–35]. The appearance in the circulation of spontaneously DNA-synthesizing cells correlated with the impairment of PHA-induced proliferation [28], the presence of B symptoms [4, 28], and a poor prognosis [36]. It appears that most PB lymphocytes responsible for the spontaneous DNA synthesis *in vitro* have a low density [37] and show the T-cell phenotype [4, 38], but spontaneously proliferating non-T cells with higher density have also been demonstrated [39]. The spontaneous DNA synthesis by PB lymphocytes from HD patients normalizes after treatment and remains low during long-term remission [4].

A number of studies have shown that lymphokine production following antigen or mitogen stimulation is frequently decreased or impaired in HD, Thus, either antigen- or mitogen-induced production of migration inhibitory factor (MIF), leukocyte inhibitory factor (LIF), lymphotoxin (LT), gamma-

Table 2. Serum IgE levels in patients with HD and non-HD lymphomas.[a]

Subject group	No. of cases	Serum IgE (IU/ml)	No. of cases with high serum IgE levels (>300 IU/ml)
Normal donors	85	115± 41	8 (9%)
Hodgkin's disease			
Untreated	119	1068±358	38 (31%)
Treated	112	224± 46	20 (17%)
Non-Hodgkin's lymphomas	25	121± 25	3 (11%)

[a]See also Romagnani *et al.* [56].

interferon (IFN-γ), and interleukin 2 (IL-2) [40–44]. In contrast, PB lymphocytes from patients with HD spontaneously released measurable amounts of LIF- and LT-like substance [41, 43] and high levels of MIF- and LIF-like activity have been detected in the serum of the great majority of patients with HD [45, 46].

2.2. B-cell alterations

Whereas cell-mediated immune responses are frequently impaired, most HD patients apparently appear to be capable of normal humoral responses [47]. The production of antibodies against antigens to which they had never previously been exposed has yielded conflicting results, some studies reporting that primary antibody production is reduced [48] and others reporting that it is unaffected [10, 49] in HD patients. On the other hand, secondary antibody responses are usually normal and evidence has been accumulating to suggest that immunoglobulin (Ig) production *in vivo* can even be enhanced in a proportion of patients. Increased levels of serum IgG, IgA, and IgD have been observed in consistent groups of untreated patients [50–53]. Antibodies to Epstein-Barr virus (EBV) and cytomegalovirus were shown to be significantly elevated in HD sera, as opposed to sera of age- and sex-matched healthy controls [54, 55]. Several laboratories, including our own, have found increased values of IgE in about one-third of untreated patients with HD (Table 2) [20, 56, 57].

High levels of circulating immune complexes (CIC) have been demonstrated in a proportion of patients ranging between 22% and 88% according to the different techniques employed [19, 58, 59]. Abnormalities of complement and its components have also been reported [60]. Antilymphocyte antibodies have been observed in the serum of a number of patients with active disease [61–63]. Antibodies directed against nonpolymorphic determinants of class II major histocompatibility complex (MHC) were detected by us in the serum of three of eight untreated patients with active HD [64]. In agreement with this finding, determinants of class II MHC antigens have recently been identified in CIC from HD patients (G. Valesini, personal communication).

Table 3. PWM- and SAC-induced IgG and IgM synthesis *in vitro* by mononuclear cells from untreated patients with HD.[a]

Subject group	No. of cases	PWM		SAC	
		IgM ($ng/10^6$ cells)	IgG	IgM ($ng/10^6$ cells)	IgG
Normal controls	47	3950±525[b]	4592±587	5265±696	3485±392
Hodgkin's disease	57	1409±265	3122±592	2459±604	2076±427
Student's *t*-test	(*p*)	<0.0005	<0.01	<0.005	<0.005

[a]See also Romagnani *et al.* [67].
[b]Mean value ±SE.

Most investigators agree that the number of B-lymphocytes, defined either as cells carrying surface Ig (sIg) or cells equipped with complement receptors (CR), is usually normal in the PB of HD patients and even increased in lymph nodes involved by HD showing the lymphocyte-predominant (LP) histologic type [4, 17, 18, 20, 21].

The ability of PB and lymphoid tissue lymphocytes from patients with HD to produce Ig *in vitro* has also been investigated. Spontaneous total IgG synthesis occurred when lymphocytes from uninvolved and lightly involved spleens were cultured, suggesting a response *in vitro* to an antigenic challenge *in vivo* [65]. The IgG produced *in vitro* by splenic lymphocytes showed cytotoxic activity on normal human T cells, mediated by an antibody-dependent cell cytotoxicity (ADCC)-like mechanism [66]. In our laboratory, the ability of PB lymphocytes from 57 untreated patients with HD to produce IgG and IgM in 7-day cultures stimulated with polyclonal B-cell activators, such as PWM and *Staphylococcus* bacteria of the Cowan I strain (SAC), was investigated [67]. The PB lymphocytes from untreated patients with HD synthesized and secreted significantly lower concentrations of IgG and IgM after stimulation with both PWM and SAC in comparison with age- and sex-matched control subjects (Table 3). Depression of PWM-induced Ig synthesis did not correlate with the excessive number of monocytes, and it was unaffected by removal of phagocytic cells or the culturing of the patients' B and T cells with monocytes from normal individuals. On the other hand, monocytes isolated from the PB of HD patients were even more effective than normal monocytes in supporting PWM-induced Ig synthesis by normal cells [67]. Synthesis of Ig induced by PWM remained subnormal after autologous irradiated T cells or allogeneic normal lymphocytes were added to patients' B-cell cultures. T cells from patients with HD appeared at least as effective as normal T cells in helping PWM-induced Ig production by normal B cells [67]. Significantly, the mean level of the spontaneous IgG synthesis was higher in cultures from HD patients than in cultures from controls, whereas the spontaneous IgM synthesis was reduced. When normal T cells were cocultured with B cells from HD patients, the spontaneous IgG synthesis declined, whereas the addition of a patients' T cells to normal

B cells resulted in an increase of the spontaneous IgG synthesis [67]. Impairment of PB lymphocytes from patients with HD to produce specific antibodies after stimulation *in vitro* with herpes zoster–varicella (HZ/V) and influenza virus has also been reported. It is noteworthy that B cells obtained from spleen of the same patients produced antibody readily, suggesting altered B-cell circulation with localization of antibody-producing B cells in the spleen and lymph nodes [68].

Taken together, these findings indicate abnormalities of Ig synthesis by cultured lymphocytes from HD patients after stimulation with polyclonal B-cell activators or antigens, and suggest that the alterations *in vitro* may be, at least in part, the result of a preexisting activation *in vivo* of both B- and T-lymphocytes.

2.3. Alterations of monocytes

The number of monocytes is usually normal in the whole blood of untreated patients with HD, but increased percentages of these cells have been found in MNC suspensions obtained after centrifugation on Ficoll-Hypaque density gradients [69]. To explain this, the possibility that higher monocyte recovery after isopyknic separation is the result of reduced adherence of these cells to foreign surfaces has been suggested [69]. As reported above, however, enhanced percentages of monocytes in PB MNC suspensions from some patients with HD more likely reflect depletion of circulating T-lymphocytes [21].

Altered function of monocytic cells from HD patients has also been reported. Monocytes showed reduced chemotactic response [70], as well as a decrease in phagocytic and candidicidal activity [71]. In addition, enhanced prostaglandin-mediated suppressor activity by monocytes from HD patients has been described and thought to be responsible for the depression of lymphoproliferative responses [72, 73] and reduction in T-colony formation [74]. However, the latter findings have not been fully confirmed by subsequent studies [75, 76]. Conflicting results have also emerged from the study of the monocyte-mediated ADCC, since both increase [77] and impairment [78] of such function have been reported.

3. Immune alterations in childhood Hodgkin's disease

Although immune function in adults with HD has been extensively studied, relatively little is known about the immunologic status of children with this disorder. Only fragmentary reports are available concerning the risk of infections and second malignancies in pediatric patients with HD [79–81]. In addition, these reports do not allow one to distinguish between the risk due to the primary disease process, splenectomy, or immunosuppression result-

ing from active cytotoxic therapy in HD patients. However, similarities with the observations of prior studies in adults suggest that the most important of these factors may be the treatment administered for the primary disease.

Immunologic studies in children with HD are also very rare. As in adults, serum IgG and IgA concentrations were significantly higher among children with HD when compared with age- and sex-matched controls, whereas serum IgM levels did not differ significantly from control values. In contrast, serum IgD levels, which were found to be elevated in adults with HD, were apparently normal in children with this disorder [82]. In a recent study, reduction of PB $CD2^+$ and $CD3^+$ cells (T-lymphocytes), as well as of the $CD4^+$ T-cell subset, has been described. In addition, enhanced proportions of both $CD3^+$ and $CD4^+$ cells were found in involved lymph nodes of children with HD (P. Paolucci, personal communication).

Thus, although fragmentary, reports available at this time suggest that immune abnormalities in childhood HD do not differ significantly from those found in adults suffering from the same disease.

4. Effect of treatment on the immune alterations

It was once presumed that the immune alterations in HD were only secondary to the disease or disease-associated factors, and that the patient would recover immunologically after therapy [83, 84]. More recent reports have clearly shown that, following treatment, at least some of the immune defects become more pronounced [23, 31, 85].

Although the increased risk of overwhelming sepsis in splenectomized patients has been recognized for many years [87, 88], the effect of splenectomy on the immune function of HD patients is not well known at this moment. No significant short-term changes in lymphocyte number, skin reactivity, and lymphoproliferative responses have been found in splenectomized patients tested before radiotherapy or chemotherapy [26, 53, 89]. However, the long-term influence of this diagnostic procedure on immunity cannot be easily evaluated because of the interference of immunosuppressive treatments, such as irradiation and chemotherapy. It has been suggested that depression of humoral immunity induced by irradiation or chemotherapy is greater in patients who have undergone splenectomy [90], but most investigators agree that impairment of humoral immunity in treated HD patients is related to aggressive treatment with both drugs and radiation rather than to splenectomy [49, 91, 92]. On the contrary, splenectomy seems to protect the patient from the therapy-induced lymphocytopenia [93].

In the last few years, it has clearly been shown that both irradiation and chemotherapy induce sustained alterations in both the number and function of circulating lymphocytes [26, 31, 86]. At the completion of a course of radiotherapy, the response *in vivo* to DNCB was lost in almost all patients

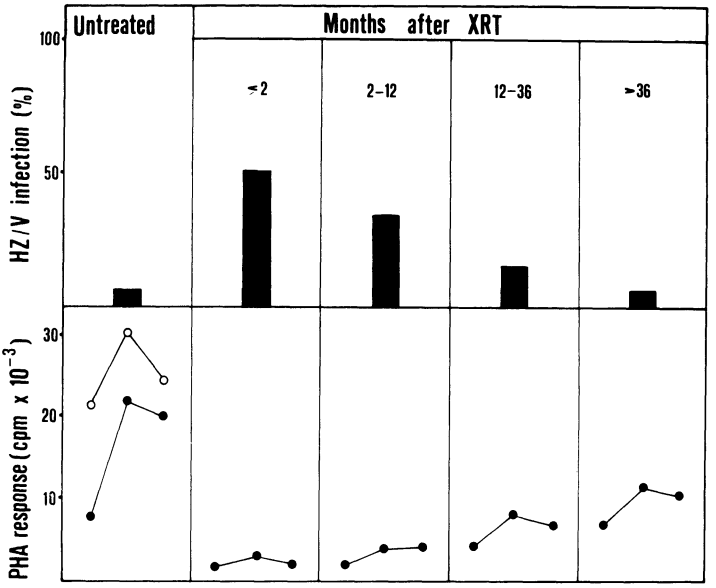


Figure 3. Prevalence of HZ/V infection and lymphoproliferative response to PHA in different groups of untreated or treated patients with HD examined at different time intervals since the completion of x-ray treatment (XRT). The results represent the mean cpm values obtained in cultures from a total number of 38 normal subjects (○) and 70 untreated patients and 91 treated patients with HD (●) following stimulation with three different PHA concentrations.

who were initially sensitive to this antigen. Many patients, however, regained their DCH during the first year after treatment [31]. DCH to recall antigens was also found to recover after discontinuation of radiotherapy or chemotherapy [94–96].

The lymphoproliferative responses to mitogens and antigens, which were significantly reduced before treatment in the majority of patients, appeared markedly impaired or absent in almost all patients after the completion of treatment. Even several months or years after discontinuation of treatment, there was little or no recovery of these responses. In a previous study, we compared the response of PB lymphocytes to PHA in several groups of patients, examined before treatment and at various time intervals after the treatment, with the prevalence of HZ/V infection. The results are summarized in Figure 3. The prevalence of viral infection, which was very low before treatment, markedly increased within the first year after the completion of treatment. Concomitantly, there was a significant decrease in the ability of PB cells from these patients to respond *in vitro* to PHA. After 1 year from the completion of treatment, the prevalence of viral infection again paralleled that of a normal age-matched population, while there seemed to be little recovery in the PHA responsiveness [16, 97].

The ability of PB lymphocytes to respond to alloantigens in MLR, which was normal or slightly reduced in untreated patients, appeared to be strong-

ly depressed during the first 2 years after treatment. There was a progressive recovery of the MLR during subsequent years, and normal responses were found in patients in complete remission for >5 years [31]. Total lymphocyte counts were markedly decreased at the completion of treatment, but a progressive restoration of the number of PB lymphocytes was seen during the first year after treatment [31]. Treatment-induced lymphocytopenia was caused by a loss of both T and B circulating cells [31]. Some months after treatment, HD patients still exhibit a striking T-lymphocytopenia [23, 31, 98–101], but many of them had B-lymphocytosis, which persisted for many years. It was considered of particular theoretical and practical relevance to ascertain the nature of the T-cell subpopulation that appeared to be so sensitive to the effect of irradiation *in vivo*. Some years ago, we approached this problem by testing the effect of radiotherapy on two distinct subpopulations of T cells (T_M and T_G) from HD patients. We found that the percentages and absolute values of T_M cells were significantly decreased in the PB of treated patients compared with the values found in either normal controls or untreated patients. In contrast, relative proportions of T_G cells were increased in the same treated patients, although their absolute number was essentially unchanged in comparison with that found before radiation therapy. There was a partial and progressive restoration of the number of T_M-lymphocytes some years after the treatment, but reduced numbers of T_M-lymphocytes were still found in patients in continuous complete remission for at least 5 years or more [23]. This finding is of interest, since T_M-lymphocytes are known to contain cells with helper activity, whereas suppressor activity has been related to the T_G-cell fraction [102]. Similar results have been reported by using a series of monoclonal antibodies defining immunoregulatory lymphoid cells. A relatively selective reduction in the $CD4^+$ (helper–inducer) population, which persisted for up to 12 months, was found in HD patients after mantle and paraaortic radiation. In contrast, the fraction of $CD8^+$ (cytotoxic–suppressor) cells remained constant after x-ray treatment [101].

Humoral immunity is also impaired in treated HD patients. Both radiotherapy and chemotherapy strongly reduced the levels of serum IgM and IgG [90], as well as specific antibody responses to *Hemophilus influenzae* or pneumococcal vaccine [92, 103]. Chemotherapy usually determined greater alteration than total nodal irradiation (TNI). In patients who received combined treatment (TNI plus chemotherapy), antibody titers were reduced to virtually undetectable levels [49, 103]. Antibody levels against pneumococcal vaccine tended to increase with time from therapy, but a deficient response appeared to persist for several years [49, 92].

It is of note that some immune abnormalities present in untreated patients, such as spontaneous DNA synthesis by PB lymphocytes, increased values of serum IgE, and serum anti-MHC class II autoantibodies have been found to normalize or disappear after treatment and do not return in HD patients during long-term remission [50, 56, 64, 86].

5. Biologic significance of the immune derangement

The biologic significance of the immune alterations in HD is still obscure. The first issue to be resolved is whether the immune alterations represent an etiologic factor or are secondary to the neoplasm. Another critical question is the recognition of a mechanism accounting for all different alterations.

5.1. Evidence suggesting preexistence of immune alterations

At least three pieces of evidence have been uncovered to suggest that the immune deficiency in HD is a preexisting phenomenon. First, the impairment of mitogen responsiveness can be detected even in the initial stages [27]. Second, some immune alterations, such as depression of lymphocyte response to mitogens and increased sensitivity of T cells to regulation by normal suppressor cells, seem to persist in long-term survivors with HD, but not in patients subjected to comparable immunosuppressive treatments for other neoplastic disease [4, 31, 104]. Finally, depression of lymphoproliferative responses to mitogens has been reported in healthy twins of patients with HD, as well as in consanguineous and nonconsanguineous relatives of HD patients [105, 106]. An increased incidence of lymphocytotoxins in the blood of relatives of HD patients has also been described [107]. These findings have led to the hypothesis that an environmentally induced, horizontally transmitted immune deficiency, like that of the recently recognized acquired immune deficiency syndrome (AIDS) [108], is a necessary prerequisite to the development of HD [106]. However, the fact that some immune alterations are detectable in the initial stages of the disease and persist in the long-term survivors does not prove that the immune alterations are an inherent characteristic of the patients in whom HD develops. They could be permanent defects acquired with the development of HD. Moreover, data showing immune alterations in healthy twins and relatives of HD patients have not fully been confirmed in subsequent studies. We were unable to find statistically significant differences in the mitogen-induced lymphoproliferative responses or the number of circulating T, T_M, and B cells among 74 relatives of patents with HD and 63 control subjects of comparable sex and age [97]. Thus, the hypothesis of a preexisting immune deficiency, which could act as an etiologic factor for the development of HD, still remains to be proved.

5.2. Mechanisms possibly responsible for immune alterations

In the attempt to explain the reason why HD patients show such a complex pattern of immune alterations, a role for several mechanisms has been adduced:

1. Lymphocyte depletion or altered lymphocyte distribution
2. Intrinsic lymphocyte abnormality

3. Enhanced suppressor activity
4. Immunosuppressive serum factors
5. Lymphocyte hyperactivity

5.2.1. Lymphocyte depletion or altered lymphocyte distribution. Although absolute lymphocytopenia has long been recognized in untreated patients with HD, its frequency and severity are insufficient to account for the immunologic impairment. Likewise, selective depletions from PB of T-lymphocytes or T_M- and $CD4^+$-cell subpopulations, which occur in a proportion of untreated patients [21, 22], cannot explain the entire complex of immune alterations. The possibility that sequestration of functional T-lymphocytes might be responsible for the immunologic defect in HD has also been suggested. This hypothesis implies that lymphocytes fail to migrate and occupy their normal environment (ecotaxopathy) because they are trapped in the lymph nodes and/or spleen. This hypothesis is supported by several findings: (a) the PHA response of spleen cells is usually normal even when PB lymphocytes exhibit impaired PHA response [28, 109, 110], (b) T-lymphocytes are increased in number in the lymph nodes and spleen and are decreased in the PB of untreated patients [22, 111, 112], (c) there is maldistribution of T_M- and T_G-cell subsets between the PB and spleen [22, 113], and (d) the percentage of $CD4^+$ cells is increased in lymphoid tissues, whereas their number is usually reduced in the PB [21, 114].

5.2.2. Intrinsic lymphocyte abnormality. The impairment of lymphoproliferative responses to mitogens and antigens has also been attributed to an intrinsic lymphocyte abnormality in HD. This hypothesis was mainly based on the demonstration of significant membrane alterations in HD lymphocytes, as reflected in enhanced lectin agglutinability and reduced cap formation [115, 116]. A functional abnormality of T-lymphocytes is further suggested by the following observations: (a) the impairment of the PHA response not only by unfractionated mononuclear cells, but also by purified T-cell populations [117]; (b) the abnormal locomotion of T-lymphocytes [118]; (c) the finding that depression of lymphocyte response in autologous MLR seems to be related to a defect of responder T cells rather than of stimulating non-T cells [32]; (d) the impaired generation of Con-A-inducible T-suppressor cells [119]; (e) the excessive sensitivity of lymphocytes from patients with active disease to the influence of normal adherent suppressor cells [104, 120, 121]; and (f) the enhanced ability of HD lymphocytes to synthesize ferritin [122].

5.2.3. Enhanced suppressor activity. Several investigations have yielded evidence suggesting that abnormal suppressor cell activity may play a role in inhibiting cell-mediated immune responses in HD. Enhanced suppressor activity has been demonstrated in MLC [123, 124], as well as in cultures in which mitogen-induced lymphoproliferative response or Ig production was

evaluated [72, 124, 125]. Abnormal suppressor cells were found to belong to the prostaglandin-releasing monocyte–macrophage population [72], but evidence has been provided that T cells may also exhibit enhanced suppressor activity [123]. More recent reports, however, do not confirm the existence of enhanced monocyte suppressor function in HD [67, 76] or suggest that it can be responsible only in part for defective responses of HD lymphocytes *in vitro* [120].

5.2.4. Immunosuppressive serum factors. The role of immunosuppressive serum factors in the immune deficiency of HD is still the subject of intense controversy. Several studies have reported that sera from HD patients exert suppressive effects on the proliferative response to PHA of normal lymphocytes [100, 126–131], but this inhibitory activity has not been confirmed in other studies [26, 28, 132, 133]. The depression of the PHA response has been attributed to the activity of serum dialyzable factors [100], PHA-binding macroglobulins [134], LIF-like substances [46], or lymphocytotoxins [126]. However, the cytotoxic capacity of antilymphocyte antibodies present in the serum from HD patients has been questioned [63]. Moreover, the ability of a patient's serum to inhibit the lymphocyte response of normal lymphocytes to Con-A stimulation has not been found to differ between lymphocytotoxin-positive and lymphocytotoxin-negative patients [61]. Thus, although antilymphocyte antibodies are really detectable in the serum of a proportion of untreated patients with HD, they do not seem to account for depression of mitogen-induced lymphoproliferative responses or other immunologic abnormalities.

E-rosetting inhibitory factors have also been described, either free in the serum or absorbed on T cells, from untreated patients with HD [135–137]. A similar or perhaps identical inhibitor was extracted from the involved spleens of HD patients and found to be a glycolipid that is undetectable in normal sera [138, 139]. Other investigators demonstrated the presence on T cells from HD patients of E-rosette-blocking protein that could be released from the surface of cells after treatment *in vivo* or incubation *in vitro* with levamisole, an antihelminthic drug with immunomodulatory properties [140–142]. The blocking protein reacted with antibody to human spleen ferritin, but contained no detectable iron and could be dissociated into 18,000-kd subunits, suggesting that it is apoferritin [141]. It is of note that ferritin, which is present in elevated amounts in the serum and lymphoid tissues of HD patients [143], shows antigenic differences from ferritin prepared from normal spleens, thus behaving as a tumor-associated antigen [144]. It is possible that apoferritin or abnormal ferritin acts as a carrier for the E-rosette inhibitory substance. This could reconcile the glycolipid and apoferritin findings [139].

More recently, we demonstrated that sera from some untreated patients with active HD caused marked inhibition of autologous and allogeneic MLR from normal lymphocytes without inducing a significant reduction of the

PHA-induced proliferative response [64]. The inhibitory activity on the autologous MLR was removed by absorption with non-T-lymphocytes, not T-lymphocytes, and was correlated with the ability of such sera to block the binding of monoclonal anti-MHC class II antibody to class-II-positive target cells [64]. Anti-class-II antibodies were detected in the same sera by a double antibody radioimmunoassay and by sodium dodecyl sulfate–polyacrylamide gel electrophoresis, using semipurified ^{125}I-labeled class II antigens prepared from two different human B-cell lines (Figure 4) [64]. Because of the well-known importance of MHC class II antigens in T-cell activation and in a number of interactions occurring among immunocompetent cells, the demonstration of these autoantibodies may contribute to explain the derangement of immunity in HD.

5.2.5. Lymphocyte hyperactivity. Another possibility that we recently suggested to explain the complexity of immune derangement in HD is that it results from lymphocyte hyperactivity, which can follow overstimulation of the immune system by unknown antigen(s) [145]. This hypothesis, which is not new, rests on a series of histologic and immunologic findings:

- Histologic evidence
  1. Follicular hyperplasia of lymph nodes
  2. Formation of germinal centers
  3. Demonstration of Reed-Sternberg cell-attached lymphocytes
- Immunologic evidence
  1. Circulating cells showing spontaneous DNA synthesis
  2. Immunoactivated T-lymphocytes in lymph nodes
  3. Spontaneous production of lymphokines
  4. Increased serum levels of IgG, IgA, IgD, and IgE
  5. Increased serum levels of antiviral antibodies
  6. Circulating immune complexes
  7. Enhanced spontaneous synthesis of IgG by cultured lymphocytes
  8. Antilymphocyte and anti-MHC class II antibodies

Reactive follicular hyperplasia in nodes around the tumor, which accounts for the many negative biopsy findings in patients ultimately proved to have the disease, as well as formation of germinal centers have been considered suggestive of B-lymphocyte hyperreactivity in lymphoid organs from patients with HD. Indeed, several immunologic data among those mentioned above are also consistent with this possibility. They include (a) the serum increase of different Ig classes [50] and of antiviral antibodies [54, 55], (b) the presence of CIC [58, 59] and of serum antilymphocyte and anti-MHC class II antibodies [62, 64], (c) the demonstration of spontaneously IgG-producing cells in the spleen [65, 66], and (d) the abnormalities of Ig production by PB cells *in vitro* [67]. Similar disturbances of B-cell function have been described in patients with active systemic lupus erythematosus and attributed to polyclonal B-cell activation (PBA) by endogenous or exogenous stimuli. PBA has also been demonstrated during the course of

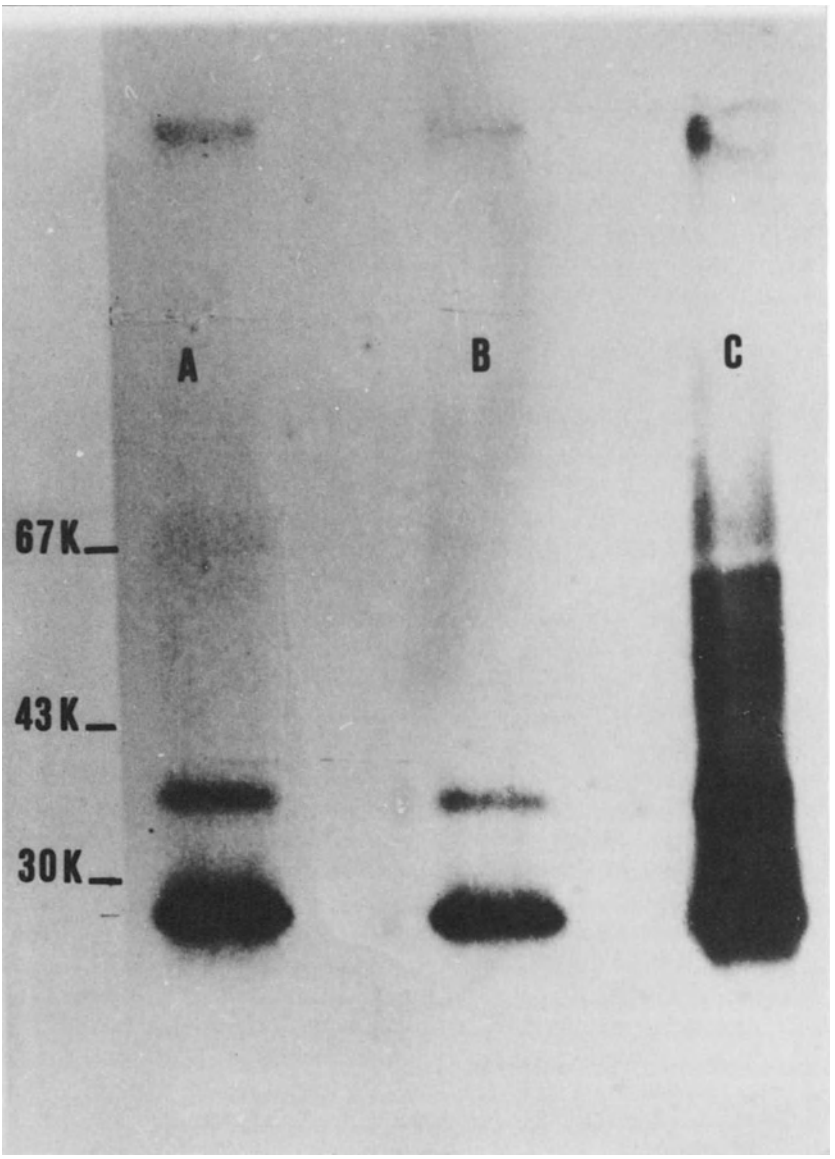


Figure 4. Detection of antibodies directed against nonpolymorphic determinants of MHC class II antigens in sera from two patients with active HD. SDS–PAGE autoradiographic pattern of protein A conjugate of HD sera (lanes *A* and *B*) after incubation with a U698M MHC class II preparation (lane *C*). The molecular weight markers were bovine serum albumin (67 kd), ovalbumin (43 kd), and carbonic anhydrase (30 kd).

some infectious diseases, such as mononucleosis. In this as well as other infectious diseases (trypanosomiasis, malaria), PBA is usually associated with DCH deficiency and defective lymphoproliferative responses to antigens and mitogens *in vitro*. Dysfunction of circulating T cells and enhanced monocyte suppressor function with overactivity of B cells have also been observed in patients with sarcoidosis, where overactivity of B cells seems to be related to hyperactivity of helper T cells, which are significantly increased in the lungs.

Some findings also suggest that overactivity of B cells in HD may derive from, or be associated with, hyperactivity of helper T cells. First, T-lymphocytes spontaneously synthesizing DNA, which are identical with those found in normal subjects under conditions of known antigenic challenge, are detectable in the PB of patients with active HD [33, 34, 38]. Second, PB T cells from HD patients show enhanced helper activity on spontaneous IgG production when cocultured with normal B cells [67]. Finally, higher percentages of $CD4^+$ cells showing the characteristics of 'immunoactivated' T cells are present in involved spleen and lymph nodes from HD patients [114]. Thus, there is sufficient evidence to suggest that increased numbers of both activated helper T cells and Ig-producing B cells are trapped in lymphoid organs, from which they can also spread into the circulation during the most active phases of the disease. The presence in the serum of enhanced levels of MIF- and LIF-like activity [41, 45, 46], as well as the spontaneous production *in vitro* of lymphokines by HD lymphocytes [41, 43], together with the reduction of mitogen-induced lymphokine production [41, 43, 44], are also consistent with the hypothesis of an activation of HD lymphocytes *in vivo*. The engagement of the immune system in the response to a persistent stimulation might explain depression of DCH to recall antigens and neoantigens, as well as reduction of lymphoproliferative responses to mitogens, as has been shown to happen in some infectious diseases and in sarcoidosis. Some of the immunosuppressive serum factors, such as lymphocytotoxins and anti-MHC class II antibodies, may merely be the result of PBA or reflect an altered turnover of surface MHC antigens, whereas other factors could be directly released from the tumor cells, as has been demonstrated in the SJL/J murine lymphoma, an animal model of HD [146].

5.3. Possible relationship between immune alterations and neoplastic transformation

From the above-mentioned data, it appears that the immune alterations in HD are not merely the consequence of a tumor-induced damage, such as that demonstrable in the majority of neoplasms. They rather seem to represent an integral part of the disease, thus suggesting the existence of a strict relationship with the mechanisms responsible for neoplastic transformation. To provide additional support for this possibility, we believe it is opportune

to discuss briefly the immune alterations in light of the present points of view on the origin of the neoplastic cell, as well as on the nature and role of other cell types usually infiltrating lymphoid organs in HD.

5.3.1 Origin of the neoplastic cell. In spite of the numerous studies performed in the last few years, the nature of cells that represent the normal counterpart of the Reed-Sternberg (RS) cell still remains undefined. As discussed in detail in other chapters of this book, at present two main possibilities can be considered. The first possibility is that the normal counterpart of RS cells belongs to the family of antigen-presenting cells, commonly defined as 'accessory' cells. There are some immunologic findings that support this possibility. First, RS cells, like all different types of accessory cells, express significant amounts of MHC class II antigens. Second, RS cells are often found to be associated in involved lymph nodes with T-lymphocytes [147], mainly showing the $CD4^+$ helper/inducer phenotype, as usually do interdigitating antigen-presenting reticulum cells in the thymus-dependent areas of lymphoid tissues [148]. Finally, cells from a permanent line (L428) obtained from the pleural effusion of a patient with HD were able to support mitogen responsiveness of T cells [149], functioned as potent stimulators in MLR [150], and presented antigen to helper T cells in an MHC-restricted fashion [151].

An alternative possibility is that HD reflects the neoplastic proliferation of activated lymphoid cells of either T-cell or, less commonly, B-cell origin. This view is mainly supported by studies on the expression of the HD-associated antigen Ki-1 [152] in reactive and neoplastic lymphoid tissue. The results of such studies indicate that the Ki-1 expression in these lesions is accompanied by the expression of lymphocyte activation markers, such as MHC class II antigens and IL-2 receptors [153].

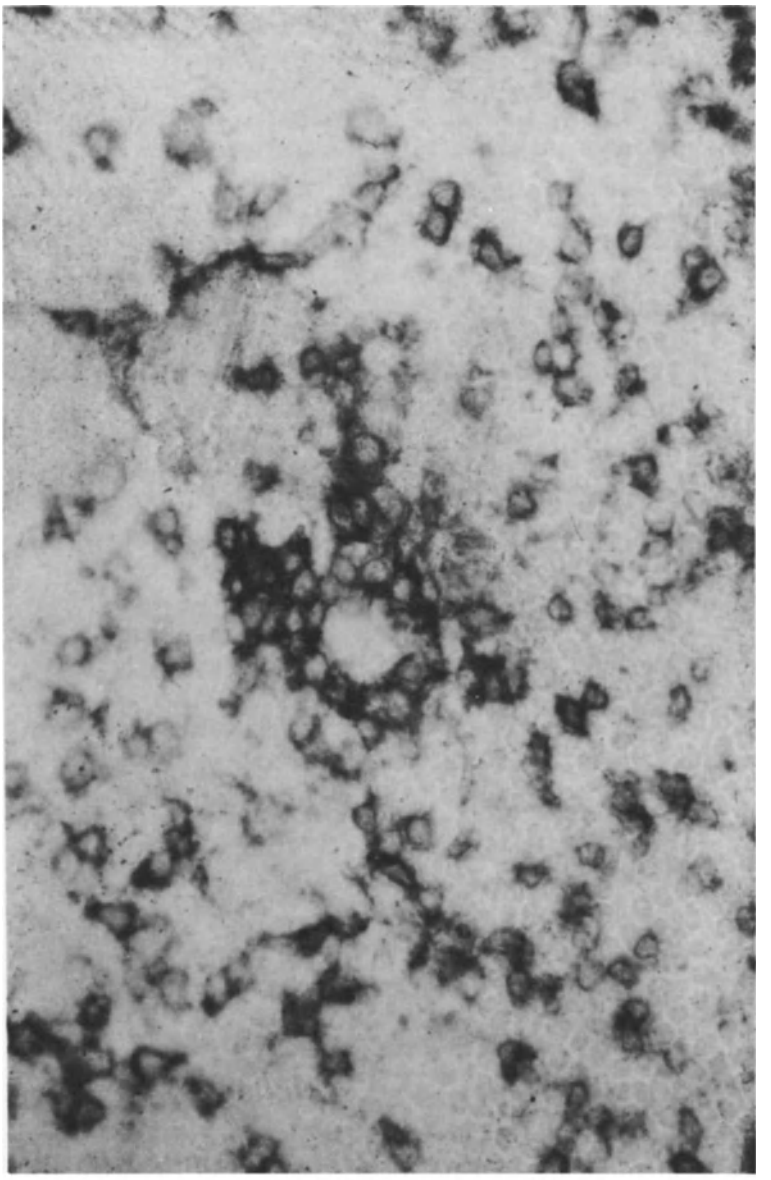
5.3.2. Nature and role of tumor-infiltrating lymphocytes. To understand the mechanisms responsible for the immune derangement in HD and to define the possible relationship between the immune alterations and the pathogenesis of the disease, it is necessary to elucidate the nature and role of lymphocytes usually infiltrating lymph nodes and/or spleens involved by the disease. The characterization of these cells has recently been attempted using both phenotypic and functional approaches.

5.3.2.1. Surface phenotype analyses. There is now general agreement that, apart from the histologic type of LP where the majority of infiltrating cells are B-lymphocytes [154], the cells that predominate in all other histologic types are T-lymphocytes [21, 24, 111, 112]. Most of these T cells possess Fcμ receptors [24, 111] and the CD4 antigen [4, 21, 114], which usually define the helper/inducer T-cell subset (Figure 5). In addition, a large proportion of these cells express the T10 antigen [114], which is present on activated T cells and a minority of them also express MHC class II antigens, again suggesting that some of the T cells are activated [146]. This conclusion is in agreement with the demonstration that T-lymphocytes present in the lymph

nodes of patients with HD show enhanced affinity for sheep red blood cells [114], increased sensitivity *in vitro* to the cytolytic effect of glucocorticoids [155], and the ability to attach nonspecifically *in vitro* to various human normal and malignant cells [155], which are considered features of 'immunoactivated' T cells. An increased number of T-activated cells (TAC) in lymph nodes involved by HD has also been reported [156]. In a recent series of experiments, we examined cell suspensions of ten lymph nodes involved by HD showing very high percentages of $CD4^+$ lymphocytes for their ability to express activation markers. We found increased values of cells bearing MHC class II determinants and T10 antigen, whereas the number of TAC^+ cells did not appear to be significantly increased. However, most T cells had the T22 antigen, which is expressed later than TAC antigen by activated T cells (Figure 6).

5.3.2.2. Functional studies. Taken together, the results of phenotypic analyses suggest that the majority of tumor-infiltrating T cells show the helper/inducer phenotype and express some activation markers. It is well known, however, that analyses of the T-cell surface phenotype do not always provide precise information on the cell function. For example, in certain instances, the phenotype of functional T cells may change in the course of cell activation. More important, monoclonal antibodies reactive against certain CD antigens do not represent markers for functionally defined T-cell subsets. On the other hand, functional studies carried out on heterogeneous T-cell subpopulations are difficult to interpret because they do not provide information on the proportion of cells expressing a given function. Recently, we attempted to overcome these difficulties by using a cloning system allowing the expansion of virtually every T-lymphocyte to investigate the functional capability of T cells present in HD spleens [157]. A total number of 221 clones derived from six different spleens were studied and compared with those of 133 clones obtained from three spleens of otherwise healthy individuals who underwent posttraumatic splenectomy. Although the majority of T-cell clones derived from HD spleens expressed the CD4 phenotype, as many as 50% of these clones displayed cytolytic activity in a lectin-dependent lytic assay, allowing detection of cytolytic cells of any specificity (Figure 7). In addition, most of the $CD4^+$ cytolytic clones obtained from HD spleens produced particularly high amounts of IL-2 [158, 159]. These data demonstrate that a dramatic expansion of an infrequent T-cell subset coexpressing helper/inducer phenotype and cytolytic activity can occur in lymphoid organs of patients with HD.

More recently, we extended these functional studies by investigating the ability of T-cell clones obtained from one lymph node and one spleen of two patients with HD to proliferate in response to autologous EBV-transformed B-cell lines. An unusually high number of T-cell clones established from both lymph node and spleen involved by HD showed the ability to respond in autologous MLR (unpublished data). Although the meaning of this finding is at present unclear, it confirms the existence of an abnormal T-cell



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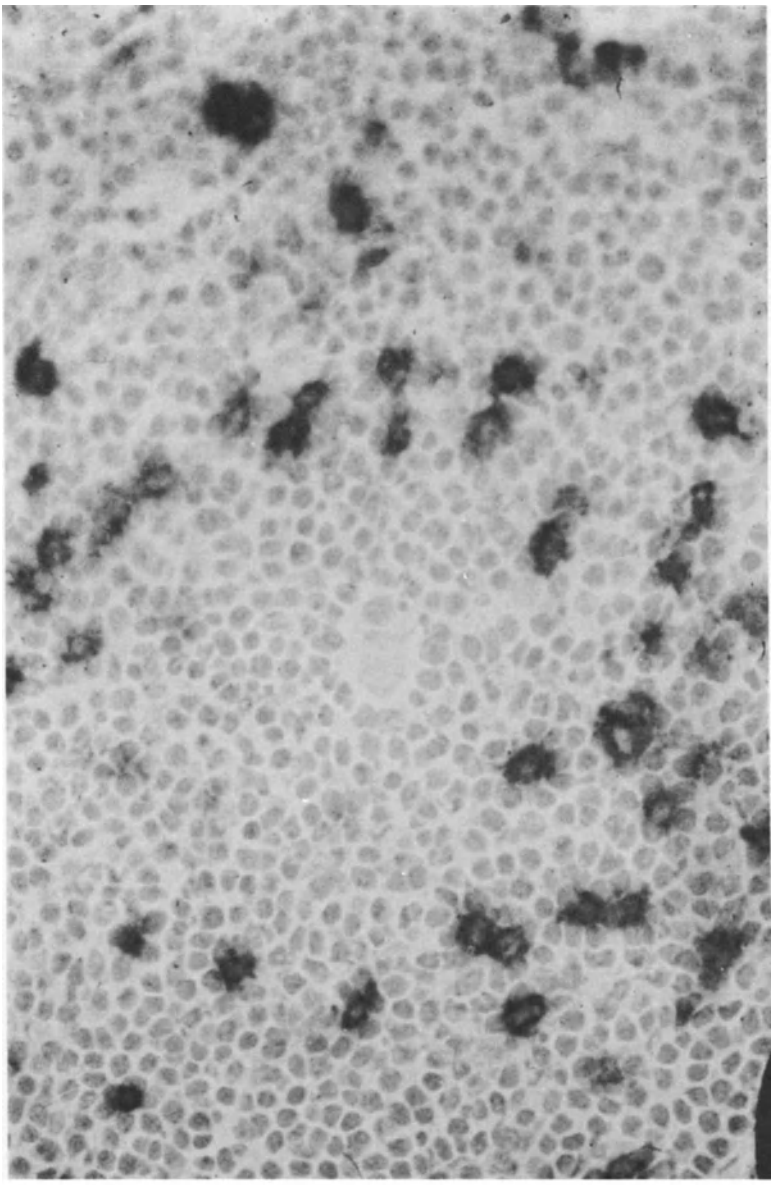

B

Figure 5. Reed-Sternberg cell-attached $CD4^+$ T-lymphocytes in an involved lymph node from a patient with HD. Immunoperoxidase staining with (*A*) anti-CD4 monoclonal antibody and (*B*) anti-CD8 monoclonal antibody. Courtesy of M. Chilosi and G. Pizzolo (University of Verona).

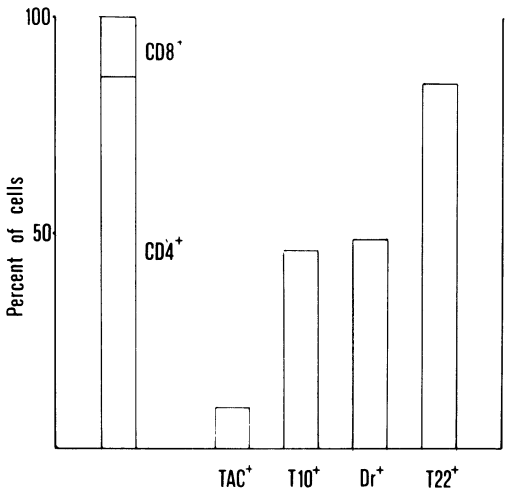

Figure 6. Expression of surface markers by T-lymphocytes of histologically involved lymph nodes from patients with HD. Cell suspensions were incubated with the following monoclonal antibodies: OKT4 (anti-CD4), OKT8 (anti-CD8), PTF 29.12 (anti-MHC-DR), anti-TAC (anti-CD25 or IL-2 receptor), OKT10 (anti-CD38), and OKT22 (reactive with a late activation antigen).

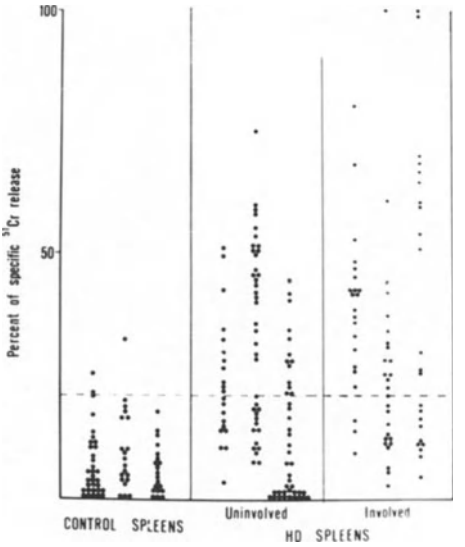

Figure 7. Cytolytic activity of CD4 T-cell clones derived from spleens of normal individuals subject to posttraumatic splenectomy and of patients with HD: 20,000 clonal T cells were tested for lectin-dependent cytolytic activity against ^{51}Cr-labeled P815 murine mastocytoma cells (at effector–target ratio 4:1) in the presence of PHA. The dotted line represents the threshold level (mean background ±3SD).

subpopulation in lymphoid organs involved by HD and suggests the possibility of altered autoreactivity in this disease.

5.3.2.3. Analysis of clonality. Although the above-mentioned results suggest that tumor-infiltrating T cells reflect, at least in part, the abnormal proliferation of an uncommon T-cell subpopulation, they do not prove whether or not the infiltrating T cells represent a monoclonal population. Recently, however, DNA derived from involved lymph nodes of patients with HD was examined by the Southern blot technique. Rearrangement of the γ-chain T-cell receptor gene was found in four cases, suggesting that T cells present in lymph nodes from these patients were clonal in origin [160].

5.3.3. Concluding hypotheses. On the basis of the studies reviewed here, some hypotheses attempting to provide a unitary interpretation of the origin of the RS cell, the nature and role of tumor-infiltrating T cells, and the immune derangement present in HD can be advanced.

The possibility has previously been suggested that the RS cell represents the neoplastic counterpart of 'accessory' cells functioning as antigen-presenting cells for helper T cells. If this is the case, tumor-infiltrating T cells may consist of a population of helper/inducer T cells in close contact with the antigen-presenting cell or, alternatively, they may be the result of a cytolytic reaction directed against the neoplastic cell. Since the RS cell has been found to be abnormally rich in MHC class II determinants, T-lymphocytes expressing on their surface the class II-reactive CD4 molecule could be favored in the development of cytolytic activity. The demonstration by our studies at clonal level that, in spite of their CD4 phenotype, about half of infiltrating T cells in HD spleens display cytolytic potential may be consistent with this possibility. However, it is difficult to reconcile this hypothesis with the complex of immune alterations present in these patients.

The other (more likely) possibility is that the normal counterpart of the RS cell is an activated T-lymphocyte. In this case, we may suggest at least three different hypotheses. First, it is possible that, as already discussed above, tumor-infiltrating T cells reflect a cytotoxic reaction against the neoplastic cell. Second, they could represent a heterogeneous population attracted by lymphokines and other soluble factors released by the activated (neoplastic) lymphocyte. However, none of these explanations is fully convincing. In particular, it is not easy to understand why the neoplastic transformation of an activated clone may result in so great a derangement of the entire immune system. Finally, it is possible that tumor-infiltrating lymphocytes are, at least in part, precursors of the neoplastic cell and that the immune disregulation leading to lymphocyte activation precedes the neoplastic transformation. This possibility has recently been suggested on the basis of unexpectedly common clinical and immunologic associations between lymphomatoid papulosis, mycosis fungoides, and some types of HD [161]. In lymphomatoid papulosis, a cutaneous eruption with histologic features of HD, there is a spectrum of activated $CD4^+$ T cells, including

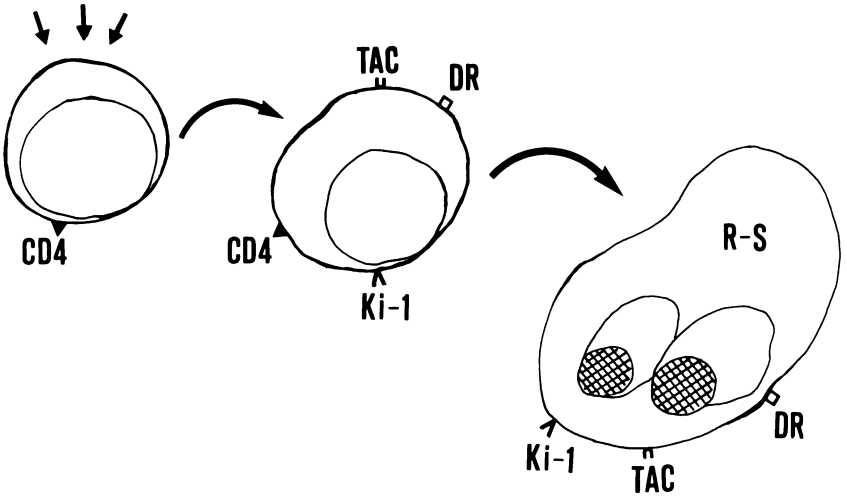

Figure 8. Scheme for the possible derivation of Reed-Sternberg cells from activated $CD4^+$ T-lymphocytes.

cerebriform cells and large transformed RS-like cells. Clonal expansion of cerebriform cells in lymphomatoid papulosis leads to mycosis fungoides. Similar expansion of large transformed cells results in HD. Progressive transformation of $CD4^+$ cerebriform cells to Ki-1 RS cells accounts for rare cases of coexistent mycosis fungoides and HD (Figure 8). In addition, this explanation accounts for the observation that, while in the histologic type of LP (where RS cells usually have B-cell markers) tumor infiltrating cells are mainly B-lymphocytes, in the other histologic types (in which a T-cell origin of RS cells is suspected) T-lymphocytes predominate among tumor-infiltrating cells. Thus, in HD, neoplastic transformation may be the final step of prolonged activation of either T-cell or, less commonly, B-cell origin.

If the latter hypothesis is valid, it appears of great importance to identify the mechanism(s) responsible for T-cell (or B-cell in the LP type) hyperactivation. With regard to the T-cell hyperactivation, one possibility we suggest is that it reflects an autologous MLR *in vivo* as a consequence of an abnormal recognition by T cells of autologous MHC class II determinants. Although there is no direct evidence supporting this possibility, it can be suggested on the basis of several observations. The first is the demonstration of autoantibodies reactive against monomorphic determinants of MHC class II antigens in the sera of some patients with active disease [64]. This indicates the existence of an abnormal immune reaction against self class II antigens similar to that already described in patients with systemic lupus erythematosus. In addition, it has been shown that ~50% of lymphoblasts generated by auto- and alloactivation reacted with the HD-associated Ki-1 antigen, whereas only <6% of lymphoblasts stimulated with mitogens and none of lymphoblasts activated by oxidative mitogenesis expressed this antigen, suggesting that HD may be the result of a malignant transformation of

autoactivated T-cell clones [162]. Finally and more importantly, preliminary data of our analysis performed at the clonal level indicate the presence of unusually high proportions of autoreactive T cells in lymphoid organs involved by HD. A disorder in autoreactivity may easily account for the immune alterations demonstrable in HD patients that, in some aspects, resemble the immune disregulation found during graft-*versus*-host-disease. In this respect, a previous theory on the pathogenesis of HD proposed the suggestive image of a 'civil war among lymphocytes' [163, 164].

It cannot certainly be excluded that chronic lymphocyte hyperactivation then resulting in neoplastic transformation may result from different mechanisms, such as infection by an oncogenic virus that integrates in the genome of activated lymphocytes. Recently, transforming genes homologous to the N-ras oncogene have been isolated from splenic nodules of two patients with HD [165]. All of these findings reasonably suggest that the modern immunologic techniques have at last the potential to solve the fascinating puzzle of the pathogenesis of HD.

6. Immunotherapeutic strategies

Two different kinds of immunotherapeutic strategies have recently been proposed as a supplement to cytostatic treatment in patients with HD:

- Use of immunologic reagents for tumor cell killing
  1. Labeled antibodies against tumor-associated proteins
  2. Autologous lymphocytes labeled with beta-emitters
  3. Lymphokine-activated killer (LAK) cells
- Immunorestoration
  1. Drug engineering
     Isoprenosine
     Tuftsin
     Levamisole
     Others
  2. Engineering with biologic agents
     Measles vaccine
     Transfer factor
     Thymic hormones
     Interferons
     Interleukin 2
  3. Cellular engineering
     Allogeneic bone marrow transplantation
     Autologous bone marrow transplantation

6.1. Use of immunologic reagents for tumor killing

The use of labeled antibodies has recently been proposed as a novel therapeutic procedure for selectively irradiating sites of disease in different

tumors. Based upon the observation that ferritin, a tumor-associated protein, is secreted by T-lymphocytes in HD, a ^{131}I-tagged polyclonal antibody to human ferritin was administered to patients with HD. The radioimmunoglobulin treatment was found to induce remission in patients with advanced HD with little toxicity [166].

An attempt to induce selective damage in sites of disease by injection of autologous normal lymphocyte labeled with the beta-emitter ^{111}In has also been made. Therapeutic doses of radiation were delivered to the lymphoid tissue in both rats and men without inducing toxicity [167].

The merits of this therapeutic strategy are unclear at this writing. Likewise, the possible value of a therapeutic approach based on the use of LAK cells, as it has been attempted in other tumors [168], although of potential interest from a theoretical point of view, remains to be established.

6.2. Immunorestoration

6.2.1. Engineering with drugs or biologic agents. Only anecdotal experience suggests the efficacy of immunomodulatory drugs in restoring the deficient immune system in HD. *In vitro* preincubation with tuftsin, a natural tetrapeptide with immunomodulatory properties, has been found to restore the deficient chemotactic responsiveness of monocytes derived from patients with HD [169]. Successful results have also been reported in immunostimulation trials with levamisole, another immunomodulatory agent. Both the frequency of infections and impaired cell-mediated immunity benefited most from the levamisole therapy in a group of HD patients [170].

Based on the observation that remission of HD had occurred following the appearance of measles in some patients, the use of live attenuated measles vaccine as an adjunct to cytostatic treatment has been suggested [171]. However, a likely possibility is that this therapeutic effect reflects the activity of virus-induced interferon (IFN) rather than of infection itself. Therefore, before exposing these immunocompromised subjects to the risk of live measles vaccine, the effect of IFN therapy should be evaluated. Some observations, indeed, suggest that administration of IFN may be of benefit in patients with HD. For example, preincubation with IFN was found to result in a clear increase in natural killer (NK) activity in patients showing depressed NK function [172]. In addition, a great clinical and immunologic improvement was achieved with intramuscular IFN therapy in a patient with LP stage IVB disease [173]. More recently, however, in a multiinstitutional trial, IFN was not observed to be of therapeutic benefit in HD [174].

Dialyzable transfer factor (TF) has been used in past years in the attempt to restore cell-mediated immunity in patients with HD. Passive transfer of DCH was achieved, with normal TF, in patients with HD in remission, but the clinical effects in these patients were difficult to assess [175, 176].

A number of studies have shown that treatment with thymic hormones

both *in vitro* and *in vivo* are capable of enhancing the E-rosette-forming capacity and the PHA blastogenic response of PB lymphocytes from untreated patients with HD [177–179]. The increase in the immune parameters was greatest in those patients with advanced disease and who presented with decreased T-cell values [178]. However, whether or not this immunomodulatory effect of thymic hormones prior to therapy may favorably alter natural history of subgroups of patients with HD remains to be established.

To our knowledge, there are no available observations at present on the possible therapeutic activity of IL-2 in patients with HD. IL-2 has been shown to display a restorative effect on depressed NK activity in HD patients superior to that of IFN-γ or IFN-γ treatment [180]. This finding may suggest a potential therapeutic application of IL-2 in HD.

From the complex of these data, however, it appears that further carefully controlled trials with adequate numbers of patients and uniform standards of disease evaluation are required to define the appropriate role of immunomodulatory drugs and biologic agents in the treatment of HD. These trials might evaluate the role of such agents in patients whose disease has relapsed after initial conventional therapy. Alternatively, studies might be performed to determine whether immunomodulatory agents in combination with chemotherapy increase the initial complete response rate or to determine whether their addition after complete response to chemotherapy increases the duration of response. On the other hand, in view of the peculiar role of the immune reactivity in this type of tumor, caution is advised in attempting to manipulate the immune system in patients with HD before the relationship between immune alterations and pathogenesis of the disease has been fully clarified.

6.2.2. Cellular engineering. In HD, conventional therapy leads to cure in such a high percentage of cases that more toxic regimens are not required for the great majority of patients. Refractory patients, however, are rarely cured, even when different conventional regimens are attempted as salvage therapy. Bone marrow transplantation (BMT) is an expanding new modality in clinical oncology. Evidence is now accumulating to suggest that some patients with relapsed or refractory HD can obtain prolonged clinical remission following intensive chemoradiotherapy and allogeneic or autologous BMT [181]. High-dose chemotherapy with either allogeneic or autologous BMT has been applied to populations of patients with advanced HD that has relapsed or is refractory to chemotherapy patients [182–185]. Although at present it is very difficult to interpret reports of massive chemotherapy and BMT in HD patients, the high percentage of remissions suggests the validity of such treatment attempts in poor-prognosis HD [181–185]. In this regard, autologous BMT seems to be a more practical approach than allogeneic BMT since it obviates the issue of limited donors and graft-*versus*-host disease, even though adding the problems of compromised marrow stem cell reserve and marrow contamination by malignant cells. A

definite answer to these questions, however, may be achieved only after controlled clinical studies.

Acknowledgments

This work was supported by grants from CNR (Finalized Oncology Project nos. 86.0056.44 and 86.01679.56) and the AIRC. P.P. is a Fellow of the AIRC.

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6. Prognostic factors including clinical markers

Bengt Glimelius

It was recognized early that Hodgkin's disease (HD) had a fulminant course in certain patients, whereas it showed a remarkably indolent character evolving over a period of several years in others [1, 2]. It was possible to identify a great number of factors that appeared to influence the prognosis.

The object of staging and the prediction of treatment response and long-term survival as accurately as possible is to deliver the most effective treatment. The recognition of certain late adverse effects has led to the commonly accepted conclusion that it is no longer justifiable to treat the patients as intensely as has often been the case during the last 10–15 years [2, 3]. Hence, there is a need for even better prognostic predictors in order to avoid overtreatment in some patients and, on the other hand, to identify patients with an aggressive disease not responding to 'conventional' therapy.

This chapter first very briefly describes general factors (*i.e.*, clinical, histopathologic, and laboratory factors) that relate to prognosis. Second, prognostic factors in nonadvanced HD and advanced HD, respectively, are reviewed and, finally, a recently developed prognostic 'survival' index is described.

1. General factors related to prognosis

It was an early observation that the extent of the disease at diagnosis—or stage—had a great impact on survival. This basic observation still holds true [3–15]. In virtually all publications, the presence of constitutional symptoms suggests a poor prognosis [2, 16, 17]. Mediastinal adenopathy is commonly seen in patients with HD and has prognostic significance [8, 18–29].

The prognostic significance of the Rye classification [30] has been confirmed in several series. The importance of histopathology as a prognostic indicator has, however, substantially decreased with the continued improvement in overall prognosis [2]. In the most recently published series, there is still, however, a minor difference in prognosis between lymphocyte predominance (LP) and nodular sclerosis (NS), on one hand, and between mixed cellularity (MC) and lymphocyte depletion (LD), on the other [2, 17,

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Table 1. Laboratory indicators of prognostic significance in patients with Hodgkin's disease.

Laboratory test	Number of patients	Included stages	Reference
Erythrocyte sedimentation rate (ESR)	1063	I–II	Tubiana *et al.* [8]
	743	I–II	Haybittle *et al.* [9]
S-Alkaline-phosphatase (ALP)	83	I–IV	Thyss *et al.* [41]
	127	I–IV	Wedelin *et al.* [31]
S-Lactate-dehydrogenase (LDH)	249	I–IV	Schilling *et al.* [42]
	127	I–IV	Wedelin *et al.* [31]
S-Copper	191	I–IV	Hgrovcic *et al.* [43]
S-Ferritin	47	I–IV	Dörner *et al.* [44]
	35	I–IV	Bezwoda *et al.* [45]
S-Thymidine kinase	72	I–IV	Eriksson *et al.* [46]
HLA-Antigen–1	52	I–IV	Hafez *et al.* [37]
Immune status[a]	47	I–IV	Van Rijswijk *et al.* [40]
	127	I–IV	Wedelin *et al.* [39]

[a]Measured as mitogen-induced lymphocyte stimulation, spontaneous DNA synthesis of lymphocytes, and/or stimulation in mixed-lymphocyte cultures.

31]. In a review of the British National Lymphoma Investigation Studies, it was found that, histologically, nodular-sclerosing HD can be divided into two grades, where cases with easily recognized areas of lymphocytic depletion or numerous pleomorphic Hodgkin's cells (NS grade 2) had a less favorable prognosis than those where such areas were not found (NS grade 1) [32]. The poor prognosis of LD HD was questioned in a recent publication by Kant *et al.* [33] due to an erroneous inclusion of cases with high-grade non-Hodgkin's lymphoma into that subtype of the disease. Although the number of patients was limited, patients with LD HD had a prognosis that did not differ from other histopathologic subtypes of HD.

Age has been reported to have prognostic significance, but is of minimal value for studies in children. Numerous reports have shown that survival is considerably shorter in elderly patients than in young ones [2, 8, 17, 34]. In most adult series, women have slightly better survival than men [2, 8, 9, 16, 35]. This latter finding could not, however, be verified in a study of 154 children [36].

The prognostic value of laboratory tests measured before the institution of therapy has been extensively studied [8, 9, 31, 37–46]. Several of these variables are closely associated with the clinical stage and age. Despite this intimate relationship with other clinical prognostic factors, several of the laboratory tests, some of which are listed in Table 1, have been found to yield additional prognostic information when analyzed by multivariate analyses of variance.

The prognostic importance of the erythrocyte sedimentation rate (ESR) was recognized early. Since then, ESR has been one of the factors showing the strongest association with survival [8, 9]. It is at present unlikely that any

of the other laboratory indicators are clinically more useful than ESR, which also has the advantage of simplicity and inexpensiveness [2].

2. Prognostic factors in non-advanced Hodgkin's disease

Although pathologic staging, including a staging laparotomy with splenectomy, can reveal occult disease in approximately one-third of the patients with clinical stages I and II, its use as a routine staging procedure has been questioned. The procedure is not without risks, although surgery-related mortality in experienced centers is virtually zero and the short-term postoperative morbidity is <5%. The main danger, especially in children, is the increased risk of overwhelming bacterial infection. There is at present a general consensus that the procedure is justified only if the findings influence the choice of treatment [2, 3, 9]. It would be advantageous if the risk of clinically occult abdominal disease, particulary in the spleen, could be more precisely identified on the basis of the pattern of clinical presentation with or without the aid of laboratory indicators. This question has been addressed in a number of recent reports. The majority of the patients have been clinically staged with bipedal lymphangiography. It is therefore not known whether the data presented are also relevant if the patients are instead, or additionally, staged with computerized tomography, ultrasonography, and/or possibly also by multiple-needle biopsies of the spleen [47, 48].

In a study by Brada *et al.* [35] encompassing 225 patients, the age, sex, and, in stage I disease, also the size and position of the involved nodes were independent predictors of finding HD during laparotomy. It was found that women had a significantly lower risk of occult abdominal disease than did men, as did older (age >20 years) compared with younger patients. In clinical stage I disease, small nodes in the neck regardless of their position, and nodes of any size confined to the suprahyoid neck as well as mediastinal presentation only, carried a low risk of abdominal disease. On the basis of their observations, low-risk (<15% positive laparotomy), high-risk (>50%), and intermediate-risk categories, respectively, could be defined: this could then form a basis for a selective use of laparotomy. Thus, according to the authors, laparotomy could be avoided in high-risk patients in favor of primary chemotherapy with or without radiotherapy, and in low-risk patients where primary radiotherapy without laparotomy could be justifiable. In the intermediate group, the information obtainable from laparotomy and splenectomy appears to be desirable in order to minimize treatment in a proportion of the cases (pathologic stages [PS] I–II) or optimize it in the remainder (PS III–IV).

When these data are compared with results from other studies, similarities were found, but also certain differences. In the study by Tubiana *et al.* [8], only sex and histology were independent prognostic factors. There was, however, a tendency for an increased risk of abdominal disease in patients

>40 years of age, in patients with multiple involved sites, and in patients with constitutional B symptoms. Logistic regression analysis indicated that only sex and the presence or absence of mediastinal involvement had significant influence. The predictive value of constitutional symptoms was also noticed in two additional studies, one of which was composed of children and young adolescents [36, 49]. In the study concerning children with HD, two intraoperative parameters—changes of splenic surface and enlargement of lymph nodes of splenic hilus/pancreatic tail—supplied significant information about splenic involvement. Thus, intraoperative decisional strategy for splenectomy could be developed that enabled the omission of splenectomy in about two-thirds of the children, leaving the possibility of obtaining detailed information about the infradiaphragmatic spread of disease [36].

The low frequency of abdominal disease in patients with mediastinal involvement only found by Brada *et al.* [35] has previously also been noted [50].

Although early studies claimed that there was an association between left-sided neck disease and abdominal disease, two recent larger series have not been able to confirm this finding [8, 17].

3. Prognostic factors in advanced Hodgkin's disease

The introduction of MOPP chemotherapy (nitrogen mustard, Oncovin [vincristine], procarbazine, and prednisone) for patients with advanced HD has significantly improved their life expectancy [51]. Although several other drug regimens have been introduced, no additional real improvement in prognosis has been achieved. A number of factors have been predictive of a high probability of achieving complete remission as well as of relapse-free survival and total survival after MOPP therapy with or without additional radiotherapy. The assessment of various prognostic factors, however, has usually been made in comparatively small patient series, which may explain why certain differences exist.

It is reasonably well established that patients who suffer a recurrence after primary radiotherapy have no worse (maybe better) an outcome than do primary HD patients [51]. In the majority of studies, the presence of constitutional symptoms has been predictive of a lower probability of achieving complete remission [51]. In other studies, age, histopathology, and/or the number of extranodal sites have had a predictive value [52–54]. The risk of relapse has varied for patients presenting with constitutional symptoms or different histologies, bone marrow involvement, or age [51, 53].

Several, but not all, studies have also noted that the dose and the rate of delivery of the chemotherapy regimens have been of importance for either the achievement of complete remission or for the patient remaining in complete remission [52, 53]. Although some reports have not been able to

confirm the deleterious effect of a low chemotherapy dose rate, it seems to be essential to retain as high a dose rate as long as possible [51].

4. Development of prognostic index

A number of prognostic factors have thus been found to influence the results of treatment of patients with HD as a group or in certain substages. Most of these prognostic factors, however, are themselves interrelated. The degree with which each factor contributes toward the prognosis is therefore, at present, uncertain. Large multivariate analyses are required to establish prognostic scores so that the most appropriate therapy for an individual patient can be selected, thus maximizing the effectiveness and minimizing morbidity. Since this requires a large number of patients uniformly staged and treated, there are only a few recent attempts in that direction.

In a review of the British National Lymphoma Investigation Studies, a prognostic index was developed on the basis of the results obtained from 743 patients (children and adults) with clinical stages IA or IIA confined to the upper half of the body. It was found that age, sex, ESR, the presence or absence of mediastinal involvement and, especially, the pathologic grade (LP + NS1 *vs* NS2 + MC) were the most important factors influencing overall survival, while the ESR, pathologic grade, and stage of the disease correlated with recurrence-free time. A prognostic 'survival' index was developed [9]: an index of <7.5 indicated a poor prognosis. This might indicate that, for these patients, chemotherapy is more appropriate than local radiation as a primary treatment. In similar study within the radiotherapy/chemotherapy group of the European Organisation on Research and Treatment of Cancer, Tubiana *et al.* [8] likewise performed a multivariate analysis of prognostic factors in 1139 patients (children and adults) in early stages of HD. Although a number of factors were shown to have an independent influence on both the incidence of relapse and the survival, two main prognostic indicators—namely, the number of involved sites and the combination of constitutional symptoms and ESR—appeared sufficient to identify the patients for whom a high recurrence-free survival could be obtained after treatment with STNI (subtotal nodal irradiation) associated with treatment of the spleen, either by splenectomy or spleen irradiation. It should be mentioned, however, that several factors of known prognostic importance from other studies such as the size of the mediastinal mass or the number of splenic nodules were not included in the analysis. Age remained the main prognostic indicator for survival after relapse in this large material.

5. Conclusion

The use of multiple prognostic factors to select patients with HD appears to provide a rational basis for a treatment decision. Several of the factors

employed—age, stage, constitutional symptoms, and tumor bulk—are objective and may be readily described. These factors may at present provide a basis for a reasonably rational treatment decision. In certain cases, however, there is a need for a more appropriate substaging in order to find the ideal treatment—*i.e.*, 'sufficient but not excessive.' A great number of parameters have been identified that could fulfill the requirements of providing an appropriate prediction and, in addition, be objective, reproducible, and inexpensive. In order to find these parameters of clinical relevance, it is of outmost importance to collect large number of patients uniformly staged and treated. With the continuing improvement in overall prognosis, survival is now so high that some of the factors previously of prognostic significance are no longer associated with a detectable influence on survival. Even those factors still having an impact on prognosis will probably do so to a decreasing extent in the future.

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7. Circulating cells in Hodgkin's disease

M. Ruud Halie, Ben E. de Pauw, and Jan W. Smit

The mode of spread of Hodgkin's disease within the body has been a subject of controversy [1–4]. One feature of lymphomas is that they originate from cells that have the potential to circulate. This should influence our thoughts about the ways the disease progresses and disseminates. The concept of lymphatic spread in the initial phase of Hodgkin's disease as favored by Kaplan has been opposed by the ideas of early hematogenous spread [2–4]. The different views have consequences for the approach to therapy. The results of local radiotherapy in localized Hodgkin's disease supported the opinion of Kaplan [5, 6]. However, further improvement in radiotherapy results has been achieved by the introduction of extended field irradiation [7]. This therapy can not be considered as being restricted to lymph nodes alone, but it also harbors an element of more systemic therapy since lymphocytes in adjacent noninvolved lymph nodes and circulating blood cells are also exposed. The finding that impaired cellular immunity occurred in stages of the disease that were considered to be restricted to one or two lymph node groups can be taken as an argument against a purely local disorder [8, 9].

In this chapter on the circulating cells in Hodgkin's disease, the implications of the presence of abnormal cells and some of the changes in normal cells in the peripheral blood will be discussed.

1. Abnormal cells in the peripheral blood

1.1. Sternberg-Reed cells

Even in patients with advanced Hodgkin's disease it is extremely rare to encounter Sternberg-Reed cells in routine blood smears. Probably Varadi found the first evidence of hematogenous dissemination in Hodgkin's disease by demonstrating the presence of Sternberg-Reed cells in blood smears [10]. His observation has been confirmed by Bouroncle and others [3, 11–13]. Typical Sternberg-Reed cells were also found by cannulation of the thoracic duct (14).

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Although several types of unusual cells have been described in the peripheral blood of patients with Hodgkin's disease, these are not identical or related to Sternberg-Reed cells.

1.2. Morphologically unidentifiable precursors

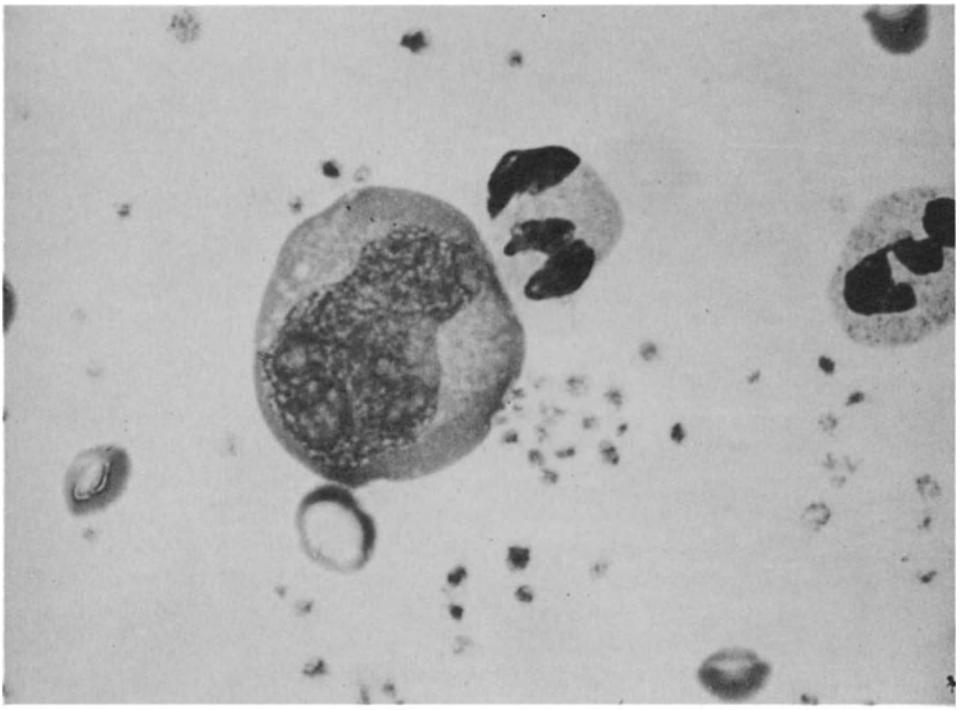
The large size of Sternberg-Reed cells may preclude direct extravasation between endothelial cells and it is tempting to assume a morphologically unidentifiable precursor of the Sternberg-Reed cells as the cause of hematogenous spread. From the studies by Zucker-Franklin *et al.*, [15], it appeared that such cells may indeed circulate even in early stages of the disease. Signs of clinical or pathologic disseminated stages were not found in these cases. This observation implies that circulating precursors do not always induce growth of Sternberg-Reed cells in normal lymphoid tissue, indicating a possible role of extrinsic factors in promoting further growth of these cells. The findings seemed to be specific in the sense that, in Hodgkin's disease, cells with morphology similar to that of Sternberg-Reed cells have been cultured and no such cells were found in cultures of normal individuals or patients with non-Hodgkin's lymphoma (NHL). However, no control studies have been performed in groups of patients in which similar multinuclear giant cells have been described in the lymph nodes, for instance, in infectious mononucleosis.

Further, the presence of these unidentified precursors has been correlated neither with clinical stages of the disease, nor with the results of therapy and prognosis. In that respect, this research does not contribute to the discussion on lymphatic *versus* hematogenous spread. It should be remembered that, in studies of solid tumors, the presence of circulating tumor cells in the blood is not necessarily associated with early dissemination [16].

1.3. Moderately basophilic blast-like lymphoid cells

The presence of these unique cells in the peripheral blood of patients with Hodgkin's disease was originally described by Halie *et al.* in 1972 [3]. The cells are medium to large sized; have a smooth, moderately blue staining of the cytoplasm in May-Grünwald–Giemsa stains; and have a perinuclear halo and very few organelles in electron microscopy. The nucleus has a fine convoluted chromatin structure with one or two prominent nucleoli (Figure 1A) [12, 13]. The cells proved to be not specific for Hodgkin's disease and have been encountered in patients with infectious mononucleosis and other viral diseases [17, 18].

In Hodgkin's disease, there is a correlation between the presence of these characteristic cells in the peripheral blood and the histologic demonstration of Hodgkin's foci in the spleen or bone marrow [4]. Therefore, these cells were considered to be indicative of hematogenous dissemination of the



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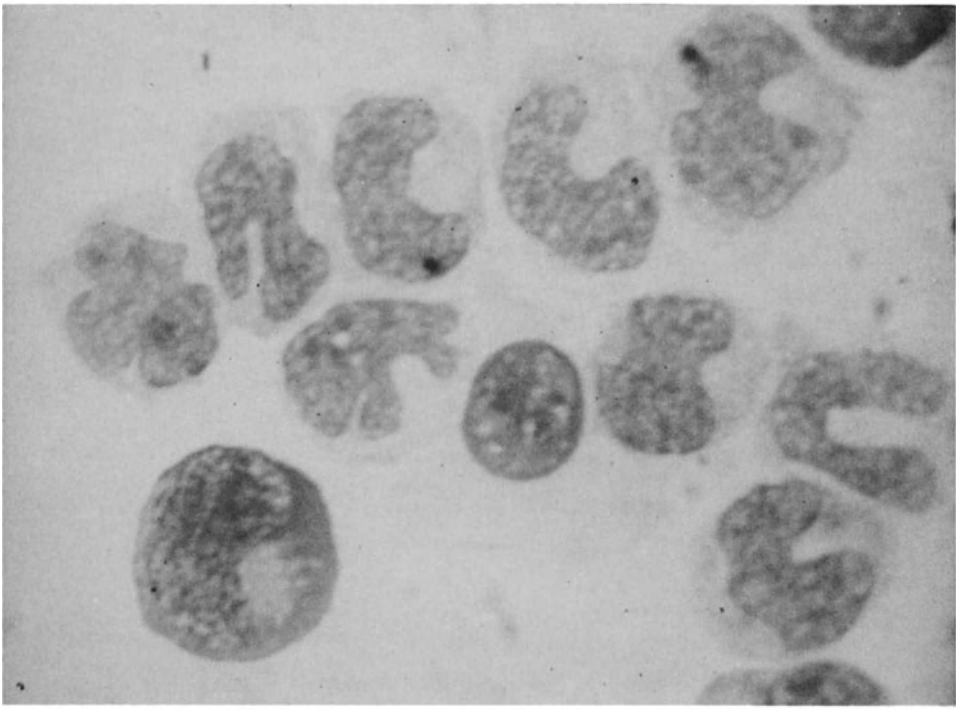

B

Figure 1. (*A*) 'Moderately basophilic cell' from the buffy coat of a patient with Hodgkin's disease. (*B*) 'Spontaneously proliferating cell' in an elutriation fraction of peripheral blood from a patient with Hodgkin's disease.

disease and, as a consequence for the therapeutic approach, chemotherapy was favored over radiotherapy in such cases.

1.4. Spontaneously proliferating cells

Lymphocytopenia has often been associated with active Hodgkin's disease in all stages and has been offered as an explanation for the impaired cellular immunity [19–21]. Not all subpopulations of lymphocytes are equally disturbed and even increased activity of certain subsets has been demonstrated [22–24]. Kuper and Bignall [25] studied seven patients with Hodgkin's disease and found increased numbers of cells in the blood capable of taking up ^{3}H-thymidine, though they were unable to identify the cells. Crowther *et al.* [26] provided evidence that the cells involved were lymphocytes, an observation that has been confirmed several times [23, 24, 27, 28].

It must be stressed that the different investigators on this subject probably have assessed different lymphocyte populations due to the techniques employed. Using nonenriched lymphocyte suspensions, Huber *et al.* [23], Bjorkholm *et al.* [24], and Shiftan *et al.* [28] reported an augmented spontaneous DNA synthesis by T-lymphocytes. This high spontaneous transformation by T cells was associated with a bad prognosis and appeared to be inversely correlated with the impairment of the *in vitro* cellular immunity.

Since the number of spontaneously DNA-synthesizing cells in the peripheral blood is rather low, methods to enrich these cells seemed warranted [29–31]. The size of the spontaneously transformed lymphocytes proved to be above average, with a specific gravity between 1.055 and 1.065 g/ml, as established by means of counterflow elutriation and continuous density centrifugation [29]. The cells concerned can be recovered from a fraction next to the monocytes in both elutriation and centrifugation techniques. This coincides with the density of the supposed hematologic stem cells in fractionating bone marrow suspension [32]. Morphologically, the main population of the spontaneously DNA-synthesizing lymphocytes show a striking similarity to the moderately basophilic cells (Figure 1A and B) described by Halie *et al.* [3] and have some resemblance with lymphocytes transformed *in vitro* by mitogens and antigens [2]. The phenomenon is not typical for Hodgkin's disease, because similar cells have been seen in the blood of patients with viral infections.

Attempts were made to characterize these cells immunologically [33]. Enriched fractions were incubated with monoclonal antibodies. An increased incidence of Ia-positive and OKT9-positive cells was found. No surface or cytoplasmic immunoglobulins could be demonstrated. More conventional markers like E rosettes, EAC rosettes and Fcγ receptors were also negative [34].

There is a positive correlation between the number of spontaneously transformed lymphocytes and the stage of the disease: spontaneous DNA synthesis seemed to increase with the stage of the disease. Within the

Table 1. Thymidine incorporation after removal of T cells and its inhibition by autologous T cells in relation to survival 8 years after diagnosis and treatment.

Subject	Thymidine incorporation by non-T cells (cpm)	% Inhibition	Disease status
1	6975	68	Alive and well
2	4250	65	Died
3	6310	82	Alive and well
4	2800	41	Died
5	405	48	Alive and well
6	3800	79	Alive and well
7	1300	23	Died
8	26,490	43	Alive and well
9	850	35	Died
10	3600	50	Alive and well

various staging groups, lymphocytes of patients with huge lymph nodes tended to have higher ^{3}H-thymidine than did cells of patients with limited enlargement of the nodes [35]. The level of spontaneous proliferations seemed to reflect the amount of tumor mass. Following therapy, the spontaneous transformation of the patients in clinical remission returned to a normal range and was independent of the number of circulating lymphocytes [36].

Further investigations showed a substantially increased ^{3}H-thymidine incorporation into high-density non-T cells after elimination of T cells from the same density fraction, indicating a suppressive effect by T-lymphocytes on the spontaneous DNA synthesis of certain subsets of cells [37]. The inhibition of non-T cells by T cells disappeared after staging laparotomy with splenectomy indicating a role of the spleen in this phenomenon.

Although increased spontaneous DNA synthesis by peripheral blood lymphocytes has been associated with a bad prognosis, it must be kept in mind that this spontaneous transformation was also related to tumor mass and advanced stages in Hodgkin's disease. Analysis of the patients after 6 years suggested that the patients with the highest spontaneous transformation within a certain stage showed better prognosis. This specially holds true for patients with high ^{3}H-thymidine incorporation after removal of T cells (Table 1).

1.5. Large atypical basophilic cells

Large, atypical basophilic lymphoid cells had already been described by Bunting [38] in 1914 and successively analyzed in more detail by Klima in 1952 [39], Crowther *et al.* [26] and others [12, 17]. Crowther *et al.* have described these cells as large lymphocytes with a strongly basophilic cytoplasma, capable of DNA synthesis and called them immunoblasts; they suggested that these cells were reactive against the tumor process. No evidence for this hypothesis has been gained since. Similar cells have been

isolated from the blood of normal subjects after immunization and prior to transplant rejection [40]. Furthermore, the cells concerned could represent the reaction against an undiscovered associated infection, since patients with Hodgkin's disease are known to be particularly prone to viral infections as evidenced by the increased incidence of herpes virus infections [41] and the frequently abnormal antibody titers against cytomegalovirus and Epstein Barr virus [42–44].

The cells described by Crowther *et al.* have been found in lymph node preparations from patients with Hodgkin's disease [45], but are probably also present in 'normal' lymphoid tissue, *e.g.*, the tonsils (J.W. Smit, unpublished, 1987).

Although the exact cause for the presence of the basophilic cells is not known, it is highly probable that they are indeed reactive cells and not tumor cells [12, 17, 26].

1.6. Large granular lymphocytes with parallel tubular structures

A second population of lymphocytes normally occurring in peripheral blood that proved to be increased in number in patients with Hodgkin's disease is composed by the so-called large granular lymphocytes (LGL) [13, 46]. This subpopulation was shown to contain parallel tubular structures (arrays) and possessed the Fc receptor for immunoglobulin G (IgG) [47, 48]. Equivalent to the parallel tubular structure (PTS) was the presence of amorphous electrodense granules. In light microscopy, both cell kinds are recognized as medium-sized lymphocytes with an abundant amount of cytoplasma and azurophilic granules.

Several investigators have studied the function of large granular lymphocytes in the normal immunologic response (see below). The cause of the increase in the LGL population in Hodgkin's disease patients was investigated by incubation of normal mononuclear cells from healthy donors with patients' sera [49]. About half of the sera induced an increase in the number of lymphocytes with PTS and/or related amorphous electrodense granules. There was a correlation with the clinical course of the disease: patients with an unfavorable prognosis nearly all demonstrated this effect, while sera of patients with a favorable outcome mostly did not show such an effect.

The effect of Hodgkin's sera on normal lymphocytes is similar to the effect of α-interferon on the number of lymphocytes with PTS and amorphous granules [49, 50]. The increase of lymphocytes with PTS from normal donors by sera from patients with Hodgkin's disease can be blocked by incubation of these sera with anti-α-interferon. Different concentrations of anti-α-interferon have to be used for each patient's serum (Table 2).

The *in vitro* induction of LGL by interferon was not accompanied by a coinciding increase in the percentages of helper/inducer T-lymphocytes, suppressor/cytotoxic T cells, or natural killer/killer cells, as determined with the monoclonal antibodies OKT4, OKT8, and Leu7, respectively.

Table 2. Blocking of the *in vitro* increase by Hodgkin's sera of the percentage of PTS-containing lymphocytes from normal donors by the addition of anti-α-interferon.[a]

	% PTS lymphocytes					
		With anti-α-IFN				
Patient sera	Without anti-α-IFN	2 μl	4 μl	8 μl	10 μl	20 μl
1	36	–	34	24		
2	34	31	29	30	33	22
3	31	29	31	23		
4	31	30	21	23		
5	32	28	23	22		
6	39	33	34	24		
7	30	29	30	20		

[a]Patients sera incubated with anti-α-IFN for 1½ h. Normal lymphocytes, incubated with recombinant α-IFN and anti-α-IFN (Boerhringer Mannheim, FRG)→20% PTS lymphocytes (mean).

Recent investigations with the monoclonal antibody Leu11b indicated that this subpopulation was indeed increased by interferon, indicating a transition of lymphocytes within the population of T-cytotoxic/effector cells that already had the appropriate membrane antigens into a further diversification of cells characterized by the PTS and development of additional antigens [50].

2. Conclusions

The results of various investigations indicate the existence of abnormal cells or abnormal numbers of normal cells in peripheral blood specimens of patients with Hodgkin's disease.

Subsequently an attempt will be made to explain the occurrence of the various cells in the light of present knowledge of the development of normal blood cells. The main conclusions from the foregoing paragraph is that abnormal cells are present in small numbers in the peripheral blood of patients with Hodgkin's disease, independent of stage. At first glance, these cells seem heterogeneous in terms of both origin and function.

Undoubtedly, when present, the Sternberg-Reed cell is the most prominent of the abnormal cell populations in the peripheral blood, indicating hematogenous dissemination of the disease. However, the number of instances in which this cell has been encountered are very few [3, 10]. In contrast to this, the finding by Zucker-Franklin *et al.* of unidentifiable precursors of Sternberg-Reed cells in the majority of patients [15], even in early stages of the disease, supports the hypothesis of early hematogenous spread.

Possible explanations for the scarcity of Sternberg-Reed cells in peripheral blood are that, in general, they are also not abundantly present in malignant tissues and that their size may prevent a frequent and easy entry into the vessels.

The moderately basophilic cells [3, 12, 13] in all probability also have a direct bearing on the dissemination of the disease. Their scarcity in the peripheral blood and the lack of adequate techniques at that time prevented characterizations other than by light and electron microscopy and cytochemical stains. Identification of these cells as to their origin was therefore not possible. Although the cells have also been found by other investigators [42, 45, 51], there have also been denials as to their existence and relation to the dissemination of the disease [17, 52]. Personal discussions with some of the latter investigators (C.A. Schiffer, personal communication, 1981) confirmed our opinion that they had been looking at different kinds of cells, mainly the basophilic immunoblasts described by Crowther *et al.* [26] and others [34].

The results of the studies by De Pauw *et al.* [35, 37] with enrichment of the spontaneously DNA-synthesizing peripheral blood lymphocytes have led us to believe that these cells and the moderately basophilic cells are identical. Morphologically the cells are similar and they have the same cytochemical characteristics. The lack of specific monoclonal T-cell or B-cell characteristics argues against a classification as a normal immunoreactive cell. In early stages of the disease, these cells could only be identified after enrichment by means of density centrifugation or elutriation [43]. It is probable that their presence in peripheral blood points to hematogenous dissemination since their presence is directly correlated with tumor mass [35, 43] and spleen involvement in the disease [18]. The extremely low number of cells probably explains why, in our earlier publications, only correlation with splenic dissemination was found [3].

The cause of this spontaneous lymphocyte transformation remains obscure. One explanation for the phenomenon may be that these are immunoreactive cells challenged *in vivo* by a hitherto unknown disease-related antigen. No proof has been found to support this hypothesis. On the other hand, these cells may be of neoplastic origin, but they are not the characteristic malignant cells of Hodgkin's disease. The high proliferative capacity and the correlation with tumor mass suggest that these cells are precursors of the malignant cells of the disease. Since Zucker-Franklin *et al.* also discovered precursor cells by *in vitro* culture, although not identified by morphologic or other methods, there is a chance that the moderately basophilic cells, the spontaneously DNA-synthesizing cells, and the Zucker-Franklin precursor cells are one and the same. Experiments are now under way to culture enriched populations of spontaneously proliferating, moderately basophilic cells according to the method described by Zucker-Franklin *et al.*

Analysis by immunologic markers, and chromosomal and gene rearrange-

ment studies of these cultured cells, should provide answers to several of the questions mentioned above.

All evidence in morphology as well as in immunologic characteristics does make it highly improbable that the precursors of PTS-containing lymphocytes are in lineage connected to one of the above-mentioned cells. They are a normally occurring lymphocyte subpopulation that is increased in patients with Hodgkin's disease [13, 46]. It is likely that this reaction is caused by a serum factor and, since there is a similarity with the *in vitro* effects of interferon, it is possible that interferon or an interferon-like substance is the factor responsible for the induction of PTS-containing lymphocytes. So far, however, increased levels of α–interferon could not be demonstrated in the sera of Hodgkin's patients that had the PTS-inducing effect. Levels of other interferons have not been measured by us so far.

In conclusion, we think that, in all stages of Hodgkin's disease, malignant precursor cells may be circulating in the blood, as evidenced by the presence of moderately basophilic cells, spontaneously DNA-synthesizing cells and the unidentified precursor cells of Zucker-Franklin *et al.* This presence does not necessarily indicate that the tumor will indeed proliferate at different sites. Other lymphocytes, such as the lymphocytes with paratubular structures, could exert a suppressive effect on the spontaneously proliferating cells, thereby suppressing the proliferation of Hodgkin's tissue elsewhere.

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8. Current management and controversies
A Surgeon's View

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The treatment of early-stage Hodgkin's disease in adults has now become almost standard. Early-stage Hodgkin's disease (stages I and II in the Ann Arbor classification) is generally treated by irradiation that extends at least one lymph node group beyond the demonstrable disease (mantle, extended mantle, which includes the periaortic nodes, inverted Y, or total nodal irradiation) [1–4]. The treatment of more extensive disease (stages III and IV in the Ann Arbor classification) remains unsettled, especially in stage III disease where chemotherapy and/or total nodal irradiation have been used. As far as chemotherapy is concerned, MOPP (nitrogen mustard, Oncovin [vincristine], procarbazine and prednisone) [5] is the 'gold standard,' although, because of the problems associated with this regimen (notably, sterility in males, the relatively high toxicity, the risk of second neoplasms, and a significant failure rate), other chemotherapy regimens are being studied.

In childhood Hodgkin's disease, the treatment has tended to parallel that used in adults; however, there is no generally accepted treatment for any stage.

One of the major problems in mounting a study (especially in early-stage Hodgkin's disease) is that the various current therapies are so successful. Long-term survival in stage I and II disease is generally quoted as being 80%–90% [1–6] with relapse-free survival being as high as 75%–80% in some studies [4–8]. It is hard to argue with such success. However, this survival is bought at a price [7], and the final accounting of the cost of current therapies may not be known for 20–30 years. For this reason, it is imperative that effective, minimally toxic therapies be designed in order to treat minimal disease with the least toxic (in terms of both long-term and short-term toxicities) effective therapy. It is also important to develop effective therapies to salvage patients who fail initial therapy or who present with late-stage disease.

One thing that is apparent is that there is a need for new prognostic markers other than stage and histology. If an independent prognostic marker could be found that would predict the patients who would be likely to

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respond to current therapies (which includes 60% of patients with stage III disease and 40% of patients with stage IV disease), then conceivably, identification of potential nonresponders with early-stage disease will enable intensification of the treatment of these patients and even (possibly) a reduction of treatment in good-prognosis stage III and stage IV patients.

Another major controversy is whether a staging laparotomy is still needed in modern-day therapy for Hodgkin's disease [9, 10]. In a treatment regimen in which all patients receive intensive chemotherapy, regardless of stage, the answer is clearly no [11]. In the situation where stage determines therapy, however, the answer must clearly be yes, since there is still a significant percentage of patients whose stage is incorrectly assessed by our current, most sophisticated, noninvasive diagnostic methods.

This chapter addresses some of these controversies. However, the bulk of the chapter is directed to the question of the staging laparotomy.

1. Radiation therapy (quick and effective, but stunting)

The most attractive aspect of radiation therapy is the relatively short duration of the therapy and the lack of systemic side effects. Most courses of radiation therapy can be completed within 6–8 weeks. During the therapy, however, disruption of the patient's normal activities can be considerable, especially when one considers that most treatment regimens require daily doses of radiation 5 days a week [3, 6, 7]. The major problems with radiation therapy in early studies of this technique were skin reactions, subcutaneous fibrosis, pericarditis, and pneumonitis. Both the incidence and severity of these have all been reduced considerably by current techniques. The major problems now reported in children are reductions in sitting height, decreased intraclavicular distance, and hypothyroidism [7]. There is also the risk of second tumors, which may be enhanced in patients who receive concurrent chemotherapy. It is still too early to tell what the 40- to 50-year risk of these complications is after current therapies have been used. Krikorian *et al.* [12] have estimated that, following total nodal irradiation and MOPP, there is a 2.3% risk of developing acute nonlymphatic leukemia and a 1.3% risk of developing non-Hodgkin's lymphoma in the first 7 years after therapy. This study was carried out in adults. If this is extrapolated at the same rate per year over 40 years, then the risks would be 13.8% for acute nonlymphatic leukemia and 7.8% for non-Hodgkin's lymphoma. These figures are more than a little worrisome.

Valagussa *et al.* [13], from Milan, recently reported the incidence of second neoplasms in 1329 patients with Hodgkin's disease (mainly adults) followed for a median period of 9.5 years: 68 second neoplasms were documented. There were no cases of leukemia in patients treated with radiation therapy alone. They gave a 12-year estimated risk of leukemia as

1.4% ± 2.3% with chemotherapy alone and 10.2% ± 5.2% with radiation therapy and MOPP. The overall risk of non-Hodgkin's lymphoma was 1.3% ± 0.6% and the overall risk for other solid tumors (excluding basal cell carcinomas) was 6.7% ± 1.4%. The actuarial risk for non-Hodgkin's lymphoma in patients treated with radiation therapy alone was 1.9% ± 1.2% (slightly higher than the risk for the whole group). The risk for second solid tumors (all of which occurred within the radiation therapy fields) was 8.9% ± 2.6% (second only to that for radiation therapy plus MOPP, which was 9.9% ± 6.9%). It must be noted that the risk for leukemia was very high (15.5% ± 7.6%) in patients who had received salvage therapy with MOPP after failing radiation therapy. However, it must be noted that most of these cases occurred in adults. There was only one child (of the 207 in the study) who developed leukemia.

2. Chemotherapy (overkill?)

A variety of chemotherapy regimens and combined chemotherapy–radiation therapy regimens have been reported in children. One of the most effective chemotherapy regimens is the MOPP regime. In pediatric Hodgkin's disease, this is usually continued for six cycles. However, the complications of this regimen can be considerable, and death from complications of the treatment has been reported in stage I and II patients who have ben treated with MOPP. MOPP is demonstrably toxic. In one series of children with early-stage Hodgkin's disease, two of 11 patients treated with MOPP alone died [14]. Other types of chemotherapy are currently being evaluated, but at this time no definitive 'best' therapy for any stage of Hodgkin's disease in children has been defined. The major complications, apart from toxicity, have been sterility in two-thirds of the male patients and the risk of second neoplasms. The risk of sterility in prepubertal boys is said to be less than in adults, although, because MOPP has been in wide use for <20 years, the definitive answer to this question will have to wait for another 5–10 years before enough children have matured sufficiently to allow the study of fertility to be completed. Female patients treated with MOPP almost invariably suffer a premature menopause, regardless of their age [15], although two earlier studies suggested that more than half of the female patients treated with MOPP may remain fertile for some time at least [16, 17].

Another regimen that has been widely used in adults and is currently being tested in children is ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine). The long-term toxicity of this regimen is not yet fully defined. However, the pulmonary toxicity of bleomycin argues strongly for caution if significant areas of the lung fields are to be irradiated in patients with this disease. Similar concerns pertain to the possibility of radiation therapy potentiating the cardiotoxicity of Adriamycin.

3. The role of surgery

At present, the surgeon is involved in almost every case of Hodgkin's disease. Almost invariably a biopsy of the involved node is required to confirm the diagnosis. Apart from this fundamental involvement, however, the surgeon's role in this disease is limited unless a staging laparotomy is required. The need for staging laparotomy is disputed. However, this controversy should be easily resolved. There is no place for staging laparotomy if all patients are to receive systemic chemotherapy as potent as MOPP or ABVD [11]. On the other hand, an initial staging laparotomy plays a vital role in the decision-making process in patients in whom one of the treatment options is involved-field or limited irradiation. In such cases, a strong case can be made for the staging laparotomy.

The role of laparotomy in evaluating massive local disease in the abdomen or pelvis, and of suspected recurrent abodminal disease, *i.e.*, secondary laparotomy, has been limited in pediatric patients because of the rare occurrence of these phenomena, but has become standard practice in some adult series. Splenectomy may also be carried out in such patients with advanced disease to increase hematologic tolerance for chemotherapy [18].

3.1. The case for initial staging laparotomy

The case for staging laparotomy in patients in which therapy depends upon the stage of disease revolves around the risks of the procedure and the inability to be certain that masses demonstrated by current imaging modalities (most commonly, lymphangiograms and CAT scans) are, in fact, tumor. The spleen and splenic hilar areas as well as, to some extent, the porta hepatis and superior celiac areas are difficult to evaluate by noninvasive techniques [19] and most radiologists agree that the results of most studies in this area are highly equivocal [20–22]. In most reported series, the staging laparotomy altered the clinical staging in 25%–46% of patients [9, 10].

A recent retrospective study of 47 children with Hodgkin's disease by Dudgeon *et al.* [22] found that, of 16 patients with abnormal lymphangiograms, only five had histologically positive nodes (11 of 16 or 69% false positive). They also found that three of 31 patients with normal lymphangiograms had positive retroperitoneal nodes for a false-negative rate of 10%. They therefore concluded that the overall accuracy of the lymphangiogram diagnosis was only 70% and that lymphangiogram is not helpful in the initial staging of pediatric Hodgkin's disease. Another recent report in a small series of 50 patients [10] pointed out that three of 12 clinical stage (CS) I patients were upstaged, as were eight of 20 CS II patients and three of 18 CS III patients. Overall, 14 (28%) of the 50 patients, were upstaged on the basis of the laparotomy. More importantly, six of the 18 CS III patients were *downstaged*. Clearly, there is abundant evidence that, even with modern technology, staging laparotomy alters the staging of significant numbers of patients.

The importance of a more detailed staging of patients with abdominal disease has been emphasized in some series. The contention that Hodgkin's disease confined to the upper abdomen (stage III_1A) should be basically treated as stage II disease, while that extending into the lower abdomen or pelvis (stage III_2A or III_3A) should receive therapy regimens designed for stage IV, has been widely accepted [23, 24]. At Stanford, Hoppe *et al.* believe that *extent* of gross splenic involvement is a major prognostic factor in stage III_1A disease and that this can be quantitated [25]. Series of sufficient size to demonstrate the significance of these observations in childhood will probably never be available, but there is no reason to think that the situation differs from that found in adults. These concepts of the significance of the details of tumor dissemination have been incorporated into the most recent pediatric cooperative group study of advanced disease (CCSG) and a laparotomy will be performed in a majority of these pediatric patients. Such refinements in evaluation are, at present, impossible without surgical visualization.

The major problem with staging laparotomy is the short- and long-term morbidity of the procedure. The major short-term problems are wound infections, dehiscences, and incisional hernias. The major medium-term problems are adhesions and adhesive obstruction. The major long-term problem is postsplenectomy sepsis. All of the studies published attest to the fact that the morbidity of the staging laparotomy is low. Nelson *et al.* [9] report an operative complication rate of 8%.

One of the most comprehensively studied group of patients is that reported from the Intergroup Hodgkin's Disease Study: 234 patients undergoing staging laparotomy and splenectomy were followed for a mean of 5.5 years and two detailed reports have been published on this group of patients 3 years apart [26, 27]. These reports detail six early postoperative complications among 234 laparotomies. There were three cases of postoperative atelectasis and/or pneumonia, one intestinal obstruction, and one ureteral obstruction (both of the latter requiring operation for relief). There were a further seven cases of adhesive obstruction, none of which required intestinal resection, although one patient did require plication of a necrotic perforation. One further patient underwent oophorectomy 3 years after laparotomy when a repositioned ovary infarcted. There were five cases of sepsis with positive blood cultures and five additional cases of probable sepsis with negative blood cultures. All of the patients with positive blood cultures grew either *Streptococcus pneumoniae* (two cases) or *Hemophilus influenzae* (three cases). If the cases of probable sepsis are included as postoperative complications, then the maximum postoperative complication rate is 9.8%. If the five cases of probable sepsis are excluded, then the complication rate is 7.7%. When such complication rates are compared with a 25%–40% chance of misstaging, it appears, to these surgeons at least, that the benefits clearly outweigh the risks of the procedure.

The ability to perform an incidental appendectomy in the course of

laparotomy without increasing the complication rate is of relatively minor significance, but the ability to transpose the ovaries into irradiation-shielded areas may be important. In the long course of a patient with relapse, it is impossible to determine where recurrent disease will be found and under what circumstances irradiation will be indicated. The probability of successful pregnancies after such transposition has been demonstrated [16, 28].

3.2. The case for partial splenectomy during staging laparotomy

The authors of this chapter have elected not to present an entirely common point of view in respect to this question. The major section is written by the primary author (K.C.P.) with subsequent comments (D.M.H.).

Overwhelming sepsis has been recognized as a complication of splenectomy since 1952 [29], and Singer [30] confirmed the extent of the risk 20 years later. Chilcote *et al.* [31] suggested that the rate of postsplenectomy sepsis in Hodgkin's disease patients could be as high as 20% with a 50% mortality. However, most of the patients reported in that particular series were stage III or stage IV patients undergoing intensive chemotherapy and/or radiation therapy. Certainly, the data from the Intergroup Hodgkin's Disease Study [27] suggest that the incidence of postsplenectomy sepsis is much less than 10% and that its severity, and possibly its frequency, can be favorably modified by pneumococcal vaccine and possibly (by extension, at least) by the *H. influenzae* type B (HIB) vaccine. An optimistic reading of the Intergroup Hodgkin's Disease Study data would be that five cases of sepsis in 234 staging laparotomies is an incidence of only 2.1% with no mortality. A contrary, more pessimistic view is that these cases were followed for a mean of only 5.5 years and a 2.1% incidence reflects a risk that is 0.38% per year. If this risk remains constant over a projected life span of a further 50 years (and several reports attest to the fact that the immune defect in postsplenectomy sepsis is permanent), then the cumulative risk could be almost 20%.

The exact extent of the risk of postsplenectomy sepsis has yet to be clearly defined. Clearly, immunization with both polyvalent pneumococcal vaccine and the HIB vaccine will not provide total lifetime protection, because not all serotypes can be effectively covered by these vaccines. Antibiotic prophylaxis should be a reasonable alternative, but the antibiotic most commonly recommended (penicillin) will not provide adequate protection against some of the organisms implicated in postsplenectomy sepsis. The other major drawback to antibiotic prophylaxis is patient compliance. It is difficult enough for most people to complete a 10-day course of antibiotics given for a sore throat or otitis media. Continuing antibiotic prophylaxis to prevent something that may never happen must be very difficult. A recent study in patients with Sickle cell disease and functional autosplenectomy highlights this problem [32]. In 88 children given both prophylactic penicillin V twice a day and polyvalent pneumococcal vaccine, there were eight

documented cases of sepsis. One of the major problems in these patients was failure to take the penicillin.

Because of this projected long-term risk, Boles *et al.* [33] proposed a partial splenectomy for staging laparotomy and demonstrated the feasibility of this concept in a series of cases. The concept that partial splenectomy protects against the risks of postsplenectomy sepsis is soundly based on experimental evidence in animal models. Although no human experiments have been reported, there have been no cases of postsplenectomy sepsis reported after partial splenectomy for trauma. There have been some reports, however, of postsplenectomy sepsis in patients who have demonstrable splenosis on liver–spleen scan after splenectomy for trauma [34, 35].

Rowley [36, 37] clearly showed that the primary immunologic defect following splenectomy is an inability to mount a rapid immune response to a new intravenously injected particulate antigen. Several studies [38–42] since then have shown that even small fragments of spleen with an intact blood supply give normal antibody responses to a challenge with intravenous particulate antigens.

The pathology of splenic involvement in Hodgkin's disease is very similar to that found when the liver is involved. Involvement can be either diffuse or focal. No one has ever suggested that anything more than one wedge biopsy and two needle biopsies from each lobe are required to detect liver disease. It is not logical to require any more than a comparable sample of the spleen, but most protocols call for total splenectomy routinely, presumably because the spleen is considered to be less essential than the liver.

The most widely quoted report, with respect to splenic involvement, was written by Dearth *et al.* from the Mayo Clinic [43]. Unfortunately, the figures most often quoted from this report misrepresent the results of that study. The article reports that 'of approximately 320 cases of staging laparotomy...there were 112 in which splenic disease was identified.' The authors report a total of 27 cases in which there were only 1–5 nodules within the spleen substance, 22 of which did not have grossly visible subcapsular nodules: 'of these 22 spleens, 14 were associated with no other abdominal involvement.' 'In 13 of the 14 spleens, the disease was localized or limited to one pole in such a way that splenic disease could have been missed by partial splenectomy.' The authors conclude that 'the risk of failing to diagnose occult splenic involvement in Hodgkin's disease could have been as high as 11.6% if partial splenectomy had been employed.' This latter statement ignores the fact that only 112 of 'approximately 320' spleens were involved in the first place. In other words, two-thirds of the spleens were removed unnecessarily. This latter figure is very similar to the risk of involvement of the spleen reported following total splenectomy by Muraji *et al.* [44], and the figures reported by Boles *et al.* [33] in patients who had a partial splenectomy. If the risk of missing splenic involvement is examined with respect to the whole group (assumed to be 320), then the risk of missing splenic involvement falls to 13 out of 320 or 4.06%. If one assumes a

random distribution of the nodules, and a hemisplenectomy, then the risk would drop to no more than seven out of 320 or 2.19%. This can be no more than the risk of missing occult liver disease or the risk of missing involved lymph nodes in patients whose abdominal lymph nodes are not grossly enlarged. Because of the normally larger lymphatic mass in young children especially, node sampling is usually blind and probably could also have a significant error. Unfortunately, this error would be very difficult to quantify.

In patients who may receive irradiation of any splenic remnant in the event of splenic involvement being detected on a partial splenectomy, there are two possible courses of management. The ideal management would be to perform the hemisplenectomy early in the staging laparotomy and request the pathologist to slice it into 2- to 3-mm slices immediately. If no involvement is detected in the fresh specimen, then it is unlikely to be found in the fixed specimen. If the splenic resection specimen is positive, then either the rest of the spleen could be resected, or the splenic remnant could be positioned so as to reduce radiation to the left kidney and the base of the left lung to a minimum. The accuracy of the subsequent radiation therapy could be greatly enhanced in these patients by marking the splenic remnant with titanium clips to provide an accurate representation of the spleen on the planning films. It would perhaps be best to examine such patients under fluoroscopy before completing the radiation therapy planning in order to determine the extent to which the splenic remnant moves during respiration.

My coauthor (D.M.H.) agrees that the risk of undetected splenic involvement, employing partial splenectomy, would be low—possibly not much higher than the risk of missing occult liver or lymph node disease. However, in the case of splenic errors, something relatively simple can be done to lower the risk—a situation not true in the other two areas. Most partial splenectomies observed (D.M.H.) were less than hemisplenectomies.

The ability of the surgeon to recognize Hodgkin's disease by gross inspection of whole or sectioned spleen segments, or of the pathologist to identify disease by rapid tissue studies, is limited. Thus, there will be a group of patients who, having had a partial splenectomy, will be determined later to require upper abdominal irradiation, either on the basis of disease in the removed splenic segment or in adjacent lymph nodes. This group may suffer the adverse effects of both forms of management, *i.e.*, they will have had a partial splenectomy as well as irradition of adjacent structures.

Relative to the incidence and severity of septic episodes in postsplenectomy patients, the following points are significant. A high percentage of septic episodes in *current* series occur during intensive chemotherapy for primary or secondary relapse. This is a group of patients who have frequent (even lethal) septic episodes with intact spleens and must be regarded as a separate category with unique problems. Further, the risk of sepsis secondary to the encapsulated organisms (*H. influenze* and *S. pneumoniae*) does appear to decrease, although it is not eliminated, with increasing age. The

lethal nature of these episodes, particularly relative to *H. influenzae*, would appear to be almost absent in adults.

In almost all of the cases of sepsis in the large pediatric series [26, 27], the patient had either not received standard pneumococcal vaccination, was not taking prophylactic antibiotics, or both.

4. Conclusions

There is still clearly a need for further studies to define the role of the various therapeutic modalities in Hodgkin's disease in children. The best plan in such studies would be to define the least toxic regimen possible. As such, it may well be necessary to use some combination of chemotherapy and/or low-dose (possibly limited) radiation therapy. Another need that has not yet been met, or even studied in any systematic fashion, is the possibility of defining another prognostic factor that is independent of stage and histology. Even with current treatments, occasional stage II patients die of progressive disease. Alternatively, 40%–50% of stage IV patients can be rendered disease free and may possibly be able to be effectively treated with less toxic therapies.

Hodgkin's disease is a neoplasm in which it is possible to achieve 'cure' (or at least a long-term disease-free survival) in a high proportion of patients. It is perhaps time to attempt to define the least toxic effective therapy. This goal is especially important in children.

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9. Indications for staging laparotomy and partial splenectomy

Harald J. Hoekstra and Willem A. Kamps

The value of staging laparotomy with splenectomy for the staging of Hodgkin's disease was first reported in 1969 by Glatstein *et al.* [1]. Several reports have demonstrated changes in the clinical stage (according to the Ann Arbor staging classification) in 15% to ~50% of the children with Hodgkin's disease who underwent a staging laparotomy with splenectomy [2–9]. A staging laparotomy is a safe surgical procedure with a low acute morbidity and a mortality rate of <1% [10]. Late complications are intestinal obstruction (4%) and overwhelming infections (10%–20%) [10–14]. The risk of postsplenectomy sepsis is ~10% and particularly high in children with Hodgkin's disease treated with combined-modality therapies of radiotherapy and chemotherapy, due to the disturbance of the immune system [12]. The mortality of this postsplenectomy sepsis is high and can reach up to 50% [12, 15]. Pneumococcal vaccine and routine prophylactic antibiotic therapy with penicillin or erythromycin has reduced the incidence of postsplenectomy infections in these children [16, 17]. To decrease the hazard of overwhelming postsplenectomy infections, partial splenectomy was introduced in the staging procedure for Hodgkin's disease [13, 18]. Other centers avoid splenectomies for Hodgkin's disease, especially in the younger children [19].

The important difference between Hodgkin's disease in children and adults that influences the treatment strategy for Hodgkin's disease in children is age. With the various combined-modality therapies of radiotherapy and chemotherapy, the overall 5-year survival is ~90%. The cervical or mediastinal lymph nodes are involved in 90% of the children with Hodgkin's disease; involvement of axillary or inguinal lymph nodes is uncommon [16]. The indications for a staging laparotomy are controversial for total as well as for partial splenectomy. The key of the staging laparotomy with or without a (partial) splenectomy is to identify those patients who do not require combined-modality therapies and can be spared the short- and long-term related treatment morbidity of these combined modality therapies.

This chapter addresses the indications of staging laparotomy and partial splenectomy for Hodgkin's disease in children.

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1. Clinical staging

In general, the pretreatment evaluation of a child with Hodgkin's disease consists of a careful history, with specific questioning for systemic symptoms, physical examination, and laboratory and radiographic investigations. Laboratory studies include a complete blood count, erythrocyte sedimentation rate, serum chemistry, and liver and renal function tests, as well as serum alkaline phosphatase and serum copper. Radiographic investigations include posterior–anterior and lateral chest radiography, and computerized axial tomography (CT) of the chest, abdomen, and pelvis. When computerized tomography is not available, whole-lung tomography as well as lymphangiography and intravenous urogram (IVU) are an alternative in the radiographic staging procedure. In some institutions, abdominal CT, lymphangiogram, and IVU are used supplementarily. Isotopic (bone and gallium) scans, abdominal ultrasound, and miscellaneous radiographs are optional and not routinely used for the radiographic staging. Bone marrow biopsies are performed in all children with Hodgkin's disease. The workup for the clinical staging of Hodgkin's disease in children is listed below:

- History
- Physical examination
- Laboratory studies
  - Complete blood count
  - Erythrocyte sedimentation rate
  - Liver and renal function tests
  - Serum alkaline phosphatase
  - Serum copper
- Radiographic studies
  - Chest x-rays
  - CT scan chest–abdomen–pelvis
    - or/and
  - Whole lung tomography
  - Lymphangiography
  - IVU
  - Isotopic scans (optional)
  - Abdominal ultrasound (optional)
  - Miscellaneous radiographs (optional)
- Bone marrow biopsies

Indications for a staging laparotomy are clinically stages I, II, and III. In stage IV, the laparotomy will not alter the stage and therapy, and therefore there is no need for a staging laparotomy and (partial) splenectomy. Splenectomy is sometimes carried out in stage IV to increase the hematologic tolerance for the chemotherapy [20].

The majority of the children will be clinically stage I or II disease localized in the cervical or mediastinal lymph nodes, with a predominance in the preteen years [5, 16]. Nodular-sclerosis and lymphocyte-predominant

subtypes are common. The lymphocyte-depleted histology is rarely diagnosed [21].

2. Staging laparotomy

There is an indication for a staging laparotomy in all protocols where the stage of the disease determines therapy. With a laparotomy, a more accurate staging can be obtained. The staging laparotomy is performed through a midline incision, extending from the xyphoid process to below the umbilicus. This incision provides an adequate exposure of the entire abdomen and retroperitoneum. Rarely used alternative incisions, such as left subcostally or midtransverse abdominally, provide limited access to the pelvis. The whole abdomen and retroperitoneum are thoroughly explored to identify any grossly abnormal involved lymph nodes. First, random wedge and deep true-cut needle biopsies are taken from both lobes of the liver. Frozen sections of all liver biopsies are examined. When Hodgkin's disease is diagnosed, the disease will be in stage IV and the treatment will be chemotherapy. There is no need for further lymph node biopsies or splenectomy. If the liver biopsies are negative for Hodgkin's disease, the next step will be lymph node sampling.

Lymph node biopsies are taken from the following areas: (1) celiac or superior paraaortic, (2) porta hepatis, (3) inferior paraaortic, (4) right and left iliac, (5) splenic hilar, and (6) mesenterium, as well as all other suspicious lymph nodes. Frozen sections of all removed lymph nodes are examined. When Hodgkin's disease is diagnosed, the disease will be in stage III, when the primary site was localized above the diaphragm. Stage III disease is treated by some investigators with chemotherapy and there is no indication for splenectomy.

If the lymph nodes are negative and the spleen is macroscopically not suspicious for Hodgkin's disease (normal spleen size and no presence of nodules), there is an indication for a partial splenectomy. The spleen is mobilized by dividing the lateral peritoneal attachments from the colon and diaphragm. The short gastric vessels are *not* divided. After identification of the tail of the pancreas, the splenic artery and vein and the vessels in the hilum of the spleen are carefully identified. The inferior splenic vessels are ligated with absorbable sutures between the hilus and the inferior portion of the spleen. A discoloring of the mid-lower portion of the spleen marks the line between devascularized and vascularized splenic tissue. With an electrocautery just outside the vascularized splenic tissue, the mid-lower devascularized portion of the spleen is resected and sent for frozen section. Hemostasis of the cut surface of the spleen can be performed, if necessary, with electrocoagulation, human fibrinogen glue in connection with a collagen sheet, or the use of an infrared coagulator. The cut surface of the spleen is 'closed' with absorbable mattress sutures and a mobilized omental

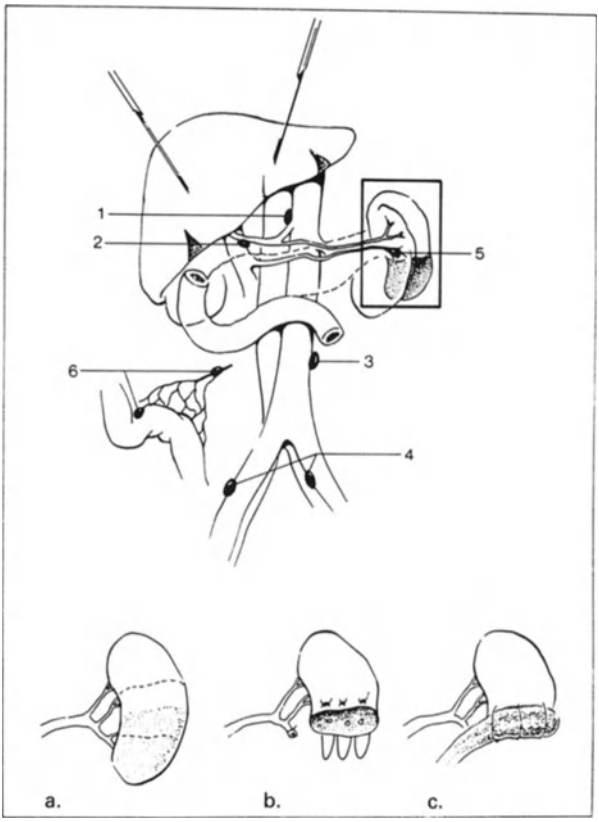

Figure 1. Sequences of procedures in staging laparotomy and the technique of partial splenectomy: (*a*) Wedge and true-cut needle biopsies of the right and left lobe of the liver. (*b*) Lymph node biopsies: 1, celiac or superior paraaortic; 2, porta hepatitis; 3, inferior paraaortic; 4, right and left iliac; 5, splenic hilar; 6, and mesenterium. (*c*) Partial splenectomy.

patch. With this technique, postoperative hemorrhages will usually be avoided. If bleeding from the splenic remnant persists, it may be necessary to ligate the main splenic artery, which involves the risk of a near total devascularization of the spleen. The spleen is replaced and the staging procedure ended. Torsion of the spleen may be prevented by fixation of the remaining spleen to the lateral abdominal wall of the abdomen [22]. When there is splenic involvement of Hodgkin's disease, the treatment will be chemotherapy and there is no need or indication for a total splenectomy. The ovaries may be relocated in any patient who will be treated with abdominal irradiation.

Figure 1 summarizes the biopsy sites during a staging laparotomy for Hodgkin's disease and the technique of a partial splenectomy. The decision tree (based on a primary site above the diaphragm) is out-lined in Figure 2.

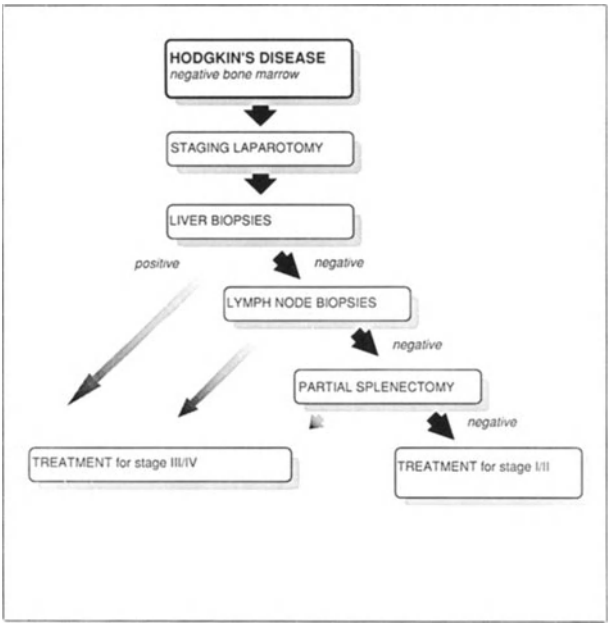

Figure 2. Decision-tree treatment of Hodgkin's disease.

3. Discussion

The role of partial splenectomy in childhood Hodgkin's disease has not been defined, nor can a definitive recommendation be made at this time. One can even speculate that an appropriate randomized study may never be undertaken to compare splenectomy *versus* partial splenectomy. To evaluate the influence of false-negative splenectomy involvement of 2% in a disease *versus* overall survival of 95% would require an extremely long follow-up.

With a partial splenectomy, there is the risk of the false-negative results reported in the literature, ranging from 0 in children to 11% in adults [13, 14]. Pringle and Hays [23] analyzed the data reported by Dearth *et al.* [11] and determined that the risk of understaging splenic involvement in adults is only 2% in stead of 11%! Therefore, partial splenectomy seems to be a reasonable alternative to total splenectomy. The experience with partial splenectomy is very limited, and no complications related to this operative procedure have been published. No overwhelming sepsis has been diagnosed after partial splenectomies.

However, one of the most important questions in partial splenectomy is: how much splenic tissue needs to be removed for an adequate staging and how much splenic tissue needs to be left behind to ensure normal splenic functions, including protection from sepsis? It is assumed that one-third to one-half of the spleen can be resected while preserving splenic function [13].

In contrast, some authors mention that only 25% of the original spleen is necessary for normal splenic function [24]. When the main splenic artery in a partially resected spleen is ligated, however, the rest of the spleen is only perfused by the short gastric arteries. A near total devascularization of this part of the spleen will be the result, without preservation of splenic function and with the risk of complications. Partial splenectomy with preservation of the hilar blood supply affords the most benefit in protection against pneumococcal bacteremia [25]. Only a few experimental studies in a rat model have demonstrated that small splenic fragments with an intact blood supply provide normal antibody response to intravenous particulate antigens and that splenic remnants after partial splenectomy regenerate [26–29]. If a partial splenectomy is performed and the splenic remnant is irradiated, the residual splenic tissue will be atrophic and nonfunctional [30].

4. Conclusion

An adequate staging of Hodgkin's disease is achieved with a staging laparotomy. Partial splenectomy seems a reasonable alternative to total splenectomy. With partial splenectomy, the risk of an overwhelming sepsis, especially in children treated with combined-modality therapies of radiation therapy and chemotherapy, is reduced and no need for pneumococcal vaccination or prophylactic antibiotic therapy exists. With a one-third to one-half partial splenectomy, there is a ±2% risk of understaging, which is lower than the current overall risk of overwhelming postsplenectomy sepsis with high mortality. Partial splenectomy is not much more difficult than standard splenectomy, but the outlined staging procedure consumes much more time than a standard routine staging laparotomy.

Acknowledgments

The authors wish to thank Mr. Douwe Buiter, Mrs. Kathelijn Fisher, and Ms. Cesia Koppe for their technical, bibliographic, and secretarial assistance.

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10. Current management and controversies
The Chemotherapist's View

Jean Lemerle and Odile Oberlin

The improvement of the therapeutic results in childhood's Hodgkin's disease, both in quantity and in quality of survival, has been obtained stepwise through clinical studies conducted around the world. It is difficult to understand the present state of the art without being aware of the main steps of this long story.

1. Historical background

It has been progressively recognized that there are more similarities than dissimilarities between the natural history of the disease and the therapeutic problems in adult patients and in children. Most of the experience gained with adults could therefore be applied to children, where the disease is considerably less frequent and large series of cases very rare. Practically, we can now consider that the main difference between the two age groups is the tolerance to treatment. Children seem to tolerate chemotherapy better; however, recently the late effects of radiotherapy on growing patients have been more closely observed and are now taken into account in most protocols, including chemotherapy.

1.1. The era of radiotherapy alone: improvement of the results with MOPP chemotherapy

With radiotherapy alone, a significant number of children could be cured during the 1960s and the early 1970s. In Toronto [1], 52 patients staged I–IIIB were treated from 1969 to 1977 with extended-field radiotherapy and had a relapse-free rate of 57% (survival, 85%). The MOPP combination of drugs (nitrogen mustard, Oncovin [vincristine], procarbazine, and prednisone) was described by Carbone in 1967 [2] and its first results were reported by De Vita *et al.* in 1970 [3], with an 81% remission rate in patients with advanced disease. In 1970, Lowenbrau *et al.* [4] reported an 87% remission rate obtained with MOPP in adult patients whose disease recurred after primary treatment with radiotherapy alone, and a 50% remission rate

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in patients who previously received radiotherapy combined with other chemotherapy regimens.

In 1982, Sullivan *et al.* [5] reported the results of the Intergroup Hodgkin's Disease in Children Study of pathologic stages (PS) I and II, where different modalities of therapy were randomly compared. The 4-year recurrence-free survival was 30%, 40%, and 95%, respectively, in patients receiving involved-field (IF) radiotherapy alone, extended-field (EF) radiotherapy alone, and IF followed by six courses of MOPP. The survival of the whole group was 96%.

In 1985, Rosenberg [6] reported long-term results of Stanford studies on PS IA and IIA, showing that freedom from progression and relapse were equivalent in patients treated either with subtotal nodal irradiation (STNI) or with IF irradiation followed by MOPP chemotherapy. He concluded that adjuvant MOPP could replace irradiation of occult disease in patients with PS IA–IIA.

After 1970, however, most of the therapeutic protocols for children as well as for adults progressively included staging laparotomy, EF high-dose (35–40 Gy) radiotherapy, and MOPP chemotherapy, which resulted in excellent remission and cure rates [7].

1.2. Complications and sequelae of aggressive multimodal therapy in children

With increasing experience and longer follow-up, the question was soon raised of the cost–benefit ratio of these intensive therapeutic modalities when applied to children.

1.2.1. Staging laparotomy and splenectomy. In 1980, Jenkin and Berry [1] reviewed the data concerning short-term or delayed morbidity associated with this procedure. Small bowel obstruction was seen in 1%–10% of the cases in seven reported pediatric series. No related death was reported. Overwhelming postsplenectomy infections were seen with a frequency that was related to the intensity of treatment, ranging from 2% to >10%, depending on the series. An incidence of 20 episodes in 18 of 20 patients, fatal in eight of 18, was reported in 1976 [8].

The conclusion by Jenkin and Berry in 1980 was that staging laparotomy with splenectomy was associated with mortality in a range of 1%–3% of cases. Others, such as Donaldson and Kaplan, reporting Stanford's experience [9], were more optimistic.

1.2.2. Soft tissue and bone growth impairments. These damages, which are due to radiotherapy and are now well known, are detailed in other chapters of this book. It should be emphasized, however, that the cosmetic damage caused to young children who receive standard full-dose mantle irradiation is hardly acceptable and should be kept in mind when discussing treatment strategies. Short trunk, thin neck, short clavicles and, occasionally, spinal

deformities and pectus excavatum are consistently observed when the patient is assessed after completion of normal growth period. Like other sequelae observed in irradiated children, these deformities are directly related to age at the time of treatment, to the dose given and the fields used, and to the time elapsed between radiotherapy and evaluation. Some optimistic statements regarding these sequelae would be revised were the follow-up longer and cover the entire growth period. Such long-term, ugly sequelae seriously affect the quality of life of survivors.

1.2.3. Cardiac and pulmonary complications. These have been less commonly observed in surviving children and are now very rare with modern radiation techniques. In young children, however, it is impossible to avoid irradiating a substantial volume of the lungs when extended fields are used.

1.2.4. Endocrine sequelae and sterility. Thyroid function impairment is common after high-dose irradiation of the neck, but in our experience it is usually limited to elevated thyroid-stimulating hormone (TSH) without clinical hypothyroidism.

As far as the gonads are concerned, attention is focused on sterility related to chemotherapy, and essentially male sterility after MOPP. Our experience [10] is that, of ten boys studied who were treated for Hodgkin's disease, seven have complete azoospermia 2–16 years after completion of therapy. They had received 2–12 courses of MOPP at ages ranging from 8 to 15 years. Three were normal and had received either one course of MOPP or vinblastine alone. These data have been confirmed by others [9, 11]. It is now increasingly clear that alkylating agents, including procarbazine, are mainly responsible for male sterility, that there is a probable dose–effect relationship [12], and that prepubertal status does not protect the testes from the drugs [10, 11]. In female patients, the damage seems less important and a number of women treated during childhood have become pregnant. Endocrine functions of the gonads are less affected, mainly in male patients who, in our experience, have all developed normal puberty.

1.2.5. Second malignant tumors. These represent a major concern for those who are in charge of treating children who have Hodgkin's disease.

The late Effects Study Group (LESG) studied 958 children with a median follow-up of 7 years [13]: 33 developed second malignant neoplasms (SMN)—16 solid tumors, 14 leukemias (13 acute nonlymphocytic leukemias and one chronic myelogenous leukemia), and three lymphomas. The acute nonlymphocytic leukemia occurred between 1 and 10 years, median 4.8, in patients who had all received procarbazine in MOPP, COPP (cyclophosphamide substituted for nitrogen mustard), or alone. All solid tumors arose in an irradiated area, the median interval being 10 years. In this large cohort, the risk of developing an SMN after successful treatment of Hodgkin's disease is 18½% at 20 years after therapy. Another LESG study on SMN

occuring after treatment of any kind of tumor showed that the excess risk of secondary leukemias following childhood cancer was almost entirely due to alkylating agents [14].

A number of publications confirm these data in adults and in children, emphasizing that (a) no leukemias occur in patients treated with radiotherapy alone [15–17]; (b) occurrence of solid tumors is increased by radiotherapy, especially when it is associated with chemotherapy [15]; (c) alkylating agents are the most carcinogenic drugs, at least for acute myelogenous leukemia; (d) leukemias are more frequent in patients >40 years of age than in children; and (e) intensive combined treatments given for relapses are associated with the highest risk of SMN, specially when MOPP is used.

1.3. MOPP challenged by ABVD

In 1985, Bonadonna *et al.* [18] updated the studies conducted in Milan on the ABVD chemotherapy regimen (Adriamycin, bleomycin, vinblastine, and dacarbazine), which had been designed as an alternative to MOPP.

In terms of efficacy, 55% of 71 MOPP-resistant patients achieved complete remission and 27% survive after 7 years. Randomly comparing ABVD with MOPP in stage IIB–IIIB patients, both regimens were found to be equivalent in terms of remission induction, survival, and disease-free survival (DFS). In another study, MOPP alternated with ABVD was superior to MOPP alone in some subsets of patients.

In children, DFS at 3 years in stages I–IIIB was found to be 97% in 39 cases treated with ABVD and low-dose radiotherapy [19]. Less toxicity than with MOPP is observed in ABVD-treated patients. Azoospermia was observed in only 54% of adults studied [20] and was always followed by recovery, findings that contrast with the very high rate of permanent sterility in male patients treated with MOPP. In 1986, Valagussa *et al.* [21] reported no leukemia at 12 years in patients treated with radiation + ABVD, compared with 10.2% when radiation was associated with MOPP. The difference is less important when solid SMN are considered.

Heart toxicity due to doxorubicin and lung fibrosis attributable to bleomycin both potentially enhanced by radiotherapy were not reported by Bonadonna *et al.* [18] and others [22] as a problem, but further prospective studies are mandatory for more firm conclusions.

2. Current management: experiences in deescalating therapy

In the early 1980s, most of the reported series of childhood's Hodgkin's disease yielded survival rates of >90%, but it had become increasingly clear to most investigators that the cost of this achievement was too high since the sequelae of 'successful' therapeutic modalities seriously impaired the quality of life of many survivors, especially the youngest ones. The problem then

was how to cure at least as many patients at a lower cost. Since both radiotherapy and chemotherapy had their well-known efficacy and drawbacks, how was it possible to avoid the latter while retaining the former?

We describe here our own experience in progressively diminishing the burden of therapy imposed on children. This was achieved on the basis of our own observations and the available published data.

2.1. Clinical staging

Being aware of the complications arising from staging laparotomy with splenectomy and of the cost of this possibly unnecessary procedure, we omitted it after 1975. Our decision was based on the following data.

In a large series of cases, infradiaphragmatic disease, either in the spleen or in the nodes or both, was found at laparotomy in 30% of patients with clinical stage (CS) IA–IIA disease with lymphangiogram considered normal [23]. In the same clinically staged patients who were treated with primary MOPP without laparotomy and supradiaphragmatic radiation, the recurrence rate was as low as 4.4% in the nonirradiated areas, which means that chemotherapy had cured radiologically inapparent disease in the majority of the cases. It was thus considered that the cost–benefit ratio of staging laparotomy was no longer good in patients treated with this chemotherapy regimen. Should radiotherapy alone be adopted for localized disease, the problem would be different. Many authors dealing with adults as well as with children have come to similar conclusions, and staging laparotomy is now seldom considered a routine procedure in children. Our own data support these views since we observed no infradiaphragmatic recurrence in 37 CS IA–IIA patients treated with MOPP followed by IF radiotherapy, the median follow-up being 7 years [24]. This policy is currently being applied in the ongoing French study [25].

2.2. Prognostic factors

Stage and general symptoms (A or B) are generally considered as the most useful prognostic factors for treatment planning. Pathologic subsets had prognostic significance when radiotherapy was the only treatment. Staging laparotomy has shown that unfavorable histology was linked with extended disease, including occult disease [26]. In patients treated with active chemotherapy, pathologic grading seems to be of very little practical significance and is hardly ever considered.

The presence of a 'large' mediastinal mass is appraised differently in different groups, and very few protocols take such a finding into consideration since multimodal therapy is given. The same applies to biologic changes, with the exception of erythrocyte sedimentation rate, which we consider as an equivalent to B symptoms when >70 at presentation, on the basis of previous studies [26].

It should be kept in mind, however, that prognostic indicators which have been excluded by intensive therapy may well regain usefulness when more selective and less aggressive treatments are considered, which is presently the case.

2.3. Primary chemotherapy: six and three MOPP, ABVD, and other regimens

Historically, patients with large mediastinal masses were the first cases in which we administered chemotherapy before radiation instead of the usual radiation ('treatment') followed by chemotherapy ('maintenance'). This was a first attempt to reduce the fields in young children in order to avoid unacceptable high-dose lung irradiation. Subsequently this was applied to all cases for several reasons: (a) prompt relief in patients with general symptoms, (b) field reduction in the mediastinal cases, (c) expected increase of efficacy of radiation directed at a smaller number of tumor cells, and (d) it enabled the assessment *in vivo* of the response to chemotherapy in individual cases and the adaptation of subsequent radiotherapy and eventually chemotherapy to this response.

During the period of 1975–1980, we reduced the number of MOPP courses from six to three. This was based on the experience of the Hôpital Saint Louis (Paris) group, which showed by surgical restaging after primary MOPP chemotherapy that three cycles were equivalent to six in terms of pathologic findings as well as for clinical remission rates and DFS [27]. We found the same in a group of 60 patients treated in 1975–1980, who had no laparotomy and received either six or three courses of MOPP [24]. In this group, 5-year survival is 93% and DFS is 86%.

We have seen that the primary three courses of ABVD [19] produced excellent results in children when followed with intermediate dose and field radiotherapy, followed by three other courses in cases with symptoms or stage III disease.

Other combined modalities that are currently being tried or evaluated are described in another chapter of this book.

The current French national protocol (Figure 1) randomly compares 2 MOPP + 2 ABVD *vs* 4 ABVD in stages I and IIA, and includes alternating 3 MOPP and 3 ABVD in all cases with B symptoms and stages III and IV.

2.4. Reducing fields and doses of radiotherapy. The option of no radiotherapy at all

The radiotherapy problems are covered in another chapter. We shall only briefly mention that reduction of the irradiated fields has been advocated by authors who pointed out that chemotherapy could control occult disease in nonirradiated areas [5, 6, 28]. It should be emphasized (a) that the definition of 'reduced' or 'involved' fields may vary from one author to the other and

STAGE (C.S.)	*CHEMOTHERAPY*	*RADIOTHERAPY*
IA–IIA (RAND.)	4 ABVD 2 MOPP–2 ABVD	20 GYS* IN INITIALLY INVOLVED FIELDS
IB–IIB–III–IV	3 MOPP–3 ABVD IN ALL CASES	20 GYS* IN INITIALLY INVOLVED FIELDS + LOMBOSPLENIC FIELD

*40 GYS IF TUMOR REDUCTION BY CHEMOTHERAPY IS <70%

Figure 1. Protocol of the French National Childhood's Hodgkin's Disease Study.

(b) that, in all of the cases mentioned, the chemotherapy regimens can be considered aggressive, containing large amounts of alkylating agents. In our 1975–1980 study, we used involved fields (40 Gy) in patients having received either six or three MOPP courses and who were CS IA or IIA, and none of these patients relapsed. In our subsequent French national protocol, therefore, we give radiotherapy in stages IA–IIA only to clinically initially involved areas. The lumbar nodes and the spleen of those with symptoms are also irradiated.

Reduction of radiotherapy doses was first proposed by the Stanford group [29] and by Jenkin *et al.* [30], and produced excellent results. In Stanford, however, the patients had surgical staging and received six cycles of MOPP, with the inconvenience related to both these modalities. In series reported by Jenkin's *et al.*, the doses were actually progressively reduced, but the fields were extended fields, and chemotherapy was six cycles of MOPP, except for stage IA.

In Philadelphia [28], pubertal status of the patients was taken into account. Postpubertal patients with surgical stages I–IIA were treated with EF high-dose radiation. The other patients were clinically staged and received six courses of COPP and then involved fields (20 Gy). Again, in this series, the limitation of radiation is balanced by large amounts of alkylating agents.

In a report from the Memphis group [31], low-dose radiation combined with COP (COPP without prednisone) was associated with a high rate of failure in stages IIB–IIIB despite the large quantities of alkylating agents given.

Jereb *et al.* report the Memorial Sloan-Kettering Cancer Center's experience [32] where stages IA and IIA had IF irradiation with no chemotherapy, but received a dose of 36 Gy, while multidrug chemotherapy (cyclophosphamide, Adriamycin, and procarbazine) was associated with IF 20-Gy radiation in more advanced cases. Again, in this series, good results in terms of survival were obtained at the cost of high doses either of radiotherapy + laparotomy or of multidrug alkylating agents + doxorubicin.

In our current study, the dose given is calculated according to the response to primary chemotherapy: when the tumor mass reduction is estimated as ≥70%, a dose of 20 Gy is given in all stages at any age. Larger doses are given in the other cases, which are a small minority.

The most radical way to avoid the drawbacks of radiotherapy is to avoid using radiotherapy at all. Several attempts have been made in children or are currently made in this direction. In all of these studies, the dilemma that we have already met cannot be avoided and, when no radiation is given, one can expect the maximum inconvenience from chemotherapy, which has to be maximum if a reasonable proportion of children are expected to be cured. Olweny *et al.* [33] gave six cycles of MOPP in all stages and obtained a 5-year survival of 75% in stages I–IIIA and 60% in stages IIIB–IV.

Jacobs *et al.* [34] gave six cycles of MVOPP (mustine and vinblastine alternating with vincristine, procarbazine, and prednisone) and obtained 11 prolonged complete remissions in 11 patients in stages I and II, but less good results in the other cases.

Schwartz *et al.* [35] randomly compared patients of all stages who received six courses of CVPP (cyclophosphamide, vinblastine, procarbazine, and prednisone) with or without the addition of 30 Gy IF radiation. The results were equally good in both arms in stages I and IIA, but patients with symptoms or mediastinal involvement needed more therapy than CVPP alone.

Behrendt and Van Bunningen, in Amsterdam [36], treated 16 patients with CS I–IIIB who had nodes smaller than 4 cm with six MOPP courses; one had 12 courses. All achieved complete remission, two relapsed, and all survive. No patient with CS I or II relapsed, median DFS being 45 and 82 months, respectively.

All of these comparatively small series indicate that six cycles of MOPP or six equivalents can probably cure the vast majority of stages I and IIA. The question is to determine whether the 100% male sterility and the few acute myelogenous leukemias that will be observed in those patients are not too high a price for avoiding even low doses of radiotherapy.

2.5. Preliminary results of the French cooperative study

Having previously established that, with clinical staging and MOPP therapy, it was possible to limit the extent of radiotherapy to initially involved areas, in 1982 we began a study aimed at exploring further reductions of therapy. One was the replacement of MOPP–ABVD by ABVD in good cases, and the other was the reduction of doses of radiotherapy to 20 Gy IF in all good responders to primary chemotherapy, whatever the stage, lombosplenic fields being added for advanced stages and B symptoms. In addition, the MOPP–ABVD combination was tried in all cases with symptoms or stages III–IV.

In July 1986, 120 patients were included and evaluable. There were 36 stage IA, three IB, 27 IIA and 15 IIB, nine IIIA and 13 IIIB, and two IVA

and 15 IVB patients, 94% were good responders to chemotherapy (>70% reduction of tumor masses) and were given 20 Gy radiation. Of the 117 who attained complete remission, 111 are still in complete remission, with a median follow-up of 28 months. The actuarial relapse-free survival is 86% at 36 months and survival is 98% at 3 years. Two patients relapsed in 20-Gy irradiated areas (three relapses in 254 irradiated areas). There has been no difference thus far between the 4 ABVD and the 2 MOPP–2 ABVD arms. Although the follow-up is short, it can be anticipated that 4 ABVD + 20 Gy IF will be considered adequate treatment for CS I–IIA patients, who represent 52% of our cases. One can wonder whether the other 40% who are not stage IV really need three MOPP courses and lumbosplenic irradiation. We feel that, in terms of cutting unnecessary therapy, this protocol is presently one of the best possible compromises that can be used to cure patients while minimizing toxicity and sequelae. This does not apply to our stage IV cases since only 44% of them survive free of disease.

3. Consensus and controversies

3.1. The state of the art

When analyzing the recent publications on treatment of childhood's Hodgkin's disease and, even more, when knowing which treatments are currently applied in the major centers or study groups, we feel that the following points are well established.

3.1.1. No staging laparotomy needed. Staging laparotomy is unnecessary when modern diagnostic radiology is available: bipedal lymphangiogram, or echography and computerized tomographic scan when in doubt about involvement of celiac or mesenteric nodes or when in doubt about mediastinal involvement.

Laparotomy is indicated when a local treatment with radiation only is considered, mainly in adolescents, but also in some cases of suspected liver involvement.

3.1.2. The majority of the cases need both radiotherapy and chemotherapy. Exceptions are the above-mentioned cases of adolescents having completed growth, who may receive only local high-dose radiotherapy in documented localized disease IA and possibly IIA. In these cases, the drawbacks of radiotherapy are minimal and those of chemotherapy may be avoided. On the other hand, very extensive stage IV disease may be better treated with intensive chemotherapy alone or at least predominant chemotherapy, but this depends widely on the cases.

It is clear to us that it is more logical to begin treatment with chemotherapy and subsequently administer adjuvant radiotherapy, yet we must admit that there is no demonstration of the superiority of this sequence.

3.1.3. Which chemotherapy? MOPP is the first widely used, and probably the most active, combination of drugs. It is the chemotherapy of reference to which the others are compared. It may also be the most toxic with respect to gonads and to carcinogenesis. Modified analogs (COPP, CVPP, COP, *etc.*) may be less toxic, but this is unlikely and would have to be demonstrated, with comparable activity being obtained.

ABVD is less toxic than MOPP, at least its toxicity is different. Gonadal toxicity seems minimal, but long-term studies are still scarce. Leukemogenesis has not been reported to be a problem with this regimen, but the heart and the lungs are exposed to damage, especially when chest irradiation is given. Activity seems comparable to that of MOPP. Long-term studies are needed to assess better the sequelae of ABVD given to children.

Other protocols mentioned in this book, combining alkylating agents including procarbazine and doxorubicin, provide excellent cure rates, but have been too recently introduced to be evaluated for long-term toxicity. In all cases, the choice of the drugs, the doses, and the duration of treatment depend on the stage and essentially on the decision made regarding radiotherapy. The less radiotherapy is given, the more chemotherapy is needed.

No 'maintenance' chemotherapy is given after irradiation.

3.1.4. Which radiotherapy? Providing that active chemotherapy is used, which cures occult disease and at least considerably 'debulks' gross disease, radiotherapy can be reduced. Fields covering only the sites of initial involvement can be used. We admit that there is no evidence that B symptoms imply a need for more extended fields as in the current French protocol. Doses ranging from 15 to 25 Gy have demonstrated good efficacy when combined with active chemotherapy. Finally, radiotherapy has to be tailored for each individual case according to stage, to age, to the chemotherapy given, and to the result of this chemotherapy.

We can see that there are very few universal guidelines for the treatment of childhood's Hodgkin's disease. The cornerstone of all therapeutic policies is the awareness of the cost–benefit ratio of the considered modalities of treatment in each given case. Cosmetic damage to the neck and shoulders may be considered more acceptable than male sterility and increased risk of acute myelogenous leukemia or *vice versa*. It is difficult to escape the '*à la carte* toxicity' choice. However, there is no reason to believe that it is impossible to build combinations of low dose-low toxicity chemotherapy that would be good enough to be safely combined with low-dose IF radiotherapy.

3.2. Pending questions

There are at least four controversial topics: nontoxic chemotherapy; no radiotherapy at all; the treatment of advanced, resistant, and relapsing cases; and high-dose chemotherapy with bone marrow transplant.

3.2.1. Nontoxic chemotherapy. Very few drugs are both nontoxic, or have acceptable toxicity, and are active in Hodgkin's disease. Vinblastine is one of them. Etoposide and teniposide have been tried. Methotrexate is being reassessed. But it is difficult to develop single-drug phase II studies in childhood's Hodgkin's disease because of the small number of recurrent cases. On the other hand, we may try to learn more about the activity and toxicity of the already-used drugs through pharmacologic and clinical detailed studies. For instance, low doses of alkylating agents may be active enough with tolerable toxicity, but we need more information on the dose–effect relationship of this family of drugs with respect to gonadal disturbance or carcinogenesis. The total dose given may well be only one of the important variables to investigate, and we should possibly also pay attention, for instance, to serum peak levels and to duration of treatment. It is probably an oversimplification to say that such-or-such drug, *e.g.*, cyclophosphamide or doxorubicin, should be discarded: we should try to use them better, which is a general problem in pediatric oncology, and a difficult one.

The most effective and least toxic agent when carefully used, at low doses, is radiotherapy. From our experience with Wilms' tumor, where the dose range of 15–25 Gy is widely used, we know that it bears acceptable sequelae when given to children of the Hodgkin's disease age, which is, in our study, a median age of 10 years.

3.2.2. No radiotherapy at all. The effect of this has been demonstrated in patients who have received chemotherapy alone. The results raise several questions. We have already mentioned the problem of the toxicity of the drugs used, and we consider it unacceptable to treat patients who have localized stage IA–IIA disease with six cycles of MOPP or equivalents when it is possible to cure them easily with much less aggressive combinations including radiotherapy. The problem is to get rid of the radiotherapy taboo. The option of using no radiotherapy at all will only make sense when nontoxic combinations of drugs will cure 95% of the cases. We have not yet reached this era. Another problem raised by the no-radiotherapy programs is to know what proportion of relapsing patients will be salvaged and at what cost. Thus far, the published series are too small and the follow-up too short to answer these questions.

3.2.3. The treatment of advanced, resistant, and relapsing cases. Stages IIIB and IV represent only 26% of the cases in the ongoing French study, and 28% and 25% in the German studies DAL HD 78 and 82 [37]. It is difficult

with such small numbers to draw definite conclusions. However, most of the recent survival data in adults as well as in children are around or under 50% for stage IV. In the French study, recurrence-free survival is 44% at 36 months. The only good results are reported by Schellong *et al.* [37], with recurrence-free survival at 30 months being 89% in stages IIIB and IV.

It is now clear that those cases should be treated more aggressively, especially in terms of primary chemotherapy. The combinations or 'hybrids' of MOPP and ABVD are being tested, but our results are not satisfactory.

For resistant and relapsing cases, after failure of MOPP and ABVD, third-line regimens have been designed and tried with some interesting results, mainly in adults. Etoposide, CCNU, ifosfamide, and even methotrexate have been combined in different ways.

The MIME combination (methyl-GAG, ifosfamide, methotrexate, etoposide) has produced a 60% response rate [38, 39]. The CEP scheme (CCNU, etoposide, and prednimustine) produced 40% and 50% response rates, respectively, after MOPP and MOPP–ABVD failures [40, 41]. Comparable to these encouraging results and those obtained with SCAB (streptozotocin, CCNU, doxorubicin, and bleomycin), which produced 35% remission in MOPP-resistant cases [42] and with APE (cytosine arabinoside, cisplatinum, etoposide) with four responses in five cases [43]. At this point, however, it seems that very few cases with previously untreated advanced disease have been submitted to these original chemotherapy protocols, which are therefore difficult to assess fully.

3.2.4. High-dose chemotherapy with bone marrow transplant. A number of small series of cases treated with intensive high-dose chemotherapy covered by bone marrow transplantation, mainly autologous transplantations (ABMT), have been reported. It is beyond the scope of this chapter to analyze these very preliminary data in detail, so we shall only mention the following.

Dumont and Teillet [44] reported 24 French cases: 18 of them were studied retrospectively, having received high-dose chemotherapy with ABMT for refractory or relapsed advanced disease. Ten received TACC (thioguanine, aracytine, cyclophosphamide, and CCNU) or BACT (the same with BCNU) and the others received CCNU and cyclophosphamide essentially. Of these 18, eight achieved complete remission, of whom three have survived to 60+ months and five relapsed at 2–5 months after ABMT.

Six other patients were recently treated prospectively with CCNU, cyclophosphamide, and etoposide and all achieved complete remission, with short follow-up.

Appelbaum *et al.*, in Seattle [45], treated eight advanced patients resistant to MOPP with high-dose cyclophosphamide total body irradiation and marrow transplantation from human leukocyte antigen (HLA)-identical siblings. Two patients remain in complete remission at 38 and 39 months. Four patients died from treatment complications.

In 1984, Jannagath *et al.* [46] reported eight cases treated with Cytoxan, BCNU, and etoposide followed by ABMT. Seven patients achieved complete or partial remission, but the follow-up has been brief.

Carella *et al.*, in Genova [47], reported 13 patients: all but one had extranodal relapses and were previously heavily treated. Two received high-dose BCNU and 11 received cyclophosphamide, etoposide, and BCNU, with autologous nonfrozen bone marrow transplantation. Complete remission was obtained in eight of 13 and partial remission in two. Ten patients were alive at 2–34 months, six being in unmaintained complete remission.

All of these results are clearly preliminary data on small numbers with short follow-up, and it is often difficult to compare these series with one another because of the scarce information on previous disease and therapy. However, they deserve attention since they indicate both feasibility and some efficacy of high doses of chemotherapy in these cases. It would seem logical to apply these treatments earlier in the course of patients whose prognosis is known to be very poor. This may at least avoid some of the observed toxicity and could result in more cures. But the best cases, the best time, and the best schedule for such salvage treatments have yet to be defined.

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11. Current management and controversies
A Radiotherapist's View

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The goal in managing patients with Hodgkin's disease is cure of the disease with minimal morbidity, yet maximal quality of life. This goal is universal; it does not represent a controversy. The issues over which there rest divided opinions relate to therapeutic orientation on how to achieve this goal and are largely issues of staging, treatment, and follow-up. Some controversies arise because of facilities available, individual expertise, or experience. Today a child with Hodgkin's disease has an ~90% likelihood of cure following accurate staging and treatment in a center with demonstrated expertise in pediatric Hodgkin's disease [1]. Such gratifying results require individualization of therapy, as no two cases of the disease are identical. The management of children requires utilization of not only principles that apply to the adult population, but also judgment with respect to age, stage, and extent of disease, tumor burden, therapeutic options, and late effects of treatment.

From a radiotherapist's orientation, cure with the least side effects of the disease and/or its treatment requires precision in staging, treatment, and follow-up. Precise attention to detail is mandatory in order to tailor the treatment to the extent of disease and, hence, individualize the therapy appropriately. When issues arise, which may be interpreted as controversial, they are usually related to details of stage or staging, and refinements in treatment. Thus, this chapter centers around those subjects that represent areas of divided opinion from the orientation of a radiotherapist concerned solely about the well-being of children.

1. Staging system

The staging system universally utilized—the Ann Arbor staging system [2]—is listed below:

Stage	*Definition*
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E).

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II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E).

III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE}).

IV Dissue or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.

The absence or presence of fever, night sweats, and/or unexplained loss of 10% or more of body weight in the 6 months preceding admission are to be denoted in all cases by the suffix letters A or B, respectively.

It is well tested, easily understood, and followed by investigators throughout the world. However, some aspects of the Ann Arbor staging system are felt to have prognostic significance and, thus, have become issues of controversy. These include the following:

1. The meaning of 'E,' extralymphatic or extranodal extension
2. The difference between multiple E's *versus* stage IV disease
3. The significance of large mediastinal masses, and tumor bulk or volume
4. The prognostic factors of stage III disease

The recognition of extralymphatic organ involvement, contiguous with involved regional lymph nodes, as having a prognosis comparable to that of localized lymph node disease [3, 4] led the members of the Ann Arbor Workshop to include the suffix 'E' to describe limited extralymphatic disease, *i.e.*, stage I_E, II_E, or III_E. The E designation was intended for extralymphatic disease, so limited in extent and/or location that it could be subjected to definitive treatment by radiotherapy [5]. For example, direct pulmonary or pericardial invasion (associated with mediastinal and/or hilar adenopathy), a chest wall mass secondary to invasion from internal mammary or infraclavicular lymph node involvement, sternal invasion from an anterior mediastinal mass, or localized bone or epidural involvement in immediate proximity to involved lymph node chains is classified as localized extralymphatic (E) disease.

The concept that localized extralymphatic E lesions do not adversely affect prognosis and should not imply dissemination has been challenged by some who report increased relapses in patients with E lesions [6]. However, others have shown that patients with E lesions treated with radiotherapy alone have comparable actuarial survival and freedom from relapse at 5 years as patients treated with radiotherapy and adjuvant chemotherapy [7]. Thus, the conclusion that localized extralymphatic lesions, when appropriately treated with radiotherapy, do not adversely affect prognosis is now well accepted. This validates the concepts of the Ann Arbor staging classification that there are real and significant differences in prognosis between localized *versus* disseminated extralymphatic involvement.

When do multiple E lesions become stage IV disease? E lesions imply direct extension from adjacent lymph node involvement while stage IV disease results from hematogenous dissemination. When one or several localized E lesions arising from a localized process can be treated definitively within a conventional radiotherapy portal, one uses the classification of E. When there are multiple lesions that cannot be explained by a local process, then the designation of stage IV is appropriate. Oftentimes individual judgment prevails in making this distinction.

The Ann Arbor staging system does assess tumor extent, but not tumor volume. Recently the concept of bulk, tumor volume, and size of disease has been recognized to have prognostic significance. There is an unfavorable influence of a large mediastinal mass on relapse-free survival and an increased incidence of intrathoracic relapse of 40%–55% either within the treatment volume, on the border of the irradiation field, or within the pulmonary parenchyma when such patients with supradiaphragmatic stage I and II Hodgkin's disease are treated with radiotherapy alone [8–11]. This recognition has led many investigators routinely to recommend chemotherapy in addition to radiotherapy for optimal treatment of bulky disease. However, the definition of bulk has been on an arbitrary basis and multiple ways of quantitating volume have been used. Some clinicians have simply measured the maximal transverse tumor diameter on a chest radiograph [12]. Others have attempted to determine the surface tumor area as reflected in the chest x-ray [13]. More recently, investigators have determined a consistent criteria of large as >0.33 as determined by the maximal transverse diameter of the mediastinum as compared with maximal intrathoracic diameter as visualized on the initial diagnostic chest x-ray [10], while others have measured the mass at the level of T_5 or T_6 on a upright posteroanterior chest radiograph [8].

Computerized tomography (CT) or magnetic resonance imaging (MRI) studies have not routinely been utilized in assessing response to therapy as a function of mass size. It is well recognized, however, that CT is of major value in the initial staging of patients [14] as well as in the radiotherapy treatment planning of patients with Hodgkin's disease [15, 16]. It may be that, when proper mediastinal imaging studies, such as CT, are routinely utilized in patients receiving radiotherapy, mediastinal mass size will cease to be a prognostic indicator when patients are treated with radiotherapy alone.

Some investigators have selected a specific peripheral lymph node size, *e.g.*, 5 cm, beyond which a region is termed bulky [17]. However, precise data relating to one-dimensional size of a single lymph node or multiple lymph nodes with respect to prognosis are lacking. For consistency of comparing institutional studies, a lymph node that is abnormal to physical examination by palpation or that is abnormal as visualized on an imaging study should be considered as involved unless proven by biopsy to be uninvolved. The determination of prognostic significance of a specific size of

lymph node involvement will require a reassessment of state-of-the-art imaging modalities and current therapeutic approaches [18].

Evolving therapeutic programs and assessment of prognostic factors have led to controversies in management of those patients with pathologic stage III disease. Comparing long-term treatment results following total lymphoid irradiation alone *versus* total lymphoid irradiation plus adjuvant chemotherapy has led investigators to recommend total lymphoid irradiation plus adjuvant chemotherapy for improved survival for subsets of these patients [19–22]. A number of subsets hae been evaluated, including the number of sites involved, anatomic substage III_1 (spleen, splenic hilar, celiac, or portahepatic lymph node) or III_2 (paraaortic, mesenteric, iliac, or inguinal–femoral), and extent of splenic involvement. Multivariate analyses reveal that bulky splenic disease ($\geqslant$5 splenic nodules) has an unfavorable prognostic factor when treated with radiation alone [23]. The significance of the anatomic subset, *i.e.*, III_1 *vs* III_2, varies among institutions and may be affected by radiotherapy techniques employed, as those failing to show a difference between the two subsets have routinely employed prophylactic liver irradiation when administering total lymphoid irradiation [23].

Thus, the issues that constitute controversies related to the staging system are those that are affected by treatment policies, specifically related to radiotherapy as a single modality *versus* radiotherapy in combination with chemotherapy. Children with Hodgkin's disease have a biology, natural history, and response to therapy that do not differ from their adult counterpart. Thus, these issues related to staging are relevant to a pediatric population if the therapeutic program selected follows the guidelines utilized for the adult population. This basically becomes important for the adolescent or young adult in whom growth and development are *not* critical with respect to the late effects of therapy. For youngsters and those prepubertal in development who have Hodgkin's disease, optimal therapy seldom involves radiation alone, thus bypassing the controversial issues related to the staging system.

2. Clinical stage

The clinical staging studies recommended in the evaluation of patients with Hodgkin's disease include:

- Complete history and physical examination by several individuals including a radiotherapist, oncologist, and surgeon
- Laboratory studies
  - Complete blood count, erythrocyte sedimentation rate
  - Renal and liver function tests, including alkaline phosphatase
  - Serum copper
  - Thyroid function tests: free thyroxin (T_4) and thyroid-stimulating hormone (TSH)

- Radiographic studies
  Posteroanterior and lateral chest radiograph
  CT scan of chest
  Lymphangiogram
  CT scan of abdomen and pelvis (optional)
  Abdominal and pelvic ultrasound (optional)
- Isotopic scans
  Bone scan: if patient has bone pain or if alkaline phosphatase is elevated
  Gallium scan (optional)

However, these staging procedures, which all aid in the detection of disease and are universally accepted within the adult population, create some difficulties of interpretation when applied to children.

The assessment of lymphoid tissue and the differentiation of involvement by Hodgkin's disease from reactive hyperplasia is particularly difficult in children. A careful history and physical examination with attention to lymphoid sites, including Waldeyer's ring, are essential. Any equivocal or suggestive enlarged lymph nodes, which might change stage and/or therapy, should be biopsied with histologic confirmation. While lymph nodes in the upper one-half of the neck and the anterior and posterior cervical chains and submandibular areas are often associated with a coexisting upper respiratory tract infection in children, firm lymph nodes in the lower one-half of the neck, including the supraclavicular fossa, are much more likely to be clinically significant. Knowledge of the recognized contiguity of spread of Hodgkin's disease, location of the lymph nodes, and experience in palpation of the nodes facilitates the decision as to whether palpable lymph nodes in a child are likely to be involved with Hodgkin's disease.

If the use of radiotherapy is considered at any time in a treatment plan, it is imperative that a radiotherapist participate in the pretreatment and staging evaluation. The size and location of enlarged lymph nodes may affect how radiotherapy will be administered, which machine and energy should be used, and what treatment field size and dose are appropriate. This evaluation must be conducted prior to administration of any therapy. A radiotherapy consultation may bring forth technical considerations with respect to the radiotherapy that may affect stage of disease or delivery of radiotherapy. An example of such is shown in Figures 1 and 2. Figure 1 reveals a CT scan of a young girl presenting with large left cervical adenopathy. This massive lymph node disease was well appreciated by physical examination. The conventional mode of radiotherapy for such disease is by using anterior and posterior opposing fields. In this patient, however, the consultant physicians recognized asymmetry in the Waldeyer's ring examination, and thus selected CT cuts were requested visualizing the nasopharynx and oropharynx. CT cuts at a higher level revealed that the obvious left neck disease was contiguous with lymphoid tissues of Waldeyer's ring on the left. Figure 2 reveals the left-sided parapharyngeal mass to be distorting the airway,

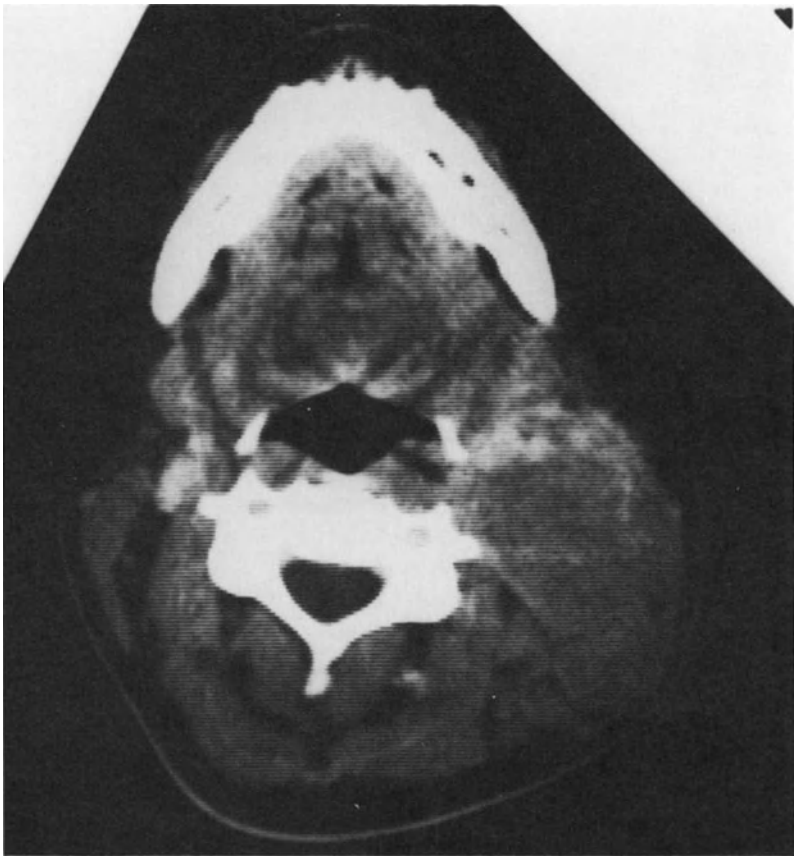

Figure 1. A CT scan through the neck revealing massive involvement of lymph node tissues of the left cervical chain in a young girl with easily palpable left supraclavicular and cervical lymph node disease. The palpable disease extent is easily encompassed by opposing anterior and posterior neck or mantle radiotherapy portals.

pushing the structures to the midline. In this situation, conventional anterior–posterior opposing neck radiotherapy portals would not have provided adequate coverage of Waldeyer's ring structures, which require use of opposed lateral neck fields abutted to and matched to the anterior and posterior low-neck ports. Without an appreciation of the Waldeyer's ring involvement and the appropriate imaging studies to demonstrate its extent, routine radiotherapy ports would have been inadequate. Although the geographic extent of disease did not alter the youngster's stage of disease, it did dictate the required radiotherapy portals to be used.

The presence of a mediastinal mass containing Hodgkin's disease as distinct from normal thymic tissue may be dificult to differentiate in a child. Thoracic CT is essential in all children, even those with an apparently

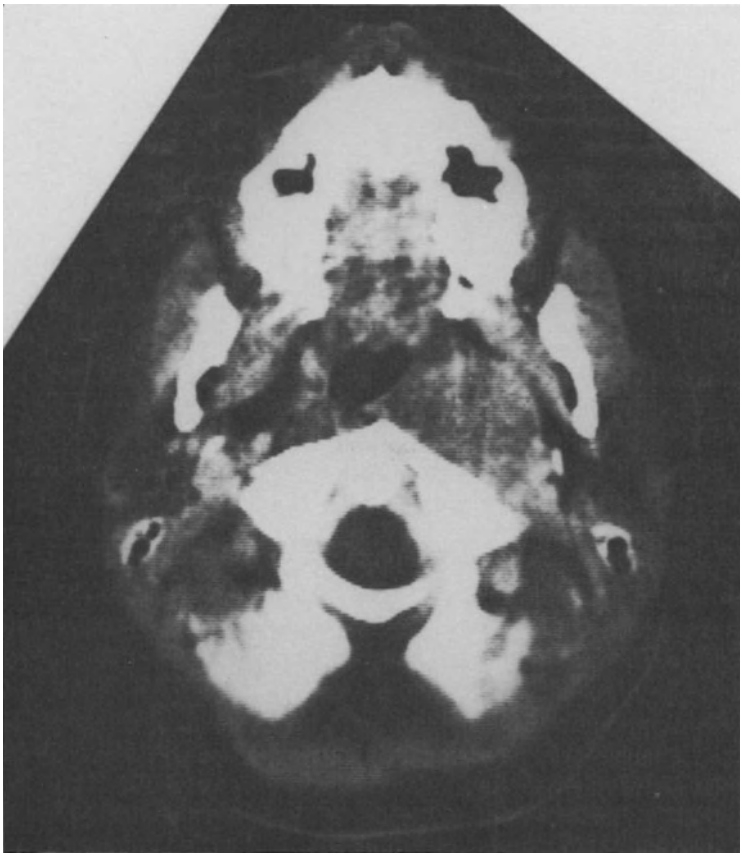

Figure 2. Higher CT cuts in the same girl as shown in Figure 1 reveal the left neck adenopathy to be extending superiorly and is contiguous with a left Waldeyer's ring, parapharyngeal mass beginning at the fossa of Rosenmuller. This extent of disease required a lateral Waldeyer's ring radiation portal to be used in order to encompass the disease adequately, in addition to the conventional anterior and posterior opposed portals routinely used to treat the neck disease.

normal chest x-ray. Any questionably abnormal mass should either be regarded as involved with Hodgkin's disease and treated as such, or biopsied to demonstrate lack of involvement with Hodgkin's disease. The thoracic CT is useful not only in determining the mediastinal extent of disease [14], but also in radiotherapy treatment planning [15, 16]. It is important to recognize that extralymphatic extension to the pericardium, pleura, or pulmonary parenchyma is commonly seen in association with massive mediastinal and/or hilar disease. Likewise, pleural effusions may be apparent, which oftentimes are secondary to lymphatic obstruction by mediastinal disease and do not necessarily represent advanced disease. The presence of such involvement affects radiation therapy portals and shielding used. The decisions regarding use of pericardial blocks, lung blocks, a subcarinal block,

larynx block, and spinal cord shielding depend upon the initial stage of disease and the comprehensive plan for therapy. For example, when chemotherapy in addition to radiotherapy is planned, the radiotherapist may elect *not* to administer prophylactic radiation to areas such as the heart or lungs in patients at high risk for extension of disease in these sites. Such compromises in radiotherapy volumes depend upon high response rates to effective multiagent chemotherapy programs. This, again, underlies the importance of all members of the therapeutic team planning therapy together at the time of diagnosis and prior to embarking upon a treatment program.

Retroperitoneal lymph node imaging studies are of particular importance in children. The lymphangiogram has proven to be useful as a guide to clinical staging, as a guide to the surgeon for surgical staging, as an aid to radiotherapy treatment planning, and as a means of following response to therapy in opacified lymph nodes by serial surveillance of abdominal radiographs [24, 25]. Yet lymphography in children is technically difficult and requires a team of individuals with expertise in performing and interpreting the lymphogram. In addition, lymphography should be performed in centers where facilities for anesthesia are available, if necessary. Because of the technical and practical difficulties in performing routine lymphography in children, some investigators have routinely preferred abdominal–pelvic CT scan as an easier and less invasive procedure. However, results of studies comparing the lymphogram with the CT scan in surgically staged children are not yet available. Early experience suggests that the CT may be complementary to the lymphogram, in that it enables visualization of upper abdominal disease in the celiac axis–porta hepatis area, which is not well demonstrated by lymphography [26, 27]. However, the resolution of current CT scans does not provide information on filling defects or lymph node architecture, such as is shown by the lymphogram (Figure 3). Rather, the CT criteria for abnormalities are based upon lymph node size, which does not differentiate reactive hyperplasia from lymphoma (Figure 4). This is of practical importance with respect to children with Hodgkin's disease as one-third of the radiographic abnormalities visualized by lymphography are attributable to reactive hyperplasia, while the remaining two-thirds of abnormalities relate to Hodgkin's disease [28]. Figures 3 and 4 reveal diffusely abnormal lymphograms with abnormal large retroperitoneal lymph nodes of a size that is easily visualized as abnormal retroperitoneal lymph nodes by CT scanning. However, the lymphogram is capable of differentiating the abnormalities of Hodgkin's disease from those of reactive hyperplasia. Interpretation of the CT is more difficult in thin children who have a paucity of retroperitoneal fat than normally is visualized in adults. Thus, there remains a controversy regarding whether to do lymphography or abdominal CT in children. It appears that both the lymphogram and CT have roles in the staging of children. Lymphography is particularly useful in younger children who have an apparently normal abdominal CT [26]. If only one radiographic imaging study is available, it appears that the lymphogram is the single most impor-

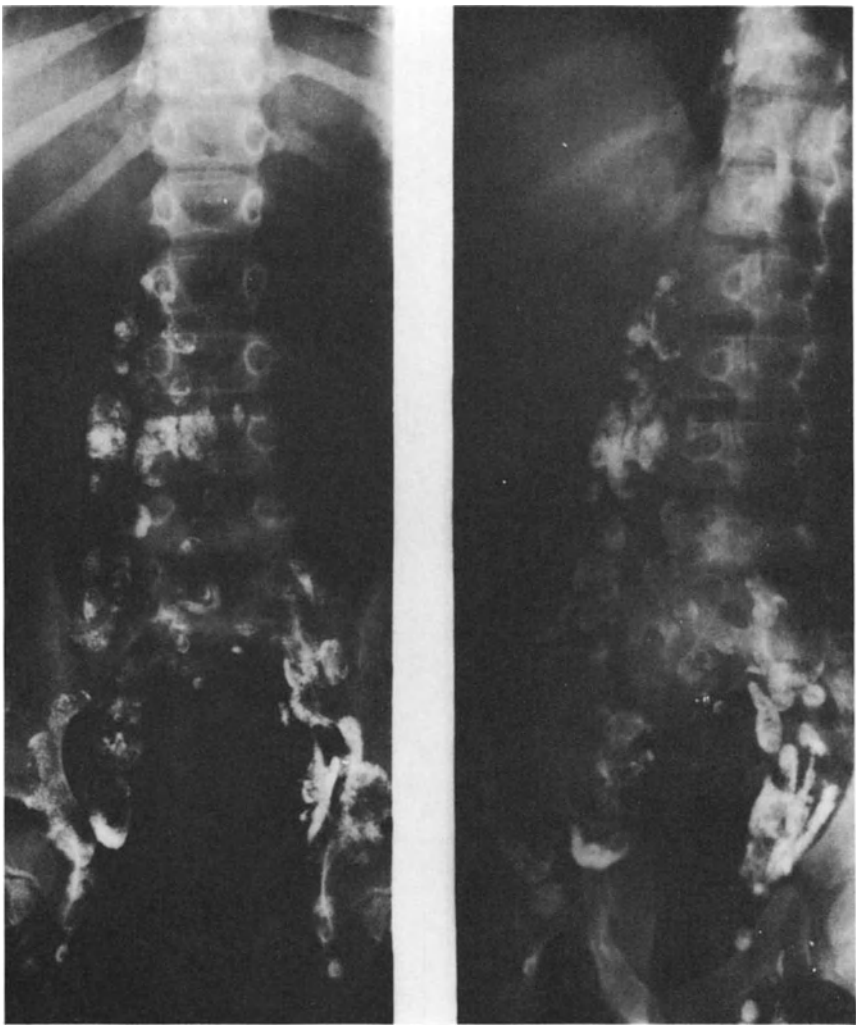

Figure 3. A lymphogram in an 8-year-old boy revealing diffusely abnormal lymph nodes in virtually all of the retroperitoneal lymph node chains. The abnormalities are of a sufficient size to also be visualized in an abdominal-pelvic CT scan as abnormally enlarged retroperitoneal adenopathy. However, the lymphogram reveals the abnormal lymph nodes to have filling defects and architectural changes characteristic of Hodgkin's disease.

tant investigation for imaging of retroperitoneal lymph nodes in Hodgkin's disease and should not be disregarded [29]. Clinical staging should be considered incomplete if the CT scan is done in lieu of the lymphogram and is the only retroperitoneal imaging study performed. Data are not yet available comparing MRI with CT or lymphography in pathologically staged children with Hodgkin's disease. It is possible that MRI may complement

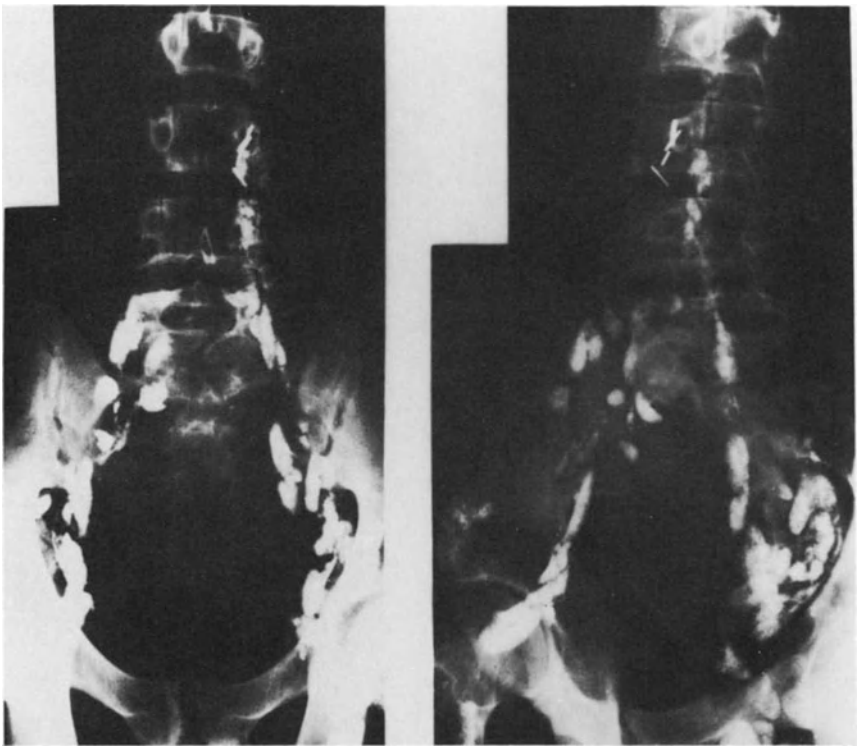

Figure 4. A lymphogram in a 15-year-old boy with supradiaphragmatic Hodgkin's disease demonstrating uniformly enlarged foamy lymph nodes, all with a reactive appearance, representing reactive hyperplasia. A CT scan of these nodes is capable of visualizing the abnormally enlarged lymph nodes, but not the architectural pattern demonstrating their reactive appearance.

the routine clinical workup of the patient with Hodgkin's disease, or may replace some of the previously recommended procedures.

Other imaging studies and scans, including gallium-67 citrate scintigraphy, liver–spleen scans, abdominal ultrasound, and miscellaneous radiographs, are often obtained in a routine workup, but have not proven useful because of the high proportion of false-positive and false-negative interpretations [28, 30].

Routine laboratory studies, including a complete blood count, erythrocyte sedimentation rate, and liver and renal function tests, are indicated for staging. Alkaline phosphatase is a useful measure for baseline and follow-up studies and, if elevated in a patient with symptoms of bone pain, requires further evaluation with a bone scan. However, the alkaline phosphatase may often be elevated as a function of active growth in a youngster or adolescent. Whenever the alkaline phosphatase is out of range for age, a bone

scan should be performed. Likewise, evaluation of serum copper content, which is a nonspecific biochemical indicator, is useful in monitoring disease activity. However, it is often elevated in young women with high estrogen activity as well as in those taking exogenous estrogen. Thus, the routine laboratory studies may be less helpful when staging a child than when staging an adult [31].

3. Surgical staging

Perhaps the greatest of all of the controversial issues among children with Hodgkin's disease remains the question of the need for surgical staging over thorough clinical staging. When performed, a staging laparotomy includes a splenectomy, wedge and needle liver biopsy, bone marrow biopsy, and biopsy of selected lymph nodes of the celiac axis, porta hepatis, and paraaortic areas as well as lymph nodes suggested on lymphography, bone marrow biopsy, and oophoropexy in girls. The concerns of staging laparotomy include an emotional one of subjecting a child to an elective surgical procedure simply for thoroughness of staging, as well as a medical one relating to the risks of serious bacterial infection among asplenic children.

With respect to the need for thorough staging, it is generally agreed that staging defines therapy. If one has complete staging revealing localized and favorable disease, then one may be able to minimize therapy. If, however, staging reveals advanced or extensive disease, then therapy cannot be compromised. When staging is incomplete, one must treat aggressively, which results in an overtreatment of some, in order to insure high cure rates. The issue becomes one of aggressive staging or aggressive treatment.

Indications for laparotomy with splenectomy depend upon treatment options. If therapy will not be altered by pathologic staging, laparotomy may not be justified [1]. It is difficult to defend staging laparotomy in children presenting with bone marrow disease, those with supradiaphragmatic disease who also have a clearly positive lymphangiogram, or those who present with extensive intrathoracic disease in whom the greatest probability of relapse is intrathoracic [11, 32, 33] and in whom general anesthesia may be dangerous. Some investigators continue to recommend staging laparotomy if the findings of laparotomy might change the need for radiotherapy [34]. Determination of the presence or absence of subdiaphragmatic disease may determine the need for subdiaphragmatic irradiation as well as whether the pelvis requires treatment. If the patient is a female and there is a possibility that pelvic radiotherapy may be required, she should undergo oophoropexy at the time of laparotomy [35]. It is uncommon to find subdiaphragmatic disease in an asymptomatic patient with intrathoracic Hodgkin's disease only, confined to the mediastinum. In such cases of patients without systemic symptoms who clearly have a negative lymphangiogram, the Stanford investigators have found a low-percentage yield from the stag-

ing laparotomy and therefore recommend extended-field radiotherapy alone if the mediastinal disease is less than one-third of the intrathoracic diameter. However, in cases with intrathoracic disease only and systemic B-type symptoms, staging laparotomy has detected occult subdiaphragmatic disease.

Staging laparotomy has been shown to be of value in the accurate staging of disease [30, 36–38]. At least one-third of children will have a change in clinical stage after laparotomy, most frequently with a finding of occult splenic disease, even in the absence of other subdiaphragmatic involvement [39]. If a laparotomy is to be undertaken, some investigators have questioned doing a partial splenectomy in lieu of a total splenectomy [40]. This notion was stimulated as a means of leaving some intact splenic tissue to protect against overwhelming sepsis. However, the high false-negative rate with partial splenectomy and the risk of failing to diagnosis occult splenic disease in the proportion remaining have generally convinced pediatric surgeons of the need for a total splenectomy followed by serial sectioning of the entire specimen [4].

The issues relevant to staging relate directly to treatment options. If radiotherapy alone as localized treatment is considered, then, obviously, one needs careful staging. If chemotherapy alone as systemic treatment is recommended, then precise staging may not be needed. Many investigators now recommend combined-modality treatment for children with Hodgkin's disease. Such programs may involve chemotherapy with radiotherapy to involved fields as defined by surgical staging [34, 42], chemotherapy with radiation therapy to involved or extended fields as defined by clinical staging [43–46], chemotherapy and radiotherapy to areas of bulky disease [17], or chemotherapy with radiotherapy to areas of surgically defined persistent disease [43, 46]. Thus, the decisions regarding who may need radiotherapy and the delineation of radiotherapy volume may determine in whom surgical staging is a requisite and whether histologic confirmation of disease extent is necessary. The studies cited have involved between three and six cycles of multiagent chemotherapy and some have used involved-field, low-dose radiotherapy. Studies comparing the efficacy of the various approaches are too preliminary at present for firm recommendations to be made. As increased emphasis on reducing therapy extends to minimizing the aggressiveness of chemotherapy as well as radiotherapy, investigators must continually reevaluate the appropriateness of cutting back on treatment.

The issues regarding potential complications from elective surgical staging for Hodgkin's disease must be addressed prior to initiation of programs that require laparotomy staging. Surgical complications defined as acute include operative deaths; late complications are those that occur late in the course, such as intestinal obstruction secondary to adhesions, and overwhelming infection secondary to the asplenic state.

When performed, surgical staging should be done by an experienced surgical team who work closely with the therapeutic team, *i.e.*, radiotherap-

ist and oncologist. The value of surgical staging is to provide information for the clinicians; thus, surgeons need to understand the issues at hand with each individual patient. This requires careful review of the diagnostic imaging studies including the lymphangiogram so that appropriate or suspicious lymph nodes will be sampled at the time of surgery. In addition, if the patient is female, consideration should be given to performing oophoropexy [35]. Additional procedures, however, not critical to the staging of Hodgkin's disease should be avoided. Thus, one should not be tempted to add an incidental appendectomy, tubal ligation, cholecystectomy, *etc.*, to a staging laparotomy. Such additional procedures only increase operative and anesthesia time, and thus the potential for complications from the procedure. In experienced hands, the mortality of routine staging laparotomy should be <0.5% [30]. At Stanford University, where more than 1500 routine staging laparotomies have been performed among patients with Hodgkin's disease, the mortality rate is zero, owing to careful patient selection, improvement in preoperative and postoperative care, and familiarity with the operative procedure.

Approximately 3% of children may experience intestinal obstruction presumably related to adhesions following the initial surgical procedure, of which ~50% require surgical correction [30, 47]. Complication rates among adults undergoing staging laparotomy exceed those among children. The low incidence in the pediatric population is related to the fact that the patients are young, and in good general health, and in most series are operated upon and cared for by a team of surgeons with expertise in performing diagnostic staging laparotomies.

The concern regarding serious bacterial infections in these asplenic patients remains, especially in children. Fulminant bacterial infections in splenectomized children are largely due to the encapsulated organisms, particularly *Streptococcus pneumoniae* and *Hemophilus influenzae*. In a survey of 1170 individual splenectomized patients for Hodgkin's disease and lymphoma from 12 different institutions, 16 instances of serious infections were uncovered (1%), six of which proved fatal (a late mortality rate of 0.5%) [48]. In a questionnaire study of children with Hodgkin's disease, two deaths due to sepsis among 374 laparotomies (0.5%) were noted [49]. In a retrospective national survey by the Children's Cancer Study Group, however, 20 episodes of bacterial sepsis in 18 of 200 children splenectomized for Hodgkin's disease were discovered (10%), with ten deaths (5%) [50]. Similarly, of 181 children with Hodgkin's disease, the Stanford group encountered 22 children with 27 episodes of serious bacterial infection (12%). However, further analysis suggested the treatment rather than a splenectomy *per se* may have been responsible for at least a significant portion of these infectious complications [51, 52]. In the Stanford pediatric series, the risk of serious bacterial infection was 1.4% among splenectomized children and 2.8% among nonsplenectomized children who received radiotherapy as

treatment for their Hodgkin's disease. However, when chemotherapy was added to radiotherapy in the treatment program, the risk rose to 18.3% for splenectomized children and 23.1% for nonsplenectomized children [51]. The rates of infection in both the splenectomized and nonsplenectomized population were significantly increased when chemotherapy was given over radiotherapy alone ($p<0.5$). Although there was no difference in the overall frequency of bacterial infection that could be attributed to splenectomy, it was nonetheless true that all of the 15 episodes of bacterial meningitis due to *S. pneumoniae* and *H. influenzae* occurred in 14 children who had been splenectomized. The concern of bacteremia following splenectomy also exists following high-dose splenic irradiation [53]. Such patients having had ~40-gray splenic irradiation have developed a functional hyposplenia [54]. Data regarding chemotherapy alone or low-dose radiotherapy regarding splenic function are not yet available. The risk of infection after splenectomy or splenic irradiation appears to be lifelong, as overwhelming bacteremia has been observed 13 years or more after all treatment among patients apparently cured of their Hodgkin's disease.

The possibility of immunization against the more widely prevalent types of *S. pneumoniae* incited interest when polyvalent pneumococcal polysaccharide vaccines became available. However, use of the vaccine among children with Hodgkin's disease has been discouraging. Mean antibody concentrations measured in children immunized after splenectomy, immunosuppressed from the disease and/or their treatment, are inadequate for protection [55]. Even when the vaccine is administered prior to splenectomy, antibody responses vary from patient to patient and from serotype to serotype, both in the level of antibody achieved and the duration of response, thus obviating effective protection [56]. Similarly, data demonstrating immunogenicity to *H. influenzae* vaccine among splenectomized children with Hodgkin's disease are lacking. As there is no readily available commercial method of evaluating antibody response following vaccination, and as data regarding efficacy are lacking, one cannot rely upon commercially available vaccines as sole protection for an asplenic child with Hodgkin's disease.

Many pediatricians now rely on the prophylactic use of penicillin in splenectomized children with Hodgkin's disease. This practice introduces the theoretical concerns of infection with penicillin-resistant organisms, questions regarding patient compliance, and concerns regarding optimal dose and duration of antibiotic therapy. As the answers to these issues are not available, pediatricians have recommended lifelong antibiotic therapy along with patient education regarding the signs and symptoms of serious bacterial infection, informing patients of the urgent need for fever workup with blood culture should a splenectomized patient develop a fever >101°–102°F. The use of routine antibiotic prophylaxis has been effective in reducing the risk of serious bacterial infection in children with Hodgkin's disease from a previous experience of 12% to 5% [34, 51].

4. Treatment options

Initial therapy for Hodgkin's disease should be planned with curative intent taking into account the age of the child, stage of the disease, tumor burden, and potential complications of therapy. Many of the guidelines determined from the adult studies are applicable to children, as the biology and natural history of the disease do not differ as a function of age. The disease in children does represent certain unique aspects, however, including potential complications and late effects among this population in whom anticipated survival time is long and in whom quality of survival is an important issue.

Radiotherapy alone may be optimal treatment for a subset of children. Selection criteria vary from institution to institution, but most clinicians agree that adolescents or young adults who are fully grown and developed, who have early-stage, favorable disease as determined by thorough clinical and pathologic staging, are appropriately treated by radiotherapy alone. Such therapy involves high-dose extended-field radiation as delivered in a center with modern radiotherapy facilities, physics and dosimetry support, and a megavoltage therapy unit such as a linear accelerator. Rarely, one encounters a case of favorable stage IA lymphocyte-predominant Hodgkin's disease arising in a favorable location, such as the high right neck or inguinal–femoral area, in which thorough staging shows no spread of disease. Such patients may be candidates for high-dose involved-field radiotherapy alone [57]. Here, the age of the child becomes a major consideration, for even high-dose involved-field radiotherapy may have serious sequelae upon bone and soft tissue growth. More commonly, the debate in such a case is whether to subject such a patient to laparotomy staging. The solution is found when one answers the question of whether therapy will be altered by the findings at staging laparotomy.

Chemotherapy alone has been utilized in a few centers representing small patient numbers and relatively short follow-up [58–60]. Among these patients, concern exists that relapse could be expected following chemotherapy alone in patients with the nodular-sclerosing subtype or in sites of previous bulky disease [18].

However, most children today are candidates for combined-modality therapy using radiotherapy and multiple cycles of multiagent chemotherapy. Historically, high-dose radiotherapy was combined with chemotherapy, as in the adult programs, but, more recently, investigators have utilized low-dose radiotherapy plus chemotherapy in children [34], in attempts to minimize the growth and developmental effects from high-dose radiation in youngsters [61]. The decision of whether to use high-dose or low-dose radiotherapy relates to the age of child at the time of treatment and his or her status of growth and development, tumor burden, and response to chemotherapy. When a child has a poor response to front-line chemotherapy, it is unwise to also compromise the dose of radiotherapy.

The appropriate volume of radiotherapy may also vary from one schedule to another. Currently, it is in vogue to use an involved field of radiotherapy when combined-modality programs are planned. However, the definition of an involved field may vary. Some investigators prefer to use the anatomic definition of separate lymph node regions adapted for staging purposes at the Rye symposium [62] as appropriate radiotherapy fields. Other radiotherapists prefer anatomic landmarks or regions that would not interfere with subsequent retreatment and not compromise symmetry. Some oncologists recommend irradiating simply the area involved without consideration of staging definitions. As there appear to be institutional variations to these definitions of a radiotherapy field, it is important that the radiotherapist involved be the one to define the radiotherapy field, as the ultimate responsibility for the radiation treatment remains with the participating radiotherapist.

The recommended number of cycles of chemotherapy varies between series and protocols. However, most institutions have given at least six cycles of chemotherapy for advanced disease. Current studies are now testing three or four cycles of chemotherapy and radiotherapy in early-stage Hodgkin's disease. The decisions regarding which multiagent chemotherapy program to choose is also in evolution. The traditional MOPP chemotherapy program (nitrogen mustard, Oncovin [vincristine], procarbazine, and prednisone) [63] has been proven to be efficacious in terms of disease control, but with unanticipated side effects of male sterility and leukemogenesis when six cycles are administered. Other programs such as ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) [64] may be associated with smaller risk of sterility or leukemia [65], but with yet unknown risk of cardiopulmonary injury. Other four-drug programs representing variations or combinations of the MOPP/ABVD program have also been tested. Further investigations are necessary to find a drug program with equal or superior effectiveness than those combinations already tested, and which has fewer side effects.

The late-effects issue becomes a major consideration with children when one considers quality of survival and number of survival years. The side effects of radiotherapy are well known [47, 66, 67] as radiotherapy is a modality capable of curing patients with Hodgkin's disease with which we now have 25+ years of experience. We are just now appreciating some of the acute and early side effects of chemotherapy. Assessment of the later complications will require more years of follow-up. Many of the older arguments regarding radiotherapy complications *versus* chemotherapy complications are now diffused by evaluating combined-modality programs that use lower doses of radiation in combination with milder chemotherapy programs. The challenge of today is one of development of new drug combinations to use in conjunction with low-dose radiotherapy for the majority of children with Hodgkin's disease.

5. Follow-up

No controversies exist regarding the need for long-term follow-up. Among the pediatric population, this is particularly important in terms of assessment of disease status as well as later complications of treatment and should be routinely performed by the radiation oncologist as well as the pediatric or medical oncologist. Late relapses are known to occur among patients with Hodgkin's disease; ~13% of relapses occur 3 years or more after completion of treatment, and initial relapses have been recognized with a disease-free interval of as long as 15 years [68].

The late effects of treatment when administered to children may not appear for many years, thus making routine and long-term assessment mandatory. The appropriate studies to perform and the interval for visits may vary, but all agree that careful follow-up is essential. Particular areas of concern with respect to the child are assessment of those organs and tissues that are more sensitive to treatment because of a child's age and growth status. The thyroid gland of a child appears to be more vulnerable to radiation injury than that of the adult as evidence of chemical hypothyroidism with elevated TSH and depressed T_4 values may appear in as many as 65% of children [69]. This injury appears to be dose related with only ~25% of children having subnormal thyroid function following low doses of radiation as compared with high doses. This injury may be reversible in greater than one-third of cases. It is important to test thyroid function by free T_4 and TSH regularly and to institute thyroid replacement in children who are chemically or clinically hypothyroid, because the effect of unopposed stimulation on the thyroid gland is unknown. Thyroid nodules may develop years after thyroid irradiation. Whereas the bulk of these will be benign thyroid adenomas, carcinoma of the thyroid has been observed after both low-dose and high-dose radiotherapy [34, 70].

Sitting heights as well as standing heights are important in the assessment of growth effects following radiotherapy and should be measured regularly, at least annually.

The assessment of residual mediastinal mass following treatment of Hodgkin's disease represents a problem and a concern particularly in those patients who present with large mediastinal masses; ~40% of such patients will have continual radiographic abnormalities following radiation or combined-modality therapy for Hodgkin's disease [71]. It is important to recognize that such masses do not by themselves represent active disease or an increased risk of relapse, and additional therapy should *not* be administered simply because of a persistent mass. Unusual thoracic radiographic findings have been observed following mantle radiotherapy and chemotherapy in children [72]. Furthermore, the appearance of increased size of mediastinal or thymic tissue following completion of six cycles of chemotherapy has been observed in children without mediastinal disease at the time of

presentation and without mediastinal radiotherapy. This rebound phenomena is presumably related to reactive changes in normal thymic lymphoid tissue. Again, it must be stressed that such interval masses do not necessarily represent growth of Hodgkin's disease. To avoid misinterpretation, it is an important principle to insist upon biopsy confirmation of any presumed primary relapse. If relapse does occur, it is important to undertake a complete clinical restaging so as to recognize the paterns of failure and impact of previous treatment. The importance of the follow-up repeat lymphogram has been described previously (see Figure 4), both as an assessment of lymph node size and character and also as a means of assessing architectural changes [73].

6. Conclusions

While there are some divided opinions regarding management of children with Hodgkin's disease, they generally relate to therapeutic orientation and are not major controversies. The radiotherapist plays a major role in the overall evaluation of all children with Hodgkin's disease, and in the therapeutic management of the majority of these children. Those issues which relate to the staging, treatment, and follow-up that affect radiotherapy should be discussed by all members of the team prior to decisions regarding management. In this way, oncologists, surgeons, and patients and their families will gain an appreciation for the concerns that represent the radiotherapist's view of the management of children with Hodgkin's disease.

Acknowledgment

This work was supported in part by grant CA 34233 from the National Cancer Institute, National Institutes of Health.

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12 Current management and controversies
The Patient's View

Margaret P. Sullivan, Sharon Lockhart, and Hallie Boren

The increasing curability of Hodgkin's disease in children, now certainly >80% [1, 2], is continuously producing cured children, teenagers, and young adults to be returned to the 'mainstream' after an absence ranging from several months to almost a year. This high cure rate is achieved through a series of diagnostic tests including biopsy, multiple laboratory and imaging studies, and surgical staging followed by complicated chemotherapy and treatment with sophisticated radiation equipment. The high cure rate is blemished somewhat by the consequences of surgical staging (primarily the splenectomy), growth retardation in irradiated tissues, and the occurrence of second malignant tumors following intensive therapy with both treatment modalities. Adverse medical consequences of surgical staging have been reported in detail [3, 4], as have late effects of radiotherapy [5, 6] and the occurrence of second malignant tumors following combined modality therapy [7, 8]. These adverse effects are of great concern to both chemotherapists and radiotherapists, and have resulted in more selective use of the staging laparotomy, reductions in the intensity of radiotherapy, and use of less toxic chemotherapy regimens.

The perceptions of the child cured of Hodgkin's disease as to the most troublesome and unpleasant aspects of the medical experience are not known. Standard instruments for the collection of such data from children have not been developed. We have sought basic information on patient perceptions of their treatment for Hodgkin's disease as a means of appraising patient management and of finding ways to modify care to make the therapeutic experience more acceptable.

1. Methods

Sixty-five patients were interviewed, 90% by telephone, to determine their perception of the 'worst thing' about (a) the diagnostic biopsy procedure and the resultant scar; (b) the diagnostic workup, including lymphangiogram; (c) therapy, both radio- and chemotherapy; and (d) daily oral prophylactic penicillin administration. Information was also sought as to the effect

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of each therapy on school, friends, and classmates. Inquiry was made as to those told of the diagnosis and whether there were anything positive in the entire diagnostic and treatment experience. Sexual activity, marriage, infertility, and divorce were not subjects of inquiry.

The patient participants were those available from our cadre of 123 children with surgically staged and treated Hodgkin's disease. Interviews were conducted by the authors: M.P., the Lymphoma Attending Physician; S.L., Pediatric Hematology Fellow in Lymphoma Clinic; and H.B., Pediatric Nurse Practitioner in Lymphoma and Long-term Follow-up Clinics. The information obtained was entered on an interview form. Repeated efforts were made to reach each surgically staged and treated patient on the roster; success was limited by the mobility of the young adult college students and employment seekers, and the nonavailability of correct direct-dialing telephone numbers for patients from other countries.

Ages of the study population at diagnosis ranged from 3 7/12 years to 15 years, median 12 2/3 years. The male–female ratio was 1.5:1.0; 61 children were of the white race and four of the black. There were seven preschool children ≤6 years of age, 22 preadolescents 7–11 years of age, and 36 adolescents aged 12–16 years. The male–female ratios for the respective groups were 1.3:1, 3.4:1, and 1.1:1. The therapeutic modalities employed further divided patients into the following treatment groups: (a) combined modality (radiotherapy [XRT] and chemotherapy [CT]), (b) CT only, (c) XRT only, and (d) CT and XRT. Time in years from completion of therapy, range and median, for children in each of the age groups is as follows: preschool, 2 1/4–13 (9 2/3); preadolescents, 1/6–15 (8 1/2); and adolescents, 1/4–16 (6). Telephone interview responses were tabulated with respect to age group and therapy delivered (Tables 1–9). As the numbers of patients in the various groups for comparison were all small, statistical tests of significance were not applied.

2. Results

2.1. Patient concerns related to biopsy (Table 1)

The diagnostic biopsy, the initial event in the patient's course of diagnosis and therapy, appears to have less significance than subsequent events that dominate the patient's perception of the total experience. A majority of patients (63%) report that they have either little or no specific recall of the actual biopsy (18%), usually of a cervical lymph node, or that they had no concerns or unpleasant memories associated with the event (45%).

Nine percent were unaware of the significance of undergoing a biopsy, and felt that it was a routine test. Eleven patients (17%) indicated that they felt frightened or worried about undergoing the procedure, and one child

Table 1. Patient concerns related to diagnostic biopsy.

Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Little or no memory of biopsy, no. (%)	No specific concerns, no. (%)	Unaware of significance, no. (%)	Frightened, worried, no. (%)	Pain of procedure, no. (%)	Biopsy scar, no. (%)
0–6	XRT & CT (2)	2 (100)	0	0	0	0	0
3–15	CT (8)	1 (12.5)	4 (50)	0	3 (37.5)	0	0
4–15	XRT (14)	5 (36)	4 (28)	2 (14)	1 (7)	0	2 (14)[c]
7–11	CT & XRT (15)	2 (13)	8 (53)	2 (13)	2 (13)[b]	1 (6)	0
12–15	CT & XRT (26)	2 (13)	13 (50)	2 (07)	5 (19)	2 (13)	2 (13)
Total	65	12 (18)	29 (45)	6 (9)	11 (17)	3 (5)	4 (6)

[a]XRT, radiotherapy; and CT, chemotherapy.
[b]One patient was frightened most by parents' fears and reactions.
[c]Numbness over scar, one patient.

indicated that her parents' visible concern and worry caused her to become frightened.

Only three patients (5%) recalled the procedure as being painful, and one patient felt that the numbness in the area of the scar was the worst aspect of the biopsy.

2.2. Lymphangiogram and the staging laparotomy (Table 2)

Like the diagnostic biopsy, the lymphangiogram and the staging laparotomy were early events in the patient's overall experience, and memories of the laparatomy seem to be replaced by later therapeutic events.

The lymphangiogram was a particularly unpleasant experience to 20 patients (30.7%), who recalled the injection of dye between the toes as very painful and/or found it difficult to remain still for a prolonged period. The percentage of patients having unpleasant recollections of the lymphangiogram seems especially high as all children <10 years of age had the procedure performed while they were anesthetized. One patient stated that, after lymphangiogram, he observed blue dye in his vomitus.

Five patients who underwent bone marrow aspiration prior to laparotomy considered this procedure to be the worst event of the diagnostic evaluation. Two of the younger patients regarded the need for needles (IVs and injections) as the worst aspect of the experience.

The actual surgical staging was associated with surprisingly few unpleasant memories. Two children remembered the anesthesia mask on their face as the most unpleasant event. The most common complaint was postoperative incisional pain, particularly abdominal pain upon laughing, coughing, or walking, cited by 18 patients (27.7%). The nasogastric tube was particularly disliked by 12 patients (18.5%). Only four patients (6%) recalled the removal of stitches as unpleasant.

Overall, the diagnostic evaluation and surgical staging laparotomy were not recalled as unfavorably as one might expect, with 11 patients (17%) being unable to recall anything. Included in this group were a 3 year old and a 4 year old. The former has no recollection of the staging laparotomy; the latter can remember the balloons tied to the stretcher that took her to the surgical suite.

2.3. Twice-daily penicillin prophylaxis (Table 3)

Over half of the patients (51%) indicated that they had no difficulty in adhering to a twice-daily schedule of penicillin prophylaxis. Ten patients (15%) stated that it was difficult to remember, but they generally took it as prescribed. An additional ten patients complained that taking the medication was a major nuisance, and that they occasionally missed doses. Five patients indicated that they took it regularly because they recognized the importance to their health. Only a small percentage of patients (3%) in-

Table 2. Patient perception of worst aspects of staging evaluation and laparotomy.

Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Not bad/ no comment, no. (%)	Needles/ injections, no. (%)	Bone marrow site,[b] no. (%)	Lymphangio-gram, no. (%)	Anesthesia mask, no. (%)	Fear and apprehension, no. (%)	NG[c] tube, no. (%)	Incisional pain, no. (%)	Stitch removal no. (%)
0–6	CT & XRT (2)	0	1 (50)	0	0	0	0	1 (50)	0	0
7–11	CT & XRT (15)	6 (40)	0	1 (6.6)	3 (20)	0	1 (6.6)	3 (20)	6 (40)	0
12–15	CT & XRT (26)	4 (15)	0	1 (3.8)	13 (50)	0	5 (19)	4 (15.3)	7 (26.9)	2 (7.6)
3–15	CT (8)	1 (12.5)	0	0	1 (12.5)	2 (25)	1 (12.5)	2 (25)	2 (25)	1 (12.5)
4–15	XRT (14)	0	1 (7)	3 (21)	3 (21)	0	2 (14.3)	2 (14.3)	3 (21)	1 (7)
Total	65	11 (16.9)	2 (3)	5 (7.6)	20 (30.7)	2 (3)	9 (13.8)	12 (18.5)	18 (27.7)	4 (6)

[a]XRT, radiotherapy; and CT, chemotherapy.
[b]Prebiopsy, mediastinal disease suggestive of lymphoma.
[c]NG, nasogastric.

Table 3. Attitude toward daily penicillin prophylaxis.

Age at diagnosis, range in years (no.)	Adherence to daily dose schedule, no. (%)							Reaction of friends, no. (%)	
	No problem	Hard to remember	Major nuisance	Taken only when sick	Never taken	Ill when omitted	Side effects	None or unaware	Aware and supportive
0–6 (7)	3 (43)	1 (14)	2 (28)	0	1 (14)	0	1[b] (14)	7 (100)	0
7–11 (22)	10[a] (45)	5 (23)	3 (14)	1 (5)	0	0	2[c] (9)	20 (91)	2 (9)
12–15 (36)	20[a] (55)	4 (11)	5 (14)	1 (3)	1 (3)	3 (8)	3[b,d] (8)	34 (94)	1 (3)
Total	33 (51)	10 (15)	10 (15)	2 (3)	2 (3)	3 (4)	6 (9)	62 (95)	3 (5)

[a]Importance to health recognized, total of five patients.
[b]Penicillin allergy, total of three patients.
[c]Bad taste, one patient.
[d]Rash with alcohol, two patients.

dicated that they never took the antibiotic as prescribed; a similar number (4%) took it only when sick. Three patients (4%) felt that they became ill when they omitted a dose, so they tried to take it regularly.

Side effects of penicillin prophylaxis were infrequent. Three patients (8%) reported allergy to penicillin; erythromycin was tolerated with no difficulty. Only one patient complained of penicillin's unpleasant taste. Two teenage patients stated that they developed a rash if they drank alcohol while taking prophylactic penicillin, which was 'difficult to explain at parties.'

A vast majority of patients (95%) indicated that their friends were generally unaware of their daily penicillin requirement. One patient avoided taking it while at school for fear of being accused of drug abuse. Only one patient reported excessive curiosity from peers about the penicillin requirement. In the few cases where peers were aware of the requirement, the reaction was supportive.

2.4. Radiotherapy (Table 4)

Fifty-seven of the patients received XRT, either alone (14 patients) or in combination with CT (43 patients). Overall, XRT was a much less unpleasant experience than CT. In fact, 15 patients (26.3%) indicated they they could recall nothing unpleasant at all about the XRT experience.

Physical side effects were relatively uncommon complaints. Nausea and vomiting occurred in 23% of the patients, particularly those receiving abdominal radiation. Two patients complained of malaise and fatigue as being the most unpleasant aspect of XRT. Two additional patients recalled esophagitis and throat pain as being the worst aspects of treatment.

Hair loss, one of the most frequent complaints associated with CT, was reported as relatively infrequent with XRT to the neck and occurred only in six patients (10.5%) in small areas at the base of the skull.

Skin changes, ranging from erythema to dryness to actual desquamation, were reported in six patients (10.5%) as the most unpleasant aspect of XRT.

In many cases, the treatment room itself or the environmental setting was the most distressing aspect of the XRT experience: 14 patients (24%) recalled the actual treatment room itself as the worst part of the therapy, citing the cold, hard table, the sense of being all alone in the cold, frightening room, and the sound of the heavy door closing as people left the room. Interestingly, these complaints were made by children of all ages, not just the younger age group. Lying still for a prolonged period of time and having to undergo treatments on a daily basis for several weeks constituted the most unpleasant aspect for two other patients.

The highly visible red treatment field lines were distressing to 12 patients (21%), who felt 'painted.' These patients also disliked not bathing the area for a prolonged time.

Other minor complaints related to the subsequent need for protection

Table 4. Patient perceptions of worst aspects of radiotherapy.

			Physical side effects, no. (%)				Treatment setting/administration, no. (%)			Late effects, no. (%)	
Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Not a bad experience, no. (%)	Nausea, vomiting, fatigue	Skin changes[b]	Esophagitis, pharyngalgia	Hair loss	Red treatment field lines	Frightening treatment room[b]	Required immobility	Need for sunscreen	Late growth defects
0–6	XRT & CT (2)	1 (50)	0	0	0	0	0	0	1 (50)	0	0
4–15	XRT only (14)	2 (14.0)	3 (21.4)	0	0	2 (14.3)	2 (14.3)	2 (14.3)	2 (14.3)	1 (7)	3 (21.4)
7–11	CT & XRT (15)	6 (40)	2 (13.3)	1 (6)	0	2 (13.3)	5+ (33.3)	2 (13.3)[a]	1 (6.7)	0	0
12–15	CT & XRT (26)	6 (23)	8 (30)	5 (19.2)	2 (7.7)	2 (7.7)	5 (19.2)	5 (19.2)	1 (3.8)	2 (7.7)	0
Total	57	15 (26.3)	13 (22.8)	6 (10.5)	2 (3.5)	6 (10.5)	12 (21)	9 (15.7)	5 (8.7)	3 (5.2)	3 (5.2)

[a]XRT, radiotherapy; and CT, chemotherapy.
[b]Included erythema, dryness, and desquamation.
[c]Cold temperature, hard table, heavy closed door, and complete aloneness.

from the sun and use of sunscreen for previously irradiated areas, perceived by three patients (5.2%) as the worst aspect of XRT. An additional three patients (5.2%) felt that the subsequent growth defects that became apparent in irradiated sites constituted the most unpleasant aspect of XRT.

2.5. Chemotherapy (Table 5)

CT was associated with complaints about events prior to drug administration, as well as effects resulting from the infusion. Eight patients (16%) acknowledged anticipatory fear and, occasionally, nausea and vomiting, from one to several days prior to their next scheduled doses of CT. These patients indicated that this anticipatory fear was worse than the actual administration of the drug. In addition, another 16 patients (31%) perceived the insertion of the IV needle for access, or the strange sensations during infusion, as the most unpleasant aspect of receiving CT.

Other complaints related to side effects of drug administration. Eight patients (16%) recalled a very unpleasant smell or taste at the time of actual infusion as the worst aspect. Clearly, nausea and vomiting, with associated weakness, was the most frequently cited memory, expressed by 40 patients (78%). A single patient reported severe diarrhea in association with one chemotherapeutic agent.

Hair loss was reported as the worst effect in nine patients (17%); however, not all regimens employed were associated with marked hair loss.

Two patients reported IV infiltration and thrombophlebitis as the worst aspect of CT administration. Only one patient reported severe systemic CT as the worst event.

Overall, CT was regarded as the worst aspect of the patient experience of the diagnosis and therapy of Hodgkin's disease.

2.6. Effect of staging and treatment on schooling (Table 6)

When all therapeutic regimens and all age groups are considered, 40% of patients felt that CT had little or no effect on school performance, while only 22% felt XRT did not affect schooling. This feeling is probably based on the routine delivery of CT through 1-day clinic visits at intervals of 2 weeks while XRT requires 4–4½ weeks in Houston for each area treated (mantle or portions thereof, upper abdomen, and/or pelvis). Nine percent of patients reported 'missing a lot of school during CT;' 17% during XRT. Respondents, however, felt CT, as compared with XRT, to be more responsible for having to repeat a grade (10% *vs* 4%), and/or dropping behind 1½ years or more or dropping out of school altogether (17% *vs* 8% for XRT). For example, one patient given both CT and XRT feels he is illiterate as a result of school missed because of CT. It is noteworthy that three of eight, or 37%, of children receiving CT only repeated a grade. Of patients ≥7 years of age given both CT and XRT, 15% had to repeat a

Table 5. Patient perception of worst aspects of chemotherapy.

Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Anticipatory fear, no. (%)	IV needle insertion, infusion no. (%)	Physical side effects, no. (%)				
				Smell/taste of CT drugs	Nausea, vomiting, weakness	Hair loss	Systemic infection	Damage to veins
0–6	XRT & CT (2)	0	2 (100)	0	1 (50)	0	0	0
3–15	CT (8)	0	5 (62)	2 (25)	4 (50)	1 (12)	0	0
7–11	CT & XRT (15)	3 (20)	3 (20)	4 (27)	12 (80)	3 (20)	0	0
12–15	CT & XRT (26)	5 (19)	6 (23)	2 (7)	23 (88)	5 (19)	1 (4)	2 (7)[b]
Total	51	8 (16)	16 (31)	8 (16)	40 (78)	9 (17)	1 (01)	2

[a]XRT, radiotherapy; and CT, chemotherapy.
[b]IV infiltration, one patient; and thrombophlebitis, one patient.

Table 6. Patient perception of effect of treatment for Hodgkin's disease on schooling.

Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Little or no change, no. (%)		Missed a lot of school, no. (%)		Repeated grade, no. (%)		Drop out or behind ≥1.5 yrs, no. (%)		Special educational programs: Homebound or tutor, no. (%)		Special educational programs: MDAH school, no. (%)	
		CT	XRT	CT	XRT	CT	XRT	CT	XRT	CT	XRT	CT	XRT
3–6	XRT & CT (2)	1 (50)	1 (50)										1 (50)
3–15	CT (8)	2 (25)	4 (28)	3 (37)[b]		3 (37)						2 (25)	
4–15	XRT (14)				4 (28)		1 (7)				1 (7)		2 (14)
7–11	CT & XRT (15)	6 (40)	3 (20)	3 (20)	3 (20)	3 (20)	2 (13)	4 (26)[c]	1 (6)	2 (13)	3 (20)	3 (20)	3 (20)
12–15	CT & XRT (26)	13 (50)	10 (33)		4 (15)	1 (4)		7 (27)[d,e]	4 (15)	8 (31)	5 (19)	2 (8)	3 (12)
Total	65	26 (40)	14 (22)	6 (9)	11 (17)	7 (10)	3 (4)	11 (17)	5 (8)	10 (15)	9 (14)	5 (8)	11 (17)

[a]XRT, radiotherapy; and CT, chemotherapy.
[b]Couldn't think very well.
[c]Two were dropouts.
[d]One feels himself to be illiterate.
[e]One feels that he is still catching up.

grade; 39% were >1½ years 'behind' or dropped out of school entirely. Finally, there was one young adult respondent who confided that he 'just could not think well' during treatment.

Voluntary participation in the M.D. Anderson Hospital School, a unit of the Houston Independent School District, was reported at disappointing levels of 17% of those given XRT and only 8% for those receiving CT. Approximately equal percentages of those receiving CT and XRT, 15% and 14%, respectively, had home-bound teachers or tutors. Some home schools did not cooperate fully in the effort to keep the patient engaged scholastically, variously advising students that only half-days of school could be tolerated 2 years after completion of therapy, 'college was not to be considered,' or the school 'felt sorry' for the patient, and passing grades would be given regardless of knowledge of the assigned material.

It is noteworthy that some patients confided that school absences related only to hair loss.

2.7. *Reactions of friends to diagnosis* (Table 7)

Friends of 94% of patients were informed of the diagnosis; 42% of those informed did not change their behavior. In one instance, the patient perversely enjoyed telling friends of the diagnosis and observing their shocked behavior. Of those friends overtly reacting to the patients' illness, 20% were consistently very supportive; an additional 11% eventually became supportive. Only one friend was said to have been indulgent. Specific examples of support included friends who 'beat up on' those heckling the patient, and friends who wore wigs to school when the patient was wearing his wig. Only 2% of friends reacted with pity; the same percentage reacted with avoidance. One patient stated that friends, although very kind and concerned, seemed afraid to touch him. Nearly 5% of patients felt their friends reacted with cruelty and derision, pulling off wigs or jeering about the hair loss. One teenage girl held her illness responsible for the loss of her boyfriend.

Patients volunteered that they thought teachers should be more active in explaining illnesses such as theirs to classmates. Two exceptional teachers allowed patients to give talks on Hodgkin's disease to their classes. In each instance, the talk was said to have been very effective. One patient was greatly comforted when the school gave permission for him to wear a cap in school.

2.8. *Confidants* (Table 8)

Only 5% of patients stated that no one outside the immediate family was told of their diagnosis; 58% stated that their illness was no secret and that they told 'anyone' about it except prospective employers or insurers.

Table 7. Reaction of friends to diagnosis of Hodgkin's disease: relationship to age at diagnosis and therapy.

Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Friends not informed, no. (%)	None noted, no. (%)	Reaction to diagnosis, no. (%)						
				Supportive			Adverse			
				Curious	Eventually	Consistently	Indulgent	Pity	Avoidance	Cruelty
0–6	XRT & CT (2)	0	0	0	1	1	0	0	0	0
3–15	CT (8)	0	2	0	1	3	0	0	0	1
4–15	XRT (14)	1	6	2	0	3	0	0	1	1
7–11	CT & XRT (15)	2	5	0	2	2	1	0	1	0
12–15	CT & XRT (26)	1	14	1	3	4	0	2	0	1
Total	65	4 (6.1)	27 (42)	3 (4.6)	7 (11)	13 (20)	1 (1.5)	2 (2.0)	2 (2.0)	3 (4.6)

[a]XRT, radiotherapy; and CT, chemotherapy.

Table 8. Confidants of patients: relationship to age at diagnosis and therapy.

Age at diagnosis, range in years	Therapeutic modalities[a] (no.)	Type of confidants, no. (%)					
		No one	Relatives	Friends	Anyone (excepting employers and insurers)	Employers	Insurers
0–6	XRT & CT (2)	0	2 (100)	2 (100)	1 (50)	1 (50)	0
3–15	CT (8)	1 (12.5)	5 (62.5)	5 (62.5)	7 (87.5)	0	0
4–15	XRT (14)	1 (7)	7 (50)	10 (71)	7 (50)	8 (57)	8 (57)
7–11	CT & XRT (15)	0	8 (53)	8 (53)	8 (53)	5 (33)	1 (6.7)
12–15	CT & XRT (26)	1 (3.8)	15 (58)	20 (77)	15 (58)	14 (54)	5 (19)
Total	65	3 (4.6)	37 (57)	45 (69)	38 (58)	28 (43)	14 (22)

[a]XRT, radiotherapy; and CT, chemotherapy.

Queries were made and tabulated separately for the different types of confidants: 69% said 'friends' were told of their illness; 57% informed relatives; and only 43% stated that they had informed or would inform prospective employers. Patients from smaller towns volunteered that it was not necessary to inform prospective employers as 'everyone in town' knew of the diagnosis. Only 22% stated that they would not inform a potential insurer for fear of exorbitant rates or rejection. Several patients obtained insurance through riders to their parents' policies and had not yet faced the problems of becoming self-insured.

2.9. Positive aspects of illness (Table 9)

Twenty-five percent of patients were unable to think of any positive aspect of the entire experience; a slightly higher number, 32%, found cure of their disease the only positive aspect.

Approximately one-quarter of the children cited the 'trips' to Houston as being positive. In addition to the clinic visit, 'trips' also included shopping, weekly pediatrics parties, and hospital-sponsored outings, as well as visits with new friends and acquaintances who quite often were hospital employees. One patient said she felt 'like Cinderella' at the hospital.

For a single patient, the medical experience resulted in a career change decision to a 'pre-med' course in college. Two patients became more mindful of their health and stated that they were 'taking better care of themselves.' The remaining 31% felt that their lives had been changed and interpersonal relationships had become more meaningful. They had become more compassionate and concerned with illness in others. Two patients confided that they had found they had an understanding which brought comfort to other patients with cancer and that patients, sometimes relatives, were able to 'open up' to them in such a way as to find solace.

3. Discussion

Those who have guided patients through the medical experience of successful treatment for Hodgkin's disease can appreciate the depth of variance between the patient's reaction to the events as they occurred and the perception of the events some 8 years later. Discrepancies appear greatest to the onlooker with respect to the staging laparotomy and the associated nasogastric tube, forced coughing, use of the incentive spirometer, ambulation, and the return of bowel mobility. In two other areas, patient reactions in follow-up clinic do not seem consistent with telephone responses. In the clinic, the requirement for penicillin often becomes an issue of control between parent and adolescent in the difficult period of teenage separation from parents; in several instances, counseling has been required. With

Table 9. Patient perceptions of positive aspects of illness.

Age at diagnosis range in years	Therapeutic modalities[a] (no.)	Nature of positivity, no. (%)					
		Nothing positive	Disease cured	Bettered care of self	Career change	Hospital activities and association	Heightened altruism an personal maturation
3–6	XRT & CT (2)	1 (50)	1 (50)	0	0	0	0
3–15	CT only (8)	3 (37)	1	0	0	3 (37)	3 (37)
4–15	XRT only (14)	2 (4)	4 (29)	0	0	7 (50)	3 (21)
7–11	CT & XRT (15)	6 (40)	5 (33)	0	0	4 (29)	3 (20)
12–15	CT & XRT (26)	4 (15)	11 (42)	2 (7)	1	3 (11)	11 (42)
Total	65	16 (25)	21 (32)	2 (3.0)	1 (2.0)	17 (26)	20 (31)

[a]XRT, radiotherapy; and CT, chemotherapy.

teenage girls, protection of irradiated skin from sunburn becomes an intense issue that is not resolved completely by the use of sunscreens. The conflict in this instance is between patient and physician rather than patient and parent. Patient acceptance of late growth defects following radiotherapy is also surprising, especially among the boys who quite often develop an interest in weight lifting as a means of ameliorating irradiation changes within the mantle field.

Despite a free exchange of information between patients and staff at this institution and a rather considerable teaching effort, patient perceptions remain unrealistic at certain times. The variance between perception and reality is dramatically shown in a thesis project done in our department wherein 49 (96%) of 51 hospitalized patients interviewed felt that they were 'getting better,' although 14 were actually in relapse [9]. Physicians of the patients rated 43% as 'getting better,' 47% as 'stable,' and 10% as 'getting worse.' Denial in such circumstances may be viewed as 'buying time' until therapy has time to become effective or until a new regimen is instituted. Coping defenses commonly utilized by cancer patients include intellectualization, rationalization, compensation, and regression, the most prominent being denial [10]. Utilization of such defenses must be considered in the evaluation of our patient interviews.

Interview responses indicate CT clearly as the most objectionable aspect of the patients' medical experience on the basis of anticipatory fear, apprehension, nausea and/or vomiting; needles and flow sensations in veins during drug injection; 'taste' of the injected agents, nausea and vomiting, and hair loss. Adults, treated for a variety of solid tumors, have responded similarly when surveyed to identify and rank side effects of CT [11]. Recollections of nausea and vomiting are cited by 78% as being the worst side effect of CT.

Many of the patients with unfavorable stage II and with stage III disease received the ACOPP regimen (Adriamycin, Cytoxan, Oncovin, prednisone, and procarbazine) in combination with radiotherapy [12]. Each of the six courses of chemotherapy required chemotherapy injections on three different days. Although highly effective, the regimen has been abandoned in favor of a less toxic regimen, CVPP (lomustine [CCNU], Velban, prednisone, and procarbazine), which is associated with far less nausea and vomiting as lomustine, the alkylating agent, is administered only once during each treatment course [13]. In addition, patients retain their hair while taking CVPP and the menstruating girls continue to have normal periods.

In our experience, single-agent antinauseant therapy has been disappointing regardless of the agent used (Thorazine, Phenergan, Torecan, or scopolamine patches). The combination of Reglan (metroclopromide), 50 mg; Ativan (lorazepam), 0.5 mg; and Benadryl (diphenylhydramine), 25 mg, given intravenously every 4 h to teenagers has been extremely effective in alleviating nausea and vomiting, with the patient being asleep, but arousable and able to void. Once intravenous drug administration is terminated, the

patient awakens and has little recall of the CT experience. This combination of medications is contraindicated during pregnancy; appropriate dose reductions are indicated for younger children.

Hypnosis may also have a role in control of nausea and vomiting. We have identified two youths (not in this study) who received antiemetics, but also appeared to hypnotize themselves for chemotherapy. These boys have no nausea or vomiting, and, awaken, as soon as timed chemotherapy is complete.

The patients' perception as to the severity of the nausea and vomiting from chemotherapy is immensely strong. The severity of the symptom has not been met with deserved developmental programs in the pharmaceutical industry.

For many of our patients, a significant interruption of schooling occurred, separating the patient from peers both scholastically and socially. The scholastic performance of 45 patients given both CT and XRT is of particular concern as 15% repeated a grade and 39% were more than 1½ years behind or dropped out of school entirely. Absences that were often far more frequent than necessary for medical reasons could be attributed to compassion or pity resulting in overprotection on the part of parents and/or teachers, a genuine lack of understanding as to the child's true medical status that did not seem consistent with expectations with so dire a diagnosis, or simply a failure to appreciate the role of school in the maturation process. Our hospital unit of the Houston Independent School System was underutilized. Cooperation of home schools was lacking in some instances. Frequently the schools at home would insist upon home-bound teaching rather than school attendance.

An early study of life styles of 124 children cured of malignancies reported education accomplishments as 'not at variance with the population of Kansas at large' [14]: 53% had gained some education beyond high school or were still attending high school, and 12% were unemployed or not in school. Subsequently, school phobia has been reported in 11% of pediatric oncology patients [15] and absenteeism has been documented at a high rate [16]. In the latter study, nonattendance was attributed to fears of rejection, parental overprotection, or failure to appreciate the value of the child's return to school.

Our hospitalized patients are now participants in a pediatric 'Star Community,' which has certain rewards for school attendance and for participation in other scheduled activities such as 'Teen Group' meeting, communal dining, 'outings,' and trips. In this 'community,' school attendance is required unless the child's attending physician, nurse, and mental health worker concur by signature in the medical record that the child is not able to attend the hospital school. Studies with a home-bound teacher are discouraged at home in favor of school attendance. Hopefully these measures will restore the educational and socialization experiences provided by schools, which are necessary in adult life.

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13. Salvage treatment for patients with multiply relapsed Hodgkin's disease

Robert S. Wimmer

The use of combination chemotherapy for patients with Hodgkin's disease has dramatically improved survival rates for this malignancy. The MOPP chemotherapy regimen (nitrogen mustard, Oncovin, prednisone, and procarbazine) introduced by De Vita *et al.* [1] can cure patients with both advanced Hodgkin's disease and Hodgkin's disease that has relapsed after the initial use of radiotherapy alone. However, it has been estimated that nearly 50% of patients in these two categories will have recurrent Hodgkin's disease during or after their MOPP chemotherapy treatments [2]. The optimal management of Hodgkin's disease patients who develop progressive disease after primary chemotherapy remains to be clearly established. An attempt at retreatment of MOPP failures was described by Fisher *et al.* [3]. This group reutilized the MOPP combination in patients who relapsed after completing an earlier prescribed course of the MOPP program. They reported a 59% second complete remission rate with this retreatment approach. A second avenue for treatment of MOPP failures was the introduction of multiagent chemotherapy combinations that were felt to be non-cross-resistant to the MOPP program. The first of these was the ABVD combination (Adriamycin, bleomycin, vinblastine, and dacarbazine) introduced by Santoro *et al.* [4], who initially reported a 50% complete response rate in patients who were previous MOPP failures. Other investigators have used the same ABVD regimen with complete response rates ranging from 0 to 59%. This marked variation is thought to result from both the degree of pretreatment in these relapsed patients and the application of the original ABVD program.

Several other combination chemotherapy regimens have been devised in addition to the ABVD schema. Most of these contain both Adriamycin and bleomycin as their primary agents. Most have complete response rates in the range of 25%–50%, compatible with treatment results using either MOPP as retreatment or using ABVD (see Table 1). It should be noted that none of these studies was performed exclusively in a pediatric population.

The traditional approach to the pediatric patient with newly diagnosed Hodgkin's disease who receives chemotherapy would be to administer either MOPP or ABVD. If relapse were to occur, the alternate program would

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Table 1. Chemotherapy of Hodgkin's disease patients relapsing after MOPP.

Author [ref]	Regimen	No. of patients	Response rate (%)	
			CR	CR + PR
Fisher *et al.* [3]	MOPP	32	56	–
Santoro *et al.* [4]	ABVD	54	59	72
Harker *et al.* [27]	ABVD	55	38	71
	B-CAVe	48	44	71
Lokich *et al.* [28]	B-DOPA	15	60	80
Vinciguerra *et al.* [29]	BVDS	10	30	50
Goldman and Dawson [30]	CVB	39	26	84
Levi *et al.* [31]	SCAB	17	35	59
Einhorn *et al.* [32]	VABCO	18	44	88

then be employed. Currently, many patients with advanced-stage disease at diagnosis are being exposed to both ABVD and MOPP from the start of treatment in regimens that administer alternating monthly cycles of these combinations. Thus, if patients have been exposed to both the MOPP and ABVD regimens and then relapse, especially if this relapse is within 6 months of completing the prescribed chemotherapy course, a 'third-line' therapy program would be considered.

An initial approach to this problem of 'salvage' chemotherapy was the use of single agents [5], mainly because of the supposedly poor bone marrow reserve and venous access problems in these patients. Recently, a number of groups have attempted to devise a third non-cross-resistant combination chemotherapy regimen that would offer a more reasonable prospect for disease control. The role for additional radiotherapy in the consolidation of chemotherapy-induced remissions, or even as the only modality of therapy for specific relapse situations, needs to be explored. Alternatively, an increasing number of institutions have investigated the use of high-dose chemotherapy and autologous or allogeneic bone marrow transplantation in patients with multiply relapsed Hodgkin's disease in a manner similar to that for other hematologic malignancies.

One of the earliest reports of a third non-cross-resistant combination chemotherapy program for multiply relapsed patients exposed to MOPP and an Adriamycin- and bleomycin-containing combination, such as ABVD, came from Santoro *et al.* [6]. They described their use of third-line chemotherapy with CEP (CCNU, etoposide, and prednimustine; see Table 2). Their initial report described 23 patients resistant to both MOPP and ABVD who were treated with CEP. A complete response rate of 26% was obtained and the partial response rate was 30%, for an overall response rate of 56%. These drugs can all be delivered orally. No treatment-induced fatalities were observed. Toxicity was described as moderate and tolerable. This group recently updated their results with 75 patients [7]. The complete remission rate for patients resistant to both MOPP and ABVD was 44%. Again, it was noted that CEP was well tolerated and no patients died from

Table 2. Third-line chemotherapy for multiply relapsed Hodgkin's disease patients: recent reports.

Author [ref]	Regimen	No. of patients	Response rate (%)	
			CR	CR + PR
Santoro *et al.* [7]	CEP	75	44	–
Cervantes *et al.* [8]	CEP	15	27	40
Straus *et al.* [9]	CAD	15	13	46
Hagemeister *et al.* [10]	MIME	47	23	63
Tseng *et al.* [11]	CEM	32	13	47
Velasquez *et al.* [12]	DHAP	19	21	68
Garbes *et al.* [13]	MTX-CHOP	11	29	57
Schulman *et al.* [14]	MOPLACE	30	21	42
Case *et al.* [15]	Mitoxantrone	33	7	34
Silverman *et al.* [16]	APE	8	38	75
Wimmer *et al.* [17]	APE	8	88	100

toxicity. As is seen with most salvage regimens, the best responses were obtained in patients who had previously responded with prolonged remissions to front-line regimens, and who relapsed with limited, especially nodal, disease.

Cervantes *et al.* [8] also reported on the use of CEP in 15 patients with advanced resistant Hodgkin's disease: 27% of their patients achieved a complete remission and 13% achieved a partial remission, for an overall response rate of 40%. Two of these patients remained in continuous remission for relatively short periods (7 and 18 months) at the time of the report. Toxic effects of the CEP regimen were scarce. Median duration of response was only 5.5 months, as opposed to 17 months for the Santoro patients. Thus, the CEP regimen provides a reasonable response rate with an oral regimen that can be easily administered on an outpatient basis. Its duration of response is relatively limited, and prednimustine is not easily available for routine use.

The CAD combination (CCNU, melphalan, and vindesine) has been used in 15 heavily pretreated patients with Hodgkin's disease in relapse [9]: two patients (13%) achieved a complete remission, one of these having received extensive radiation therapy only as prior therapy, and five patients (33%) achieved a partial remission, for an overall response rate of 46%. Myelosuppression with this regimen was recorded as serious, but was more tolerable when doses were attenuated later in its use. It was concluded that the CAD combination was active in patients who had previously received combination therapy.

A large series of patients with Hodgkin's disease in relapse have been treated with the MIME chemotherapy combination (methyl-GAG, ifosfamide, methotrexate, and etoposide) [10]. All but one of these patients had received both a prior MOPP or MOPP-like combination and an Adriamycin-containing combination. Complete remission was obtained in 11 patients (23%) and a partial remission was seen in 19 patients (40%). The median

time for freedom from progression was 25 months and again depended upon the extent of disease. Patients with only nodal relapses survived longer than those with extranodal disease. The MIME combination produced considerable myelosuppression. Ifosfamide-induced hemorrhagic cystitis was a relatively common problem. This program appears to produce response rates that are comparable or even somewhat better than other combinations, and has been used in a reasonable number of patients as a third-line regimen. Two of the agents in the combination, methyl-GAG and ifosfamide, are not commercially available at present.

Another oral third-line chemotherapy regimen for resistant Hodgkin's disease is CEM (CCNU, etoposide, and methotrexate), reported by Tseng *et al.* [11]. Again, most patients had been treated with MOPP and ABVD, and the majority had prior irradiation. Four patients achieved complete response (13%), with a median duration of 33+ months and 11 achieved a partial response (34%), for an overall response rate of 47%. Myelosuppression was moderate and tolerable. The conclusion was that this was an easy program to administer and had activity comparable to other third-line regimens.

As a prelude to autologous bone marrow transplant in the majority of their patients, Velasquez *et al.* [12] employed the DHAP combination (dexamethasone, high-dose cytosine arabinoside, and cisplatinum) as salvage treatment for patients with relapsing Hodgkin's disease. A total response rate with DHAP of 68% in a heavily pretreated Hodgkin's disease population was obtained, with four patients (21%) achieving a complete response and nine patients (47%) achieving a partial response. Toxicity was said to be acceptable. The authors felt that DHAP was an effective treatment in relapsing Hodgkin's disease.

Eleven patients with Hodgkin's disease refractory to standard chemotherapy were treated with six cycles of intermediate-dose methotrexate with leucovorin rescue followed by cyclophosphamide, Adriamycin, vincristine, and prednisone [13]. All had received MOPP or a variant thereof, but only four had received an Adriamycin-containing regimen. Overall response rate was 57%, with four patients (29%) achieving a complete response. One of these complete-response patients has continued in disease-free remission for over 8 years. One patient died during therapy of overwhelming sepsis from pancytopenia. Again, the small numbers of patients show a response pattern similar to most of the regimens previously described.

An early report of the use of the MOPLACE combination in previously treated Hodgkin's disease patients has been presented [14]. The regimen consists of cyclophosphamide, etoposide, and prednisone, followed by methotrexate with leucovorin rescue, cytosine arabinoside, and vincristine. Forty patients have been entered on an ongoing study. The current complete and partial response rates are each 21%, for a total response rate of 42%. Several episodes of severe or fatal pulmonary toxicity have been encountered. Mylosuppression has been severe. The pulmonary toxicity may

be related to methotrexate and bleomycin in the face of prior radiotherapy. The abstract concluded that this is an active combination in heavily pretreated Hodgkin's disease patients, but it is a regimen that may have to be modified.

The only recent large-scale single-agent phase II trial for patients with refractory Hodgkin's disease has been with the drug mitoxantrone [15]. Thirty patients were treated with mitoxantrone on an every 3-week schedule. There were three complete remissions (9%) and nine partial remissions (27%), for a total respone rate of 36%. Three patients who had previously received Adriamycin developed cardiac toxicity, one of which was fatal congestive heart failure. It was concluded that mitoxantrone can produce a significant response rate in refractory Hodgkin's disease with acceptable toxicity.

The only purely pediatric experience with a third-line chemotherapy regimen for multiply relapsed Hodgkin's disease patients has been with the APE regimen (cytosine arabinoside, cisplatinum, and etoposide). Silverman *et al.* [16] originally reported its use in eight adult patients, six of whom responded (three complete responses and three partial responses). Myelosuppression was said to be severe, but tolerable. Wimmer *et al.* [17] recently reported the use of the APE chemotherapy regimen in eight pediatric patients with relapsed Hodgkin's disease. All eight patients had been treated with a minimum of MOPP, ABVD, and radiotherapy, usually with at least two relapses before initiating APE chemotherapy. One of these patients relapsed after an autologous bone marrow transplant. Seven of the eight patients achieved a complete remission. The remaining patient achieved a partial remission for 1 year with only two cycles of APE chemotherapy prior to removing himself from treatment for social reasons. Toxicity was well tolerated without life-threatening problems. Expected pancytopenia resulted in several hospital admissions for fevers with neutropenia, but no documented sepsis. Nausea and vomiting were consistently reported to be much less than previously experienced with MOPP or ABVD. No renal, auditory, hepatic, or neurologic toxicity was appreciated. Performance levels were excellent. Thus, virtually all patients achieved a complete response with quite manageable toxicity. Further evaluation of the APE chemotherapy regimen is currently being carried out by the Pediatric Oncology Group.

Few of the multiply relapsed Hodgkin's disease patients mentioned above will be cured with any of the third-line chemotherapy regimens described. Currently, as with other hematologic malignancies and solid tumors, the role of bone marrow transplantation is being explored in an attempt to provide curative therapy for high-risk Hodgkin's disease patients. A number of centers have reported their experience with autologous bone marrow transplantation for relapsed Hodgkin's disease [18–21]. A variety of cytoreductive chemotherapy regimens were used, with long-term disease-free survival rates generally in the 15%–25% range. O'Reilly *et al.* [22] recently reported on 20 patients transplanted for progressive Hodgkin's disease. Their patients

attained a complete remission rate of 80%, with a 65% continued complete remission rate at the time of the report. However, the median follow-up for these patients was a very short 8 months. In the only report of allogeneic transplantation in patients with resistant Hodgkin's disease, the Seattle group reported that two of eight patients remain alive in unmaintained remission following transplant with a standard-high-dose cyclophosphamide and total body irradiation transplant protocol [23]. Thus, intensive chemotherapy followed by either autologous or allogeneic bone marrow reconstitution appears to be able to salvage a small percentage of patients with progressive Hodgkin's disease. Increasing the effectiveness of the cytoreductive chemotherapy, decreasing the toxicity of the transplant procedure, and providing the transplant at an earlier period before the emergence of resistant disease would certainly result in increased survival rates. The exact role for transplant as opposed to salvage chemotherapy alone awaits more extensive testing.

A word of caution must be imparted before considering that multiagent salvage chemotherapy or bone marrow transplantation offers the only chance for cure for patients with relapsed Hodgkin's disease. Three recent reports discuss the role of potentially curative radiation therapy in selected relapsed Hodgkin's disease patients [24–26]. Patients who relapse in nodal areas after receiving chemotherapy alone as their initial treatment, especially if that initial chemotherapy produced a remission that lasted longer than 1 year, should be considered for wide-field comprehensive salvage radiotherapy with a curative intent. Whether the addition of second- or third-line chemotherapy to this radiotherapy plan is feasible or necessary needs further investigation.

In summary, a significant minority of newly diagnosd patients with Hodgkin's disease will eventually require salvage therapy for one or more relapses. Exposure to both the MOPP and ABVD regimens and potentially curative radiotherapy should be considered before the administration of a 'third-line' chemotherapy regimen or bone marrow transplantation. Preliminary reports suggest an emerging role for aggressive salvage chemotherapy or transplant in the patient with relapsed disease. Additional studies of these experimental procedures are obviously necessary. As always, a multidisciplinary approach to the problem of the Hodgkin's disease patient with progressive disease should be utilized in order to allow the best chance for quality survival.

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14 Late effects of Hodgkin's disease treatment in children

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Table 1 lists the major delayed consequences of therapy for Hodgkin's disease and their causes in order of severity, beginning with those probably fatal, to those that interfere with function and finally those that are minor. One can not help but note two points: (a) any single major complication is preventable or avoidable by modifying treatment, and (b) it is not often possible to escape altogether the risk of major complications. Since many of the late effects either threaten life or impair quality of survival, it is important to consider them in the selection of therapy.

There are now data showing that with available therapy we can effectively reduce morbidity and mortality without compromising survival from the Hodgkin's disease itself. For example, in pediatric studies of combined modality, a reduction of radiation dose and field volume lessens growth abnormalities and thyroid, cardiac, and pulmonary dysfunction with no apparent compromise of efficacy [1–4]. Mauch *et al.* calculate that with nitrogen mustard, Oncovin, prednisone, and procarbazine (MOPP) in combination with radiation therapy (RT), reducing the radiation field to less than the total nodal volume reduces the risk of fatal complications from 11.9% to 0.8% [5]. However, as we manipulate treatment to avoid late effects, we must make certain that the complications of the new therapy are less severe than those of the standard therapy. For example, in the exchange of AVBD (Adriamycin, vinblastine, bleomycin, and DTIC) for MOPP, we exchange probable sterility and possible leukemogenesis for potential cardiac and pulmonary damage.

The results of studies demonstrating efficacy with dose reductions of chemotherapy in order to reduce side effects are emerging [6–8]. Cumulative dose reduction is accomplished by alternating non-cross-resistant regimens or simply reducing doses by 50% when radiation is added. The 'Vancouver hybrid' consists of 33% less Adriamycin, bleomycin, and nitrogen mustard than standard AVBD–MOPP with comparable therapeutic results [9], and the vinblastine–bleomycin–methotrexate regimen used at Stanford avoids altogether most troublesome problems of chemotherapy [10]. The early results of these approaches are tantalizing, but some caution

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Table 1. Late effects of treatment for Hodgkin's disease.

Late effect	Cause
Life-threatening	
Acute non-lymphoblastic leukemia	MOPP: alkylating agents
Other second malignant neoplasms	Radiation, chemotherapy
Overwhelming bacterial infection	Splenectomy
Serious	
Cardiac dysfunction	Radiation/adriamycin
Pulmonary fibrosis	Radiation/bleomycin
Sterility/gonadal dysfunction	MOPP or MOPP equivalent; radiation
Musculoskeletal abnormalities	Radiation/steroids
Usually minor	
Thyroid dysfunction	Radiation
Herpes zoster	Radiation; chemotherapy
Lymphocyte dysfunction	Radiation; chemotherapy
Psychosocial	

is necessary in interpreting them: inability to detect differences in effectiveness between lesser therapy and standard therapy may be a function of a short follow-up period, an attenuated population, and excellent results with current available therapeutic options. As Hodgkin's disease is rare in children, our studies often lack the power to detect the small differences necessary to prove that two apparently good therapies are not equally good.

This chapter reviews recent literature in the area of late effects and presents the results of detailed investigations of long-term survivors treated at the Children's Hospital of Philadelphia. An attempt is made to estimate risks of serious sequelae and to suggest alternatives. Finally we propose a schema for the systematic late follow-up of surviving patients depending on therapy received and known risk factors.

1. Second neoplasms in Hodgkin's disease

Following the recognition, in the early 1970s, that an increasing number of patients with Hodgkin's disease were likely to be cured, came reports that these survivors were at risk for the development of second malignant neoplasms (SMN). One of the earliest, by Arseneau *et al.* from the National Cancer Institute, suggested in its title that the second cancers had a 'possible association with intensive therapy' [11]. By intensive therapy was meant MOPP or COPP (cyclophosphamide instead of nitrogen mustard) for at least 6 months combined with intensive radiotherapy. The observed-to-expected ratio of second tumors was 29 in the 35 patients treated in that manner, while the overall ratio was between 3 and 4, and was similar in the subgroups treated with less intensive radiotherapy and/or chemotherapy. In a very recent update from that same institution, 13 cases of acute leukemia

were noted among 198 patients treated with MOPP a median of 14 years ago; most also received radiation therapy [12]. Although other malignancies have also been seen in that population, the authors conclude that none have occurred at a frequency greater than that seen in age-matched controls. However, no data are given for these assertions and we await a subsequent manuscript for the details.

Following that initial report from the National Cancer Institute, there was a flurry of activity to determine the incidence of SMN in major cancer centers and cooperative groups in which large numbers of Hodgkin's disease survivors were being followed. Stanford reported that, among 680 consecutive patients, leukemia occurred in six and all had received combined radiotherapy and chemotherapy [13]. There were no leukemias among 320 patients treated with radiotherapy alone or 30 patients treated with chemotherapy alone, and the actuarial probability of developing leukemia with multimodal therapy was ~4% at 7 years. The secondary leukemias, in general, responded poorly to therapy.

Very few of these analyses included children, however, and the rarity of Hodgkin's disease in the pediatric population precluded the early emergence of data regarding children. Nevertheless, the reports of SMN in adults treated for Hodgkin's disease confirmed the original findings of Arseneau *et al.* (referred to above). The Southwest Oncology Group reported 32 SMN, 21 acute leukemias, and 11 solid tumors among 659 patients, with a 6%–7% risk of developing leukemia at 7 years and a positive correlation with age [14]. Patients older than 40 years at the time of treatment had a 21% risk of developing leukemia at 7 years. Cancer and Leukemia Group B evaluated almost 800 Hodgkin's disease patients achieving complete remission between 1966 and 1974 and found ten who developed acute nonlymphocytic leukemia (ANLL) [15]. They found nitrogen mustard not to be a significant hazard, but chlorambucil was associated with an excess risk >200. Nonleukemic SMN were not found to be associated with any chemotherapeutic agent, but radiotherapy was found to increase significantly their incidence. In 1981, Boivin *et al.* reported on a Hodgkin's disease cohort treated from 1940 to 1975 in which there occurred 27 SMN, among them six leukemias, and also found that there were no leukemias after radiotherapy alone. In the subgroup treated with both intensive radiotherapy and chemotherapy, however, the relative risk of leukemia was 170 [16].

In 1980, a report from the National Institute in Milan, Italy, revealed a variation in the incidence of second neoplasms depending on whether the patients received a newly developed regimen of chemotherapy (ABVD) or the MOPP regimen [17]. In that group of 764 patients with a 10-year follow-up, none of 236 treated with radiotherapy alone developed ANLL. But the incidence of solid tumors among those patients was ~15%. In 492 patients treated with radiotherapy and chemotherapy, the incidence of solid tumors was 6% and acute leukemia 3.5% with a 10-year follow-up. Interes-

tingly, only patients treated with nitrogen mustard, cyclophosphamide, or chlorambucil as the alkylating agent or with procarbazine developed leukemia, the highest incidence being among patients treated with MOPP. Those given the new combination of AVBD developed no second leukemias. In a more recent publication from that group, and with a median follow-up time of 9½ years, 68 new cancers developed among 1329 patients treated from 1965 to 1982 [18]. Although there were no cases of leukemia following radiotherapy and AVBD with a median follow-up exceeding 8 years, the risk of leukemia was 4.8% in patients treated with radiotherapy and different alkylating-agent-containing regimens and almost 10.2% in patients treated with radiotherapy and MOPP. Only a single case of leukemia was seen in 207 children. There was an association between increasing age and the risk of ANLL. The 43 solid tumors occurring in this group of patients included eight with basal cell carcinoma; the majority of solid tumors (25) occurred in previously irradiated areas and included six cases of sarcoma and ten cases of lung cancer.

A recent report from Yale estimates the 10-year actuarial risk of ANLL, non-Hodgkin's lymphoma (NHL), and solid tumors in their institution, and presents a comprehensive review of the literature concerning this complication [19].

Other neoplasms reported, probably occurring excessively, in Hodgkin's disease patients include non-Hodgkin's lymphoma [20], chronic granulocytic leukemias [21], and cancers of the lung [22, 23], breast [24], thyroid [25, 26], testes [27], and spinal cord [28]. Solid tumors appear to be strongly associated with radiation therapy. These tumors occur within a median latent period of 7 years. This short median interval may be an artifact of the limited follow-up periods in most series relative to the usual latent periods for radiation carcinogenesis.

Data concerning children with SMN after Hodgkin's disease have generally come from individual cases [29–31], although two series have been reported [32, 33]. In the first, no cases of ANLL were seen, but the incidence of SMN was 4% with an undisclosed median follow-up.

The second, from the Late Effects Study Group (LESG), in which a cohort of almost 1000 children had been followed for a median of 7 years, reported an overall risk of SMN rising from 4% at 10 years to 18% at 20 years. There were equal numbers of leukemias or lymphomas and solid tumors, with the leukemias occurring within a median time of 5 years after chemotherapy and the solid tumors arising in the field at a median of 12 years after radiation. In another report from the LESG, alkylating agent therapy was found to be associated with ANLL in a strong dose–response relationship [34]. These data confirm that children, like adults, have an excess risk of SMN following treatment for Hodgkin's disease. It is still too early to determine the excess lifetime risk of SMN for these survivors since few have had the opportunity to arrive at the average age of death in our society.

2. Overwhelming bacterial infection

Staging laparotomy with splenectomy came into wide use in the United States in the early 1970s. Enthusiasm for the procedure was tempered in 1976 by the review of Chilcote *et al.* in which 20 of 200 asplenic children with Hodgkin's disease developed overwhelming bacterial infection, ten of whom later died [35]. Most cases of overwhelming sepsis occur within 2 years after splenectomy, but isolated episodes have been reported 5, 10, or even 12 years later [36–38]. Splenic irradiation to 3600 cGy or more can ablate splenic function to the same extent as surgery [39]. It is not yet known whether 2000 cGy will be associated with functional asplenia, but there are no case reports of typical overwhelming sepsis among patients treated with lower doses of irradiation, and one does not generally see Howell-Jolly bodies in erythrocytes of children who received the lower dose to the spleen. Late follow-up of patients treated in Toronto with ~2000 cGy suggests that splenic function remains intact [40]. Donaldson and Kaplan made the point that splenectomy is not the only factor that predisposes pediatric Hodgkin's disease patients to bacterial infections; extensive disease and use of chemotherapy or combined modality therapy also favor infection [1].

Recent studies have demonstrated a considerably lower incidence of postsplenectomy sepsis than Chilcote's original study [2, 7, 41]. This reduction can probably be attributed to multiple factors: physician and patient awareness, avoidance of splenectomy in very young children and in patients with advanced disease destined to receive chemotherapy, and the use of pneumococcal vaccine and penicillin prophylaxis. Most studies of the use of pneumococcal vaccine in Hodgkin's disease patients show that patients who are immunized before or immediately after splenectomy develop protective titers to the majority of pneumococcal antigens [42]. However, postimmunization decline in titer is greater in Hodgkin's disease patients than in controls. In contrast to those immunized before splenectomy, patients who receive the vaccine within 3 years after completing therapy show abnormally low titers to most pneumococcal antigens; responses to serotypes 1, 6, 7, 8, and 9 are especially low [42, 43]. Booster immunization after treatment or after splenectomy fails to elicit a booster response. Some, but not all, who are immunized more than 3 years after therapy have normal responses. In general, the adequacy of response is inversely related to the intensity of therapy.

Recently, Siber *et al.* have studied simultaneous *Hemophilus influenzae* type B, tetravalent meningococcal, and polyvalent pneumococcal vaccination in Hodgkin's disease patients before and after splenectomy and after treatment [44]: 6–12 months after therapy, most patients immunized before splenectomy maintain protective levels of anticapsular antibody to *H. influenzae*, but over half fail to maintain protective levels to pneumococcus types 6, 7, and 9. Those treated with chemotherapy or combined modality

show the poorest responses. Among patients immunized after therapy, half treated with combined modality fail to sustain a protective response to *H. influenzae* B. Those treated with irradiation alone or chemotherapy alone have titers lower than their own pretherapy titers, but most develop protective levels of antibody.

Based on these studies, Siber *et al.* make the following recommendations for immunization of Hodgkin's disease patients:

1. Patients who are to have splenectomy or splenic irradiation should receive the vaccines as soon as the diagnosis is established and surgery planned. The vaccines should be given at least a week before therapy starts. In adults, the vaccines may be effective when given in the immediate postsurgical period. In children, on the other hand, efficacy is unlikely because children may require intact splenic function for a normal primary response to thymus-independent antigens such as polysaccharide.
2. Pneumococcal, *H. influenzae* B, and meningococcal vaccine can be given simultaneously as there is little antigenic competition between the polysaccharides of the three organisms.
3. Booster immunizations are under investigation and are not recommended at this time.

Studies of polysaccharide–protein conjugate *H. influenzae* vaccines are currently under way at the Children's Hospital of Philadelphia. These are of special interest for asplenic pediatric patients who are likely to respond better to protein–polysaccharide antigens than to polysaccharide alone and who are probably at greater risk of *H. influenzae* infection than adults.

A multicenter controlled trial has now proven that penicillin prophylaxis is effective in preventing infection and death from pneumococcus in children with sickle cell disease [45]. Because Hodgkin's disease patients, although older than most sickle cell (SS) patients, are even less likely than SS patients to sustain antibody titers to pneumococcal vaccine, because penicillin prophylaxis entails little financial cost and is of low risk, and because it is unlikely that a Hodgkin's disease study comparable to that in SS patients will emerge in the near future, we recommend penicillin prophylaxis indefinitely in patients who have had surgical or irradiation-induced splenectomy. However, compliance with penicillin is likely to fall off with time, penicillin does not offer protection against all encapsulated bacteria, and the available vaccines do not necessarily confer immunity. Thus, splenectomized Hodgkin's disease patients remain at risk of overwhelming bacterial infection. Obviously, we must continue to investigate ways in which splenectomy can be avoided without compromising therapeutic results.

3. Cardiac complications

Radiation in the 3600 to 4400-cGy dose range induces cardiac disease in some Hodgkin's disease patients. Clinically detectable cardiac damage takes

the following forms: asymptomatic pericardial effusion, constrictive pericarditis with tamponade, coronary artery disease, valvular disease, and abnormal radionuclide, echocardiography, or stress testing in the absence of clinically detectable disease [46–50]. The reported incidence of complications ranges from 3% to >90%, depending on radiation technique, length of follow-up, patient selection, and sensitivity of tests used to measure cardiac function. Whether or not age is a variable is not known, but all those treating children have concerns that the late effects of irradiation on young hearts may require decades to become apparent. The incidence of cardiac damage in 120 pediatric patients at Stanford is 16% overall: 18.5% in 85 patients treated with >3600 cGy and none in 35 patients treated with <2500 cGy [1].

Pericardial effusions are usually discovered by an enlarged cardiac silhouette on routine chest radiograph within 1–2 years after irradiation. Clinical hypothyroidism may contribute to this syndrome. Usually these effusions resolve spontaneously, but sometimes pericardiocentesis is necessary to relieve symptoms or for diagnostic purposes to rule out malignant or infectious causes [46].

Constrictive pericarditis, in contrast, may be a life-threatening emergency. Generally constrictive pericarditis occurs 4–12 years after irradiation. Often there is associated focal myocardial damage [46]. When treatment consists of a single anterior mantle field to 3600–4400 cGy or the same plus 400–1000 cGy to the posterior field, the incidence of constrictive pericarditis is 30% [46, 51]. However, if alternating anterior–posterior fields are used, and if subcranial blocks and apical shielding are added, constrictive pericarditis is rare [1, 46].

More insidious than pericarditis is coronary artery disease. Radiation-induced coronary artery disease has been well described in animals, but it has been difficult to estimate its incidence in survivors of Hodgkin's disease. There are isolated reports of sudden cardiac deaths, but noticeably lacking are figures to document a disproportionate increase in infarcts and premature deaths in young adult survivors. This lack of evidence may be deceptive. In their study of 957 long-term survivors of Hodgkin's disease, Boivin and Hutchison conclude that the relative risk of death is 1.5 in irradiated patients, 'which does not differ significantly from unity' [47]. Among 545 irradiated patients aged 0–44 years at the time of irradiation, there were five deaths from coronary artery disease as compared with no deaths among 106 patients who had no irradiation. Of particular note are deaths at 18, 20, and 25 years of age—6, 2, and 11 years after irradiation. In two cases, the cardiac disease was the immediate cause of death. In the Stanford experience of 120 patients, there were two cases of coronary artery disease in pediatric patients [1].

Using extensive cardiopulmonary testing, Mayo Clinic investigators evaluated 11 long-term survivors of pediatirc Hodgkin's disease 6–16 years after irradiation [50]. Only three patients were entirely normal. One had

had constrictive pericarditis and four had thickened cardiac valves. Patients had received 1950–5500 cGy irradiation; the authors could find no apparent correlation between dose and damage in this small series. In contrast, all five patients in the Stanford series who had valvular or myocardial damage received doses in the higher ranges [1].

Among 25 young adults irradiated for Hodgkin's disease 5 or more years previously, none had an abnormal physical examination, electrocardiogram, cardiac silhouette on chest radiograph, or treadmill stress test [51]. However, six had reduced left ventricular ejection fractions and enlarged right ventricles on gated equilibrium radionuclide ventriculography; four of the six had apical hypokinesia. The implications of these laboratory findings on longevity and function remain to be seen.

At this time, it does not appear that MOPP or MOPP-equivalent chemotherapy increases cardiac morbidity. Furthermore, in the cohort of 233 consecutive patients followed for a median of 37 months, the Milanese investigators have failed to detect significant cardiac damage in patients treated with either AVBD–RT–AVBD or MOPP–RT–MOPP [52]. The studies may have lacked sufficient power to detect significant differences and, more importantly, the follow-up may be too short to detect delayed cardiac or pulmonary fibrosis. Although data to document an effect of anthracycline-containing combinations on cardiac complications are not yet available, one can only predict that this class of drugs will increase them.

4. Pulmonary complications of Hodgkin's disease treatment

Pulmonary complications following treatment for Hodgkin's disease are listed below:

- During treatment or within 1 year
  - Acute radiation pneumonitis [1, 46]
  - Bleomycin hypersensitivity [53]
  - *Pneumocystis carinii* pneumonitis [1]
  - Steroid withdrawal pneumonitis [54, 55]
  - Chronic radiation pneumonitis [1, 4, 46]
- Later than 1 year or more after treatment
  - Pleural effusions [1]
  - Radiation fibrosis [1, 46]
  - Bleomycin fibrosis [53]
  - Pulmonary function test abnormalities [50–52]
  - Apical mediastinal radiographic abnormalities [51, 56]
  - Chronic pneumonitis [1, 46]

Radiation pneumonitis is a self-limited syndrome that appears 2–6 months after mantle irradiation in 4%–20% of patients [46]. The syndrome consists of cough with or without fever; chest radiographs show a widened mediasti-

num with shaggy borders around mediastinal structures. Sometimes enlargement can be sufficiently sudden and great as to simulate disease recurrence [56]. Signs and symptoms of acute radiation pneumonitis generally resolve in weeks to months. In <5% of cases, the syndrome is severe with high fever and dyspnea necessitating hospitalization and empiric use of steroids, which appear to have benefited some patients [54]. Very rarely, the pneumonitis may be fatal or may result in chronic restrictive disease.

Radiation pneumonitis will occur in 15% of patients who receive 600 cGy whole lung irradiation in addition to mediastinal radiotherapy and 30% of those who receive 600–3000 cGy to the whole lung [46]. Certain maneuvers can reduce pulmonary damage: use of thin lung blocks in patients treated with whole lung irradiation, reshaping of lung blocks and fractionation of doses to allow shrinkage of field in patients with large masses, sitting position during treatment to avoid artifactual exaggeration of mass size, and use of preoperative chemotherapy.

A number of factors may confound the diagnosis of radiation pneumonitis or exacerbate the condition. These confounding factors result from chemotherapy–radiation therapy interaction. *Pneumocystis carinii* pneumonitis occurred in five of 115 pediatric patients during or after MOPP chemotherapy that followed previous mantle radiotherapy [1]. Two cases were fatal. *Pneumocystis* pneumonitis can be prevented with trimethoprim–sulfamethoxazole prophylaxis [57]. It has been observed that rapid withdrawal of prednisone during MOPP therapy of patients who had previously been treated with radiotherapy can precipitate severe or fatal radiation-like pneumonitis or interstitial pneumonitis [55]. Thus, any patient receiving MOPP at any time after mediastinal irradiation should taper the steroid after the 14-day therapeutic dose. The radiomimetic effects of Adriamycin or bleomycin contribute to 'radiation' pneumonitis in patients receiving postirradiation AVBD. Finally, bleomycin and cyclophosphamide each have their own intrinsic pulmonary toxicity that can cause chemical pneumonitis.

Bleomycin hypersensitivity reaction occurs during or months after bleomycin therapy. It can appear as nodular infiltrates or diffuse interstitial disease [53]. The radiographic picture can simulate disease recurrence or infections. There is also a dose-dependent bleomycin pulmonary damage that may result in permanent restrictive disease. It is generally accepted that this restrictive disease does not occur after <200 U/m^2 and is more likely to occur in older patients [49]. But, in fact, there are few data about the relative bleomycin sensitivity of the lungs of young children compared with adults. Among the 13 pediatric patients treated with AVBD in Philadelphia, one 8-year-old boy has developed moderately severe restrictive disease following 120 U/m^2 bleomycin given over 6 months; he did not have mediastinal irradiation. It is too soon to determine whether his pulmonary disease will improve or progress. The incidence of delayed pulmonary reactions is not known.

Jochelson *et al.* observed that 88% of 65 patients had residual mediastinal

abnormalities on chest radiograph as long as one year after mantle irradiation [58]. The mediastinum was more than 6 cm wider than normal in 27 patients. Four years later, 40% still had abnormally wide mediastinal shadows. Morgan *et al.* noted radiographic changes consistent with paramediastinal and apical fibrosis in 60% of their young adult patients 5 years or more after mantle therapy [59]; 89% had minor abnormalities of pulmonary function tests. The most severe abnormality was a reduction in diffusing capacity to ~72% of normal. Carbon monoxide diffusion capacity of 64% of predicted was observed in the patients who had received chemotherapy in addition to radiotherapy compared with those who had received radiotherapy alone (78% of predicted). All patients were asymptomatic. In their study of 11 long-term survivors of irradiated childhood Hodgkin's disease patients, Kadota *et al.* found five with restriction of lung volume to 62%–82% of predicted. Six of 11 showed reduced exercise tolerance on testing, but none was symptomatic [50]. Donaldson observed chronic pleural effusions in two patients 6 and 8 years after treatment [1]. Whether any of these laboratory abnormalities will resolve or become clinically significant years later remains to be seen.

5. Gonadal dysfunction

MOPP, MOPP analogues, and irradiation damage the gonads. The predominant injury is to the germinal cells as manifested by elevated follicle-stimulating hormone (FSH) and azospermia in the male, and amenorrhea or anovulatory menstrual cycles in the female. Leydig cell dysfunction and exaggerated luteinizing hormone (LH) and FSH response to LH-releasing factor (LRF) occur with more extensive testicular injury [59]. Elevated gonadotrophins and reduced testicular volume correlate with oligo- or azospermia and can be used as indirect parameters of gonadal function in boys who are reluctant to have sperm analyses. Gross assessment of gonadal function is easier in the female. A totally normal menstrual history is a reasonably reliable indicator of reproductive capability, and giving birth to normal children would seem to attest to acceptable gonadal function, but even ability to menstruate and reproduce may fail to predict premature aging of the ovary.

With the use of modern dosimetry and shielding techniques, the testes receive 5%–10% of the dose to lymphatics in pelvic irradiation [39]. The relative radiosensitivity of the prepubertal and pubertal testis is not known. Donaldson and Kaplan found three of five irradiated boys capable of fathering normal children; two had reduced sperm counts [1]. Perdick and Hoppe studied 18 men 16–45 years old (mean, 27 years) at the time of pelvic irradiation in doses of 2750–4500 cGy [60]. This dose was sufficient to cause

temporary azospermia in the majority of men. One (17%) of six had >20 million sperm within 18 months of treatment, four (66%) of six were normal between 18 and 26 months and seven (88%) of eight were normal after 26 months. Although patients in this study were not examined before treatment, it is encouraging that so many were normal, since as many as 71% may have had inadequate sperm before treatment. Pretreatment oligospermia correlates with advanced stage of disease and fever [61].

Ovarian function is also compromised by irradiation. However, oophoropexy reduces the risk of damage. In late follow-up of 27 women who had had pelvic irradiation for Hodgkin's disease between the ages of 12–38 years, Horning *et al.* found that 47% had normal menses, 47% had irregular menses, and 6% (one patient) had no menses [62]; 32% had menopausal symptoms. There were seven pregnancies in these patients. In the Stanford series of children and adolescents, all seven girls who had pelvic irradiation and oophoropexy had menses [1].

In 1980, Schilsky *et al.* [59] reviewed the gonadal effects of chemotherapy. All alkylating agents cause some gonadal injury to males, but the agents probably differ one from the other. Prepubertal, pubertal, and postpubertal testes also differ in their sensitivity to alkylating agents. Early studies of boys treated with cyclophosphamide for nephrotic syndrome suggested that the prepubertal testis may be less sensitive to this agent than the pubertal or postpubertal organ [62], but more recent studies cast doubt on this conclusion [63–65]. Damage may be dose dependent as well as or rather than age dependent. Cumulative doses of 6–14 grams (g) of cyclophosphamide were associated with normal sperm counts whereas 12–39 g caused azospermia in boys and young teenagers [63]. MOPP caused azospermia 4–11 years after therapy in all boys <15 years of age at treatment [1]. Green *et al.* noted elevated gonadotrophins in two prepubertal boys after 'MOPP-equivalent' therapy while two of five pubertal males had normal values [66]. In 32 patients with lymphoma, seven of ten treated with cyclophosphamide, vincristine, and prednisone recovered normal LH and FSH, and three of four recovered sperm counts; only one of six treated with MOPP recovered [67]. To explain discrepancies between MOPP studies and those using cyclophosphamide, Schilsky *et al.* propose that procarbazine may be contributing to male gonadal dysfunction, but it is also possible that nitrogen mustard is more damaging than cyclophosphamide or that dose intensity influences the rate of damage. There are rare cases in which young men have fathered children 8 years or more after MOPP [68].

Chemotherapy damages the ovary less than the testis, and younger females are less affected than older women. Horning *et al.* found 56% of young women treated with MOPP had normal menses, while 15% had no menses [62]. Addition of pelvic irradiation to MOPP increased gonadal toxicity with only 20% having normal menses and 55% being amenorrheic. Young age at the time of treatment was associated with less gonadal

damage. There were seven pregnancies among 13 patients treated with chemotherapy and five among 11 combined-modality patients. Donaldson and Kaplan found that eight of ten chemotherapy-treated girls and 14 of 15 combined-modality-treated girls had normal menses [1]. Whether chemotherapy causes premature ovarian aging in girls is not known, but data from young women treated with alkylating agents for breast cancer suggest that there is cause for concern. In those girls and women who have been castrated by radiation or chemotherapy, most physicians favor replacement to avoid the cardiovascular and orthopedic consequences of absent estrogen.

There has been interest in the effects of chemotherapy on the offspring of patients treated for cancer as children or young adults. Li and Jaffe suggested there were no problems [69]. However, when Holmes and Holmes compared 93 pregnancies in 48 Hodgkin's patients to 228 pregnancies in their 69 siblings, they concluded that there may be an excess of fetal abnormalities in offspring of women previously treated with combined modality and excess abortions in the wives of men treated with combined modality [70]. Methods of data analysis in the Holmes' study were subsequently challenged by Simon and, in fact, no other study has as yet confirmed an excess risk to offspring of long-term survivors of Hodgkin's disease [71].

There are ways to prevent gonadal toxicity and to maintain gonadal function. It has been shown that AVBD does not damage the male or female gonad [52]. Mantle therapy has no effects on gonads. Three courses of MOPP plus mantle or extended mantle therapy appear to be less damaging than six courses of MOPP [7, 8, 71]. Three courses of MOPP and three of AVBD are under investigation as an alternative to six of either combination since much of the organ damage of the alkylating agents and antitumor antibiotics is dose dependent. Sperm banking and cryopreservation of sperm can overcome the problems of fertility in the males with adequate pretreatment counts [70–72]. Of those with more than 20×10^6 motile sperm, 46% were able to sire children within 6 months; success is greater when insemination is coordinated with ovulation as judged by urinary luteinizing hormone [73]. It is generally recommended that women who have received chemotherapy try to become pregnant earlier rather than waiting because of the potential for an early menopause [74]. The use of oral contraceptives during cytotoxic therapy has met with mixed results and probably warrants further investigation [75, 76]. Finally, Glode *et al.* showed that pretreatment and continued administration of [D-leu^b] des-Gly-NH_2 proethylamide gonadotrophin-releasing hormone protects male rats from histologically detectable gonadal damage [77]. This is an intriguing approach, but further investigation will be necessary to ascertain that surviving spermatogonia are normal, that offspring are normal, and that gonadotrophin-releasing hormone analogues can be used with chemotherapeutic agents without affecting their metabolism.

6. Musculoskeletal abnormalities

The standard doses and fields of radiation used to treat Hodgkin's disease impair growth of bone and soft tissues. Growth impairment is most apparent when young children and teenagers are irradiated. Sitting height, intraclavicular distance, circumference of the neck, and overall height are most affected. Wilimas *et al.* found that, among 34 patients irradiated at <16 years of age, 12 had standing heights at or below the third percentile and 17 had sitting heights below the third percentile [78]. Growth retardation was greater in boys than girls and in patients whose treatment fields were larger than the mantle. Mauch *et al.* observed similar results in that 16 of 23 patients treated when 3–12 years of age had abnormally short sitting heights; however, standing heights in his patients were within the normal range [79]. Donaldson and Kaplan found reduction in sitting height in 17 of 30 patients treated with 3600 cGy [1]. In contrast, among 44 children given <2500 cGy and chemotherapy, there were none with abnormal standing height and only six with abnormal sitting heights. These patients did have some soft tissue and skeletal abnormalities, but these were considerably less severe than in those treated with higher doses. Cramer and Adrieu eliminated height abnormalities by eliminating mediastinal irradiation in children without mediastinal disease [2]. Thus, growth abnormalities can be reduced with smaller fields or lower doses of radiation.

Chemotherapy alone does not appear to cause long-term growth retardation or soft tissue damage. However, the radiomimetic effects of anthracycline antibiotics increase the radiation injury to soft tissue and bone. Among the Philadelphia patients, three of nine children or adolescents who received radiation and 50–300 mg/m^2 of adriamycin have had exaggerated soft tissue responses [4]. The most severe was in a 14-year-old girl who received 3900 cGy to the mantle and 300 mg/m^2 of doxorubicin. Two years later, she could not swim because she could not lift her head out of the water and she could not drive because she could not turn her head to look over her shoulder. Soft tissues of the neck were hard and indurated. Range-of-motion limitations have improved sufficiently over time so that, by 8 years after treatment, she is able to swim and drive, although her physical examination continues to show hardening of soft tissues.

The combination of chemotherapy and radiotherapy contributes to the development of avascular necrosis of the head of the humerus and/or the head of the femur. Proznitz *et al.* found nine cases in young adults among 92 patients who received their MOPP-like regimen and 2000–4400 cGy irradiation [80]. The reported incidence ranges from 1.3% to the 10% of Proznitz *et al.* [81]. Corticosteroids alone can cause aseptic necrosis, and the patients treated by Proznitz *et al.* received more corticosteroids than most patients who receive six courses of MOPP. Other musculoskeletal abnormalities include asymmetry of tissues when only one side has been irradiated, usually

Table 2. Thyroid abnormalities after irradiation for Hodgkin's disease.[a]

Total no.	Percent (no.) ↑ TRH	↑ TSH nl T4	↑ TSH ↓ T4	Hyperthyroid	Ref
Adults					
235		44	20		[82]
69	26	29	6		[87]
50		(1)	18	(1)	[88]
25	40	52	8		[51]
Children					
32	19	55	16		[92]
44 (95)[b]		68	6		[83]
27		37			[84]
24		88	17	(1)	[85]
18[c]		16	(1)	(1)	[4]

[a]Patients received ≥3600 cGy except for references [77] and [4].
[b]Data are extrapolated from a population of 95 patients with childhood cancer, 44 of whom had Hodgkin's disease treated with a mean-thyroid radiation dose of 3990 ± 1290 rad.
[c]Patients received 2100 cGy to thyroid.

manifested as torticollis in children treated with involved-field radiotherapy to the neck. Osteoradionecrosis and osteochondromas also occur in irradiated bones.

7. Thyroid abnormalities

Potentially curative doses of radiation can damage the thyroid. As many as 80% of patients may develop some form of thyroid dysfunction, the most prevalent being compensated chemical hypothyroidism—that is, elevated thyroid-stimulating hormone (TSH) and normal free thyroxin (T_4). Clinical hypothyroidism occurs less commonly (Table 2) [51, 82–92]. Some investigators have found patients with normal T_4 and normal TSH, but abnormal response to thyroid-releasing hormone stimulation test [82]. The interval between irradiation and development of hypothyroidism ranges from 3 months to 6 years [82].

Factors that predispose patients to hypothyroidism are high doses of irradiation, preirradiation lymphangiogram, and perhaps young age. There is a small but significant increase in the incidence of hypothyroidism in patients who have had lymphangiogram. An interval of <10 days between lymphangiogram and irradiation favors the development of hypothyroidism [87], whereas, after an interval of >30 days, lymphangiogram apparently plays no role. It is thought that the iodine in the lipoidal dye used in lymphangiograms suppresses thyroid function, causing a compensatory rise in TSH that in turn stimulates the gland and renders it more susceptible to

radiation-induced damage. Most larger studies do find that young children have a higher incidence of hypothyroidism than older patients. In a sample of 27 patients, however, Green *et al.* found the incidence of chemical hypothyroidism to be 72% in 14 patients <13 years who did not have lymphangiogram and 15% in 13 patients >13 years [84]. Their data, both with respect to age and the negative role of lymphangiogram, contrast with those of other series. There are no reports demonstrating an effect of chemotherapy on the incidence of hypothyroidism.

Thyroid function data for Hodgkin's disease patients who have received doses in the 2000- to 2500-cGy range are not yet available. However, current follow-up of patients at Children's Hospital of Philadelphia shows that two of 18 who received <2100 cGy developed compensated chemical hypothyroidism; one is clinically hypothyroid and one has Grave's disease [4]. The number of thyroid problems is approximately half that of patients who received >3600 cGy to the thyroid. Hypothyroidism is probably underestimated since patients who have elevated TSH values are placed on thyroxin.

Hypothyroidism is not the only thyroid abnormality. Most series cite at least one patient with hyperthyroidism and Grave's disease [82, 83]. In addition, palpable or radiographically demonstrable lesions are not infrequent, but they may be overlooked. Kaplan *et al.* discovered palpable abnormalities in 32 of 95 patients who had received thyroid irradiation as children [83]. These abnormalities were diffuse enlargement in 7% and nodularity in 28%. Nelson *et al.* found that 15 of 50 Hodgkin's disease patients had abnormal thyroid scans 2–16 years after irradiation [88].

Most investigators recommend that patients with compensated chemical hypothyroidism receive thyroxin supplementation. Arguments in favor of early treatment of chemical hypothyroidism are that it will prevent development of clinical hypothyroidism and that is may prevent the development of carcinoma. Animal studies show that chronic stimulation by TSH of a chemically ablated thyroid gland predisposes animals to carcinoma. Also, administration of thyroid hormone reduces the number of recurrences of thyroid cancer in patients with radiation-induced combined papillary and follicular thyroid carcinoma [89, 90]. Thyroid replacement is not expensive, is easily monitored, and, if taken correctly, is relatively free of side effects. Arguments against universal administration of thyroxin are that there is no information on how long to continue replacement and that some chemical hypothyroidism and rare clinical hypothyroidism may resolve spontaneously [85]. Elevations that occur in the first 2 years may reflect transient post-irradiation elevations. In fact, Devney *et al.* found that three of ten cases of chemical hypothyroidism and one of three of clinical hypothyroidism resolved spontaneously; in half of these patients, hypothyroidism occurred within 2 years of irradiation [85]. Until there are more data to select those chemically hypothyroid patients requiring suppression, most physicians administer thyroid hormone indefinitely. The use of pre- and paralym-

phangiogram and intratherapy prophylactic thyroid hormone is under investigation.

The evaluation of patients for treatment-induced thyroid dysfunction includes TSH and T_4 every 6 months for 7 years after treatment. If patients are taking estrogens, a T_3 resin uptake should be obtained to determine free T_4, and careful physical evaluation by a competent examiner should be performed yearly. The low mortality for thyroid carcinoma (<1%) reflects, to some extent, early detection. Thyroid scans are not universally recommended for patients with chemical or clinical hypothyroidism, but should be obtained in those with palpable abnormalities. Ultrasound appears to be a safe, sensitive way to follow thyroid structure in those patients with abnormalities [86]. Our ability to relegate thyroid abnormalities to the category of minor late effects is dependent on careful follow-up and reevaluation.

8. Immunologic abnormalities

Hodgkin's disease itself impairs immunity, especially cell-mediated immunity. Following treatment, some disease-related abnormalities such as cutaneous anergy disappear, while others such as inverted T-cell helper-to-suppressor ratio become more abnormal [93–102].

In general, severity and duration of residual immunologic abnormalities are directly proportional to the intensity of therapy—that is, they are greatest for combined modality and least for involved-field irradiation. Most detailed studies of the late effects of treatment on the immune system have been performed on groups that include both children and adults. In 11 patients, 12–63 years of age, treated with extended-field irradiation, Posner *et al.* found a reduced absolute lymphocyte count and T-cell number, and increased B-cell number. Helper-to-suppressor ratio was 2.08 at diagnosis, 0.45 by 1–4 months after treatment, and 1.06 by 5–12 months later [98]. Among 11 patients of all ages treated with radiation and chemotherapy, or both, Hutchins *et al.* [93] also found a decreased helper-to-suppressor ratio and, in addition, found that patient monocytes inhibited the one-way mixed-lymphocyte culture (MLC) and that patients failed to respond normally in MLC to the addition of allogeneic T cells. Fisher *et al.* [94] demonstrated that T-cell suppression after therapy differed from that before therapy in that, after treatment, abnormalities of T-cell response are not mediated by prostaglandin and monocytes. Anergy improves regardless of disease control.

Tan *et al.* have compared the immunologic function in surviving children with that of adults and have found differences [99]. Children, in contrast to adults, do not manifest progressive lymphopenia and their T-cell number remains normal or increases. The abnormal response to phytohemagglutinin is lost in children. These results suggest either that children's immune

systems are more resilient or that different mechanisms controlling suppression and recovery are in effect. Natural killer (NK) activity in pediatric Hodgkin's disease patients is low before treatment. What happens after therapy is controversial. Kohl *et al.* [96] found it reduced 9–12 months after therapy in five children, whereas Kamiya *et al.* [97], in a study of 23 patients off treatment, found NK activity normal. In the former study, controls were young adults rather than children. Finally, in children and adults with Hodgkin's disease, serologic responses to Epstein-Barr virus (EBV) are abnormal with disproportionately high titers to the viral capsid antigen, persistent antibody to early antigen, and low titers to the nuclear antigen. These abnormalties remain indefinitely and may cause confusion in determining whether a patient has an acute or previous infection. The abnormal serologic response to EBV is another manifestation of defective cell-mediated immunity [100–102].

For the most part, abnormalities of lymphocyte function that persist beyond treatment are laboratory phenomena, the clinical significance of which is not obvious. One exception is the increased risk of acquiring varicella zoster [103–107]. This viral infection occurs most often within the first 6 months after treatment, that is, in the same time period that Posner *et al.* [98] had observed the most severe immunologic abnormalities. Factors that influence the incidence of zoster are age and intensity of therapy. For some years, it has appeared that children are more susceptible to zoster than adults, and that patients given combined modality have a higher incidence. These impressions have been confirmed in a multicenter collaborative study of varicella zoster, in which 116 cases occurred among 717 patients within 36 months of diagnosis [103]. The rate of varicella zoster was 26.6% in 63 patients <16 years, 18.7% in 613 patients 16–64 years, and 6.2% in those >65. When the various forms of therapy were compared, there was an incidence of 11% in those treated with irradiation, 13.2% in those with chemotherapy, and 27.3% in those treated with combined modality. Rates ranging from 32% to 83% are noted among pediatric patients treated with combined modality (Table 3) [1, 28, 105].

Zoster was once a debilitating and sometimes life-threatening consequence of therapy, but the use first of adenine arabinoside and more recently of acyclovir has made it a relatively minor complication [108, 109]. Acyclovir is the antibiotic of first choice. Patients should be reminded about zoster, first at diagnosis, and later when they have completed therapy, and they must be instructed to call at the time of first symptoms so that specific antiviral therapy can be started promptly.

A second viral infection that is a nuisance in Hodgkin's disease patients is verruca vulgaris. As in other compromised hosts, these warts are often seen in greater number, and are larger and more complex than those in healthy children. It is difficult to estimate the frequency of unusually troublesome warts in children treated for Hodgkin's disease.

Table 3. Incidence of zoster in Pediatric patients with Hodgkin's disease according to therapy.

EF radiation	Combined modality	Ref
7/17[a] (41%)	5/6 (83%)	[103]
12/50 (24%)	7/22 (32%)	[37]
16/63 (25%)	34/79 (43%)	[1]

[a]Number affected per number at risk.

9. Psychosocial sequelae

It was expected that the physical and emotional trauma of treatment of childhood cancer would necessarily bring about psychosocial devastation. One of the first attempts to address the late psychosocial effects of childhood cancer was Fergusson's evaluation of a heterogeneous group of 45 long-term survivors in Philadelphia [110]. Her conclusion was surprising: psychosocial damage was not a major consequence of treatment. With few exceptions, subsequent studies have confirmed this conclusion [111–115].

There are now a small number of studies that focus specifically on the psychosocial problems among survivors of Hodgkin's disease. Fobair *et al.* interviewed 403 young adults treated for Hodgkin's disease between ages 5 and 65 years [115]. Most patients complained of subnormal energy levels in the year following treatment. Younger patients were likely to recover within a year. Older patients and those who were depressed for one or another reason and those with advanced-stage and heavier treatment had prolonged fatigue. Twenty-six percent of patients felt that treatment had altered their appearance and 18% noted loss of libido. Again younger patients suffered less than older ones. Forty-two percent experienced therapy-related difficulties at work, most often denial of insurance and other benefits and failure of attempts to enter military service.

Forty-three patients treated for Hodgkin's disease at least 5 years previously at ages 7–19 years were interviewed by a staff psychiatrist at St. Jude Children's Research Hospital [115]. Karnofsky status was 100 in all. Psychiatric problems occurred at some time in 17% and drug or alcohol abuse in 17%; 95% felt that they had benefited from the experience of having had cancer and that they had an improved outlook in life. Lingering problems included job discrimination (21%) and inability to obtain health insurance (39%) or life insurance (80%). Problems with work, the military, and insurance are recurring themes in all series [115]. Among the long-term survivors in Philadelphia, most of the patients who have not experienced problems with insurance were not asked specifically about cancer when applying and did not volunteer unsolicited information. Fobair *et al.* made a plea for enforcement of federal regulations concerning fair labor and employment practices, and they express concern about the effect of prepaid health plans on the ability of persons who are potential health risks to obtain employment and health insurance [115].

10. Follow-up care

Major potential sequelae of treatment should be discussed before treatment starts as part of the process of informed consent and again at the end of treatment as part of patient education. The last day of treatment or a follow-up visit within a month are opportune times to begin explaining follow-up and to review major late effects. The specific purposes of follow-up are to screen for relapse and to assess and possibly treat delayed consequences of therapy. Only a few of the latter are likely to occur in the first year. Fobair *et al.* recommend that patients be warned of the lingering fatigue and perhaps the depression they may feel for a year or more [115]. We also describe signs and symptoms of zoster and advise patients to call when they occur so we can administer acylovir. Similarly, those patients who are asplenic need to be reminded of the gravity of a sudden febrile illness and we emphasize the importance of lifelong penicillin prophylaxis. Families should be told to keep their insurance if it covers the patient and to obtain whatever school or group insurance policies are available at special rates if future coverage is in jeopardy.

Most recurrences occur within 2–3 years of stopping treatment and most serious late effects occur after 2 years. Thus, the early emphasis of history, physical examination, blood studies such as erythrocyte sedimentation rate or ferritin, and radiologic tests is on detection of Hodgkin's disease and establishing posttherapy baselines (Table 4). The frequency and extent of laboratory testing depends on the risk of relapse. We recommend a chest radiograph at least every 3 months for 3 years, every 6 months for 2 years, and yearly thereafter until 15 years from diagnosis. A computed tomographic scan of the abdomen and pelvis and a concurrent ultrasound provide a baseline for follow-up. We then repeat the ultrasound every 6 months for 3 years and yearly thereafter until 5 years. The erythrocyte sedimentation rate and a blood count are obtained at each visit in patients who have received chemotherapy or yearly in these who have had irradiation only. Thyroid studies (T_4 and TSH) should be obtained in those who have had thyroid irradiation.

Gonadotrophins should be obtained in the first year in females over 10 years of age and males over 14 years who have had chemotherapy or pelvic irradiation. Girls who have had normal menses throughout and continue to have normal menses need not be tested, but should be advised of the possibility of early ovarian aging. Boys or young men should be encouraged to have sperm counts performed, especially if they are sexually active and not using contraception or when they are planning to marry. Sperm counts that are low should be repeated some years later before the conclusion is drawn that the patient is infertile.

Stress echocardiography (or more sensitive testing) and pulmonary function tests should be performed 7 years from diagnosis and, if possible, at 15 years. If they are abnormal, patients can be advised about immunizations,

Table 4. Follow-up of patients treated for Hodgkin's disease.

Month	Hx	PE	CBC[a]	ESR	T_4/TSH[b]	LH/FSH[c] sperm count	CXR[d]	US/CT	ECHO	PFT
0	.	.	.	.	.		.	.		.
3	.	.	.	.			.			
6	.	.	.	.	.			.	.	
9	.	.	.	.			.			
12	.	.	.	.	.	.	.	.	.	
15	.	.	.		.		.			
18	.	.	.				.	.		
21	.	.	.				.			
24	.	.	.	.	.		.			
27	.	.	.				.			
30	.	.	.	.	.		.	.		
33	.	.	.				.			
36	.	.	.	.	.		.	.		
42	.	.	.	.			.			
48	.	.	.	.	.		.	.		
54	.	.	.	.			.			
60	.	.	.	.	.	.	.	.		
72	.	.	.				.		.	.
84	.	.	.				.			
96	.	.	.				.			
108	.	.	.			.	.			
120	.	.				.	.			
180	.	.	.				.		.	.

Hx, history; PE, physical examination; CBC, complete blood count; ESR, sedimentation rate or other patient appropriate acute-phase reactant; T_4/TSH, thyroid hormone/thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; CXR, chest radiograph; US, ultrasound; CT, computed tomography; ECHO, echocardiogram (or more sensitive test of cardiac function); and PFT, pulmonary function tests.

[a]CBC in chemotherapy or combined-modality patients as noted; in others yearly.

[b]T_4, TSH in patients who have received thyroid irradiation only.

[c]LH, FSH in patients who have received alkylating agents or pelvic irradiation.

[d]US and CT below the diaphragm every 3 months in patients with disease below the diaphragm; every 6 months in others for first 3 years.

exercise programs, diet, and other interventions to maximize the risks of progressive or more serious complications. The information from the study of these patients is essential for the ongoing evaluation of the most effective, least damaging therapy for the next generation as well as the obvious benefit for the patient.

Physicians and patients are uncomfortable with discussions of second malignant neoplasms, but if the subject has been discussed in the first phases of disease it is not unreasonable to reopen it at the end of treatment. Every attempt should be made to emphasize the relative rarity of these tumors and the extent to which therapy has been designed to avoid second tumors

without jeopardizing curability of Hodgkin's disease itself. The role of the follow-up visit for patients who have stopped therapy is to provide counsel and guidance so that they may live the fullest and most productive lives possible and to help them care for themselves.

Acknowledgments

This work was supported in part by a contract from the Commonwealth of Pennsylvania (SPC 789311). The authors wish to thank Mr. Jack L. Elias for his assistance in the preparation of the manuscript of this chapter.

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15. Areas of neglect and controversy in the dental care of children with Hodgkin's disease

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In childhood, Hodgkin's disease presents as a painless mass in the neck in 90% of cases. As can be clearly seen in this volume, the roles of radiotherapy and chemotherapy have not yet been defined, but virtually all children will be treated with one or both of these modalities.

While the fact that these children will need supportive dental care is not in question, the protocols that may be used are open to discussion. Dental care is an underdeveloped area in this type of patient. Indeed, some review articles, in discussing complications of cancer therapy, either do not mention the oral cavity or do not discuss it in any detail [1, 2]. Further, the full extent of dental complications arising in long-term survivors is only now being recognized and documented.

Dental care can be split into three areas:

1. At diagnosis
2. During treatment
3. Long-term aftercare

Controversies in treatment strategies and areas of neglect are discussed in this chapter.

1. Dental care at diagnosis: an area of neglect

Patients presenting with Hodgkins disease may have the whole range of normal dental problems ranging from caries through orthodontic treatment to periodontal disease. Poor oral hygiene is often a complicating factor as a result of the previous period of ill health. It is important at this stage to eliminate potential problem areas that will be difficult or impossible to treat during the period of active cancer therapy. This implies that a thorough clinical and radiographic dental examination should be carried out to document the base-line oral condition fully. This should include careful charting of all hard and soft tissue lesions to enable prophylactic measures during medical treatment to be related to changes in oral conditions. Dental care at this stage should aim at:

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1. Eliminating infected areas, *e.g.*, untreated apical infections
2. Treating carious cavities, *e.g.*, placing permanent or semipermanent (glass-ionomer cement) restorations
3. Removing sources of mucosal irritation, *e.g.*, orthodontic appliances, sharp fillings, and calculus
4. Providing comprehensive oral care instruction to the patient and/or parents
5. Taking full mouth impressions and making plaster study models
6. Noting unavoidable problem situations that have to be dealt with during treatment, *e.g.*, early 'white spot' enamel lesions, soft tissue damage or infection (tooth eruption), mouth breathing, and thumb sucking (although rarely a problem in the age range associated with Hodgkin's disease)

2. Dental care during medical treatment: includes areas of controversy

In the late 1970s and early 1980s, a number of groups began to address the problem of the oral cavity [3–6]. Programs were developed for the oral hard and soft tissues. As already stated, Hodgkin's disease occurs mainly in the younger age groups and is usually treated with a combination of radiotherapy and chemotherapy. Unfortunately, almost all publications on oral care focus on the problems of the (adult) irradiated patient. Further, the frequency of oral complications after chemotherapy is almost threefold greater in pediatric patients than in adults [7]. This has also been our experience [8].

There has, in consequence, been increased concern about the need for a broader-based program of oral care. In this context, there are four main areas of controversy:

1. The extent of flouride usage
2. Oral hygiene: the use of antibacterial agents as an adjunct to normal oral hygiene regimens
3. The use of artificial saliva
4. The extent to which nursing staff can provide this type of dental care

2.1. Use of fluorides

The degree to which all patients, irrespective of age, oral condition, or treatment modality should be given a conventional standard fluoride program is an open question. Although the risk of caries, particularly radiation caries in irradiated patients [9], should not be taken lightly, it should be emphasized that regimens requiring daily use of trays containing (acid) fluoride gels in small mouths are clearly stressful and at times impossible to carry out. Studies have shown that children under ~6 years of age are unable to control their swallowing reflex and may ingest up to 70% of

fluoride if this applied as a gel in a tray [11, 12]. *In vitro* studies have also shown the value of lower concentrations [12]. This has been confirmed by recent *in vivo* work which has demonstrated that brushing with an 0.4% F^- gel for only 1 min once a week in healthy subjects provides very significant remineralization [13]. Systemic fluoride supplements are also clearly unnecessary in view of the amounts of fluoride normally ingested from toothpaste and other fluoride regimens. They can only serve to increase the plasma fluoride level [14] and the risk of toxic effects [15].

These results give weight to the philosophy of Fejerskov et al. [16] on the more rational use of fluorides: in short, fluorides should be used only when necessary at the lowest dose required to achieve primary or secondary prevention with the least possible stress to the patient.

Although the degree of xerostomia in adults can be correlated with the amount of radiation received [17], it has been our experience that these rules do not always apply in children. These young patients rarely suffer complete xerostomia and should receive treatment appropriate to their oral state. Patients with severe qualitative and quantitative reductions in saliva would thus receive intensive fluoride therapy ranging from daily to weekly use of a *neutral* fluoride gel in custom-made trays [18] during and immediately after the period of radiation treatment. A more variable program can apply to these patients in the long term after radiation therapy. In those patients on chemotherapy only, the caries risk is not so high [19, 20], and the patient may be better served by a more conservative approach that reduces unnecessary treatment. Particularly the use of custom fluoride trays in mouths affected by mucositis is an extremely stressful procedure.

For the past 3 years, we have treated non-irradiated children on chemotherapy with a conservative regimen based on good oral hygiene (see below) and, in the first instance, using only fluoride-containing toothpaste twice daily. Fluoride treatment is only increased if there is evidence of increased caries activity as indicated by an alteration in the size or number of white-spot initial caries lesions compared with the original diagnosis. In this instance, a neutral 1% sodium fluoride (0.45% F^-) gel is then lightly *brushed* on, and flossed interproximally if possible, on a weekly basis.

We will be reporting on 3-year results in the near future, but this area of prevention, particularly with respect to children, should be the object of more research.

2.2. Oral hygiene and soft tissue care

The potential unpleasant and deleterious mucosal side effects of chemotherapy in adults, which have recently been reviewed [21], include mucositis, cheleitis, and gingival and mucosal bleeding with or without superimposed infection such as moniliasis and herpes. To this should be added the major side effects of irradiation, namely, xerostomia, radiation caries, mucositis, loss of taste, and increased oral infection [22].

In general, oral prevention protocols for adults are based on subjective observations as a result of experience and these have not been verified by long-term clinical studies [3, 21, 23–25]. In the pediatric situation, again there are very few studies and topical soft tissue treatment is based on extrapolation from adult data or philosophies. The data and treatment philosophies discussed by these authors can, however, be helpful.

Recently the management of common oral complications of chemotherapy has been excellently delineated by Peterson [26] and McGaw and Belch [27]. It is in the area of routine daily care and prophylaxis, however, that controversies remain. That scrupulous oral hygiene is a primary requirement in these patients is generally accepted. How this can be achieved is less universally agreed upon. Techniques range from very careful use of the toothbrush, with or without warm water irrigation [5], to the extensive use of chemical plaque control (reviewed in a recent editorial [28]).

The removal of food debris that may act an irritant to the soft tissues is one facet of the problem. They can be removed most efficiently by mechanical means, *e.g.*, toothbrushing/flossing. The extent to which oral microflora can be controlled, however, is an area of particular interest, particularly in young patients since primary teeth erupt until the age of ~2½ years, and primary tooth loss and the eruption of permanent teeth occur from the age of ~6 to 12 years. During these times, one or more areas of the mouth will be particularly prone to gingival inflamation and infection, and will require specific preventive care in view of the added risk of septicemia [29]. Studies have shown that the severity and duration of mucositis can be correlated not only with levels of dental plaque present around erupting teeth, but also with the levels of oral hygiene around the remaining teeth in the mouth [30].

There are at present a number of mouth-rinse regimens to help combat this situation. These include the use of cetylpyridinium chloride [3], saline [25], 0.1% chlorhexidine [27, 31], warm sodium bicarbonate [32], and carbomide peroxide in glycerol [33].

It is the routine use of an antibacterial mouthwash that is one clear area of controversy. In recent years, the use of chlorhexidine has been extensively documented for both high-risk (mentally handicapped) patients [34, 35] and in periodontics [36]. Although there have been occasional negative results [37], most long-term studies have shown 30%–50% reductions of total salivary flora without a concomitant shift toward resistant strains [38]. Repeated chlorhexidine treatments have also been shown to increase both its retention and effect on bacteria [39]. It is, therefore, only to be expected that these results would be extrapolated to the treatment of cancer patients. Katz [40] found that, in combination with fluoride, the oral health of irradiated patients was fully maintained with excellent patient acceptance and compliance. More recently, it was tested against a placebo control rinse in leukemic patients and found to provide superior oral health whether measured in terms of plaque, gingivitis, or mucositis levels [27].

In spite of these results, it is notable that its use is not universal, and the question of whether such an antibacterial mouthwash should be used still has to be answered. Indeed, in some centers, routine monitoring of both the type and quantity of bacteria present is by no means standard.

2.3. Artificial saliva

Severe long-term hyposalivation does not usually occur either during or after treatment with radiotherapy and/or chemotherapy. If this symptom does occur, artificial saliva can be prescribed. Those based on mucin (Saliva Orthana) rather than on carboxymethyl cellulose (Glandosane, Orex, or V.A. Oralube) are often preferred by patients. Mucin-containing preparations have lubricating and wetting properties very similar to those of natural saliva [41].

2.4. The use of nursing staff

The question posed in this section about which member of the treatment team should carry out routine oral care is probably the most controversial since it involves personal feelings related to territory and competence. Little that is relevant has been published, and there are no protocols or guidelines.

The basic question is: how many of these basic oral care procedures need the services of trained *dental* personel and how much can be implemented by the nursing staff? On the basis that the type of care to be provided—toothbrushing, swabbing, rinsing, spraying, fluoride application, *etc.*—has been fully taught, there would appear to be no reason why routine preventive care cannot be carried out by nursing staff. This has the distinct advantage that it can become ward routine and is neither forgotten nor disruptive [42]. It also allows the nursing staff to become actively involved, thus increasing motivation, and is also extremely cost effective. As with all procedures, it must be regularly monitored, in the first instance by an oral hygienist, and is no substitute for regular oral examination by a dentist.

It is clear that answers to this problem will vary from country to country and between hospitals in the same country, depending on the law and its interpretation, payment systems, and the personalities involved. However, the patient has a right to, and should receive, routine prophylactic oral care during normal waking hours. For patients with severe oral problems, care may even be necessary every few hours on a 24-h basis.

3. Long-term aftercare: an area of neglect

In the last few decades, great strides have been made in the medical treatment of these children, and the long-term survival in Hodgkin's disease

Table 1. Dental evaluation: areas of neglect and controversy.

	Current practice	Recommended practice[a]
Area of neglect		
Dental care at diagnosis	Varies according to unit	Full history and examination Treat: Infection Caries Soft tissue inflammation Remove orthodontic appliances, rough edges on fillings, *etc.* Give oral hygiene instruction Make study models Chart: Initial lesions Soft tissue damage Note: Thumb sucking Mouth breathing Erupting teeth
Areas of controversy		
During active medical treatment		
Fluoride use		
Fluoride toothpaste	Normally used	Recommended as base level for caries prevention Supervised use only, under the age of 4 years
Acidulicated fluoride gels	Used in some institutions	Not recommended; *neutral* gels are preferred
High concentration 1.2% NaF, and 0.4% SnF_2 gels	Frequently used	Lower concentration, *e.g.*, 0.4% NaF may be equally effective
Custom trays for fluoride application	Commonly used	Should only be used if clinically indicated in irradiated patients if mucosal condition allows, application with a toothbrush and floss may be equally effective
Systemic fluoride supplementation, *e.g.*, tablets	Commonly used	Not recommended in combination with local agents in view of the amounts of fluoride unintentionally swallowed

Antibacterial mouthwash	Used in only a few centers	Should be used more widely, in conjunction with normal oral hygiene measures, under controlled conditions to provide conclusive data
Artificial saliva	Varies according to unit	Recommended: mucin-containing substitutes, *e.g.*, saliva orthana Alternative: carboxy methyl cellulose based, *e.g.*, Glandosane, Orex, V.A. Oralube
Area of neglect Aftercare	Varies according to unit	Regular 4 or 6 monthly examinations. Higher risk of: Abnormal skeletal or soft tissue growth Hypodontia Shortened and/or malformed crowns and roots Caries Careful documentation required to provide a data base of future dental requirements

[a]'Recommended practice' is part of the standard treatment protocol of the Pediatric Oncology Center, Groningen.

is now well over 70%. The dental health of these patients during and after treatment is therefore of importance since it can affect their future quality of life.

The long-term effects on the oral system of childhood cancers, or their treatment, has received little attention. In a review article on the late effects of cancer in children [43], only three of the 229 references concerned the oral cavity, and these were related to the results of radiation of the head and neck.

In a recent study of children, most of whom were over the age when tooth formation occurs, possible chemotherapeutic effects on five of the 23 patients being treated for tumors outside of the head and neck region were reported [44]. Increased levels of dental malformations were found in a study of 64 children treated with chemotherapy with and without prophylactic radiation to the central nervous system [45]. More recently, in a study of 45 children, all of whom had developing permanent incisors at the time of chemotherapy, it was found that only two were free of some type of dental abnormality [46].

The dental problems which may be encountered can be summarized as follows:

1. Altered growth to the skeleton and soft tissues [47]
2. Hypodontia [45]
3. Shortened malformed roots [48]
4. Malformed and/or hypoplastic crowns [46]
5. Increased risk of caries in irradiated patients [44] and the possibly in patients treated with chemotherapy [46]

It is clear that patients should be placed on long-term recall, regularly evaluated, and receive counseling and dental care as the need arises (Table 1). Because of the small numbers of patients evaluated in the studies completed to date, it would be of advantage if knowledge and data could be pooled to gain a better insight into long-term dental needs.

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II

Institutional Experience

16. Hodgkin's disease in Indian children

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The dramatic improvement in the treatment of Hodgkin's disease (HD) is due to a better understanding of its biologic behavior and pathologic subtypes, accurate staging, and more effective treatment with chemotherapy and radiotherapy.

While the disease pattern and response to treatment in children from the Western Hemisphere have been widely reported by Schnitzer *et al.* [1], Fuller *et al.* [2], Smith *et al.* [3], and Donaldson *et al.* [4], there is a great paucity of information regarding childhood HD from India.

The overall crude age-adjusted incidence rate is low in developed countries, as reported by Waterhouse *et al.* [5]. In contrast, the incidence of childhood HD in Western India is quite high and comprises ~25% of all such cases. As reported by Talvalkar *et al.* [6], the incidence rate in the 0- to 9-year age group in the Greater Bombay population is higher than the corresponding Connecticut (USA) rate, but much less than that reported from Colombia (California).

It conforms to the type I pattern seen in tropical and subtropical areas as described by Correa and O'Conor [7] and is characterized by high rates in children, marked male preponderance, and poorer prognostic subtypes, and by presenting initially with an advanced clinical stage. This pattern as seen in India is similar to the clinical picture as seen in Portugal [8], Turkey [9], Africa [10, 11], and Israel [12]. This could be related to environmental and socioeconomic status, as reported by Gutensohn and Cole [13] and by Gutensohn and Shapiro [14]. Further, it closely follows that in adults in our country as previously reported by Dinshaw *et al.* [15]. This is in contrast to American children reported by Young *et al.* [16], in whom HD differs significantly from adult HD, with an increased incidence of the nodular-sclerotic (NS) subtype and a much lower incidence of mixed-cellularity (MC) and lymphocyte predominant (LP) varieties.

A retrospective study of all HD in infancy and childhood diagnosed at the Tata Memorial Hospital during 1975–1982 was undertaken to assess the prognostic roles of histopathology and clinical extent of disease. They have been analyzed in relation to the clinical presentation, staging procedures, histology, and results of changing concepts of management.

Kamps, W.A. (editor) HODGKIN'S DISEASE IN CHILDREN

Table 1. Age distribution: 212 new cases (1975–1982).

Age (years)	No.	%
0–4	18	8.5
5–9	96	45.3
10–14	98	46.2

Table 2. Histopathologic distribution: 212 new cases (1975–1982).

Path	Total no.	0–4 years	5–9 years	10–14 years
LP	67	7	32	28
NS	21	2	6	13
MC	88	7	44	37
LD	19	–	7	12
UH	17	2	7	8
Total	212	18	96	98

LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; and UH, unclassified histology.

A total of 212 cases of HD in children 14 years and younger were registered at the Tata Memorial Hospital from 1975 to 1982, and investigated and treated at the two Joint Lymphoma Clinics. They comprised 25% of all HD patients registered during that period.

While 45% (96 patients) were between 5 and 9 years old and 46% (98 patients) between 10 and 14 years old, only 8.5% (18 patients) were 4 years old or younger. The youngest recorded age was 3 years. As in most other series, there was a marked male preponderance with 178 male to only 38 female patients, comprising a ratio of 5:1 (Table 1).

Pretreatment studies included a complete history and physical examination; complete blood counts; erythrocyte sedimentation rate determination; liver function tests; blood urea, serum uric acid, and urine examinations; and chest x-rays.

Bons marrow aspirations are unsatisfactory for demonstrating HD. Thus, bone marrow was biopsied using Jamshedi needles in 195 patients with positive findings in only 15 cases (7%).

Lymphangiograms and simultaneous intravenous pyelograms were done in only 40 patients due to practical difficulties of sedation in young patients. Fifteen patients (38%) showed evidence of unsuspected disease below the diaphragm.

Liver and spleen acintiscans were not routinely carried out as they are of doubtful value. Scanning with computerized axial tomography and ultrasound is just beginning to make an impact in our country. Its noninvasiveness will be of great advantage in monitoring the disease in these children.

The MC histologic subtype was the commonest and was seen in 88 patients (41%), followed by the LP variety in 67 patients (32%) (Table 2).

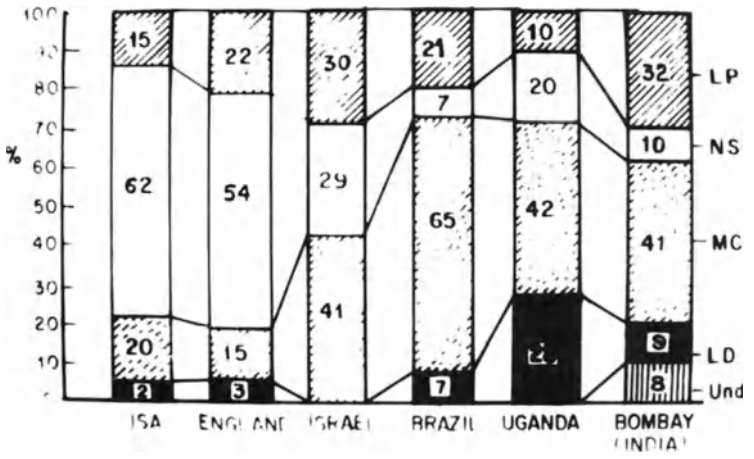

Figure 1. Comparison of histologic presentations.

Table 3. Clinical stage: 212 new cases (1975–1982).

Stage	No. (%)	A	B
I	51 (24)	36	15
II	55 (26)	34	21
III	67 (32)	27	40
IV	39 (18)	5	34
Total	212	102	110

The NS and lymphocytic depleted (LD) types were seen in only 21 patients (10%) and 19 cases (9%), respectively. In 17 patients (8%), it was not possible to subclassify the disease. Thus, 50% of all cases were in the poorer prognostic subtypes of MC and LD. There did not appear to be any significant difference in the different age groups apart from an increased tendency toward NS and LD in the older adolescent, 10- to 14-year, group. Figure 1 demonstrates the shift from the predominant favorable pathologic subtypes LP and NS present in the Western Hemisphere to the more unfavorable varieties of MC and LD prevalent in the subtropical and tropical countries.

All the patients were clinically staged according to the Ann Arbor classification [17]: 51 children (24%) were in stage I, 55 patients (26%) in stage II, 67 cases (32%) in stage III, and 39 cases (18%) in stage IV (Table 3). Of all children, 50% presented with early clinical stages I and II, and 36 (34%) had associated systemic symptoms. On the other hand, 74 children (70%) had systemic symptoms in stages III and IV.

This high percentage of advanced clinical stage is primarily due to a delay

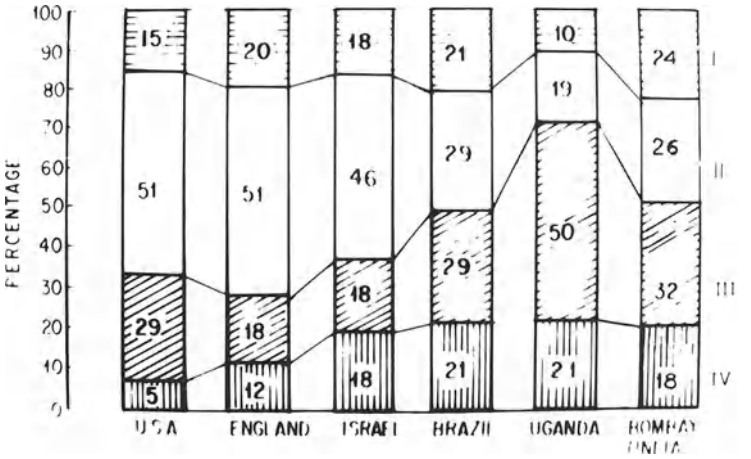

Figure 2. Comparison of clinical presentations.

in diagnosis and probably attributed to a high incidence of tubercular lymphadenopathy in this pediatric age group. It may also strengthen the suggestion of a higher incidence of MC type due to a progression and conversion of the more favorable LP variety to MC and LD subtypes with passage of time.

Figure 2 demonstrates the prevalence of the earlier clinical stages in the Western countries, and an advanced clinical stage in the more economically depressed areas.

The decision for routine laparotomy staging in children presents a difficult problem. Unsuspected disease below the diaphragm has been detected in 21%–35% of young children, as reported by Fuller *et al.* [2], Donaldson *et al.* [4], and Botnick *et al.* [18].

In this series, 26 children underwent a staging laparotomy. There were 23 boys and three girls, with the youngest being 4 years. A change in clinical staging was recorded in 12 patients (46%). However, more importantly, 11 patients (58%) were upgraded from clinical stages I and II to a more advanced clinical stage:

- Stages I and II: upgraded in 11 of 19 cases
- Stage III: upgraded in one of four cases

The total change in clinical staging in 46% of children is even more pronounced than in all patients with HD who were laparotomised for staging as reported previously by Dinshaw *et al.* [19]. There was no serious immediate postoperative complication or mortality. A major point of dispute is whether all children with localized disease should be subjected to intensive staging procedures. Only if the policy of treatment involves using radical radiation therapy alone, such invasive staging procedures are mandatory.

The optimum treatment for the child with HD still remains controversial.

Table 4. Analysis of treatment: 129 evaluable cases (1975–1982).

Stage	RT	CT	CT + RT
IA + IIA	20	16	11
IB + IIB	2	4	9
IIIA	2	14	5
IIIB + IV	1	30	15

Mantle RT—31 cases
TNI—4 cases
Involved field—31 cases
CT × 6 courses—70 cases
CT 6 courses—35 cases
Complete response—108 patients (84%)

The majority of our children were of the poorer prognostic subtypes both histologically and clinically, in whom staging procedures revealed an extremely high incidence of 58% unsuspected infradiaphragmatic disease. Further, an increasing awareness of the immediate and long-term complications of radiation therapy in young children made us decide on a treatment policy of combination chemotherapy and involved-field radiation to residual bulky nodes in the majority of our cases. The poor general condition of most children when initially seen precluded the opportunity for a staging laparotomy. Chemotherapy obviated the need for a staging laparotomy. While children have excellent tolerance to drugs with minimal side effects, the disadvantages of chemotherapy include sterility in the older child and an increased danger of secondary tumors. However, the major advantage is avoidance of a staging laparotomy and postradiation sequelae in young children. In the event of a relapse at a later stage, radical radiation therapy could still be administered with a curative intent with minimal side effects and growth retardation.

A radical course of radiation with megavoltage rays was delivered up to a dosage of 30–40 Gy in 3–4 weeks using a mantle technique in 31 cases and total nodal irradiation in four cases. Involved-field radiation was directed to residual areas of bulky disease in 31 patients who were treated primarily with chemotherapy.

Chemotherapy using the standard COPP regimen was administered to 105 patients. The dosage was cyclophosphamide, 400 mg/m^2, and Oncovin (vincristine), 1.4 mg/m^2, intravenously on days 1 and 8; and procarbazine, 100 mg/m^2, and prednisone, 40 mg/m^2 orally from day 1 to day 14. These combinations were given in six courses once monthly to 70 patients and in 7–10 courses in 35 cases.

In this series, 129 children were available for analysis after having completed a planned course of minimum adequate treatment with chemotherapy and/or radiation. All cases were evaluated at the completion of radiation therapy or at the end of six courses of chemotherapy (Table 4). Complete response was defined as complete disappearance of all clinical and radiologic evidence of disease. Partial response was noted where tumor shrinkage was

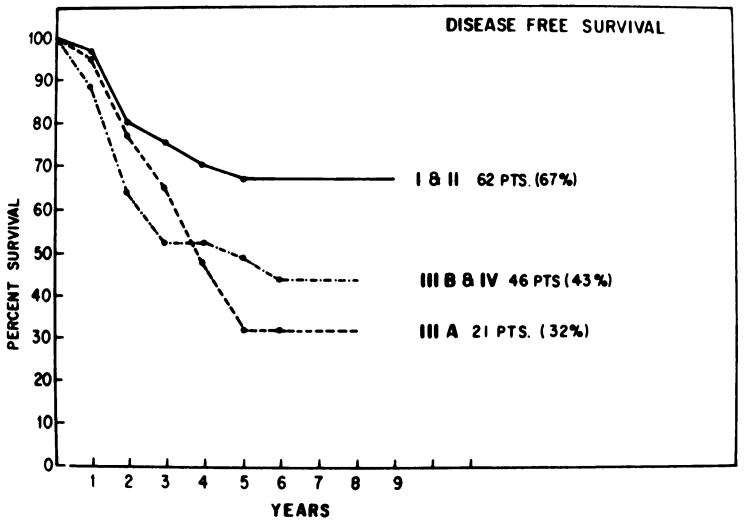

Figure 3. Actuarial life-table analysis of 129 evaluable cases (1975–1982).

≥50%. There was complete response to treatment in 84% of all children given a minimum adequate course of treatment.

The disease-free survival rates were calculated by the actuarial life-table method, with a minimum follow-up of 3 years to a maximum of 10 years. The disease-free status for stages I and II (A and B) was determined to be 67%; it was 32% for stage IIIA and 43% for stages IIIB and IV, respectively (Figure 3).

The latest ongoing prospective study randomizes the use of alternate COPP–ABVD–COPP in six cycles *versus* COPP alone, along with definitive involved-field radiation in all patients with unfavorable histology and disease status higher than IB and IIB. (The ABVD combination is Adriamycin, bleomycin, vinblastine, and dacarbazine.) The favorable clinical stages IA and IIA continue to be treated with COPP alone.

Excellent results have been published by Fuller *et al.* [2] with 80% and 67% survival rates at 5 years and 10 years in stage I and II cases treated with involved-field radiation alone. This has been confirmed by Cham *et al.* [20] with 89% survival rates at 3 years, and by Tan *et al.* [21] with an 84% disease-free status at 8 years. Chemotherapy given alone in Ugandan children with HD has had excellent results comparable to those seen in adults. Complete remissions were reported by Ziegler *et al.* [22] and Olweny *et al.* [11] in 88% of cases with 70%, 78%, and 62% 5-year survivals for stage I–II, III, and IV cases, respectively.

Jenkins *et al.* [23] treated 57 study patients with unfavorable stage I and all stages II–IV with combination chemotherapy and low-dose extended-field radiation. The results were even more impressive with 92% and 84% 5-year and 10-year survivals.

The Stanford series reported by Donaldson and Kaplan [24] proved that the results were better in children than in young adults in stages I and II (A and B) and very much better in stages III and IV with 89% survivals at 5 years. The HD intergroup study reported by Sullivan *et al.* [25] in 305 patients reported disease control in 95% at 4 years with MOPP and involved-field radiation alone. It also concluded that extended-field radiation, when used alone, produced better disease-free intervals than involved-field radiation alone in the early clinical stages.

The advances in the multidisciplinary approach have dramatically improved the prognosis of this previously rapidly fatal disease. The widespread adoption of staging systems, both clinical and pathologic, the increased accuracy of the extent of disease, and more appropriate modalities of treatment have all been reflected in the changing concepts of treatment. However, complications demand that continued efforts be made to optimize treatments to provide maximum survival with minimum morbidity in these young children.

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17. Treatment of childhood Hodgkin's disease with chemotherapy alone

Experiences from the Royal Children's Hospital, Melbourne

Henry Ekert

The essential feature of childhood is growth and development, culminating in a mature adult. Pediatric oncologists face a particular dilemma when planning the best methods of treatment of life-threatening disease. The cure of children should be achieved at the lowest possible cost to their growth and development. Truly cured individuals are those whose physical and mental health is comparable to their age- and sex-matched peers in their social strata. In Wilms' tumor and acute lymphocytic leukemia, the intensity of treatment, which has irreversible consequences on growth and development, is being decreased. In childhood Hodgkin's disease, similar attempts are under way to eliminate the consequences of irradiation of growing tissues and postsplenectomy infections, and to reduce the cumulative toxicity of chemotherapy, surgery, and irradiation (Table 1).

1. Chemotherapy

Our approach has been the use of chemotherapy as the only treatment modality. This can be justified on several grounds. In advanced (stage III and IV) Hodgkin's disease, chemotherapy studies using nitrogen mustard, Oncovin (vincristine), procarbazine, and prednisone (MOPP), initiated in 1970 by DeVita at the National Cancer Institute, show an 80% remission rate, with 63.5% of patients remaining in remission with a minimum follow-up period of 5 years [1]. Results of chemotherapy with other regimens, *e.g.* ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) [2], have been similar, while alternating courses of MOPP and ABVD are claimed to have long-term disease-free rates of $\simeq$70% [3]. It seems reasonable to extrapolate from these data that chemotherapy alone may be even more effective in stage I and II disease than in stages III and IV. That this may be so is suggested by the studies of chemotherapy as the only modality of treatment reported in 1978 from Uganda [4], where radiation facilities were not available. Out of 48 children with Hodgkin's disease stages IA–IVB, 42 achieved complete remission with six courses of MOPP; 11 subsequently relapsed. In this small group of patients, all of 18 children with stages I–IIIA

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Table 1. Complications of irradiation in the treatment of childhood Hodgkin's disease.

Complication	Frequency
General appearance	Very common
↑ TSH levels	≃ 65%–78% with doses >26 Gy
Aseptic necrosis of bones	≃ 1% A single report of frequency of 20%
Pneumonitis	≃ 2%
Cardiac	16 of 120 with high-dose mantle field
Testicular and ovarian	With pelvic irradiation
Varicella	21%
Second malignancy	Relative risk ratio of 3.3 (ratio of observed: expected)

achieved complete remission CR, and four of 18 relapsed but complete remission was reinduced with MOPP. Subsequently, the UK Children Solid Tumor Group [5] reported on combined chemotherapy and irradiation in 80 children, of whom 13 received chemotherapy alone using vinblastine, chlorambucil, procarbazine, and prednisolone. Two of these patients subsequently relapsed, and one died of progressive disease. Ekert and Waters [6] reported a 93% disease-free survival in 18 children treated with MOPP alone.

In using chemotherapy as the only modality of treatment, there are certain advantages, and some complications.

The major advantages are: (a) elimination of dysmorphic features; (b) elimination of the need for staging laparotomy with splenectomy; and (c) elimination of irradiation of sensitive tissues such as heart, thyroid, lung and breast.

The major disadvantages are: (a) unknown, but possibly high potential for infertility in prepubertal and pubertal children; (b) high indicence of early side effects characteristic of the agents used for treatment, *e.g.*, gastrointestinal and hematologic; and (c) higher long-term incidence of hematologic second malignancy, particularly acute myeloid leukemia, when compared with irradiation alone.

When reduced to the essentials, the judgement as to the choice of treatment is subjective and involves the patients, their family, and their medical treatment team. In my experience, fear of surgical staging and the long-term consequences on growth, inherent in an irradiation approach, outweigh those related to chemotherapy, so that, so far, all patients and their families have preferred the chemotherapy option.

For the reasons previously outlined, we considered the option of using chemotherapy as the only treatment modality most compatible with our desire to cure children with the least serious side effects on the quality of their lives after treatment had finished. At the time of writing, the study population consists of 34 children, of whom 25 are boys and nine are girls: 22 were in the age group 10–15 years, ten between 5 and 9 years, one under the age of 5, and one over the age of 15. The staging of the patients was clinical, using conventional techniques, including organ imaging and bone

marrow trephines, but not lymphangiography. In the early years of the study, we were still undertaking staging laparotomy and splenectomy. Nine of these patients were pathologically staged. The distribution of patients according to stage was: stage I, 11; II, 10; III, 7; and IV, 6. Eight of the children, all in stage II, III, or IV, were considered to have B symptoms.

A subdiaphragmatic presentation occurred in four patients. Bulky mediastinal disease, defined as a mediastinum–thoracic ratio of >0.33, was present in ten patients. In all patients, the diagnosis was histologically confirmed prior to commencement of therapy. Nodular sclerosing histology was present in 25, mixed cellularity in six, lymphocyte predominant in two, and lymphocyte depleted in one.

No patient received irradiation prior to chemotherapy, even in the presence of massive mediastinal disease. Treatment consisted of MOPP, given as

vincristine	1.5 mg/m^2	D 0 + 7
nitrogen mustard	6 mg/m^2	D 0 + 7
procarbazine	100 mg/m^2	D 0–14
prednisolone	50 mg/m^2	D 0–14

Prednisolone was given with each course of chemotherapy. Courses of chemotherapy were administered in the outpatient department at monthly intervals. In patients treated prior to 1982, a minimum of six courses were given if the disease was stage I or II, and 6–12 if stage III or IV. From 1982, no more than six courses were given and, in patients with stage I disease, the number was reduced to four. Between 1982 and 1983, we decided to use ABVD as the initial form of treatment because of its reported lower incidence of long-term consequences [7]. Six patients received this form of therapy, four with stage I and II disease and two with stage III and IV disease. Two (stage I and III) failed to achieve remission, and one (stage I) relapsed immediately after ceasing treatment. These patients were subsequently treated with MOPP, and two achieved complete remission and remain in remission for 3 years, while one failed to respond to MOPP.

Of the 31 patients treated with MOPP, 27 had received no prior therapy, and four had relapsed on previous treatment, three during or at completion of ABVD, and one 6 years following mantle therapy and chemotherapy with vincristine and cyclophosphamide. The response to MOPP, according to the stage of disease, is shown in table 2.

All patients with stage I disease achieved a complete remission and none relapsed. Two patients died in complete remission and will be discussed later. All but one patient with stage II disease achieved complete remission, and one relapsed 6 months after cessation of treatment and required involved-field irradiation. The patient whose disease failed to remit had bulky mediastinal disease and failed to respond to ABVD and, subsequently, mantle irradiation. He is currently alive with stage IV pulmonary disease. In stage III disease, all but one patient achieved complete remission and

Table 2. Response according to stage in 31 patients treated with MOPP as initial treatment (27) or following relapse (4).

Stage	No. pts	No. CR	Median CCR (months)	No. and site relapses	No. deaths
I	11	11	22	0	2 (in CCR)
II	8	7	45	1 C[a]	0
IIIA	4	4	68	0	0
IIIB	3	2	9	0	0
IVA	2	2	64	0	0
IVB	3	3	119	0	0

[a]C, cervical.

Table 3. Response to chemotherapy.

Presentation	No. pts	No. CR	Median CCR (months)	No. and site relapses	No. deaths
Cervical or cervical and mediastinal	20	20	45	1 C[a]	2
Bulky mediastinal	10	8	51	0	0
Subdiaphragmatic	4	4	89	0	0

[a]C, cervical.

none has relapsed. The patient who failed to achieve complete remission had bulky mediastinal disease, which was initially treated with ABVD and subsequently with MOPP. Failure to respond to MOPP led to mantle irradiation, but disease has progressed and he now has stage IV (pulmonary) disease. All patients with stage IV disease entered complete remission and none has relapsed.

The results of treatment with chemotherapy (MOPP or ABVD) according to mode of presentation in all 34 patients is shown in table 3. The only patients failing to achieve complete remission were two with bulky mediastinal disease. In three of these ten patients, there were residual lesions on chest x-ray and CT scans at the completion of chemotherapy. Exploratory thoracotomy was undertaken in these children prior to considering further therapy. In two, there was evidence of persistent Hodgkin's disease while, in one, there was only fibrous tissue. This patient had no further therapy and has remained disease free for 8 years. It is notable that eight of ten children with bulky mediastinal disease achieved complete remission with chemotherapy only and none has relapsed.

The disease-free survival from Hodgkin's disease in the 34 patients treated with MOPP or ABVD is 88%, with a median follow-up of 52 months. Freedom from relapse in the 31 patients treated with MOPP is 90% (two failures of complete remission, and one relapse) (Table 3). The event-free survival in the 31 patients treated with MOPP is 83% (two failures of complete remission, one relapse, and two deaths) (Figure 1).

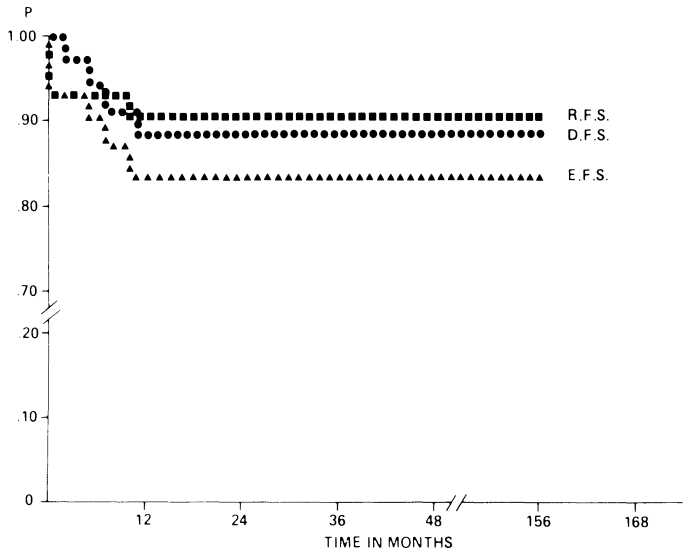

Figure 1. Survival of patients treated with MOPP: R.F.S., relapse-free survival; D.F.S., disease-free survival; and E.F.S., event-free survival.

2. Complications of Treatment

There were two deaths among stage I patients. Both had strikingly similar disease courses. At the completion of six cycles of MOPP in the first patient and four cycles of MOPP in the second, there was hematologic toxicity that was considered to require transfusion of packed red cells in the first patient, and platelet and packed red cells in the second. A week later, this was followed by sudden onset of a devastating illness consisting of widespread maculopapular rash, bloody diarrhea, dehydration, and pulmonary consolidation. In the first patient, at autopsy there was necrotizing enterocolitis, bone marrow hypoplasia, and hyaline membrane pulmonary consolidation with cytomegalovirus (CMV) inclusions. In the second patient, there were similar findings, but no evidence of CMV. The pathologic diagnosis of both of these patients was that of acute graft-*versus*-host disease, a complication of transfusion in Hodgkin's disease that has previously been reported [8]. As a consequence of these two unfortunate experiences, we now either avoid transfusion or irradiate blood products prior to transfusion in children with Hodgkin's disease and hematologic toxicity.

One other patient with stage IV disease developed 'T'-cell acute lymphocytic leukemia 40 months after cessation of therapy. Whether this represents a drug-induced lymphoma or a propensity of Hodgkin's disease to develop non-Hodgkin's lymphoma is unknown in her case, but she has responded well to chemotherapy and, at the time of this report, is 36 months in complete remission.

The other complications of treatment were due to gastrointestinal and hemopoietic side effects of therapy. All patients suffered from nausea and vomiting. Pain with venepuncture related to nitrogen mustard occurred in ~50%. Hemopoietic toxicity, resulting in more than 1 week's interruption of treatment, occurred in 74 of 222 courses of chemotherapy. Herpes zoster infection occurred in ten patients.

We do not as yet have detailed endocrinologic assessment of the patients. Gynecomastia at time of puberty occurred in one patient. He had normal levels of follicle-stimulating and luteinizing hormone and was considered to have gynecomastia not related to treatment. All girls who had entered menarche have resumed normal menses on ceasing chemotherapy.

All children successfully treated with MOPP alone are now robust, healthy-looking boys and girls, undertaking normal life-style activities. All are within normal limits for height and weight, and do not have dysmorphic features. The majority remember with some revulsion their MOPP days and dread the thought that they may need retreatment.

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18. Pediatric Hodgkin's Disease
Later Results and Toxicity—the Toronto Experience

Derek Jenkin and John Doyle

Both radiation treatment and/or combination chemotherapy, classically with MOPP (nitrogen mustard, Oncovin (vincristine), prednisone, and procarbazine) are very effective in the eradication of Hodgkins disease. The relapse rate after treatment may be decreased by combining these modalities. Whether this is an appropriate strategy is a question of balance between cure of the disease and the early and late toxicity of treatment, with the comparison for limited disease being between initial bimodal treatment or sequential treatment in which radiation is used alone as the primary treatment and treatment is intensified at the time of first relapse, when necessary, using combination chemotherapy and usually additional radiation treatment. The importance of this question has been obvious ever since the curative role of combination chemotherapy with MOPP was established in the early 1970s. Because severe late toxicity may be delayed for many years, there is not yet a clear answer to the question, even in the much larger adult population with this disease.

In 1982, we reported a study of the treatment of children with Hodgkin's disease conducted from 1973 to 1979 in which staging laparotomy was omitted; children with favorable clinical stage I (CS 1) were treated with involved-field radiation (IF RT) alone and all other patients with six cycles of MOPP combined with low-dose extended-field radiation (EF RT). Combined therapy was commenced with MOPP. EF RT was given after completion of the first three cycles of MOPP and treatment was completed with a final three cycles of MOPP. Only one of 27 patients with CS 2 or CS 3 disease relapsed with a median follow-up time of 4.3 years. In this study group, the overall 5-year survival (SR) and relapse-free survival (RFS) rates were 92% and 82%, respectively. This was contrasted with our previous experience from 1963 to 1973, when our treatment policy was to undertake staging laparotomy and to treat patients with pathologic stage (PS) 1–3A with EF RT alone, and to reserve bimodal treatment with a variety of chemotherapies for PS 3B–4. These 'nonstudy' patients had 5-year SR and RFS rates of 92% and 58%. Details of the chemotherapy and radiation treatment programs have been given previously [1].

We now update this experience and demonstrate the durability of the

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Table 1. Clinical stage distribution for study and nonstudy patients.

	Study patients		Non-study patients	
CS	No.	(%)	No.	(%)
1	15	(26)	8	(15)
2	22	(39)	31	(59)
3	5	(9)	11	(21)
4	18	(26)	3	(6)
Total	57		53	

treatment results and examine the steadily increasing cost in relation to late toxicity.

1. Patient data base

From 1969 to 1979, 110 consecutive previously untreated children 16 years old or younger were registered at either the Hospital for Sick Children (HSC) or the Princess Margaret Hospital (PMH), Toronto. Since PMH was the only regional radiation treatment facility, we believe these to be unselected patients from the metropolitan Toronto region with a population base of ~3.5 million. Most of these patients were treated by the pediatric hematology/oncology team, but a proportion of children 14–16 years old were referred to the adult lymphoma team at the PMH from adult hospitals in the region.

The patient data were reviewed in December 1986. Follow-up intervals ranged 7–17 years.

From 1973 to 1979, 57 study patients were treated, initially either with MOPP and low-dose EF RT (45 patients) or IF RT alone (12 patients, favorable CS 1).

From 1969 to 1979, 53 nonstudy patients were treated (43 from 1960 to 1972 and ten from 1973 to 1979). Those patients in PS 1–3A received EF RT alone as the first treatment with combination chemotherapy being reserved for subsequent relapse. Patients in PS 3B–4 were treated with a variety of combinations of EF RT and chemotherapy. The majority of individual chemotherapy regimens used first, particularly in the earlier years, would now be regarded as ones yielding only a small chance for cure.

The clinical stage distribution for these two groups of patients is presented in Table 1. These stage distributions were not the same. The study patients were more likely to be in CS 3B–4, 30% *vs* 12%, or CS 1, 26% *vs* 15%. Because the intensity of investigation of Hodgkin's disease has increased over the years, the decreased proportion of nonstudy patients classified as having advanced disease may be partly or completely spurious. There is some suggestion of this in that the proportion of study patients with

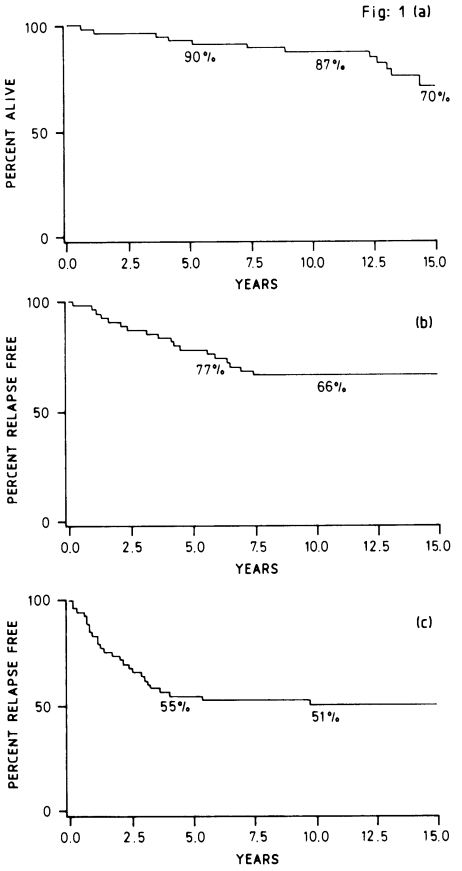

Figure 1. Nonstudy patients (all stages, n=53): (*A*) survival, (*B*) survival free of a second relapse, and (*C*) relapse-free survival.

B symptoms, 27%, was not significantly different from that of nonstudy patients, 31%.

2. Results

2.1. Nonstudy patients (n=*53)*

The overall 5-year SR, free of second relapse (2 RFS), and RFS rates were 92%, 77%, and 55% and, at 10 years, 87%, 66%, and 51% respectively (Figure 1). For CS 2+3 (n=42), the 5-year rates were SR 90%, 2 RFS 74%, and RFS 50%. Two of the three patients in CS 4 remained alive relapse free and one died of progressive disease.

The overall survival rate included death from disease and toxicity. No incidental deaths from other causes occurred in this series. Patients who

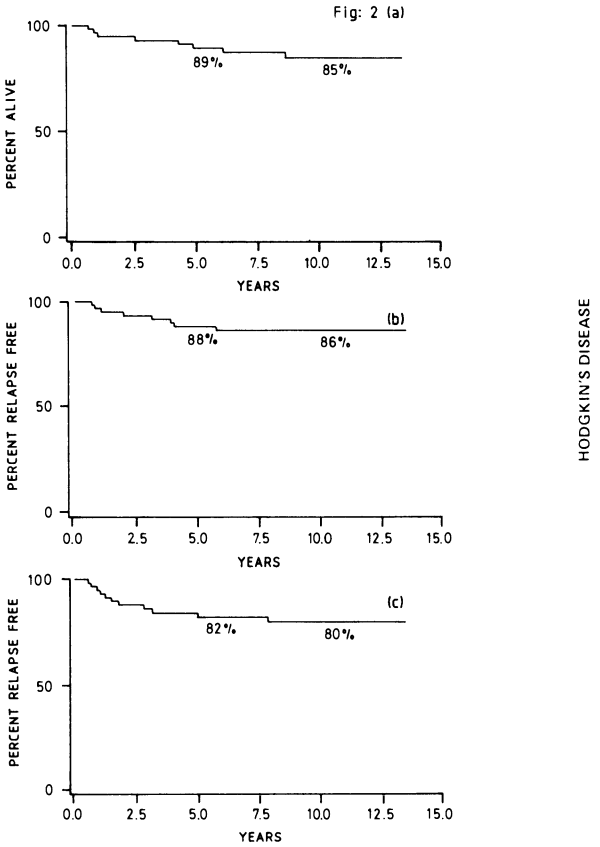

Figure 2. Study patients (all stages, n=57): (*A*) survival, (*B*) survival free of a second relapse, and (*C*) relapse-free survival.

died of toxicity are counted as an adverse event in the relapse-free data at the time of death.

2.2. *Study patients* (n=57)

For all stages combined, 5-year SR was 89%, 2 RFS 88%, and RFS 82% and, at 10 years, 85%, 86%, and 80%, respectively (Figure 2). For CS 2+3 (n=27), 5-year SR was 93%, 2 RFS 93%, and RFS 89%. For CS 4 (n=15), 5-year SR was 80% and RFS 60%.

2.3. *Clinical stage I*

In the study group, three of 15 CS 1 patients were treated bimodally, that is, as if they were in CS 2, because of unusual extent of involvement of a single region. All other patients and the eight CS 1 patients in the nonstudy group were initially treated with RT along. Because of the small numbers and

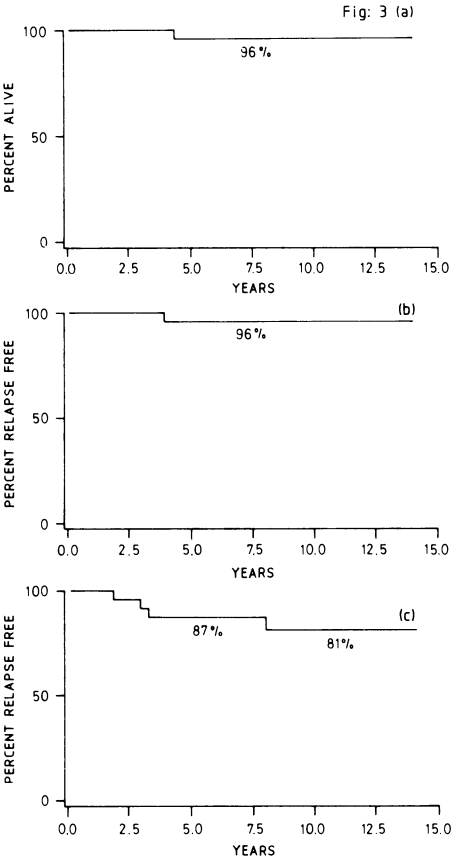

Figure 3. Clinical stage 1 (all study and nonstudy patients, $n=23$): (*A*) survival, (*B*) survival free of a second relapse, and (*C*) relapse-free survival.

minor differences in radiation treatment and methodology, these are analyzed as a single group. Five-year SR was 96%, 2 RFS 96%, and RFS 87% (Figure 3). None of the three patients treated bimodally relapsed. A subgroup of 17 patients were treated with IF RT alone, defined either as irradiation of a single region or of the mantle. The 5-year SR was 94%, 2 RFS 94%, and RFS 82%. The one patient who died of Hodgkin's disease had a first relapse that included gross bone involvement and the disease had an acute course. This patient was the only one of the four patients who relapsed who was not salvaged and apparently cured by the second treatment.

3. Toxicity

Most of our patients have continued in follow-up in the Toronto region. The early and late unusual toxicities that may be elicited by chart review are

Table 2. Distribution of toxic events between study and nonstudy patients (OPSI overwhelming postsplenectomy infection).

	Study		Non-study	
Toxic event	Episodes	Fatal	Episodes	Fatal
Second malignant tumor	4	1	3	3
Thyroid adenoma	1		4	
Severe viral infection	5	2	2	2
Ovarian failure	1		4	
Slipped femoral epiphysis	1			
Gynecomastia	1			
Hypothyroidism	1			
OPSI	1		1	
Small bowel obstruction			1	
Pneumonectomy			1	
Herpes zoster	4		4	
Total	19	3	20	5

listed in Table 2. Excluded are the normal acute toxicities of combination chemotherapy, including bacterial infection and the acute toxicity of RT. Also excluded is the delayed growth effect of RT. No patient in this series has a significant functional disability as a consequence of a growth defect due to RT. We believe our incidence of herpes zoster is significantly underreported.

The most important toxicity seen in this series related to second tumor induction and severe viral infection. Eight toxic deaths were related to one or other of these complications and one additional toxic death from bacterial pneumonia occurred during a fourth complete remission.

4. Second malignant tumors

4.1. Acute leukemia

Three nonstudy patients died as a consequence of induction of acute nonlymphocytic leukemia (ANLL). All three patients had received intensive sequential treatment for relapse and all died during complete remission of their Hodgkin's disease: two after two relapses and one after one relapse of Hodgkin's disease.

- *Case 1 CS 3A.* Primary treatment EF RT. Lung relapse at 7 months, vinblastine (VLB) maintained for 35 months. Second relapse at 77 months, MOPP × 7. ANLL at 120 months.
- *Case 2 CS 3A.* Primary treatment EF RT. First relapse (bone) at 1 month during EF RT. VLB + chlorambucil maintained. Second relapse at 37

months, MOPP × 8 with chlorambucil maintenance. ANLL at 106 months.
- *Case 3 CS 2A.* Primary treatment EF RT. First relapse at 9 months (bone). MOPP × 10 with chlorambucil maintenance + IF RT. ANLL at 49 months.

Clearly both unusually intensive leukemogenic chemotherapy and ER FT was given to all these patients. At 15 years, the actuarial incidence of acute leukemia was 6%.

4.2. Non-Hodgkin's lymphoma

One CS 4B study patient with nodular-sclerosing Hodgkin's disease was treated with MOPP and EF RT. A first relapse at 7 months was with non-Hodgkin's lymphoma that was not subsequently controlled. This patient suffered from a partial immune defect. The histology of both the Hodgkin's disease and non-Hodgkin's lymphoma was classic.

4.3. Thyroid carcinoma

Follicular thyroid carcinoma occurred in two study patients during their first complete remission.
- *Case 1 CS 4B.* MOPP + EF RT. Thyroid carcinoma at 7 years.
- *Case 2 CS 2A.* MOPP + EF RT. Thyroid carcinoma at 10 years.

Both patients were treated surgically and remained in continuing complete remission of both their Hodgkin's disease and thyroid carcinoma.

4.4. Basal cell carcinoma

A CS 2A study patient treated with EF RT and MOPP developed a small basal cell carcinoma in the skin overlying the scapula during the first complete remission at 11 years. The lesion was excised.

The second malignant tumors in this series occurred at 7 months and 4, 7, 9, 10, 10, and 11 years from diagnosis.

5. Benign tumors: thyroid adenomata

Five patients developed thyroid adenomata at 8, 9, 9, 11, and 13 years from diagnosis. Four of these patients have been treated surgically and one patient has refused resection. Four patients were in the nonstudy group. In one patient, thyroid adenomata occurred in a first remission, in two patients in a second remission, and in two patients in a third remission.

None of these patients developed thyroid cancer and, conversely, our two patients with thyroid cancer were not known to have benign adenomata previously. All had undergone neck irradiation. The actuarial incidence of

thyroid neoplasms, benign or malignant, at 5, 10, and 15 years was 0%, 7%, and 12%, respectively.

6. Severe viral infections

Seven patients, five study and two nonstudy, developed severe viral infection and four of these patients died. All had received MOPP therapy either as a first treatment or for relapse. Six patients developed this complication during or within 6 months of MOPP therapy; the infection was fatal (chicken pox, pneumonia [probably rubeola] and encephalitis) in three of these patients and was nonfatal (hepatitis, hepatitis B, and disseminated herpes zoster) in three. In one patient, viral infection was delayed (a fatal viral myocarditis during first remission at 43 months). Overwhelming viral infection was not seen in our patients treated with EF RT alone, and it is assumed to be a complication of the specific immunosuppression associated with MOPP therapy. The viral deaths occurred at 7, 12, 13 and 43 months from diagnosis.

7. Other toxictty

Ovarian failure will always occur after ovarian irradiation in Hodgkin's disease. Radiation was not administered to the pelvis in any girl in CS 2+3 in our study group. Fortunately, pelvic node involvement in pediatric Hodgkin's disease is uncommon, except for the occasional patient who develops the disease in the inguinal nodes.

The patient who developed a slipped femoral epiphysis had received radiation for CS 1 disease in the inguinal region. In Toronto, gynecomastia is a rare complication of MOPP therapy. Two patients developed overwhelming postsplenectomy infection (pneumococcal and meningococcal). The episode of small bowel obstruction, which required surgical correction, was attributed to a previous staging laparotomy. The total omission of staging laparotomy from our patients would have prevented three episodes of life-threatening toxicity. The patient who underwent pneumonectomy had been treated for recurrent bronchial disease with relatively high-dose large-volume radiation and developed symptomatic pulmonary fibrosis.

8. Relapse toxicity

The survival hazard associated with the occurrence of a first or second relapse of Hodgkin's disease is crucial information in determining the appropriate intensity of the first treatment.

Of fifty-three nonstudy patients, 24 (45%) have relapsed. The 5- and

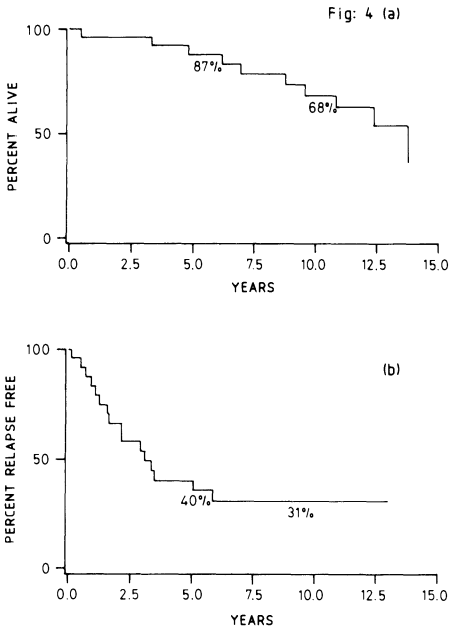

Figure 4. Nonstudy patients (n=24): (A) survival and (B) relapse-free survival measured from the day of first relapse.

10-year SR and RFS for these 24 patients measured from the day of first relapse were 87% and 68%, and 40% and 31%, respectively (Figure 4). To date, of the 24 patients with a first relapse, 15 have had a second relapse and one patient has died of ANLL in the second remission. Of the 15 patients with a second relapse, seven are currently alive, two after multiple additional relapses and five without further relapse. Two patients died during the third complete remission of ANLL and six died of progressive disease. In retrospect, these patients may not have been treated optimally for relapse, but did receive MOPP or ABVD at some time. Thus, the death hazard associated with relapse or toxicity in these patients is unlikely to be <50%. In addition, there is substantial cumulative toxicity from repetitive treatment for relapse.

In contrast, nine (18%) of 57 study patients have relapsed. The 5-year SR and RFS for these nine patients measured from the day of first relapse are 44% and 33%, respectively (Figure 5). Six of nine patients with a first relapse have had a second relapse and all six have died of progressive diease. Of the three patients who survived relapse, one was in CS 1 and was initially treated by IF RT alone, but relapsed at 5 years and was treated with MOPP + EF RT and survived 5 years later; one patient in CS 2A developed a single nodal site of relapse at 21 months, was treated with IF RT, and is alive 10 years later; and the third patient in CS 4B relapsed at 11 months, was treated with ABVD alone, and is alive, relapse free, 8 years later.

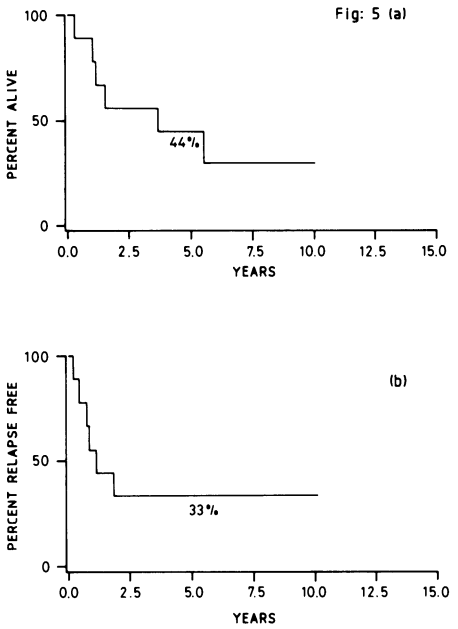

Figure 5. Study patients (n=9): (A) survival and (B) relapse-free survival measured from the day of first relapse.

9. Conclusions

We conclude that initial bimodal treatment of patients with CS 2–3 Hodgkin's disease is associated with a survival advantage compared with initial EF RT for patients in CS 2–3A, and that the significant morbidity and mortality associated with these treatments is comparable during the first decade following diagnosis. Clearly the thrust of future investigation must be to maintain the excellent treatment results in CS 1–3 while reducing treatment morbidity and in CS 4 to further improve treatment effectiveness.

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19. The Pediatric Oncology Group
Studies in Hodgkin's Disease

Brigid G. Leventhal

1. The Pediatric Oncology Group

In 1979, the Pediatric Division of the Southwest Oncology Group expanded greatly when almost all of the institutions whose pediatricians had participated in the activities of Cancer and Leukemia Group B joined them. In 1980, the Pediatric Division of the Southwest Oncology Group (SWOG) elected to separate from the parent organization and establish the Pediatric Oncology Group (POG). Several new institutions have joined the Group since then so that, in 1984 [1], the POG consisted of >65 participating institutions (member, affiliate, *etc.*) from many geographic areas of the United States as well as some areas outside of the United States. Members of the group have expertise in all modalities of therapy and broad expertise in the biologic sciences. This chapter describes some activities of the pediatric groups that joined to form the POG as well as of the Group itself. Because the Group is relatively new, many of these studies are not mature.

2. Stage I and II of Hodgkin's disease

2.1. Intergroup Hodgkin's disease study [2]

All of the major pediatric oncology study groups joined together to conduct a randomized study of the management of early-stage Hodgkin's disease in 1975. This protocol involved a randomization by one group of institutions to involved-field radiotherapy (IF) *versus* involved-field plus six courses of MOPP (nitrogen mustard, Oncovin [vincristine], procarbazine, and prednisone) (IF + MOPP), and by two other groups of institutions to extended-field radiotherapy (EF) *versus* involved-field plus six courses of MOPP. Thus, it was a three-armed study with two experimental and one common control arm.

Broadly speaking, the purpose of the study was to define the minimum effective therapy for this group of patients. It was already known that a certain fraction of patients would be cured with radiation therapy alone, and

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there was interest in determining whether that fraction would be greater with EF than with IF treatment. It was suspected that a greater fraction would be cured if chemotherapy was given as simultaneous front-line therapy, but the high salvage rate of patients who relapse after radiotherapy [3] had made investigators wonder whether, for a patient population as a whole, the overall survival rate might not be just as good if some patients were allowed to relapse after radiation and then be salvaged, thereby sparing significant numbers of patients the acute and late toxicities of chemotherapy. The specific objectives then were to compare the initial disease-free and overall survival in the three treatment groups, to evaluate retrievability after first relapse and to compare the incidence and severity of late effects in the three groups.

At the time of the preliminary report [2], 305 patients had been entered into the study. The details of the treatment regimen are available in the report. In terms of length of initial disease control, the best regimen, as expected, was IF + MOPP, with 95% of the 118 patients assigned to this arm project to be in remission at 4 years ($p = 0.002$ *vs* IF alone). Patients receiving EF tended to have a longer disease-free interval than those receiving IF ($p = 0.004$), but the proportion still disease free in each group was projected to be ~40% by 4 years. This figure was much lower than the results reported from single institutions in children with stage I and II Hodgkin's disease treated with radiation alone where 70%–80% of patients are disease free after 5 years. The overall survival data on this study has not been updated recently, so that, although at the time of the preliminary report only eight of 279 patients had died, it has not been possible to assess the effect of the 'rescue' strategy on overall survival.

Despite the Intergroup Study, then, the debate continues as to whether it is a better strategy to give patients radiotherapy first and then allow them to relapse with later chemotherapy rescue, thereby avoiding the toxicity of chemotherapy in a certain percentage of patients, or whether this will result in the developent of resistant tumors as well as higher toxicity in some of the patients who will either fail to be rescued or suffer a higher incidence of certain toxicities such as growth inhibition or induction of second malignancies [3–6]. All investigators agree that the principal objective remains the development of minimal curative therapy for children with this disease.

2.2. Current POG studies in early-stage Hodgkin's disease: POG 8625

The POG has elected to investigate whether low-dose IF radiotherapy, when combined with chemotherapy, produces better long-term results than chemotherapy alone in this group of patients. The complete-remission rate for patients with early-stage disease treated with chemotherapy alone is not known. In adults, chemotherapy alone has produced results comparable to combined-modality therapy [7, 8]. Seven of seven children treated in Uganda [9] with six courses of MOPP were in CCR at 5 years and, in other small

series [10, 11], nine of nine and ten of ten patients with early-stage disease achieved durable complete remission after treatment with six courses of MOPP alone. ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) is a chemotherapy combination reported to be equieffective with MOPP in advanced disease and non-cross-resistant [12]. Patients with advanced disease treated with 1 year of alternating MOPP–ABVD have been reported to have a 90% cure rate [13]. The ability to substitute ABVD for MOPP might well lead to a lower incidence of sterility in male patients since a 50% sterility rate has been reported after three courses, which rises to 100% in adults after six courses [14]. Thus, to achieve curative doses of combination therapy with reduced doses of each individual agent, alternating MOPP–ABVD was chosen as the chemotherapy for this protocol. The radiotherapy dose is 2500 rad to involved areas. This dose is based on the work of Donaldson [6], who found that, at this dose, there was excellent disease control with less marked abnormalities in bone growth and no incidence of pulmonary reactions when compared with the standard dose.

Patients entered on this protocol are pathologically staged. All patients receive four courses of chemotherapy—*i.e.*, MOPP, ABVD, MOPP, and ABVD—and are then restaged to determine whether they are in complete remission. If complete remission has been achieved, they are then randomized to receive either another MOPP–ABVD or 2550 cGy IF radiation. This study was activated in 1986 and is still actively accruing patients. The specific objectives of the protocol are to compare the effectiveness of chemotherapy alone with chemotherapy plus low-dose IF radiation in terms of disease-free and overall survival, and to assess the acute and chronic toxicities of these two forms of therapy. There are no reported long-term studies of MOPP/ABVD in children, and careful follow-up of these patients is essential to assure that we are not substituting late treatment-induced morbidity (*e.g.*, perhaps pulmonary dysfunction) for short-term disease control.

3. Advanced-stage Hodgkin's disease

3.1. POG 7612

Under the direction of Dr. M. Sullivan, the POG conducted a study in stage III Hodgkin's disease comparing low-dose B-MOPP (bleomycin + MOPP) with A-COPP (Adriamycin + cyclophosphamide + OPP) with both groups of patients receiving sandwich radiotherapy (M. Sullivan, personal communication). This study was an attempt to dissect out the original observations made by the SWOG showing that bleomycin added to MOPP in the treatment of adults with advanced-stage Hodgkin's disease increased the complete remission rate [15] and that adriamycin increased the effectiveness of this combination even further [16]. This childhood study is currently in

preparation for publication. All such studies with modest variations of the MOPP regimen in adults have recently been summarized and felt to show no essential difference in results from those achieved with MOPP alone [17].

3.2. Current POG study for advanced disease: POG 8725

The current protocol for advanced-stage disease in the POG is similar to that in early-stage disease and asks whether the addition of low-dose total nodal radiation therapy to combination chemotherapy will improve the duration of complete remission and survival when compared with combination chemotherapy alone. All patients receive eight courses of chemotherapy: MOPP/ABVD, MOPP/ABVD, MOPP/ABVD, and MOPP/ABVD. If they are in complete remission at the end of that time, they are then randomized to receive either no further therapy or low-dose total nodal irradiation. Because it is conceivable that radiotherapy is of greatest benefit in patients with bulk disease or possibly with nodular sclerosing histology [7], patients are stratified for the presence or absence of large mediastinal mass or other bulky disease.

This protocol was based on promising pilot data reported in 20 patients with advanced disease treated with similar chemotherapy, all of whom achieved complete remission that had lasted a median of 20 months at the time of the report [18]. Although total nodal radiation has been deemed extremely effective therapy in disseminated disease [4], there was concern that this radiation would not be tolerated by patients who had been pretreated with this amount of chemotherapy [19]. The first study that was mounted (POG 8426), therefore, was a feasibility pilot in which all patients received eight courses of combination chemotherapy followed by low-dose total nodal irradiation (2100 rad to all lymphoid tissues, including the spleen). Nonlymphoid organs would be irradiated if involved. The results of this pilot study are being analyzed, and it is hoped that the randomized study can soon be undertaken.

4. Studies in relapsed Hodgkin's disease

Because it is anticipated that most patients will have received MOPP, ABVD, and radiation therapy in some order as standard initial therapy, it seemed important to attempt to devise a combination for salvage therapy of such patients that included agents with single-agent activity that were not cross-resistant with the agents included in these combinations. Preliminary data have suggested that a combinationof cytosar, cisplatin, and etoposide is quite effective. In the initial analysis of this regimen, six of eight patients with recurrent disease achieved a complete remission for a median of 9+ months [20]. In view of this promising early data, a formal protocol is being drafted to evaluate this regimen further. Since the POG has a number of

institutions that can perform autologous bone marrow transplantation, the prospect of eventually intensifying such therapy and using autologous marrow rescue is an attractive one.

Acknowledgment

This work was supported by grant CA 28476.

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20. Current practice in Hodgkin's disease
The United Kingdom Children's Cancer Study Group

John Martin and Martin Radford

The United Kingdom Children's Cancer Study Group (UKCCSG) is the principal organizer for studies in malignant disease in childhood in the British Isles. The group initially undertook a retrospective study of children with Hodgkin's disease in the United Kingdom and, after discussion of the data obtained, the UKCCSG Hodgkin's study protocol was agreed upon and introduced in January 1982.

1. Objectives of study

1. To establish a uniform practice for management of Hodgkin's disease in the British Isles.
2. To establish whether children can be safely managed without staging laparotomy and splenectomy.
3. To establish whether the combination of chlorambucil, vinblastine, procarbazine, and prednisone (CLVPP) is an effective alternative form of chemotherapy to the combination of mustine, vincristine, procarbazine, and prednisone (MOPP).
4. To document prospectively the long-term side effects of the management, especially on growth and subsequent fertility.

Staging laparotomy and splenectomy have usually been used to confirm the extent of the disease. We were concerned with the dangers of serious and sometimes fatal bacterial infection that may occur in children who have had a splenectomy, and especially if they also receive chemotherapy [1, 2]. The development of newer scanning techniques led us to the decision to investigate children as fully as possible using these methods and not to undertake laparotomy and splenectomy.

The standard approach to the treatment of Hodgkin's disease has been to use radiation therapy for localized disease and combination chemotherapy, with or without radiation therapy, for generalized disease. Good results have been obtained by these methods [3]. However, complications of treatment and the risk of second malignant disease, especially in children who receive bimodal therapy, led us to decide to use less treatment and a

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single modality treatment whenever possible. In the best group of patients (stage IA), we decided to use local involved-field radiation only. This avoids the risk of subsequent infertility due to alkylating agents. It is acknowledged that there would be a small number of children who would relapse, but it is known that such children should have an excellent response to subsequent chemotherapy.

2. Methods

Eligibility for the study is all children <15 years of age with biopsy-proven Hodgkin's disease. To avoid selection, all participating centers have to notify all children <15 years of age with Hodgkin's disease, and give reasons for any children who are not entered into the study.

2.1. Investigations

The initial investigations were undertaken as indicated below:

- Hemoglobin
- White cell count with differential
- Platelet count
- Erythrocyte sedimentation rate
- Bone marrow aspiration and biopsy (if hemogram abnormal in clinical stage III or IV)
- Immunoglobulins
- Liver function tests (bilirubin, alkaline phosphatase,and enzymes)
- Viral antibody screen
- Chest x-ray (if abnormal for tomograms or computerized tomography (CT) scan)
- Abdominal ultrasound examination
- Lymphangiogram
- Abdominal CT scan

} two of three must be performed

- Biopsy of involved node (S)
- Liver biopsy (if involvement suspected)

The previous retrospective study indicated that bone marrow aspiration and biopsy was invariably normal in clinical stage I and II disease, and therefore necessary only in stage III and IV disease where the hemogram is abnormal.

Lymphangiography, especially in small children, was not available in all centers and, at the time the study commenced, not all centers had access to whole body CT scanning. All patients were to have minimal investigations for abdominal disease of two of three from lymphangiography, abdominal ultrasound examination, and abdominal CT scanning.

Histology was examined at local centers and is being reviewed centrally.

The longitudinal endocrine and growth studies, listed below, are an important part of the protocol:

- Initial: height and weight; pubertal status and bone age (Greulich and Pyle)
- Follow-up: at 3- to 6-month intervals
  - Regular height and weight
  - Regular pubertal assessment using Tanner's scales
  - In males, regular assessment of testicular size using Prader orchidometer and note presence or absence of gynaecomastia
  - If puberty fails to progress normally, perform follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone or estrodiol tests
  - Where patient received neck irradiation for thyroxine and TSH
- Postpuberty and when treatment completed
  - Males
    - Sperm counts × 2
    - Plasma testosterone
    - Serum FSH and LH
  - Females
    - With regular menses, plasma progesterone on day 21 of cycle
    - With amenorrhea, serum FSH and LH, and oestrodiol and progesterone levels
- Repeat assessment where azoospermia or amenorrhea is present

The studies were designed in collaboration with the Endocrine Department at the Christie Hospital (Dr. S. Shallet) and kept to an acceptable minimum to aid investigation and patient compliance.

2.2. Treatment

2.2.1. Stage IA. These children are treated with involved-field radiotherapy, 35 Gy in 20 fractions over 4 weeks. The majority of these patients have cervical disease and, for reasons of subsequent symmetry of growth, both sides of the neck are treated with anterior and posterior opposing fields extending from the mastoid processes to just below the clavicle. The larynx is shielded anteriorly and the cervical spine by a posterior strip.

2.2.2. All other stages. Except those with a large mediastinal mass, all other stages are treated with chemotherapy alone using CLVPP:

- Chlorambucil: 6 mg/m^2 orally for 14 days
- Vinblastine: 6 mg/m^2 intravenously on days 1 and 8
- Procarbazine: 100 mg/m^2 orally for 14 days
- Prednisolone: 40 mg/m^2 orally for 14 days
- Minimum 28-day interval first day of each course

Treatment consists of the number of courses to achieve clinical remission, plus four further courses—a minimum of six or a maximum of eight courses

are given. Nonresponders by the end of three courses, or where there is evidence of progressive disease, fail the study and are changed to alternative therapy at the discretion of the local clinician.

2.2.3. Children with a large mediastinal mass. This is defined in the study as a mass greater than one-third of the transverse thoracic diameter at the level of the mass. In these patients, chemotherapy is given as above, but is followed by radiotherapy to the mediastinum to the original volume of mediastinal disease. Anterior and posterior longitudinal fields are used extending from the suprasternal notch to the level of the tenth thoracic vertebra. The thoracic spine may be shielded on the posterior field after a dose of 20 Gy has been given. A calculated dose of 35 Gy is given to the midplane over a 4-week period.

2.3. Follow-up

All children are under continuous observation at one of the registered treatment centers. Any major event, *e.g.*, relapse, is reported to the trial coordinators. Regular follow-up forms are completed, initially at 6 monthly intervals, but currently once per year.

3. Results: current situation

As of June 1986, *i.e.*, 4½ years from commencement of study, 167 children had been entered from 18 centers. Numbers registered per center varied from two to 19. There were 119 boys (71.3% of the total) and 48 girls (28.7%). The youngest registered child was 2 years of age at diagnosis and a peak was seen at 12 years. It is probable that, while most younger children are seen in the pediatric oncology centers involved in the study, a number of older children are treated in adult units. Therefore, older children are probably under-represented in our series.

Currently, staging information is available on 152 children (see Table 1).

A preliminary analysis has been completed for children entered into the study from January 1982 through January 1984, *i.e.*, with a minimum follow-up of 20 months.

3.1. Stage I

A total of 20 children were entered in this period. They consist of 18 boys and two girls with an age range of 4–14 years (mean, 9 years): 15 presented with enlarged cervical lymph nodes and the remaining children with nodes in the axilla or supraclavicular fossa and a single inguinal node presentation. None had 'B' symptoms. Histology was lymphocyte predominant in ten

Table 1. Staging information on 152 children

	n	Total	Percentage
Stage I			
All IA		44	27.8
Stage II			
IIA	37	49	32.9
IIB	12		
Stage III			
IIIA	24	39	25.3
IIIB	15		
Stage IV			
IVA	7	20	13.9
IVB	13		

patients, mixed cellularity in five, nodular sclerosing in three, and unclassified in two patients.

Of these 20 children, 17 remain disease free and the three remaining patients are alive after relapse and subsequent treatment with chemotherapy. There have been no deaths in this group. Of the three relapses, two were localized cervical relapses, one within and one at the edge of the original radiation field. Both of these children (boys aged 9 and 11) had lymphocyte-predominant histology and remained stage I at relapse. The third relapse was in a boy aged 11 who presented with cervical nodes. He was also lymphocyte predominant. Two years following diagnosis, he relapsed with multisystem disease involving nodes, lungs, and mediastinum. Repeat biopsy showed histology still to be of the lymphocyte-predominant type. He has been retreated with chemotherapy.

Thus, the majority of stage I patients remain well after local treatment only. The three relapsed patients all responded well to retreatment with chemotherapy using CLVPP. Analysis of the relapsed children shows no set pattern and could not have been predicted.

Five further children, all registered from one center, were pathologically staged. Their investigations included laparotomy and splenectomy. All were of nodular-sclerosing histologic type. Four of these children remain well, with no recurrence. One, a girl aged 12, who presented with supraclavicular fossa nodes, relapsed with a solitary pulmonary nodule. Histologic confirmation was not obtained. She responded well to chemotherapy (CLVPP), and remains well and disease free.

3.2. Stage II

A total of 25 children were entered in this period: 12 boys and 13 girls. Of the 25 patients, 21 presented with cervical and/or supraclavicular nodes, and three of the four remaining patients had axillary nodes; 14 had nodular

sclerosing, nine had mixed cellularity, and two had lymphocyte-predominant histology. All patients received chemotherapy with CLVPP.

After follow-up of 30–54 months, 18 remain alive and have had no recurrence of disease, and the remaining seven are alive after relapse. There are no deaths. Six relapses occurred in 14 patients with a mediastinal mass and only one in 11 patients without. Of the relapsed patients, two had relapses after chemotherapy and radiation therapy 16 and 13 months from diagnosis. The remaining five either relapsed while receiving chemotherapy or were considered nonresponders by local investigators.

3.3. Stage III

A total of 25 children entered were stage III, of whom 21 were boys and four were girls. Of the 25 patients, 22 presented with cervical or supraclavicular nodes, two with inguinal nodes, and one in the axilla. Histology was mixed cellularity in 13 children, nodular sclerosing in nine, lymphocyte predominant in two, and unclassified in one patient.

Of the 25 patients, 18 remained disease free at the time of analysis. Three were alive after relapse and treatment with alternative chemotherapy. Two children were judged nonresponders to CLVPP, but remain alive after different chemotherapy. Two children with stage III disease have died of infection, one of septicemia after course 2 and one of measles giant-cell pneumonia after seven courses. Preliminary analysis suggests that those children going into clinical remission after one or two courses of CLVPP predominantly remain well, while those requiring more courses to achieve clinical remission have a less favorable outcome.

3.4. Stage IV

A total of 15 children entered were of this stage: eight were boys and seven were girls. Of the 15 patients, nine had nodular-sclerosing histology, three mixed-cellularity, and one each of lymphocyte-predominant, lymphocyte-depleted, and unspecified types. Of the 15 children, ten remain alive and well with no recurrence of disease. Three children are alive following relapse and two children have died, one of disease and the other of infection. In this stage also, patients who responded rapidly to CLVPP remain well while slow responders have a poorer prognosis.

4. Preliminary conclusions

Preliminary analysis of the first 90 patients with a minimal follow-up period of 30 months shows that clinical stage I patients treated with only involved-field radiation are doing well. The three stage I recurrences all responded well to chemotherapy. Stage II patients, especially with mediastinal mass,

are doing less well. Stage III and IV children who responded rapidly to chemotherapy with CLVPP are remaining well with a very low recurrence rate. Those with a slower clinical response appear to have a less good prognosis. Analysis of further patients may confirm this trend. If so, an earlier change to alternative chemotherapy would appear to be indicated.

This study continues with a steady accrual of patients. Further detailed analyses of larger cohorts will become available.

Acknowledgment

The United Kingdom Children's Cancer Study Group is supported by the Cancer Research Campaign.

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21. Results of therapy for Hodgkin's disease in chilhood

The Argentine Group for Treatment of Acute Leukemia

Federico Sackmann-Muriel, Mabel Maschio, Maria Teresa Santarelli, and Santiago Pavlovsky

In Argentina, no studies had been organized to evaluate the results of therapy on Hodgkin's disease in childhood before the Argentine Group for Treatment of Acute Leukemia (GATLA) was created. As an historical comparison, we have an early evaluation of two series diagnosed and followed at the Children's Hospital of Buenos Aires. The first one, from 1940 to 1966, included 43 children. Minimal investigations were performed during this period, consisting primarily of physical examination, chest x-ray, and hemogram. Low-dose (<2500 rad) localized radiotherapy from an orthovoltage unit was the usual treatment. Some children also received single-agent chemotherapy, mainly cyclophosphamide or vinblastine. Ten (23%) out of these 43 children are alive disease free with a median follow-up of 25 years, with a range of 20–41 years. The second one, from 1967 to 1972, included 35 children. All the patients during these periods had lymphangiography and laparotomy with splenectomy and multiple biopsies performed to determine stage. Higher dosage of extended radiotherapy (3000–4000 rad) delivered by an orthovoltage unit followed by a multidrug chemotherapy—mainly COPP (cyclophosphamide, Oncovin [vincristine], procarbazine, and prednisone) or MOPP (nitrogen mustard, Oncovin, procarbazine, and prednisone) were used but without any prospectively designed protocol. Of these 35 children, 15 (43%) are alive disease free with a median follow-up of 16 years, with a range of 14–19 years [1, 2].

In this chapter, we summarize the results of therapy of a total of 254 children <16 years of age with histologically proven Hodgkin's disease. They were registered in three consecutive studies undertaken by the GATLA from November 1972 to December 1985, and evaluated up to December 1986 (Table 1).

The first protocol for treatment by the GATLA of Hodgkin's disease in childhood started in November 1972 with the purpose of exploring new combinations of chemotherapy that would be less toxic and easier to manage. A randomized, controlled study was designed to compare differences in efficacy using six courses of cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP) *versus* the same drugs plus CCNU (CCVPP). Dosage in every monthly cycle were: cyclophosphamide 600 mg/m^2 i.v. and

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Table 1. Percent of complete remission (CR), disease-free survival (DFS), and survival (SV) rate at 60 months according to clinical stages and protocol of treatment.

Stage	Year	Treatment[a]	No. pts	%CR	%DFS	%SV
I–IIA	1972–77	RT + CVPP (m)	7	100	100	100
	1972–77	RT + CCVPP (m)	5	60	60	100
	1978–86	CVPP + RT + CVPP	41	97	73	97
	1978–86	CVPP	54	96	79	100
I–IIB	1972–77	CVPP + m	15	87	79	100
IIIA	1972–77	CCVPP + m	8	62	69	75
	1978–86	CVPP + RT + CVPP	18	100	88	100
	1978–86	CVPP	28	93	27	91
IIIB	1972–77	CVPP + m	22	73	36	88
IVA–B	1972–77	CCVPP + m	16	56	33	83
	1978–79	CVPP + RT + CVPP	7	43	33	70
	1978–79	CVPP	7	43	33	38
	1979–84	ACOP–VBP	26	73	43	82

[a]m, maintenance with the same regimen used during induction for 3 years; and (m), chemotherapy is used only as maintenance.

vinblastine 6 mg/m^2 i.v. on day 1, procarbazine 100 mg/m^2/day orally, and prednisone 40 mg/m^2/day orally on days 1–14. The CCVPP group received also CCNU 75 mg/m^2 on day 1 in alternate cycles.

Children with clinical stage I or IIA received radiotherapy (4000 rad) to involved areas as induction treatment and were subsequently randomized to receive maintenance therapy. Children in all other stages received only combination chemotherapy as induction therapy, at random. Maintenance therapy consisted of one cycle of either CVPP or CCVPP every 2 months during the first year, every 4 months during the second year, and every 6 months during the third year. Patient data have been published in detail [2, 3]. It is necessary to point out that all of this studies are part of a larger clinical trial that included adults, whose results are not included here.

A total of 73 children under the age of 16 years were entered into this study between November 1972 to August 1977 at nine participating institutions. Median age was 8 years with a range of 2–15 years. The male–female patient ratio was 2.32:1. Children were clinically staged. Though some children had staging laparotomy, this was not a requisite for the protocol, but bipedal lymphangiography was performed in all the patients.

Overall complete remission rate of this study was 73% (53 of 73 children). The 10-year actuarial curves of disease-free survival and survival were 49% and 74%, respectively.

Complete remission was achieved in ten (83%) out of 12 children in stages I–IIA. The 10-year actuarial curves of disease-free survival and survival were 80% and 100%, respectively. There is no difference between the CVPP- and CCVPP-maintained groups.

Analysis of all other cases—that is, stages I–IIB, IIIA–B, and IV, who

received only combination chemotherapy as induction—is as follows: complete remission was obtained in 26 (74%) of 35 children receiving the CVPP regimen as induction and in 14 (58%) of 24 children receiving the CCVPP as induction (p=NS).

The 10-year actuarial curves of disease-free survival and survival of 35 children randomized to receive CVPP were 44% and 69%, respectively. On the other hand, the 10-year actuarial curves of disease-free survival and survival of the 24 CCVPP-treated group of children were 42% and 69%, respectively (p=NS).

We concluded from this study that the addition of CCNU to the CVPP regimen showed that this combination neither increases the percentage of complete remissions nor prolongs disease-free survival or survival of children with Hodgkin's disease. Moreover, we have showed that the CCVPP regimen is associated with more hematologic, gastrointestinal, and neurologic toxicity. The CVPP regimen is equally effective, less toxic, and therefore, it has to be preferred. In addition, the usefulness of maintenance therapy was nuclear.

In September 1977, the GATLA initiated a second study whose main objective was to test the effectiveness of combination chemotherapy alone compared with the radiochemotherapy approach in localized and generalized Hodgkin's disease. Following our previous experience, the same 6 monthly courses of CVPP regimen was elected as induction, and a lower dose (3000 rad) of involved-field radiotherapy was used. Radiotherapy was administered to the involved lymph node areas at diagnosis between the third and fourth cycles of CVPP. Children were clinically staged and no maintenance therapy was administered.

An interim evaluation of this study (January 1979) showed that this combination chemotherapy was not as effective as expected in stage III and IV Hodgkin's disease. Since then, a new protocol has been designed for advanced Hodgkin's disease (see below). However, children with advanced disease treated before that date are evaluated in this presentation and obviously this inclusion impairs the overall results.

A total of 155 children <16 years of age were entered into this study from September 1977 to December 1985 at 11 participating institutions. The median age was 8 years with a range of 2–15 years. The male–female patient ratio was 2.52:1. The clinical stages were: stage I, 54 children; stage II, 65 children; stage III, 30 children; and stage IV, 6 children. Median follow-up is 87 months. Patient data have been published in detail [4–6].

Overall complete remission rate in this study was 90% (142 of 155 children). The 7-year actuarial curves of disease-free survival and survival of the whole group were 64% and 79%, respectively.

Complete remission was achieved in 62 (94%) of 66 children treated with CVPP plus radiotherapy whereas complete remission was achieved in 78 (89%) of the 88 children treated with CVPP alone (p=NS). The 7-year actuarial curves of disease-free survival and survival of children treated with

the combined approach were 74% and 76%, respectively. On the other hand, the 7-year actuarial curves of disease-free survival and survival of children treated with CVPP chemotherapy alone were 58% and 88%, respectively. There were not statistical significant differences between the disease-free survival and survival curves of children treated with radiochemotherapy and chemotherapy alone.

The data of this study, which included adults also, was extensively reevaluated. Cox multivariate analysis of factors affecting continuous complete remission, disease-free survival, and overall survival in clinical stages I–II showed two clearly different prognostic groups considering age, sex, stage, symptoms, histology, number of lymph node areas, bulky tumors, and mediastinal widening [7]. All of the following factors at diagnosis imply a 'favorable' prognosis: <3 lymph node areas affected, lymphocyte-predominant, nodular-sclerosis, and mixed-cellularity histology, size of the lymph nodes <5 cm, and nonbulky mediastinum <33% thoracic width). On the contrary, 'unfavorable' prognosis is implied by one of the following factors at diagnosis: >2 lymph node areas affected, lymphocyte-depleted histology, size of the lymph nodes ≥5 cm, or bulky mediastinum (>33% thoracic width).

We concluded from this study that (a) allocation of clinical stage I–II Hodgkin's disease in two prognostic groups according to age, number of lymph node areas, size of the lymph nodes, and histology is a useful prognostic indicator; (b) in children with 'favorable' stage I and II disease, there is no necessity to add radiotherapy to CVPP; and (c) children with 'unfavorable' stage I–II and IIIA disease have better disease-free survival when they are treated with radiotherapy plus CVPP.

As mentioned before, in November 1979, the GATLA opened a third study of Hodgkin's disease, but eligible children had only histologically documented stage IIIB and IVB disease. The chemotherapy program was more aggressive than the previous one, and consisted of Adriamycin 45 mg/m^2 i.v., cyclophosphamide 400 mg/m^2 i.v., and vincristine 2 mg/m^2 i.v. on day 1; prednisone 40 mg/m^2 orally for days 1–5; vinblastine 6 mg/m^2 i.v. on day 21; procarbazine 100 mg/m^2 orally on days 21–26; and bleomycin 5 mg i.m. on days 21–26 (ACOP–VBP). This cycle was repeated every 28 days for six times and no maintenance treatment was given.

From November 1979 to October 1984, a total of 26 stage IIIB and IVA/B children entered this study: 15 were in stage IIIB and 11 in stage IVA/B. Mean age was 9 years with a range of 3–15 years. The male–female patient ratio was 7.67:1.

The complete remission rate was 73% (19 of 26 patients). The 5-year actuarial curves of disease-free survival and survival were 43% and 82%, respectively.

We conclude from this study that the results achieved are not impressive, and they could be improved despite the advanced stages of disease in these children. In November 1984, we initiated a new study using a more aggres-

sive combination chemotherapy: cyclophosphamide, Adriamycin, vincristine, prednisone, and etoposide. The mean observation period of this study is as yet too brief to report treatment results.

In relation to the long-term sequelae of the treatment of Hodgkin's disease in childhood, it is noteworthy to mention that none of the children in these studies has yet developed a second malignant disease. In addition, we want to mention that a study is being conducted to evaluate the hypothalamic–hypofiso–gonadal function in these long-term survivors. A preliminary evaluation has been published [8].

Acknowledgments

We gratefully acknowledge the data management of Ana Becú and typographical assistance of Candelaria Vieyra.

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22. The German cooperative therapy studies
An Approach to Minimize Treatment Modalities and Invasive Staging Procedures

Günther M. Schellong*

In West Germany, consecutive multicenter studies on childhood Hodgkin's disease have been undertaken since 1978. The first two of these (HD–78 and HD–82) were closed to patient entry in 1981 and 1984, respectively, while the third one (HD-85) is still open. From June 1978 through March 1987, 506 children under the age of 16 years entered these studies at 68 centers (including some hospitals in Austria and the Netherlands), representing ~70% of the children with Hodgkin's disease in the F.R.G.

The overall objective of these consecutive studies was to minimize radiotherapy and chemotherapy step by step, as well as invasive staging procedures in the context of a combined-modality treatment concept. In particular, we aimed at reducing radiotherapy to the involved fields, using intermediate and low radiation doses, with the rationale that appropriate chemotherapy could be sufficient to eradicate occult microfoci in adjacent lymphatic areas. Concomitantly, the extent of chemotherapy and the exposure to alkylating agents were limited, depending on the stage of disease.

Another purpose was to reappraise the need for splenectomy and laparotomy. The detailed analyses of the staging findings in study I, in which conventional exploratory laparotomy and splenectomy had been performed, allowed restriction of splenectomy to selected cases in study II by means of an intraoperative decisional strategy. In addition, laparotomy is limited in study III by using clinical parameters.

1. Study I (HD-78)

1.1. Objectives

- To prove the efficacy of two cycles of OPPA chemotherapy (see below) as induction treatment for children with all stages of Hodgkin's disease.
- To prove that the reduction of the radiation dose to 18–20 Gy for the apparently noninvolved adjacent fields is sufficient, if radiotherapy is combined with risk-adapted chemotherapy.
- To determine by statistical analyses which combination of clinical and

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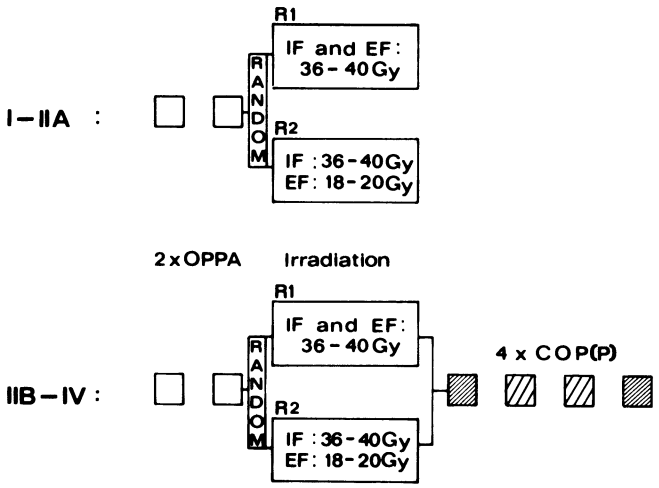

Figure 1. Therapy protocol of study I (HD-78). IF, involved field; and EF, extended field.

intraoperative findings would most probably predict or exclude splenic involvement, and to develop a decisional model that allows the restriction of splenectomy selectively to patients with a high probability of splenic involvement.

1.2. Methods

1.2.1. Treatment protocol (Figure 1) [1, 2]. Patients were stratified according to pathologic stages (PS I and IIA *vs* PS IIB, III, and IV). All were administered induction chemotherapy with two cycles of OPPA, *i.e.*, vincristine (1.5 mg/m^2 i.v. on days 1, 8, and 15; maximal single dose 2.0 mg), procarbazine (100 mg/m^2 p.o. on days 1–15; maximal daily dose 150 mg), prednisone (60 mg/m^2 p.o. on days 1–15), and doxorubicin (40 mg/m^2 on days 1 and 15). Following these two courses of induction chemotherapy, all children received radiotherapy with 35–40 Gy to the involved regions. In addition, they were randomly allocated to obtain extended-field irradiation therapy with a dose of either 36–40 Gy or 18–20 Gy. No additional treatment was given for stage I–IIA disease. In more advanced stages, radiotherapy was followed by adjuvant chemotherapy with four cycles of COPP, *i.e.*, cyclophosphamide (500 mg/m^2 i.v. on days 1 and 8), vincristine (1.5 mg/m^2 on days 1 and 8; maximal single dose 2.0 mg), and procarbazine (100 mg/m^2 on days 1–14; maximal daily dose 150 mg) plus, in the first and fourth cycles, prednisone (40 mg/m^2 p.o. on days 1–14).

1.2.2. Diagnostic procedures. Exploratory laparotomy and splenectomy were required per protocol. Only children under the age of 5 years and a few patients with stage IV disease did not undergo staging laparotomy. To

Table 1. Study I (HD–78): distribution of stage according to the Ann Arbor classification in 170 protocol patients.

Stage	No. of patients	%
IA	37 (3)[a]	21.8
IB	4	2.4
IIA	32	18.8
IIB	17	10.0
IIIA	32 (1)[a]	18.8
IIIB	35	20.6
IVA	4	2.4
IVB	9 (2)[a]	5.3
	170 (6)[a]	100.0

[a](□), no. of patients in whom only clinical stage was obtained.

reduce the risk of developing overwhelming bacterial infections, all children were given cotrimoxazol during chemotherapy and radiotherapy, followed by prophylactic penicillin for at least 2 years. Most patients received pneumococcal vaccination prior to splenectomy.

Lymphangiography, computerized tomography (CT), and sonography (SG) were not mandatory and therefore only performed in a minor proportion of the patients.

1.2.3. Statistical methods. The life-table analyses of survival were based on the respective total groups of protocol patients. Only the time of death was evaluated. The analyses of event-free survival cover the respective total group, too, but evaluate all events leading to failure of remission achievement (early death, progression) or to termination of survival in remission (first relapse, death in remission).

For the multivariate analyses of the significance of different clinical and intraoperative parameters for predicting splenic involvement, the Cox linear logistic model was used.

1.3. Results

A total of 174 protocol patients were enrolled in the study between June 1978 and November 1981 at 47 centers. Patient data have been published in detail [1]. Four patients had to be excluded from the evaluation because the radiotherapy could not be given according to the protocol guidelines due to refusal of the parents. The median age of the 170 protocol patients was 12$^{2}/_{12}$ years with a range of 2$^{4}/_{12}$– to 16$^{3}/_{12}$ years. The male–female patient ratio was 1.79. Pathologic stage according to the Ann Arbor classification was determined in 164 patients (Table 1). Six were not laparotomized. In one-third of the patients (56 of 164), stage had been altered after laparotomy and splenectomy; 23% were restaged as more severe disease and 11% as less advanced disease.

The individual significance of 16 clinical and surgical findings for predict-

Table 2. Study I (HD–78): risk groups according to splenic involvement (154 patients).

Group	Changes in splenic surface	Enlargement of lymph nodes at hilus of spleen/tail of pancreas	Incidence of splenic involvement
1	+	+/–	19/20 = 95%
2	–	+	22/36 = 61%
3	–	–	19/98 = 19%

ing splenic involvement was evaluated in 154 patients [3]. A statistically significant association to splenic involvement was established for only six of these variables (three clinical and three intraoperative). Multivariate analysis indicated that two intraoperative parameters, *i.e.*, changes in splenic surface and enlargement of lymph nodes at the splenic hilus/tail of the pancreas, provided almost the entire information available on splenic involvement, so that the other parameters could be disregarded. Three risk groups were defined accordingly (Table 2) and, in study II (HD-82), splenectomy was avoided in patients of the lowest risk category.

1.3.1. Effectiveness of OPPA induction therapy [1]. A total of 146 patients had provable disease after biopsy was made; 104 (71.2%) were in complete remission after two OPPA cycles. If only peripheral lymph nodes are evaluated, 91.4% achieved a complete remission. Of 87 mediastinal tumors, 41 were totally and 15 subtotally reduced.

1.3.2. Treatment results. One child with stage IVB disease and severe clinical symptoms died on day 10 of treatment. One further patient with stage IVB had progression in the lungs and skeleton during therapy. Complete remission occurred in 168 (98.8%) of 170 patients. Seven patients died in continuous remission 5–17 months after initiation of treatment, three due to pneumonia, two due to septicemia, and one each due to varicella and graft-*versus*-host reaction after granulocyte transfusion. These seven patients had had advanced stages of disease (Table 3) and six of them had received high-dose extended-field irradiation (randomization arm R1). As of March 1987, ten patients have relapsed. Five patients were lost to follow-up, one of them after relapse. The remaining 147 complete responders have been in continuous first remission for 64–105 months. There are 154 patients still living. So far, no second malignancies have been observed.

The probability for event-free survival after more than 8 years is 89% for the overall group (Figure 2), 92% for stages I–IIA and 86% for stages IIB–IV. The probability for survival is 94% (overall group), 99% (stages I–IIA), and 90% (stages IIB–IV), respectively.

Between the two randomization arms, no significant differences are found with respect to stages I–IIA (event-free survival 91% *vs* 92%) (Figure 3). In stages IIB–IV, the probability for event-free survival is significantly poorer

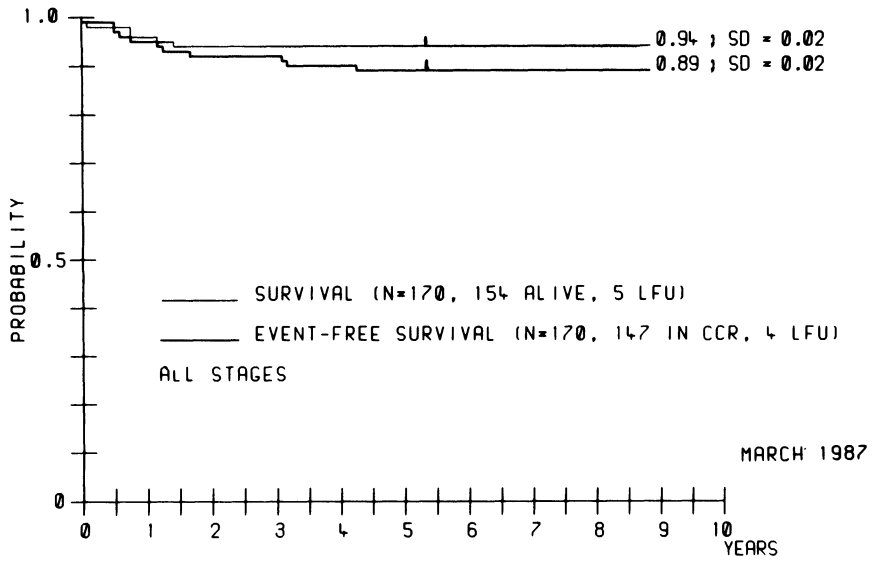

Figure 2. Survival and event-free survival of 170 patients in study I (HD-78). The tick marks represent the last patient of the study.

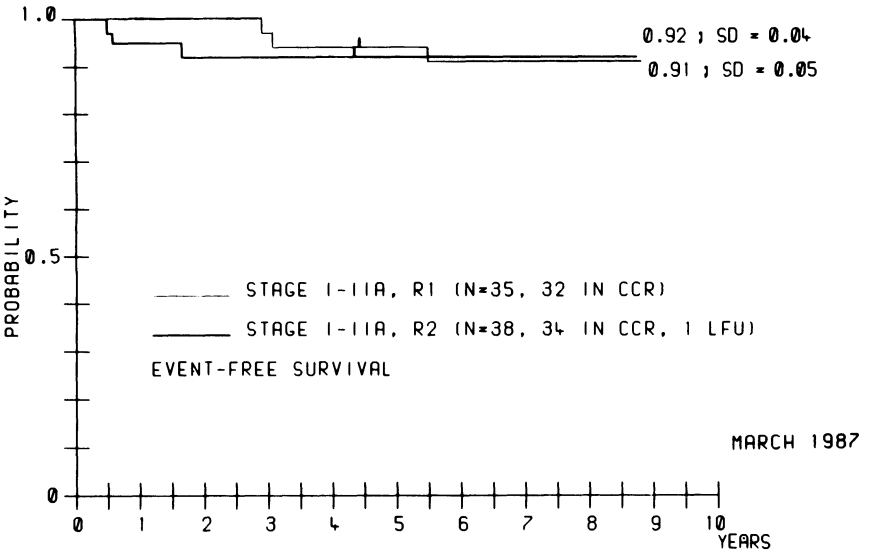

Figure 3. Event-free survival in 73 patients with stage I–IIA disease (randomization arm R1 *vs* R2) in study I (HD–78). The tick marks represent the last patient of the respective group.

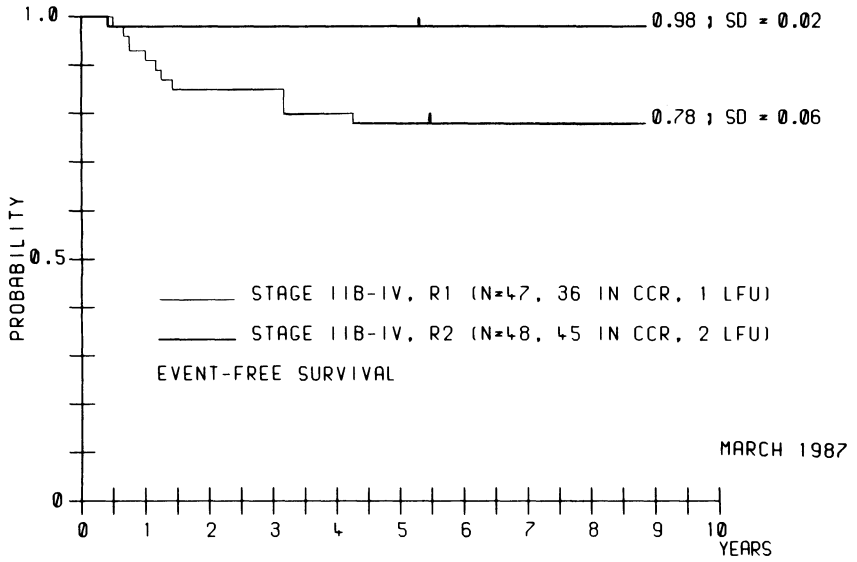

Figure 4. Event-free survival in 94 patients with stage IIB–IV disease (randomization arm R1 *vs* R2) in study I (HD–78). P = 0.005

Table 3. Study I (HD–78): treatment results in the two randomization arms R1 and R2.

	Patients with stages I–IIA		Patients with stages IIB–IV	
	R1	R2	R1	R2
Radiation therapy completed	35	38	47	48
Complete remission	35	38	47	48
Death in remission	0	0	6	1
Recurrent disease	3	3	4	0
Lost to follow-up	1[a]	1	1	2
In first remission	32	34	36	45
Alive	34	36	39	45

[a]After relapse.

in randomization arm R1 (78%) than in arm R2 (98%, $p = 0.005$) (Figure 4). This difference is due to a higher number of intercurrent deaths (6:1) and relapses (4:0) in the patients with high-dose extended-field irradiation (Table 3).

1.4. Conclusions

- Two cycles of OPPA chemotherapy are an effective induction treatment for children with all stages of Hodgkin's disease.
- The radiation dose for the apparently noninvolved adjacent regions can be

reduced to at least 18–20 Gy, if a risk-adapted chemotherapy is given concomitantly.
- Of 16 clinical and surgical findings, two intraoperative parameters, namely, changes in splenic surface and enlargement of lymph nodes in the splenic hilus/pancreatic tail, predict or exclude splenic involvement with the highest probability. It is suggested that splenectomy can be omitted without splenic irradiation, if both parameters are negative and chemotherapy is given.

2. Study II (HD-82)

2.1. Objectives

- To prove the sufficiency of involved-field irradiation in the context of a combined-modality treatment with risk-adapted chemotherapy (OPPA/COPP) in children with all stages of Hodgkin's disease.
- To reduce radiation doses to 35, 30, or 25 Gy for the involved fields, depending on the extent of the preceding chemotherapy.
- To omit splenectomy in patients with highly improbable splenic involvement, using an intraoperative decisional strategy based on the results of the statistical analyses in study I.
- To find out by statistical analyses which combination of clinical findings (including sonography (SG) and CT scan) would most probably predict intraabdominal involvement, and to develop a decisional model that allows the restriction of laparotomy selectively to patients with a high probability of intraabdominal disease.

2.2. Methods

2.2.1. Treatment protocol (Figure 5) [2, 4]. Patients were stratified according to the pathologic stages into three groups (PS I–IIA *vs* PS IIB–IIIA *vs* IIIB–IV) receiving two, four, or six cycles of chemotherapy, respectively. In PS I–IIA patients, chemotherapy consisted of two OPPA cycles. Those with more advanced stages also received two courses of OPPA followed by two (PS IIB–IIIA) or four (PS IIIB–IV) cycles of COPP. After completion of chemotherapy, radiotherapy was given to the involved fields only. The radiation dose was 35, 30, or 25 Gy, depending on the number of preceding cycles of chemotherapy. In patients with PSIIB−IIIA or PSIIIB−IV, the fields showing residual tumor after completion of chemotherapy received a dose increased by 5 Gy, i.e., 35 or 30 Gy, respectively. Definitions of the involved fields were restrictive. In this study, there was no randomization.

2.2.2. Diagnostic procedures. Staging laparotomy was mandatory, whereas splenectomy was performed only selectively by use of an intra-operative decisional strategy (Figure 6) developed on the basis of the statistical analy-

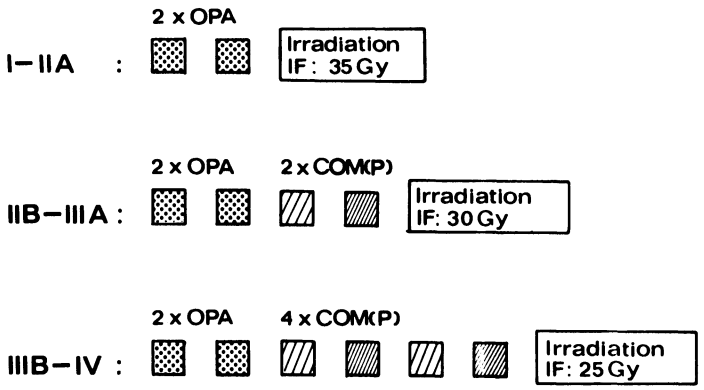

Figure 5. Therapy protocol of study II (HD–82). IF, involved field.

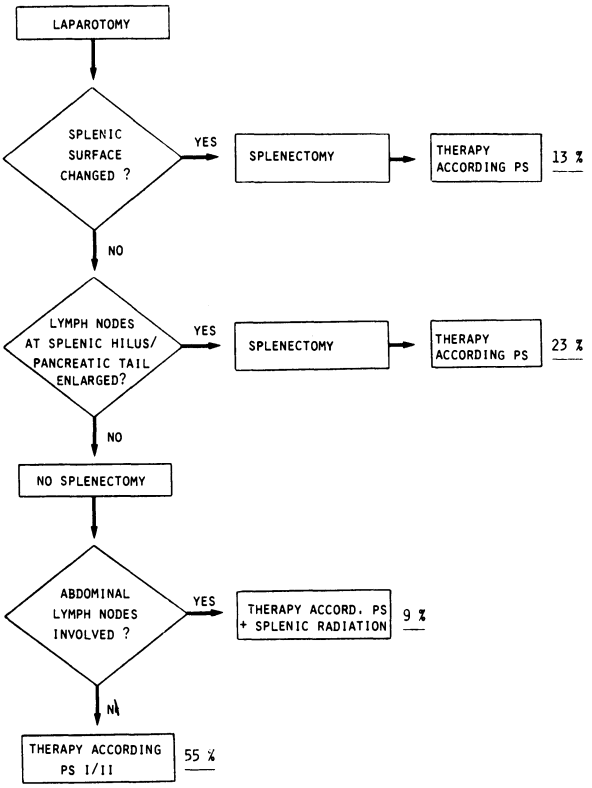

Figure 6. Intraoperative decisional strategy for selective laparotomy derived from the statistical analysis in study I.—The percentages given represent the relative incidence expected in accordance with the retrospective analysis.

Table 4. Study II (HD–82): distribution of stage according to the Ann Arbor classification in 207 patients.

Stage	No. of patients	%
IA	48 (1)[a]	23.2
IB	4	1.9
IIA	49	23.7
IIB	26	12.6
IIIA	28	13.5
IIIB	36	17.4
IVA	2	1.0
IVB	14	6.8
Total	207 (1)[a]	100.0

[a](□), one of 48 stage IA patients not laparotomized.

ses in study I [3]. Children without changes of splenic surface and without enlargement of lymph nodes at the splenic hilus/pancreatic tail were not splenectomized.

Lymphangiography was performed only in a few patients, whereas abdominal SG and/or CT were applied in about two-thirds of them.

2.2.3. Statistical methods. See study I.

2.3. Results

A total of 207 children under the age of 16 years were enrolled in the study between December 1981 and December 1984 at 53 centers. Patient data have been published in detail [4]. Median age was 12.0 years with a range of 3.0–15 11/12 years. The male–female patient ratio was 1.70. The distribution of pathologic stages is presented in Table 4.

At laparotomy, the criteria of the decisional strategy were observed in 174 (84.1%) of 207 patients; 69 children (39.7%) were splenectomized. The predicted value, according to our retrospective analyses, was 36%. Splenic involvement was proven histologically in 50 (72.5%; predicted 73%) of 69 removed spleens. In six (5.7%) of 105 nonsplenectomized patients, the spleen was included in the infradiaphragmatic irradiation. The percentage of nonsplenectomized patients differs among the three treatment groups: 83%, PS I–IIA; 53%, PS IIB–IIIA; and 28%, PS IIIB–IV.

The individual significance of 13 clinical parameters including SG and CT findings for predicting intraabdominal disease was evaluated [5]. A statistically significant association with intraabdominal involvement was established for seven of these parameters. Multivariate analyses indicated that three parameters—namely, abdomen in SG and CT 'abnormal,' B symptomatology,and enlargement of hilar lymph nodes of the lung—contain almost the entire information concerning abdominal involvement. For practical purposes, one can omit B symptomatology because the combination of the other

Table 5. Study II (HD–82): risk groups according to abdominal involvement (145 patients).

Group	Abdominal SG and/or CT abnormal	Enlargement of lymph nodes at the hili of the lungs	Incidence of abdominal involvement
1	+	+/−	33/48 = 69%
2	−	+	13/24 = 54%
3	−	−	6/73 = 8%

two parameters leads to the smallest number of false-positive results, while the number of false-negative results is only slightly increased. In study III (HD-85), laparotomy is restricted to patients with abnormal findings in SG/CT and/or enlargement of hilar lymph nodes of the lung(Table 5, groups 1 and 2).

2.3.1. Treatment results [4]. Of 207 patients, four had to be excluded from the evaluation of the treatment results because of major violations of the radiotherapy protocol. All 203 patients achieved complete remission. In the further course, three children died of intercurrent disease (one of varicella and two of sepsis). All three children had undergone splenectomy and were in the middle- and higher-stage groups. As of March 1987, five children have relapsed (PS IIA, IIB, IIIB, $IV_{H+}B$, and $IV_{L+}B$). All five had presented with the histologic type of nodular sclerosis. Three relapsed children had been splenectomized; in the other two patients, the spleen had been included in the infradiaphragmatic irradiation field. A total of 195 patients are in continuous first remission, 26–62 months after institution of therapy, and 198 children are alive.

The life-table analyses for the entire group of 203 protocol patients show a projected 5-year survival rate of 96% as well as an event-free survival rate of 96% (Figure 7). The projected disease-free survival rates for the three therapy groups after 5 years are 99%, 96%, and 90% (Figure 8).

2.4. Conclusions

- A stage-dependent chemotherapy (two, four, or six cycles OPPA/COPP) is highly sufficient to eradicate occult microfoci, so that only involved-field irradiation is needed. Furthermore, it is possible to dispense with proving an isolated splenic involvement unrecognizable during laparotomy, because smaller foci in the spleen are eradicated by two cycles of OPPA even without irradiation of this organ.
- There is a high probability of preventing local recurrence by combining radiation doses of 35, 30, or 25 Gy with the applied risk-adapted chemotherapy of two, four, or six cycles of OPPA/COPP.
- The excellent therapy results justify cautious attempts at further treatment reductions.
- The strategy of selective splenectomy, based on the results of the statistical

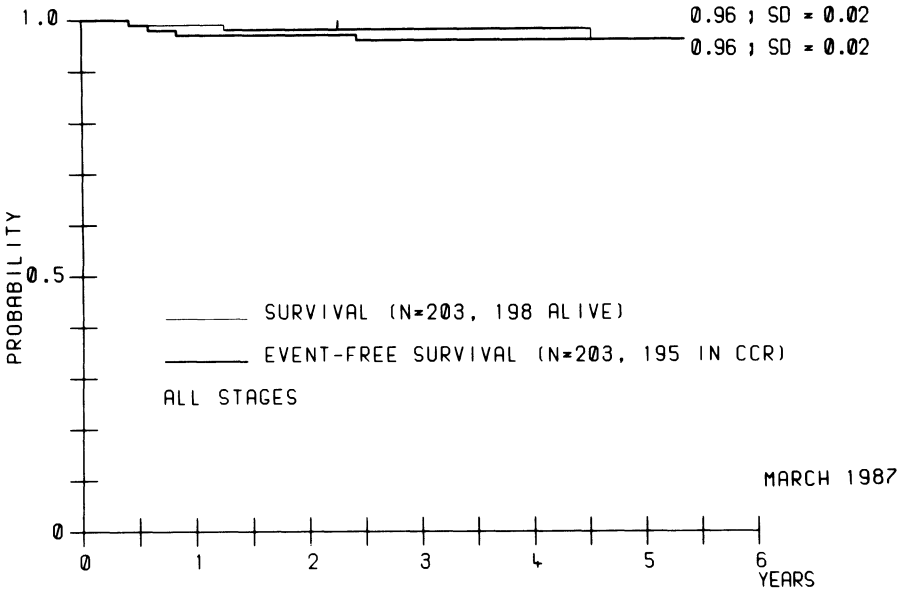

Figure 7. Survival and event-free survival of 203 patients in study II (HD–82).

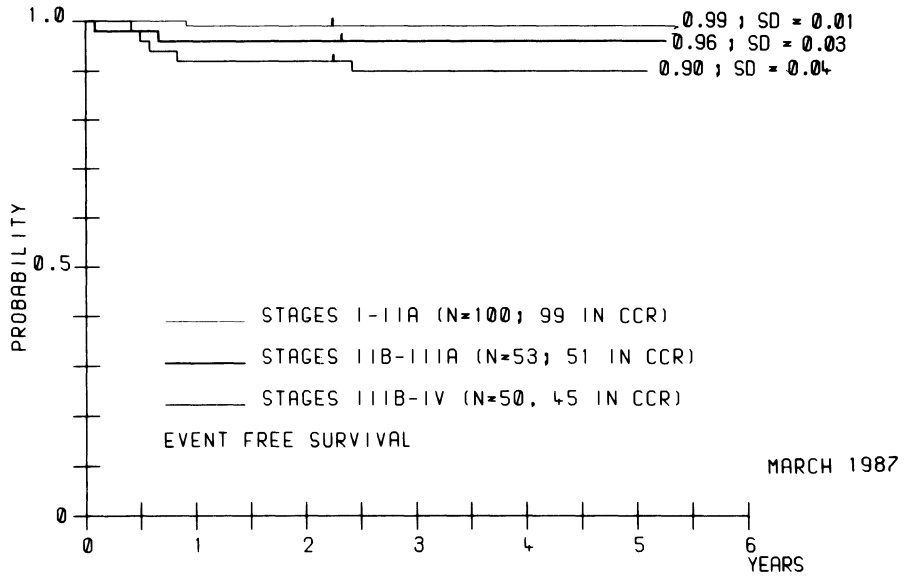

Figure 8. Event-free survival in the three treatment groups of study II (HD–82). The tick marks represent the last patient of the respective group.

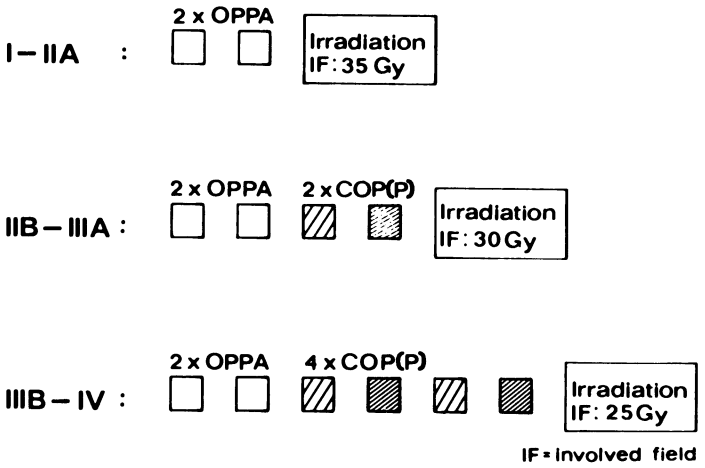

Figure 9. Therapy protocol of study III (HD–85). IF, involved field.

analyses in study I, is very useful in the context of a combined-modality treatment.

- Of 13 clinical parameters, SG and CT findings in combination with enlargement of lymph nodes at the hilus of the lungs predict or exclude intraabdominal involvement with the highest probability. It is suggested that laparotomy can be omitted without infadiaphragmatic irradiation if both parameters are negative and chemotherapy is given.

3. Study III (HD-85)

3.1. Objectives

- To eliminate procarbazine from the OPPA/COPP chemotherapy within the otherwise unchanged treatment regimen of the preceding study II.
- To avoid laparotomy in patients with highly unprobable abdominal disease, using a decisional strategy developed from the data of study II.

3.2. Methods

3.2.1. Treatment protocol (Figure 9). The overall therapy plan remains the same as in study II, *i.e.*, stratification in three risk groups according to stage of disease, number of chemotherapy cycles, and involved-field irradiation with 35, 30, or 25 Gy, respectively. Procarbazine is eliminated from OPPA (resulting in OPA) and replaced by methotrexate (40 mg m^2 i.v. on days 1 and 8) in COPP (resulting in COMP).

3.2.2. Diagnostic procedures. Laparotomy is performed only selectively by use of two criteria derived from the statistical analyses of the data in study

II, namely, pathologic abdominal findings in SG/CT and/or enlargement of lymph nodes at the hili of the lungs. Children without these findings are not laparotomized. In patients with surgical staging, selective indication for splenectomy according to our decisional model is applied. Lymphangiography is not used.

3.3. Results

Patient recruitment was started in January 1985 and will presumably continue until December 1988. As of March 1987, 125 children have been enrolled in the study. Of these patients, 52 (41.6%) were not laparotomized; in 37 (51%) of 73 children with surgical staging, the spleen has been preserved. Among the three treatment groups, the percentage of only clinically staged children differs: 67%, PS I–IIA; 5%, PS IIB–IIIA; and 6% PS IIIB–IV.

Since the mean observation period of the study patients so far is only 13 months, it is not yet possible to report on treatment results.

Acknowledgment

This work was supported by the Bundesminister für Forschung und Technologie of the Federal Republic of Germany.

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23. Hodgkin's disease in children and adolescents

Experiences from the Memorial Sloan-Kettering Cancer Center, New York

Charlotte T.C. Tan

The treatment of Hodgkin's disease has changed during the last few decades with the ultimate goal of increasing the 'cure' and, at the same time, reducing the morbidity. Hodgkin's disease is relatively rare in children as compared with that in adults. In spite of this, a total of 431 children and adolescents with biopsy-proven Hodgkin's disease have been seen at Memorial Hospital. This sizable experience provides a unique opportunity to observe the changing management of this disease in children during recent decades. These patients were grouped according to the year of diagnosis as follows: 1929–1959, 80 children; 1960–1969, 86 children; and 1970–present, 265 children. In the first period, lymphangiography was not available and radiation therapy was limited to clinically involved areas. Chemotherapy was available only during the last half of the period and consisted mainly of alkylating agents and adrenal steroids. Between 1960 and 1969, lymphangiography had come into general practice, extended-field radiation therapy was widely utilized, and the success of chemotherapy had increased by the use of vinca alkaloids and procarbazine. The present group began in 1970. Patients are managed in accordance with current concepts of surgical staging, protocol radiation therapy, and/or multiagent systemic chemotherapy.

In this chapter we present: (a) the general characteristics of the three groups of patients, (b) the present group of patients who had surgical (pathologic) staging, and (c) the results of patients treated by current protocols with involved-field (IF) radiation alone, with multiple chemotherapy alone, and with combined multiple chemotherapy and IF radiation.

1. General patient characteristics

1.1. Age at diagnosis and sex incidence

There were 272 boys and 159 girls, a 1.8:1 ratio. Peak incidence occurred at ages 13 and 14 years. There was only one boy diagnosed at the age of 2 years.

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1.2. Initial presentation

The initial sites of disease in these 431 patients show that involvement of cervical nodes (65%) was most common, followed by supraclavicular nodes (30.6%). Axilla (7.6%) and inguinal (6%) sites were less frequent. Approximately 50% of the patients had more than one nonadjacent area of peripheral node involvement. Mediastinal disease as the initial site was seen in 28 patients (6.5%). Extranodal sites of initial disease presentation were seen in lungs (3.9%), bones (3.7%), liver (1.4%), and CNS or skin (0.7%).

1.3. Histologic classification

All patients had their initial biopsy material reviewed and the diagnosis of Hodgkin's disease confirmed by the Pathology Department of Memorial Hospital. A total of 378 patients' histologic slides were available for further review and classification according to the Lukes and Butler scheme. These showed 63% nodular-sclerosing, 26% mixed-cellularity, 9% lymphocyte-predominant, and 1.3% lymphocyte-depleted type.

2. Clinical staging

All patients were clinically staged by roentgenographic studies of chest, abdominal lymphangiography, computerized tomographic scan of the thorax and abdomen and, recently, by magnetic resonance imaging (MRI). Gallium-67 scan is useful in initial workup and is sensitive to detecting early recurrences [1].

While no laboratory test is uniquely abnormal in Hodgkin's disease, several common nonspecific tests may serve as indicators of the presence and extent of disease both at the time of diagnosis and during follow-up. In the presence of active disease, there may be elevation of sedimentation rate, serum ferritin and copper levels, the serum iron and zinc may be decreased, with a normal total iron-binding capacity.

3. Surgical staging

Newly diagnosed patients are staged surgically by exploratory laparotomy. The surgical procedures required for pathologic staging consist of splenectomy, wedge liver biopsies, and biopsy of the paraaortic nodes and bone marrow [2]. Complete staging is essential for determining the choice of treatment modalities.

A total of 167 patients had the surgical staging done at Memorial Hospital. Of these, in 119 patients the staging was not changed from the clinical staging. The staging was reduced in ten patients. In 38 patients, however,

Table 1. Hodgkin's disease in 431 children according to year of diagnoses, staging, and treatment.

Group	No. of patients	Disease staging	Irradiation			Chemo alone	MDP IF
			Local	EF	TN		
I	80	Clinical A 46 B 34	76	1		3	
II	86	+Lag A 41 B 45	27	51	6	2	
III	167[a]	Pathologic I II III IV A 33 43 36 2 B 4 16 21 12	(IF) 60	10	11	(MDP) 9	77

[a]Additional 34 had prior treatment, 30 had nonprotocol, and 34 had consultation.

the pathologic staging rose from that of the clinical staging because of Hodgkin's disease involvement in the spleen in 38, splenic hilar nodes in 17, porta hepatis in eight, celiac axis nodes in six, paraaortic nodes in four, and liver in one patient. Children who had a splenectomy routinely received prophylactic penicillin orally and, during the last 10 years, pneumococci and *H. influenzae* vaccine were also given. There were no major surgical complications.

The incidence of sepsis after splenectomy was very low. After 1970, at the Department of Pediatrics the number of blood cultures taken on pediatric patients with cancer averaged 850/year. We randomly looked at six separate years (1970, 1971, 1980, 1981, 1982, and 1986) and found only ten children with Hodgkin's disease who had positive blood cultures during these 6-year periods. These positive blood cultures included *Pseudomonas aeruginosa* in three, *Hemophilus influenzae* in two, streptococci in two, and one each had staphylococci, *Candida albicans* and *Acinetobacter*.

4. Treatment

Table 1 summarizes our total experience in the changing management of childhood Hodgkin's disease during the last few decades [3–7]. The present group III began in 1970. Only the patients who had surgical staging done at Memorial Hospital are analyzed and presented here. Excluded are the large number of patients referred for consultation only, nonprotocol patients, and those who had prior treatment outside. Currently, treatment modalities include:

1. *Radiation alone to the involved or mantle field* for pathologic stages IA and IIA

2. *Multiple chemotherapy alone*
   a Previously treated patients who relapsed from initial radiation and/or chemotherapy received multiple chemotherapy alone
   b A small group of the newly diagnosed patients, mostly with stage IV disease, had multiple-drug chemotherapy alone
3. *Newly diagnosed* patients with B symptoms, stages III and IV are being treated with three cycles of multiple drug chemotherapy followed by IF irradiation and then three more cycles of chemotherapy.

The results with 172 children and adolescents who have been treated with the current treatment modalities and have had a follow-up period more than 3 years are presented.

4.1. Protocol radiation

Patients with pathologic stages IA and IIA with disease above the diaphragm were given involved- or mantle-field radiation [8–10]. The dose range was 3500–4000 cGy (median, 3600 cGy) with a daily dose of 200 cGy. The megavoltage used for IA neck presentation was CO^{60} or electrons. For IA other presentation and for all IIA, accelerator 6 MV was used from 1970 through 1980 and 10 MV after 1981.

Of the 52 children who received involved- or mantle-field radiation for stages IA and IIA with nonbulky mediastinal and supradiaphramatic disease, 12 patients relapsed in a median of 16 months (range, 6–54 months) from diagnosis; in the majority of the cases, the relapse occurred by 32 months. The site of relapse in six of the patients occurred in field/marginal and in four outfield but above the diaphragm. The other two recurred in the lungs. Both of these patients had hilar involvement. Figure 1 shows a relapse rate of 24%, but the salvage rate was 94% (11 of 12 patients), resulting in an overall 98% survival with a long-term follow-up.

4.2. Multiple-drug protocol (MDP)

In 1970, we designed a multiple drug protocol for children with advanced Hodgkin's disease or ones who have relapsed after initial radiation and/or chemotherapy. This protocol consists of adriamycin followed by vincristine, procarbazine, prednisone, and cyclophosphamide (Figure 2). Cycles are repeated every 6–8 weeks for a total of 6–7 cycles.

Figure 3 shows the 45 previously treated patients who relapsed after initial radiation and/or chemotherapy and then received 6–7 courses of MDP. Of the 42 evaluable patients, 35 achieved a complete remission, five a partial remission, and two had no response. Twenty-seven of the complete responders are alive and disease-free. Two-thirds of the survivors are alive more than 9 years after the start of MDP.

Because of the high response rate in the previously treated patients, we used this protocol also for the newly diagnosed patients. Figure 4 shows the

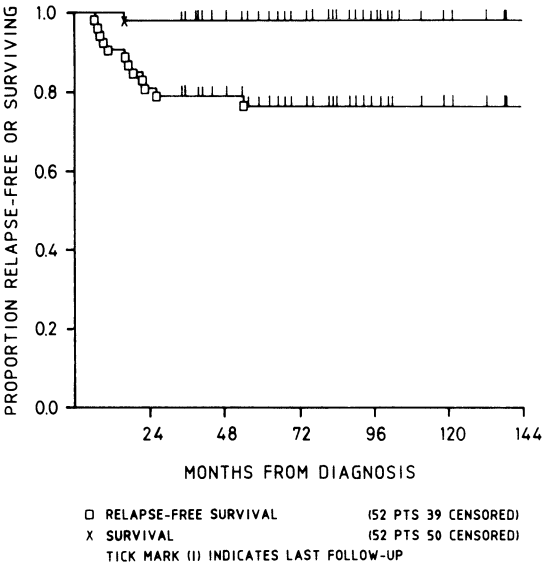

Figure 1. A proportion of patients surviving pediatric Hodgkin's disease, pathologic stages IA and IIA (nonbulky mediastinal supradiaphragmatic disease) treated with involved-field or mantle-field irradiation: □, relapse-free survival (52 patients, 39 censored); and x, survival (52 patients, 50 censored). Tick mark indicates last follow-up.

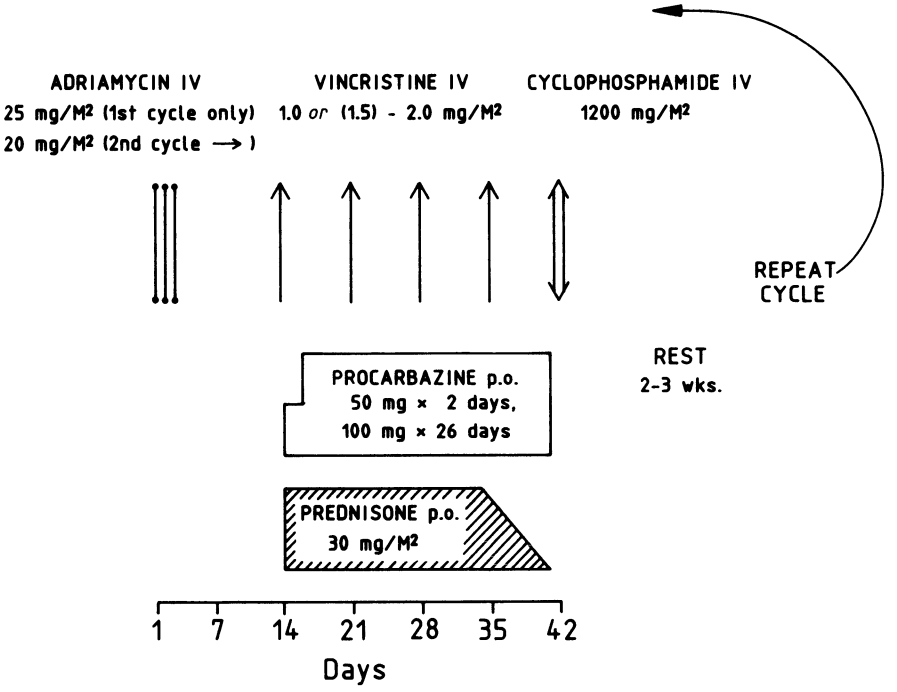

Figure 2. Chemotherapy protocol for advanced Hodgkin's disease in children.

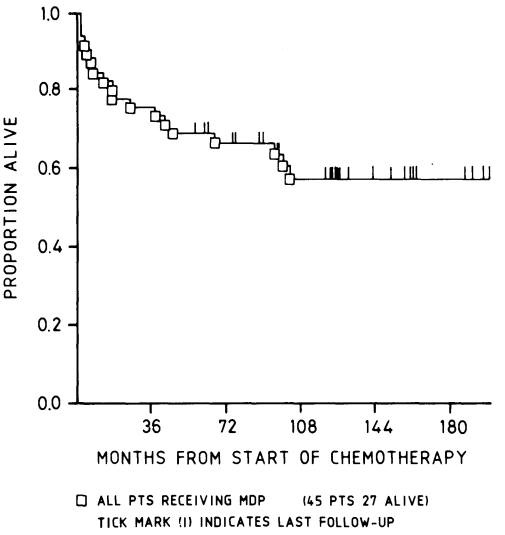

Figure 3. Proportion of patients alive: previously treated, receiving MDP: □, all patients receiving MDP (45 patients, 27 alive). Tick mark indicates last follow-up.

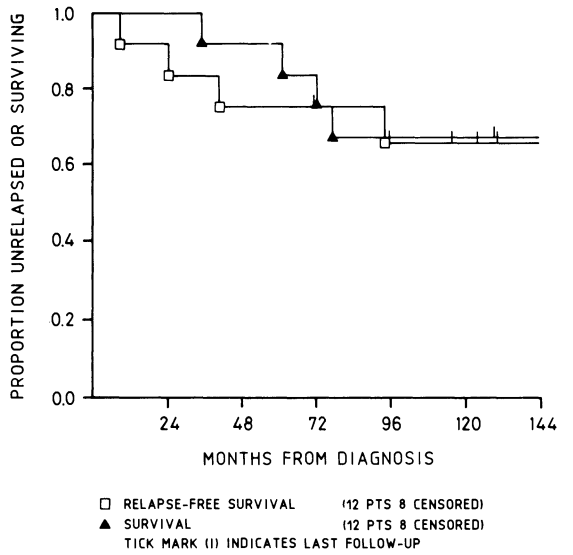

Figure 4. Proportion of survivals in newly diagnosed patients with pediatric Hodgkin's disease receiving MDP with no radiation therapy: □, relapse-free survival (12 patients, 8 censored); and ▲, survival (12 patients, 8 censored). Tick mark indicates last follow-up.

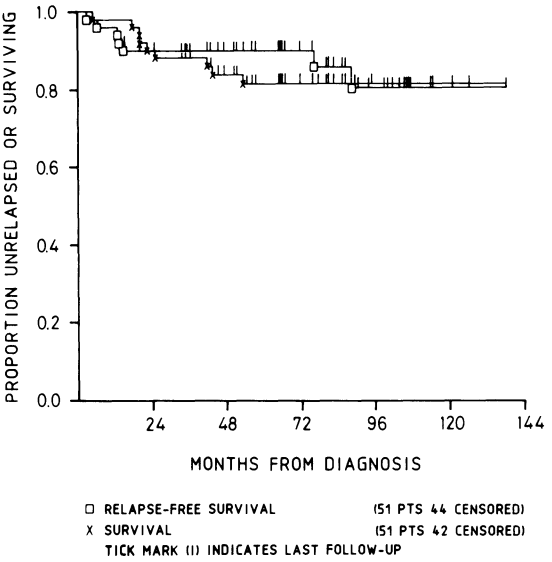

Figure 5. Proportion of survivals in newly diagnosed patients receiving MDP + IF (low) + MDP: □, relapse-free survival (51 patients, 44 censored); and x, survival (51 patients, 41 censored). Tick mark indicates last follow-up.

12 newly diagnosed patients who received MDP only, without radiation therapy. This includes two patients with IB, one patient each with IIIA, IIIB, and IVA, and seven patients with IVB disease. All achieved complete remissions. Seven are alive and have remained disease free. Four patients had relapses, three of whom died; the other patient died of acute myeloblastic leukemia and with no evidence of Hodgkin's disease. At 8–10 years, the relapse-free interval and survival was 66%.

4.3. Multiple-drug protocol and high involved-field radiotherapy

During the period of 1974–1976, 12 newly diagnosed patients received three cycles of MDP followed by 3000–4000 cGy to the involved field, and then three more cycles of MDP. This is indicated as high IF radiotherapy (RT). Six of these 12 patients were stage IIIB, two were IIB, and one each with IB, IIIA, IVA, and IVB. All 12 patients have remained relapse free for more than 10 years. The hematologic depression that resulted from this treatment modality, however, was severe in these patients.

4.4. Multiple-drug protocol and low involved-field radiotherapy

From 1977 until April 1984, 51 children received three cycles of MDP followed by 2400 cGy IF, indicated as low IF RT, and then another three cycles of MDP. Of these 51 patients, seven were IIA, 10 were IIB, 16 were IIIA, 10 were IIIB, one was IVA, and seven were IVB. Figure 5 shows an

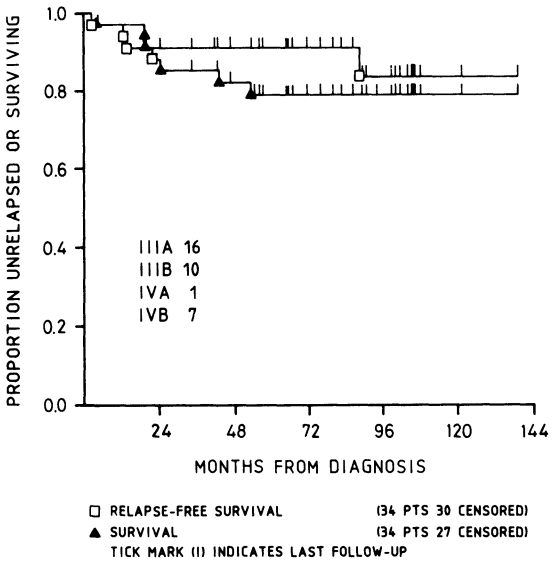

Figure 6. Proportion of survivals in newly diagnosed, stage III and IV patients receiving MDP + IF (low) + MDP: □, relapse-free survival (34 patients, 30 censored); and ▲, survival (34 patients, 27 censored). Tick mark indicates last follow-up.

80% relapse-free interval and survival at 8–10 years. Figure 6 shows that, in the 34 patients with stage III and IV disease, both the relapse-free interval and survival were essentially the same.

Figure 7 shows the 53 patients with stage III and IV disease who received three different treatment modalities: 10 received MDP only, 34 received MDP and 2400 cGy to the involved field, and the other 9 patients received MDP and 3000–4000 cGy to the involved field. Comparing the three groups with respect to event-free survival, the overall p value, based on the Log-rank test was 0.15, which might suggest a trend. However, the number of patients is small and there are proportionately more stage IV patients in the MDP-alone group, which may explain the lower percentage of survival. There was more hematologic toxicity in the patients who received high-dose IF RT, and it appeared to offer no advantage.

4.5. Retrieval chemotherapy

Patients who failed MDP have been entered on a retrieval protocol that consists of six cycles of non-cross-resistant drugs, using velban, BCNU, bleomycin, and chlorambucil. Of a total of 14 evaluable patients, eight have achieved a complete remission. Of these, seven are alive. The duration of remission ranged from 2 months to 8 years, a median of 1 year.

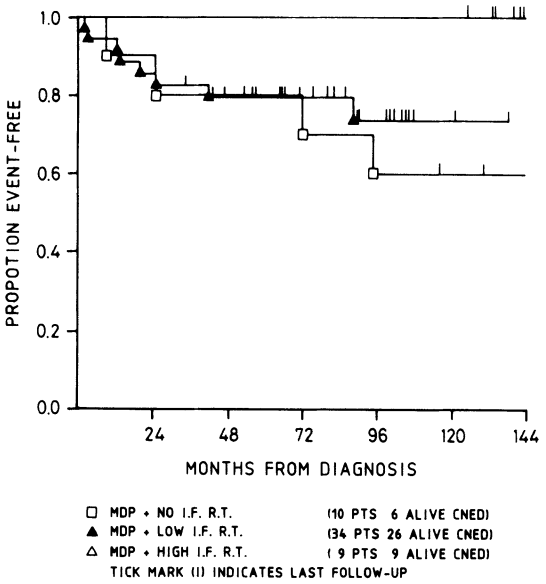

Figure 7. Proportion of surviving stage III and IV patients receiving MDP alone (MDP and low IF and MDP + high IF RT: □, MDP + no IF RT (10 patients, 6 alive censored); ▲, MDP + low IF RT (34 patients, 26 alive censored); and △, MDP + high IF RT (9 patients, 9 alive censored). Tick mark indicates last follow-up.

5. Discussion

This is a review of the children and adolescents with Hodgkin's disease who have been treated at a single cancer institute. For the past 3 decades, patient follow-up has been done by the author and others as a multidisciplinary team. The current group, diagnosed since 1970, has been treated in accordance with current concepts of surgical staging, protocol radiation therapy, and a multiple-drug protocol. Laparotomy has been done by one team of pediatric surgeons at this center [2]. Of the 167 patients who had a staging laparotomy done at this center, the pathologic disease staging rose from the clinical staging in 38 patients (23%). We studied the weight of the spleen according to the age of the patient and found there was no correlation between the size or weight of the spleen with disease involvement. For example, a 14-year-old child had a spleen weighing 25 g that was positive, while another 14-year-old child had a spleen weighing over 400 g that was histologically negative for Hodgkin's disease. Likewise, gallium scan or computerized tomographic scan of the abdomen did not always predict the presence of disease in the abdomen or spleen.

Recently we have done MRI in 15 children with an attempt to correlate its findings with the surgical pathology of the spleen. At present, it appears that this modality is relatively insensitive to detecting smaller disease (<0.8–

0.9 cm). In addition, the positive MR examinations consistently underestimated the extent of involvement with Hodgkin's disease, correctly diagnosing the presence of nodules >0.8 cm in diameter, but missing (frequently multiple) nodules of smaller diameter in the same spleen. Negative MR examination of the spleen does not rule out the presence of tumor in this organ in Hodgkin's disease (R.T. Heelan *et al.*, unpublished). Further refinement of the technique in MRI may improve its diagnostic value.

Presently, we feel that splenectomy with histologic examination of the spleen is important and, if the spleen is involved, its removal will then avoid irradiation to the splenic pedicle area. A definitive, accurate surgical staging is necessary to define the extent of disease and thus determine the treatment modality. There has been no increased incidence of overwhelming infection in the splenectomized patients. There were only ten splenectomized patients in a 6-year period who developed positive blood cultures while receiving chemotherapy.

The treatment methods found best for adult patients with Hodgkin's disease may be less suitable for children. With the provision of an accurate definition of the extent of disease at diagnosis by surgical staging, it is then possible to use a more restricted field of irradiation in children, so long as survival is not jeopardized. The purpose is to minimize the late effects of extended-field irradiation and/or chemotherapy, such as disturbances in growth and development and/or secondary malignancies. Since 1970, our treatment policy for patients with stages I and II has been the use of restricted fields (involved or mantle fields). In our group of 52 patients with stages IA and IIA, supradiaphragmatic and nonbulky mediastinal disease was treated with restricted irradiation fields. Although the relapse rate of 24% seems to be high, the salvage rate of this group is 94% (11 of 12 patients), resulting in an overall 98% survival with long-term follow-up. This indicates that the restricted-field radiation offers high survival rates with the benefit of sparing >75% of the pediatric population, not only large field radiation, but also multiple-drug therapy. This relapse rate of 24% may have been decreased further by carefully designed blocks and by using a standard mantle field instead IF RT.

At Memorial Center, our initial experience with adriamycin alone showed that, in all nine children with Hodgkin's disease who relapsed after the initial therapy, there was rapid tumor regression. Therefore, in our multiple-drug protocol, we used adriamycin initially and followed with a combination of vincristine, procarbazine, and prednisone. In all of these patients treated, signs of tumor regression occurred following the first course of adriamycin, with further regression on continuation of chemotherapy. Instead of mechlorethamine hydrochloride used in the MOPP protocol (nitrogen mustard, Oncovin, procarbazine, and prednisone), we used cyclophosphamide as the alkylating agent. The result of the MDP in the 45 previously treated patients was encouraging: 35 achieved complete remission and 27 of the complete responders are alive and disease free. Two-thirds of the survivors are alive more than 9 years after the start of MDP.

A group of 12 newly diagnosed patients, ten with pathologic stages III and IV were treated with MDP alone without radiation therapy. In this group of patients with far-advanced diseases, a relapse-free interval and survival of 66% at 8–10 years is considered acceptable. Two groups of patients received a combination of MDP and IF RT. In the earlier period, 12 patients received 3000–4000 cGy to the involved field. Since 1977, patients have been treated with MDP and 2400 cGy to the involved field. It is difficult to compare these three treatment modalities (that is, MDP with no radiation, MDP with high IF, and MDP with low IF) because these are not randomized studies and the number of patients is small, with a various number of patients in advanced stages. A randomized study would be necessary in order to determine any advantage of the different treatment modalities.

The total cumulative dose of adriamycin in MDP is 360 mg/m^2. With the addition of IF RT, we have not observed clinical evidence of myocardial dysfunction or congestive heart failure in these patients. The treatment is administered in the Outpatient Department. With the exception of occasional admissions, with fever and neutropenia, in general the treatment is well tolerated.

Of the 172 patients, five developed secondary malignancies, three which were acute nonlymphoblastic leukemia at 14, 28, and 68 months after the start of chemotherapy and irradiation. The other two patients developed osteogenic sarcoma, and adenocarcinoma of the esophagus 6 and 12 years after the start of treatment, respectively.

The changing treatment modalities may have improved the long-term disease-free survival. Close clinical follow-up of these patients is important in detecting early relapse. Biochemical parameters, such as sedimentation rate, serum iron, ferritin, copper, iron, and zinc, which each by itself may be nonspecific, may help to detect early disease recurrence in some patients [11]. We have also followed these patients using various immunologic studies in the hope of correlating the laboratory finding with the disease activity clinically, as well as to understand better the biology of the disease [12–16].

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24. Results of therapy for Hodgkin's disease at St. Jude Children's Research Hospital

Judith A. Wilimas and Elizabeth I. Thompson

The first protocol for treatment of Hodgkin's disease at St. Jude Children's Research Hospital began in 1968 to test the relatively new concept of combined-modality therapy. Of the 56 patients entered in study, 40 remain alive in continuous complete remission at a median of 15 years. These patients have participated in several studies of late effects of therapy.

The second study entered 125 patients between 1972 and 1979. Stage I patients received extended-field radiotherapy (35–37 Gy). Stage II and IIIA patients were randomized between radiation therapy (RT) alone and radiation plus chemotherapy (CT), consisting of weekly vincristine and cyclophosphamide for 1 year and four 1-month courses of procarbazine. Stages IIB, IIIB, and IV received the same chemotherapy for 18 months and were randomized to RT or no RT. Randomization was closed in 1977 and subsequent patients received combined-modality therapy until 1979. Results are: stage I—three relapses in 31 patients (one death in remission); stages IIA and IIIA—six relapses in 18 patients treated with RT (one death from sepsis), and three relapses in 37 patients treated with RT + CT (one accidental death); and stage IIB, IIIB, and IV—12 relapses in 15 patients treated with CT, and eight relapses in 24 patients treated with CT + RT. Overall, 90 patients remain in continuous complete remission.

The third study was begun in 1979 to determine whether equivalent disease control with decreased toxicity could be achieved in stages II, III, and IV with CT and RT of 20 Gy. Chemotherapy and radiation ports (mantle, periaortic, or inverted Y) were the same as in the 1972–1979 study. Stage I patients continued to receive extended-field radiotherapy. Stage IIA patients with small (<33% thoracic width) or no mediastinal mass (SMM) received standard dose (35–37 Gy) RT to involved and next contiguous lymph node areas. Stage-specific results are: stages I and IIA (SMM)—five relapses in 42 patients; stages IIA and IIIA—two relapses in 31 patients; and stages IIB, IIIB, and IV—eight relapses in 24 patients. Of 97 patients, 82 remain in continuous complete remission. In 1981, because of reports of improved disease control for patients with stage IV disease with alternating cycles of MOPP (nitrogen mustard, Oncovin, procarbazine, and prednisone) and ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine), a toxicity trial consisting of alternating COP–ABVD plus 20 Gy to involved fields

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was opened for these patients. By 1984, six of 22 patients with stages IIB and IIIB receiving COP (cyclophosphamide, Oncovin, and procarbazine) plus 20 Gy had relapsed while none of eight stage IV patients treated with COP–ABVD–20 Gy had relapsed. Although numbers were small, acute toxicity in the COP–ABVD group was minimal. We, therefore, elected to begin treating patients with stage IIB and IIIB disease with COP–ABVD and 20 Gy involved-field radiation, hoping to achieve better disease control and avoid staging laparotomy. Acute toxicity has not been a major problem, but these children will need to be carefully monitored to assess long-term effects of such treatment. To date, 25 patients have been entered on this therapy. With a median follow-up of 2 years, one patient who had bone marrow involvement at diagnosis has relapsed.

Since carefully designed therapy results in overall cure rates approaching 90% in Hodgkin's disease, late effects of therapy are a major concern, particularly among children [1, 2]. Careful documentation of physical and psychosocial effects of treatment protocols may allow us to predict effects of new therapies more accurately [3]. We have conducted several studies of late effects in our patients who have been off therapy for 5 or more years. These studies have focused on three main areas: physical effects including growth and thyroid function, reproductive effects in women, and psychosocial effects.

Serial measurements of height were available on 34 of 40 patients in the first study, who were <16 years of age when they received 35–37 Gy mantle and/or abdominal RT. Not surprisingly, almost all of these children had a decrease in their height percentile from the time of diagnosis. This occurred even in patients who received only mantle RT, although the most striking decreases in height occurred in the younger patients treated with RT to the entire spine. Of the 34 patients, 11 had a height 5–10 years after therapy that was less than the 3rd percentile for age.

A similar analysis performed on 29 patients who received 20 Gy revealed that none of the patients had a height less than the 3rd percentile 3–7 years after therapy. However, the median age at diagnosis of these patients was 12.8 years as compared with 10 years in the earlier series, so less effect of RT on bone growth might be anticipated.

Serial thyroid function studies were analyzed on 188 long-term survivors who had received radiation to the neck, generally as part of a mantle field. Patients were begun on synthroid when thyroid-stimulating hormone (TSH) levels were >10 μU/ml. Currently on thyroid supplementation are 18 patients: 14 for elevated TSH, three following thyroid ablation for hyperthyroidism, and one who was hypothyroid before therapy for Hodgkin's disease. Five patients have developed thyroid nodules; all of these have been benign. Continued follow-up of these patients will be necessary. We are currently attempting to determine whether the relatively low incidence of thyroid abnormalities can be associated with omission of lymphangiograms.

A recent survey of ovarian function in long-term survivors of Hodgkin's disease revealed that 19 of 53 women responding to the questionnaire had overian failure (lack of menses without hormonal stimulation, elevated luteinizing hormone and follicle-stimulating hormone levels). Of these 19 patients, 17 had received total abdominal or inverted 'Y' RT ± CT, one received multiple CT agents, and one received 18 months of COP plus paraaortic RT. Only four of the women receiving inverted-Y RT had normal ovarian function. Many women in our studies experienced temporary cessation of menses during therapy and for periods of up to several years following therapy, but then resumed normal menses. Persistent ovarian failure seemed to occur much more frequently due to RT than to CT.

Little information is available concerning psychosocial late effects of Hodgkin's disease. The psychiatrist at our institution, Dr. Abby Wasserman, recently conducted a pilot study interviewing 40 patients off therapy at least 5 years. Results of this study are reassuring in terms of the paucity of serious psychopathology. Mean age of these patients at diagnosis was 13 years; mean age at the time they were interviewed was 25 years. Side effects of treatment including nausea, vomiting, hair loss, infections, and hospitalizations were most frequently perceived as the worst thing about having had Hodgkin's disease. Due to the illness and therapy, these patients missed a mean of 6 months of school; 16 patients reported unpleasant school experiences such as being teased about being bald or thin, or being treated as outcasts. In spite of this, educational levels attained by these patients exceeded those expected in age-, sex-, and state-matched populations. Most of the girls were concerned about their reproductive status while the boys expressed little interest in pursuing such studies. Interestingly, almost all of the patients felt that they had benefited in some way from the experience of having cancer. Current concerns of these young adults focused on job discrimination and difficulties in obtaining health or life insurance. This study has identified specific areas of concern. Future studies of the physical and psychosocial sequelae of therapy in these patients may allow modifications and refinements in therapy aimed at improving the quality of life in these patients.

Acknowledgments

This work was supported by grant CA 21765 (CORE) from the National Cancer Institute and by the American Lebanese–Syrian Associated Charities (ALSAC).

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25. Clinical investigations of children with Hodgkin's disease at Stanford University Medical Center

A Preliminary Overview Using Low-dose Irradiation and Alternating ABVD/MOPP Chemotherapy

Sarah S. Donaldson, Michael P. Link, I. Ross McDougall, Bruce R. Parker, and Stephen J. Shochat

Clinical studies of the efficacy of diagnostic and therapeutic regimens in the care of pediatric patients with Hodgkin's disease represent a major component of the longstanding, ongoing lymphoma program at Stanford University Medical Center. This program encompasses laboratory investigators into the nature of the lymphomas as well as evaluation of prospective clinical protocols. This chapter describes the current clinical investigations in pediatric Hodgkin's disease at Stanford initiated in May 1982, and serves as a preliminary overview of the project to date.

1. Background

In 1970, we became particularly concerned about youngsters with Hodgkin's disease when we were referred two children, one only 21 months and a second four years of age, with newly diagnosed Hodgkin's disease. Recognizing the bone growth abnormalities known to accompany high-dose, extended-field radiation [1] and the early effectiveness of combined-modality therapy in adults, a pilot protocol was designed to ascertain whether MOPP chemotherapy (nitrogen mustard, Oncovin (vincristine), procarbazine, and prednisone) could be used to replace a portion of the needed radiation dose in pathologically staged children with Hodgkin's disease. A total of 54 children were treated using the approach of low-dose irradiation and MOPP chemotherapy. The actuarial freedom from relapse of these patients is 90% and survival is 88% with a maximum 15-year follow-up and a median follow-up of 6½ years [2]. This approach of low-dose radiotherapy and chemotherapy is well tolerated and effective. Recognizing the complications of therapy among children treated with Hodgkin's disease [3], our goals in therapy have become: cure of a high proportion of these children without serious bone growth impairment; reduction of radiation- and chemotherapy-induced heart, lung, liver, and gonadal injury; and freedom from infections, sterility, and second malignant tumors. Our experience with low-dose radiation and six cycles of MOPP chemotherapy revealed an absence of the radiation-induced injury, which we had previously observed following high-

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dose extended-field radiation in children, but a concerning problem of infertility in young males, which was thought related to the degree of exposure to the alkylating agents in the MOPP combination. As well, we discovered unanticipated incidence of leukemia, with three of the 54 children developing acute leukemia. Our experience with nearly 7-year median follow-up now provides long-term experience that validates the effectiveness of low-dose radiation and chemotherapy and demonstrates the need for long-term follow-up. The unexpected late effects from the combined-modality therapy, felt largely to be related to the six cycles of MOPP chemotherapy, demanded a reappraisal and a plan for new drug therapy to be used in conjunction with low-dose radiotherapy.

With a 97% local control rate, which we observed with low-dose radiation (25, 20, and 15 Gy) and six cycles of MOPP and no difference in local control whether 15, 20, or 25 Gy was administered [2], we felt justified in our subsequent studies to further limit the radiotherapy to a dose of 15 Gy to areas of original known disease, and boost to 25 Gy only those sites of initial bulky disease or sites that failed to regress after two cycles of chemotherapy.

Surgical staging has been utilized in the Stanford studies since the late 1960s, even though we recognize the potential complications of postsplenectomy septicemia in children. We continue to recommend surgical staging in selected patients in order to define the sites necessary to irradiate in an involved-field irradiation program. Despite our concern over morbidity from surgical staging, there have been no serious complications from laparotomy and no fatalities from postsplenectomy bacteremia, since the routine use of pneumococcal vaccine and prophylatic penicillin in all patients. The concern of sterility as well as secondary oncogenesis including leukemia induction observed with low-dose radiation and six cycles of MOPP encouraged us to limit the exposure to MOPP by utilizing the ABVD/MOPP alternating regimen. The ABVD combination (Adriamycin, bleomycin, vinblastine, and DTIC) is reported to be less leukemogenic and less sterilizing than MOPP [4] and data suggest that reduction in exposure to alkylating agents may reduce the incidence of secondary leukemia and increase the likelihood of fertility in males. The ABVD/MOPP regimen may also be more efficacious than either combination used alone.

2. Methods

The patient population eligible for the current pediatric study, which opened in May 1982, includes all children with newly diagnosed, previously untreated Hodgkin's disease who have a bone age of $\leq$15 years and who will be treated and followed at Stanford University Medical Center and the Children's Hospital at Stanford. Children with a bone age >15 years are treated using adult protocol studies. A staging workup includes the following:

1. Careful history and physical examination with agreement by pediatric oncologists and radiation oncologists as to which lymph nodes are thought to be abnormal. Suspicious lymph nodes are biopsied.
2. Complete blood count, platelet count, erythrocyte sedimentation rate, and serum copper determination.
3. Chemical screening and battery including alkaline phosphatase.
4. Posteroanterior (PA) and lateral chest x-ray.
5. Thoracic computerized tomography (CT) scan.
6. Bipedal lymphography.
7. CT scan of abdomen and pelvis.
8. Bone scan with appropriate bone radiographs if a child is symptomatic or has abnormally elevated alkaline phosphatase beyond that expected by his age and growth pattern.
9. Bone age films.
10. Pulmonary function tests.
11. Percutaneous needle bone marrow biopsy in all children who have evidence of subdiaphragmatic disease, constitutional symptoms, bone disease, or significantly elevated serum alkaline phosphatase.

Staging laparotomy, splenectomy, selected lymph node and liver biopsies, and open bone marrow biopsy are routinely performed with the following exceptions:

1. Clinical stage IV patients.
2. Children with positive percutaneous bone marrow biopsy.
3. Children with clinical stage IA high right neck disease (above the angle of the mandible) with lymphocyte-predominant histology, in whom one is willing to treat with high-dose radiotherapy alone.
4. Children with clinical stage IA or IIA Hodgkin's disease confined to the thorax, who have a clearly negative lymphogram and in whom one is willing to give high-dose, extended-field radiotherapy.
5. Patients presenting with supradiaphragmatic disease who have a clearly positive lymphogram and in whom an involved radiotherapy field would not be altered by a staging laparotomy.

Patients are staged by the Ann Arbor staging system [5], with favorable and unfavorable staging guidelines utilized.

All initial diagnostic biopsy slides, as well as subsequent materials obtained during surgical studies, are reviewed by members of the Division of Surgical Pathology, and categorized using the Rye modification of the Lukes and Butler classification of Hodgkin's disease.

Upon completion of the diagnostic studies and for the purposes of resolving major questions of interpretation or procedure, a patient's history and physical examination, laboratory, radiographic, and surgical findings are reviewed at a lymphoma staging conference. This conference brings together physicians from Pediatric and Medical Oncology, Radiation Therapy, Diagnostic Radiology, Nuclear Medicine, Pathology, and Surgery. After review of the appropriate data, the child's treatment is determined

including the volume of radiation and plan of interdigitation of chemotherapy and radiation therapy.

The techniques of radiation involve standard radiation fields as defined, including a mantle, minimantle, hemi-minimantle, Waldeyer's field, spade, and inverted Y. Involved field (IF) radiation implies treatment to the involved lymph node regions only (as defined at the Rye symposium) [6]. In patients with cervical, infraclavicular, or axillary disease, all three regions are treated in continuity. Both hila and the mediastinum are irradiated when any portion of those regions is involved. Prophylatic radiation of the pericardium is omitted. Attention is given to sparing normal structures such as the larynx, and the humeral and femoral heads, whenever possible. In patients who have splenic disease, a splenic hilar and paraaortic field is utilized. Splenic and abdominal nodal radiotherapy is given to patients with clinical stage III and IV disease. Pelvic radiation is not given to young women unless a pretreatment oophoropexy is performed.

The radiation dose to involved sites is a minimum of 15 Gy. In patients with massive initial disease, or those with residual disease following two cycles of chemotherapy, localized boosts are given to a total of 25 Gy. Boosts are normally given at the completion of the planned therapy. If necessary, emergency or urgent radiotherapy is administered prior to completion of staging for immediate relief of large symptomatic masses.

Patients receive combined modality therapy in an alternating fashion: first, two cycles of chemotherapy, then one region of radiotherapy, followed by two cycles of chemotherapy, and then (if necessary) a second region of radiotherapy, until six cycles of chemotherapy are given and all involved areas are irradiated.

The chemotherapy employed involves alternating ABVD and MOPP. The ABVD chemotherapy is administered as:

Adriamycin	25 mg/m^2 IV, day 1 + 15
Bleomycin	10 mg/m^2 IV, day 1 + 15
Vinblastine	6 mg/m^2 IV, day 1 + 15
DTIC	375 mg/m^2 IV, day 1 + 15

The MOPP chemotherapy is administered as:

Nitrogen Mustard	6 mg/m^2 IV, day 1 + 8
Vincristine (Oncovin)	1.4 mg/m^2 IV, day 1 + 8
Procarbazine	100 mg/m^2 PO, day 1–14
Prednisone	40 mg/m^2 PO, day 1–14

The treatment is repeated every 4 weeks except when alternated with radiotherapy. Prednisone is given in the first MOPP cycle only, when patients have received mediastinal radiation. The ABVD and MOPP is alternated every other cycle with the initial cycle being ABVD. Every effort is made to give full doses of all drugs with each course. Short delays in therapy are often necessary to administer chemotherapy courses at full dose

Table 1. Combined treatment modality of alternating ABVD and MOPP with low-dose radiotherapy.

IA, IIA I_EA, II_EA IB, IIB I_EB, II_EB	ABVD/MOPP → IF radiotherapy → ABVD/MOPP → ABVD/MOPP
IIIA, III_EA, III_SA, $III_{SE}A$ IIIB, III_EB, III_SB, $III_{SE}B$ IV, multiple E's	ABVD/MOPP → IF radiotherapy → ABVD/MOPP → IF radiotherapy → ABVD/MOPP → IF radiotherapy
IV_M	Alternating ABVD/MOPP × 6 → consolidative IF radiotherapy

[7]. The combined-modality treatment of alternating ABVD and MOPP with low-dose radiotherapy is shown in Table 1.

3. Measurement of effect and toxicity

At the completion of therapy, children are examined carefully for any evidence of disease. This includes a physical examination and repeat radiographic studies including KUB (kidneys, ureters, and bladder) to be certain that all opacified involved lymph nodes have returned to normal appearance. Any noninvasive diagnostic studies, which initially demonstrated disease, are repeated. A bone marrow biopsy is obtained in all children who had involvement of the liver or marrow at the time of presentation. Surgical restaging is not done.

4. Follow-up

All children are followed in a conjoint lymphoma clinic staffed by members of the Division of Radiation Therapy and Oncology, and by members of the Division of Pediatric Oncology at the Children's Hospital at Stanford. The routine follow-up examinations after completion of therapy are every 2 months for the first year, every 3 months for the second year, every 4 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter. Routine follow-up studies include: PA and lateral radiograph of the chest, KUB as long as lymphographic contrast material remains, complete blood count, erythrocyte sedimentation rate, serum copper, platelet count, alkaline phosphastase, weight, and standing and sitting height. Free thyroxin (FT4) and thyroid-stimulating hormone (TSH) are obtained every 6–12 months. Thyroid antibody studies are performed annually. Follicle-stimulating hormone, LH, and testosterone are studied annually. When boys are postpubertal and able to provide semen for sperm counts, a semen analysis is obtained. If abnormal, it is repeated every 2–3

years to assess whether normal values return. Repeat lymphography is obtained during the first 3 years of follow-up whenever patients have inadequate residual contrast for adequate examination of nonirradiated retroperitoneal nodes or when there is a concern over potential relapse. If a thyroid nodule is found on physical examination, the patient undergoes workup including fine-needle aspirate, iodine-123 scintiscan, and ultrasound. If the clinical findings are suspicious, operation is advised. After careful evaluation at each clinic visit, patients are scored as being disease free, having equivocal evidence of disease, or having known active disease. Patients are observed continuously for long-term complications of therapy. Should any child have suspicion of relapse, pathologic confirmation of relapsing disease is required and patients are clinically restaged.

Replacement thyroid therapy is given to children who become chemically hypothyroid (elevated TSH and low or low-normal FT4) and monitored regularly. In those children who become hypothyroid during the first year after treatment in whom it is probable that the lymphangiogram load of iodine has played a role, thyroid replacement is stopped after 1 year for 6–8 weeks to determine whether thyroid function has spontaneously returned to normal (using clinical evaluation, FT4 and TSH). In those children whose hypothyroidism occurs 1 year or more after radiotherapy, periodic (*i.e.*, annual) attempts are made to lower the dose of thyroid replacement and, if possible, discontinue it. This will allow us to determine precisely the frequency of permanent hypothyroidism and, more importantly, ensure euthyroid children are not taking thyroxin needlessly [8].

Gated nuclear left ventricular angiograms are performed regularly in any patient with history or physical findings suggestive of cardiac dysfunction. Pulmonary function studies are done at the completion of therapy and at yearly intervals thereafter in patients who present with mediastinal disease or have mantle irradiation in addition to chemotherapy.

5. Results

To date, 33 children have been entered into this study. The chronologic ages of the children range from 5 to 17 years, which represent a bone age range of 5–14 years. The mean age for the group is 11 years. Of the 33, 15 (45%) are 10 years of age or less. There are 23 boys and ten girls for a male-to-female ratio of 2.3:1.0.

The stages of the children are shown in the insert in Figure 1; 24 had stage III and IV disease, while nine had stage II disease. Of the nine with stage IV disease, eight were stage IV on the basis of extensive pulmonary involvement with or without pleural and pericardial involvement, and one had bone marrow and bone involvement. None had recognized hepatic involvement. Eight of the children were classified as unfavorable on the basis of having massive mediastinal disease (>0.33 intrathoracic diameter)

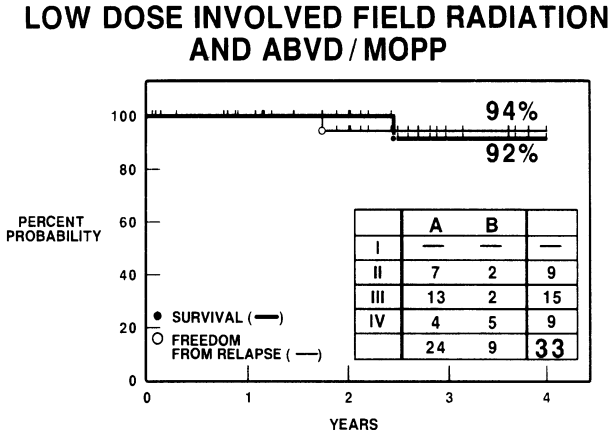

Figure 1. The actuarial survival and freedom from relapse for the total patient population. The stages of the patients are shown in the insert.

[9]. An additional seven children were considered unfavorable on the basis of having bulky splenic disease (five or more nodules) [10]. Only nine (27%) of 33 presented with systemic symptoms of fever, night sweats, or weight loss of >10% of the normal body weight. Seven of these nine had stage III or IV disease.

The histologies of the group revealed the following subtypes: one had lymphocyte predominance, 25 had nodular sclerosis, six had mixed cellularity, and one had interfollicular. Thus, in this series, 94% had either nodular-sclerosis or mixed-cellularity subtypes.

Staging laparotomy with splenectomy was performed in 25 (76%) of the 33 children. The eight exceptions included seven children with massive mediastinal disease staged as IV on the basis of multiple extralymphatic extension to the lung, pleura, chest wall, and/or pericardium, and one was stage III with supradiaphragmatic palpable disease and a clearly positive lymphangiogram. Of the 25 cases who were subjected to staging laparotomy, 15 (60% of the group) had subdiaphragmatic disease detected by staging laparotomy and thus a change in the definition and extent of the involved field of radiation.

The actuarial survival and freedom from relapse for the study population is shown in Figure 1. The projected survival is 92% and freedom from relapse is 94% with a maximum follow-up of 4 years and a median follow-up of 2 years.

There has been one treatment failure. One child with clinical stage IVB disease involving the lung, pleura, and pericardium, unfavorable on the basis of massive intrathoracic disease, had a recurrence in the mediastinum at 22 months after diagnosis. She received an additional cycle of chemotherapy that rendered her clinically free of disease and then was given an autologous bone marrow transplant. The bone marrow transplant was com-

plicated by poor engraftment, cytomegalovirus, and *Pneumocystis carinii* pulmonary infections. She died 5 months after transplantation from these complications, and evidence of microscopic residual Hodgkin's disease in the hila and lung was confirmed at autopsy.

The overall response to chemotherapy has been excellent. All patients have been clinically free of disease at the completion of their planned therapy. Patients with massive disease at presentation who have had persistent radiographic abnormalities after chemotherapy have been given boosts of radiotherapy to a total of 25 Gy. Patients not subjected to staging laparotomy who have positive lymphangiograms received radiotherapy to their spleen and upper-abdominal lymph nodes. The response rate to the planned therapy has been 100%.

Complications from therapy have been minimal. There has been no operative mortality. One out of 27 who had staging laparotomy developed a postsurgical pancreatitis that resolved spontaneously. There has been one episode of small bowel obstruction that resolved with supportive management. All children who have splenectomy are given prophylactic penicillin and most are given pneumococcal vaccine in addition. There have been no episodes of serious bacterial infections using this program.

To date, no cases of cardiac, pulmonary, hepatic, or thyroid injury, or growth abnormalities have been observed. However, we recognize that the duration of follow-up has been too brief for most of these potential late effects to be recognized. Furthermore, an analysis of gonadal function is too premature to know whether there will be some preservation or recovery of spermatogenesis following the alternating ABVD/MOPP chemotherapy program. Notably, no second malignant tumors have yet been observed, but the duration of follow-up has been too short to assess accurately either leukemogenesis or solid tumor induction.

Efforts are directed toward cure of Hodgkin's disease with a minimal amount of morbidity. In terms of the pediatric population, morbidity requires long-term follow-up. To test the efficacy of this study, children will need to be followed for many years. Whereas 77% of relapses occur within the first 3 years following treatment, we have seen initial relapses as late as 15 years after radiotherapy alone [11]. Thus, assessment of efficacy requires long-term follow-up of relapse status as well as late effects. Growth and development abnormalities are not expected to occur until well after children have completed their adolescent growth spurt and are into their pubertal status. Whereas leukemias have been observed 2–3 years after completion of therapy, solid tumor induction often takes 10 years or more to appear. Thus, secondary tumor involvement will require many years of follow-up for this complication to be assessed. We will continue to investigate risk factors, with the long-term goal of tailoring therapy to patients' stage and extent of disease, minimizing treatment whenever possible, keeping in mind a long-term goal of quality of life for these children for whom cure of disease is likely.

Acknowledgments

The authors thank Saul A. Rosenberg, MD, and the late Henry S. Kaplan, MD, for their guidance and support, Lois Hall for secretarial assistance, and Anna Varghese for data analysis. This work was supported in part by grant CA 34233 from the National Cancer Institute, National Institutes of Health.

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Summary

26. Hodgkin's disease mongraph

Stephen C. Peiper and Costan W. Berard

The entity (or entities) that we recognize as Hodgkin's disease has several clinical and pathologic features that set it apart from the non-Hodgkin's lymphomas and other malignancies in general, and place it in its own unique pathophysiologic group. This tumor was first described by Thomas Hodgkin in 1832 and thus was one of the first malignant tumors to be studied using morbid anatomic techniques. Hodgkin's disease was also one of the first malignant tumors frequently found to be responsive to the available chemotherapeutic and radiotherapeutic modalities [1, 2]. The potential ability to recognize subgroups of patients capable of being cured stimulated the interests of clinical scientists, including pathologists, to study this disease more intensively [3–6]. Continued efforts in the analysis of the pathology of Hodgkin's disease gave insights into the patterns of its histopathology and anatomic progression. This accelerated the development of guidelines for the histologic features that were predictive of favorable and unfavorable clinical outcomes in 1966 and of treatment regimens tailored to the disease status of the patient, based on staging guidelines established at Ann Arbor, Michigan, in 1971. Thus, Hodgkin's disease has been the frontrunner of hematologic malignancies in which the understanding of anatomic and pathologic features plays an important role in designing therapy and predicting the clinical outcome.

In contrast to our empirical understanding of the clinically relevant pathologic features of Hodgkin's disease, we know little about the biology or the cytogenesis of its malignant element, the Reed-Sternberg cell, and its variants. These cells have well-defined and characteristic morphologic features that are neither specific for malignancy nor of a particular lineage of immunopoietic cells. Reed-Sternberg cells may be a morphologic manifestation of activated cells of the lymphoid or mononuclear phagocyte lineages in various reactive lymphadenopathies. The morphology of Reed-Sternberg cells, therefore, does not yield insight into their derivation, as was the case for the non-Hodgkin's lymphomas. This ambiguity has provided a challenge to the anatomic pathologist to characterize the Reed-Sternberg cell and to identify its normal counterpart.

Many approaches have been used to deduce the cell of origin and to

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characterize the differentiated phenotype of Reed-Sternberg and Hodgkin's cells [3–6]. Morphologic studies have revealed conflicting ultrastructural features of Reed-Sternberg cells and have failed to resolve whether they are derived from lymphocytes or mononuclear phagocytes. Cytochemical analysis indicates that these cells contain acid phosphatase, but does not provide definitive evidence regarding the cell of origin. Similarly, conflicting studies of the immunoglobulin content of Reed-Sternberg cells have shown the presence of polyclonal and monoclonal immunoglobulin molecules, interpreted as indicative of derivation from mononuclear phagocytes and B-lymphocytes, respectively. The availability of large panels of monoclonal antibodies, including several antibodies specific for each of the various hematopoietic lineages, has not helped to clarify this issue as was originally hoped. Reed-Sternberg cells have been shown to express a primitive phenotype and not to react with any of the lineage-specific monoclonal antibodies. These cells consistently have been shown to express HLA class II antigens, the receptors for interleukin 2 and transferrin, and antigens recognized by the Ki1 and the LeuM1 monoclonal antibodies. Finally, application of molecular biologic techniques to study the configuration of the genes encoding the polypeptide subunits of immunoglobulin and T-cell receptor molecules has not produced conclusive evidence of a rearrangement, as would be observed in B-lymphocytes and T-lymphocytes, respectively. It therefore appears that Reed-Sternberg cells have a phenotype consistent with that of a primitive cell that has undergone activation, but do not express phenotypic markers that are characteristic of differentiation to lymphocytes or mononuclear phagocytes. These cells appear to represent a phenotypic novelty that defies the ability of currently available technologies to clarify their derivation. The hypothesis underlying several of the chapters in this monograph is that malignant cells have normal counterparts that can be demonstrated to fit into a differentiation pathway based on their phenotype. Reed-Sternberg cells and their variants may not have a normal phenotypic counterpart, as is provocatively proposed by Dr. Bucsky in this monograph [5]. It is unclear whether compilation of additional phenotypic data will help to solve this conundrum.

The lymphocyte-predominance subtype of Hodgkin's disease may represent a distinct clinicopathologic entity. It frequently has a nodular pattern of growth, as is observed in B-cell malignancies, and the Reed-Sternberg cell variants express four protein antigens characteristic of B-lymphocytes (CD19, CD20, CD21, and J chain). Dr. Poppema *et al.* present the results of cell fusion studies that have a controversial interpretation [3]. Cells from a lymph node involved by nodular sclerosing Hodgkin's disease were fused with a mouse myeloma cell line and hybrids that bound the Ki1 and LeuM1 monoclonal antibodies were assumed to be Reed-Sternberg cell hybrids. These clones were found to have rearranged immunoglobulin light-chain genes that were different for each clone, although no rearrangement was detected in the original lymph node. This is interpreted as evidence for a

polyclonal B-cell derivation of nodular sclerosing Hodgkin's disease, implying that this may be a premalignant state that may subsequently undergo malignant transformation. This finding is provocative, but requires confirmation by an independent strategy, particularly because the rules for gene expression and rearrangement have not been established for somatic cell hybrids. Reactivity with Ki1 and Leu M1 is not specific for Reed-Sternberg cells; both may react with activated lymphoid cells and thus the Ki1–LeuM1 —positive hybrids with rearranged immunoglobulin light-chain genes may represent fusion with activated B-lymphocytes. It will be necessary to identify stringent phenotypic and/or genotypic criteria for Reed-Sternberg cells to facilitate the interpretation of such studies.

It could be argued that the cell of origin of the Reed-Sternberg cell is an intriguing issue, but that perhaps a more relevant one is the functional biology of this cell type. The diagnosis of Hodgkin's disease is not based solely on the identification of the neoplastic element, as is the case with the vast majority of malignant tumors, but is also dependent upon the presence of the appropriate background of (reactive) immune and inflammatory cells. Indeed, Reed-Sternberg cells typically compose a very minor proportion of the tumefaction in Hodgkin's disease, estimated at ~1%. It can be concluded that these cells represent a profoundly immunocompetent species of neoplastic immune cells whose major biologic manifestation is the ability to elicit an inflammatory infiltrate, a feature of activated cells of the efferent limb of the immune system. Perhaps an in-depth understanding of the pathophysiology of Hodgkin's disease will provide insight into alternative strategies for therapy and the nature of the malignant element(s).

It is probable that the infiltrate of reactive cells characteristic of involvement by Hodgkin's disease is elicited directly or indirectly by cytokines secreted by Reed-Sternberg and Hodgkin's cells. The reactive infiltrate characteristic of Hodgkin's disease is polymorphic and varies in accordance with the histologic subtype. A major component of this infiltrate consists of morphologically normal small lymphocytes that have a membrane immunophenotype characteristic of activated helper T4-lymphocytes (positive for T1, T3, T4, T10, and class II HLA antigens). These lymphocytes are frequently found to be adherent to the Reed-Sternberg cells in single-cell suspensions. The nature of this interaction is unclear. It may be a manifestation of an immunologic response to a tumor cell or represent a vestige of a physiologic intercellular interaction between activated helper T cells and the malignant cognate of an antigen-presenting cell.

The monokine interleukin 1 (IL-1) has been directly implicated in the pathogenesis of Hodgkin's disease [7]. Reed-Sternberg cells and their variants in the lymphocyte-predominance and nodular sclerosing histologic subtypes have been found to contain IL-1 by immunocytochemical staining with antibodies to recombinant human IL-1. Although mononuclear phagocytes are the primary source of IL-1, the production of this polypeptide is not limited to cells of this lineage. The association of IL-1 with Reed-

Sternberg cells should therefore not be interpreted as evidence favoring a derivation from cells of the mononuclear phagocyte system. This association is a very stimulating finding because IL-1 is a hormone-like polypeptide [8] that has several biologic activities that could explain some of the clinical and pathologic manifestations of Hodgkin's disease. This protein was first described in mice as a product of monocytes capable of enhancing the mitogenesis of thymocytes. It has subsequently been shown to enhance selectively the proliferation of helper T-lymphocytes, the population that comprises the majority of lymphoid cells present in the infiltrate of Hodgkin's disease. IL-1 stimulates the proliferation of fibroblasts, and thus could play a role in the fibrosis that frequently accompanies Hodgkin's disease. It also is able to enhance the proliferative effect of the colony-stimulating factors on primitive hematopoietic progenitor cells and is a chemoattractant for mature granulocytes and macrophages. IL-1 could exert a strong effect in eliciting a polymorphic infiltrate composed of helper T-lymphocytes, neutrophils, eosinophils, and histiocytes that is characteristic of Hodgkin's disease. IL-1 also has effects on distant target organs that may account for clinical and laboratory features of this malignancy. Its action on the thalamus results in pyrexia and it stimulates hepatocytes to synthesize and secrete acute phase reactants.

Another characteristic constituent of the infiltrate of Hodgkin's disease is neutrophilic and eosinophilic granulocytes. Moreover, approximately one-third of patients with Hodgkin's disease have an elevation in circulating granulocytes, which may coincide with medullary granulocytic hyperplasia. Cells of the lymphoid and mononuclear phagocyte lineages may elaborate factors that stimulate the proliferation and localization of granulocytic cells. Two such factors are granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor (GM-CSF). Both are polypeptides capable of inducing the proliferation of hematopoietic colonies that are composed of granulocytic cells (G-CSF) or mixtures of granulocytic and monocytic cells (GM-CSF) and of potentiating the effector cell functions of mature granulocytes and monocytes. Stimulation of monocytes with gamma-interferon or endotoxin induces the production of G-CSF and activations of T-lymphocytes induces the production of GM-CSF. The monokines IL-1 and tumor necrosis factor are capable of inducing the production of G-CSF and GM-CSF by fibroblasts and endothelial cells. It is possible that the biologic activities of colony-stimulating factors selected by neoplastic or reactive mononuclear phagocytes and lymphocytes may play a role in the pathogenesis of the involvement of granulocytic cells in Hodgkin's disease.

The availability of cell lines representative of Reed-Sternberg cells will greatly enhance our understanding of the functional biology and the cellular derivation of this cell type. Intensive efforts have been made to derive such a cell line from tissues involved by Hodgkin's disease. The cell lines derived

from patients with Hodgkin's disease are described in detail in the chapter by Drs. Burrichter, Schaadt, and Diehl [4]. All of the lines have been derived from patients with advanced-stage disease; seven of eight are from patients with the nodular sclerosis type and one from a patient with the lymphocyte-depleted type. The authors appropriately point out that only three of the eight lines that have been established express a phenotype characteristic of Reed-Sternberg and Hodgkin's cells *in situ*. Six of the eight lines express the phenotypic hallmarks of Reed-Sternberg cells: class II HLA antigens, determinants recognized by the LeuM1 monoclonal antibody, and the polypeptide recognized by the Ki1 monoclonal antibody. The phenotype of three of the six diverges from that of Reed-Sternberg cells based on the acquisition of reactivity with monoclonal antibodies to T-lymphocyte antigens and/or the M1 monoclonal antibody. Five cell lines express features of lymphoid cells (3-B, 2-T), two express features of cells of the mononuclear phagocyte system, and one does not have features of B- or T-lymphocytes. It must be assumed either that Hodgkin's disease is a heterogeneous malignancy that may be derived from various cell types, that it is derived from a primitive cell capable of differentiating to various cell types, or that some of the cell lines are not representative of Reed-Sternberg cells. Further progression of our understanding of Hodgkin's disease depends upon the ability to establish stringent criteria in order to identify cell lines representative of the malignant elements of Hodgkin's disease.

Hodgkin's disease is the most common lymphoreticular malignancy in the United States and Europe. This disease has elements of heterogeneity that include a bimodal age distribution and four histopathologic variants. Hodgkin's disease is curable with radiotherapic and chemotherapeutic regimens, unlike the low-grade non-Hodgkin's lymphomas. The malignant element in Hodgkin's disease, the Reed-Sternberg cell, composes a minor proportion of the tumor burden, but, in spite of this, it evokes local and systemic effects, indicating that it is indeed an immunocompetent species. The Reed-Sternberg cell can be likened to the conductor of a symphony. In its microenvironment in the lymph node, Reed-Sternberg cells are capable of eliciting a polymorphic infiltrate composed of helper T-lymphocytes, plasma cells, mononuclear phagocytes, neutrophils, eosinophils, and activated fibroblasts. The Reed-Sternberg cells contain IL-1, which may play a role in the pathogenesis of this reactive infiltrate. Patients with Hodgkin's disease may also have systemic manifestations, which often include an acquired immunodeficiency state. The Reed-Sternberg cell itself is a mystery; it has the phenotype of an activated primitive cell, but does not express features of differentiation to lymphocytes or mononuclear phagocytes.

Reed-Sternberg cells have been found to be aneuploid, but more specific cytogenetic studies are not available. Intensive efforts have been made to generate cell lines representative of Reed-Sternberg cells and several candidates are available. Analysis of such lines will facilitate the study of the

mediators of the local and systemic alterations observed in Hodgkin's disease, and monoclonal antibodies to these lines may help to solve the mystery of the normal cognate of Reed-Sternberg cells.

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27. Clinical overview of Hodgkin's disease

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The purpose of this overview is not to look for consensus, not to resolve important therapeutic questions and certainly not to recommend a 'middle of the road' noncontroversial (a highly unlikely possibility) treatment schedule for each stage of Hodgkin's disease. The purpose is to acknowledge that there are some very important unresolved issues and that children with Hodgkin's disease need to be treated on research protocol [1–4].

What are the more common issues being addressed by current pediatric oncologists [5–14]? We have elected to choose four that are relevant to early and, in some cases, late stages of Hodgkin's disease:

1. Is there a chemotherapeutic alternative for MOPP (nitrogen mustard, Oncovin, prednisone, and procarbazine)?
2. Can the role of radiation therapy be further reduced or even eliminated?
3. Can some or even all patients be managed without the traditional staging laparotomy?
4. What are the medical and psychosocial consequences of being treated and cured of Hodgkin's disease? Do the current supportive care measures have the potential to reduce these?

No one institution or cooperative group can address all of the first three questions. The contributors to this volume have stated their current priorities. A representative of each of the three treatment modalities (chemotherapy, radiotherapy, and surgery) was also asked to write a chapter, not only of their own descriptive, but also of their perception of the other two descriptives [1, 3, 4].

From these chapters and the institutional reports, it is obvious that no consensus has yet been reached. However, they all have one common thread: for early stages of Hodgkin's disease, eliminate unnecessary therapy or procedures while maintaining a high percentage of long-term survival and, for advanced Hodgkin's disease, improve long-term survival.

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