Hodgkin's disease—I: identification and classification

Patrice Carde

This is the tenth in a series of articles examining recent developments in cancer

The rare disease described in 1832 by Sir Thomas Hodgkin has during the past 30 years been a model for the development of diagnostic and therapeutic procedures. The story starts in 1963 with the claim by Easson that Hodgkin's disease, a type of disseminated cancer, was curable. Several workers showed that if radiotherapy fields were sufficiently large and radiation doses sufficiently high cure was possible. From the beginning an unusual degree of cooperation prevailed between pathologists, radiotherapists, surgeons, radiologists and, later, medical internists and statisticians. From 1957 to 1971 the principles of lymphangiography, surgical staging, clinical staging, pathological classification, isotopic scanning, megavoltage radiation therapy, monochemotherapy, and polychemotherapy were combined in a comprehensive multidisciplinary approach. Statistical analyses, the search for prognostic factors, and controlled trials evolved accordingly.¹ As a consequence survival rose dramatically.

Since the introduction of adjuvant chemotherapy around 1970, however, there has been no evidence of improvement in survival (table I) as documented by the international data bank overview of Hodgkin's disease. The 8671 patients treated from 1970 to 1979 had a similar survival (60% at 20 years) to the 5096 treated after 1980.^{2,3} This observation, made in a large cohort of patients treated in expert centres and confirmed in successive cohorts of patients with localised disease during 1972-86, contrasts with the usual optimistic statements.^{4,5}

The first reason for the failure to improve survival is the high mortality still associated with Hodgkin's disease in certain groups of patients. A better understanding of the pathogenesis (roles of Epstein-Barr virus, oncogenes, genetics), biological characteristics (lymphokine production, immunophenotype), and initial prognostic factors of this disease may make the identification of high risk groups easier. Early recognition of the patients in whom treatment is likely to fail or those likely to have a recurrence may provide an opportunity, before irreversible iatrogenic toxicity occurs, to switch to an alternative treatment, with some chances of success.⁶

The second reason for survival not improving is the increasing incidence of deaths that are not related to the disease itself but to the consequences of modern treatments. Patients in the international data bank overview who remained free of disease still had a risk of death more than twice that of a population of the same age and sex. As within six years after diagnosis the risk of dying of unrelated causes overrides that of dying of Hodgkin's disease, and in patients in their early 50s, 20 years after diagnosis the cumulative number of unrelated deaths equals that of deaths from Hodgkin's disease. After 10 years, when virtually no deaths from Hodgkin's disease occur, the standardised mortality ratio is still four to eight times greater in these patients than controls. Less than 5% of these deaths are related to secondary leukaemia or myelodysplasia (for which the causative factor is chemotherapy) or to non-Hodgkin's lymphoma (unknown causes); most of the deaths are from cardiac or pulmonary related diseases (which are caused by radiotherapy, with or without chemotherapy) or secondary solid tumours (due to radiotherapy, immune defects, or chemotherapy).^{2,3,7,8} Thus the costs and benefits of chemotherapy and extended field radiotherapy have to be carefully balanced in patients with early stage Hodgkin's disease.

Finally, even though current science may only marginally improve a survival rate as high as 60% at 20 years, it may, and must, urgently improve the quality of patients' lives.² The toxicity and stress associated with staging (for instance, by laparotomy, which has no impact on survival), prolonged treatments, and, most of all, gonadal damage and infertility should be quantified and prevented.⁹

Pathology and immunopathology

Both the presence of the Hodgkin and Reed-Sternberg cells and a characteristic cytological environment are required for a pathological diagnosis of Hodgkin's disease. The Rye classification remains the standard: in 5096 cases diagnosed since 1980 in the international data base the proportions of histological subtypes were lymphocyte predominance 6.3%, nodular sclerosis 63.9%, mixed cellularity 24.6%, lymphocyte depletion 1.9%, and unclassified 3.2%.² However, morphologically this is an extremely diverse disease.¹

Recent progress in pathology, immunophenotyping, and cytokine recognition has challenged the concept of Hodgkin's as a single disease. Nodular lymphocyte predominant Hodgkin's disease has been shown to be of a B cell phenotype and to synthesise J chains; high grade B non-Hodgkin's lymphomas evolve commonly from this subtype, which now could be considered a B cell non-Hodgkin's lymphoma. Within the nodular sclerosis category the British National Lymphoma Investigation has described morphologically a more aggressive subtype.¹⁰ Lymphocyte depleted categories of Hodgkin's disease actually represent anaplastic large cell lymphomas exhibiting Ki-1 (CD 30) positivity by morphological and immunological criteria, and some cases of anaplastic non-Hodgkin's lymphoma exhibit all of the features of Hodgkin's disease, including surface receptors for interleukin 9.¹² An admixture of cases of non-Hodgkin's lymphomas with nodular

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TABLE I—Proportion of patients with Hodgkin's disease achieving complete remission, relapse free survival (in complete responders), and survival at five and 15 years according to Ann Arbor Stage^a

Clinical stage	No of patients	% With complete remission	% With relapse free survival at five years*	% With relapse free survival at 10 years*	% Survival at 5 years	% Survival at 15 years
I A:						
1970-9	1516	98	80	75	90	70
After 1980	949	98			90	
II A:						
1970-9	2488	95	74	70	88	70
After 1980	1511	94			90	
I B/II B:						
1970-9	1081	87	73	69	80	62
After 1980	721	83			81	
III A:						
1970-9	940	87†	75	63	78	57
After 1980	510	87			83	
III B:						
1970-9	1001	77†	65	61	64	42
After 1980	641	75			70	
IV:						
1970-9	544	62	66	62	54	35
After 1980	752	63			62	

*In complete responders.

†All results for clinical stage III together.

sclerosis lacking mature T or B immunophenotype cannot be distinguished from nodular sclerosis Hodgkin's disease. Cytokine production and histology may be correlated: interleukin 5 receptors and eosinophilic granuloma, secretion of transforming growth factor β in nodular sclerosis Hodgkin's disease.^{13 14} Cell lines were also shown to secrete tumour necrosis factor, macrophage colony stimulating factor, and prostaglandin E2. Such correlations may provide clues to the cell of origin of Hodgkin's disease or the prognosis of the disease; they may also help explain the causes of B symptoms; the role of interleukin 1, and interleukin 6 in the pathogenesis of the characteristic fever and correlated sweats has been investigated.^{15 16}

Cytogenesis, genetics, and epidemiology

The histopathogenesis of the Reed-Sternberg cell still resists analysis, but there have been some recent insights. Immunophenotyping and genotyping of these cells and derived cell lines, the use of viral probes for the polymerase chain reaction or in situ hybridisation techniques, and results of karyotyping together tentatively indicate a syndrome which fits well with the epidemiology.^{12 17 18} Briefly, Reed-Sternberg cells have an immature lymphoid genotype (usually heavy rather than light immunoglobulin gene rearrangements, which are a characteristic of pre-B cell precursors, and T cell receptor gene rearrangements, which are characteristics of pre-T cells). This contrasts with the concomitant phenotypic expression of late "activated" lymphoid cells. The activation markers on these cells (CD 25, CD 30, CDw70, and HLA-DR) are similar to those expressed on Epstein-Barr virus transformed cell lines. This suggests that Reed-Sternberg cells could represent the malignant transformation of immature lymphoid cells that have been infected by the Epstein-Barr virus, a potent activator of lymphoid cells, at the very moment when immunoglobulin or T cell receptor genes are rearranged. Indeed, different techniques have not only shown the presence of the Epstein-Barr virus genome in the cells but have also proved it to be in a clonal form, implying that the virus entered the tumour cells before clonal expansion.¹² In parallel, increased levels of IgG and IgA antibodies against capsid antigens have been recorded, indicating a role for the Epstein-Barr virus during the development of Hodgkin's disease, at least as a cofactor. One possible mechanism is that it acts through a paracrine network of cytokines, mimicking the interaction between the epithelial neoplastic cells and benign lymphoid infiltrating cells seen in nasopharyngeal carcinoma, another cancer related to Epstein-Barr virus.

The lymphocyte predominant category, now considered as a B non-Hodgkin's lymphoma, is set apart; it is probably associated with the evolution of Hodgkin's disease from non-Hodgkin's lymphoma and also with the t(14;18) translocation juxtaposing the BCL2 proto-oncogene, which is implicated in preventing programmed cell death (apoptosis), on to the gene for the Ig heavy chain.

Initial presentation and investigation

The two main histological types of Hodgkin's disease (nodular sclerosis and mixed cellularity) in fact represent two different diseases. The nodular sclerosis type is much more common (70%), occurs at a younger age, and is more common in women; in these cases the nodal disease usually develops at sites related to the drainage of the upper respiratory tract—that is the mediastinum and neck. The mixed cellularity type of disease (30%) more often affects the spleen and the infradiaphragmatic nodes as well as the liver, lung,

Work up recommended in localised supradiaphragmatic presentations

Mandatory	Clinical history and examination Ann Arbor or Cotswolds classification Blood counts, erythrocyte sedimentation rate, liver function, HIV serology Chest radiography, computed tomography of thorax, lymphography (or computed tomography of abdomen and pelvis as second choice) Bone marrow biopsy and aspiration
Recommended	Lactate dehydrogenase activity Ultrasonography of liver and spleen
Investigational	Computed tomography of abdomen in addition to lymphography Magnetic resonance imaging Gallium scanning, technetium bone scanning Immunoscintigram with antiferritin or antiCD30 Serum concentration levels of soluble CD8, CD25, CD30, IL-6 Epstein-Barr virus serology

and bone marrow, presumably by haematogenous spread.¹⁹ Thus staging should be adapted to the histological type as well as to the apparent spread of the disease.

In localised disease the staging (box) has two purposes: firstly, to ensure that the usual locoregional nodal presentation (clinical stages I-II; 60-65% of cases at first diagnosis) represents the actual spread of the disease and thus that limited radiotherapy fields carry a high likelihood of cure; secondly, to estimate through a series of well validated prognostic factors, the potential for the disease to spread outside the radiation fields and therefore the need for adjuvant chemotherapy.^{4 20-23} Lymphangiography has proved a more sensitive and specific staging investigation than computed tomography in visualising the retroperitoneal and iliac node groups in all comparative studies on Hodgkin's disease and should remain central to investigations in localised supradiaphragmatic disease.²⁴ The risk of splenic disease is highly correlated to positive results on lymphangiography and, therefore, indirectly, it is more sensitive than computed tomography for determining the risk of dissemination through the blood. Unfortunately, lymphangiography, which is time consuming and requires skill and training, tends to be replaced by the easier to perform computed tomography. Biological tests have not all been assessed through large multivariate analyses. Measurement of the erythrocyte sedimentation rate is simple, cheap, well documented, and predicts relapse both initially and during follow up.^{20 25-27} Lactate dehydrogenase, which has not been assessed in Hodgkin's disease, and serum concentrations of soluble antigens CD 30, CD 8, CD 25, and interleukin 6 all require multivariate analyses to assess their value.²⁸

Staging laparotomy

In localised disease staging laparotomy is no longer required. It was first used to assess the incidence and sites of spread of infradiaphragmatic disease when other tests (including lymphangiography) gave negative results.²⁹ Up to 62% of patients with supradiaphragmatic stage I-II disease had positive results on laparotomy, which made them pathological stage III-IV.¹² This finding explains why in the European

Organisation for Research and Treatment of Cancer H1 study more than 50% of patients with mixed cellularity Hodgkin's disease relapsed when radiotherapy alone was given to patients with apparent supradiaphragmatic disease.³⁰ The clinical presentation was then correlated with the findings of laparotomy.^{31 32}

When prophylactic radiotherapy under the diaphragm became routine positive findings at laparotomy, particularly from the spleen, were used as prognostic factors because they correlated with the risk of relapse in patients treated with radiotherapy alone.²¹ Patients with positive results were then offered a more intensive treatment (either inverted Y radiotherapy with the drawback of the gonadal irradiation in women, or chemotherapy, or sometimes both). Later, some groups decided not to perform laparotomy at all and to accept a higher relapse rate. By this time it was clear that laparotomy had no impact on survival owing to the efficacy of salvage chemotherapy for patients relapsing after initial radiotherapy.³³ Others decided to omit laparotomy only in patients with poor initial prognostic factors (about 50% chance of survival) since they were due to receive intensive treatment anyway.^{4 34 35} Finally, even in the best prognostic group the role of laparotomy has been challenged by the results of a trial in which the type of staging (clinical or laparotomy) was randomised: the six year freedom from progression was only 5% higher in those given laparotomy but paradoxically these patients had a lower survival trend owing to laparotomy related deaths.⁴ Furthermore, the emergence of better tolerated and less toxic regimens makes chemotherapy more acceptable, and the associated increase in freedom from progression compensates for the omission of laparotomy. The same is true for patients with stage III disease, in whom downstaging is less of a problem.

Assessment of response

In disseminated disease, when chemotherapy based treatment is indicated, accurate staging of all sites of disease covers two different aims: firstly, to gather prognostic information; secondly, to reassess the same sites after chemotherapy to rule out residual disease. This is required because chemotherapy is less effective at controlling Hodgkin's disease in nodes (around 70% complete response in affected nodes with 30-40% relapse) than is radiotherapy (almost 100% control with rare relapse). Conversely chemotherapy may be superior in visceral disease.

For the same reason much attention has been paid to the early assessment of the response to chemotherapy to identify patients who are very likely to fail, thereby

enabling alternative forms of treatment to be started early on, before the patients are overtreated with ineffective but debilitating regimens.⁶ Unfortunately, residual masses may contain Hodgkin's disease or only fibrosis, and assessment remains difficult both during and after treatment.³⁶ Special imaging techniques may help to direct a confirmatory biopsy. Gallium scanning seems to reliably predict a negative biopsy result only in the mediastinum.³⁷ Nuclear magnetic resonance diagnoses initial marrow disease,³⁸ but has little to add when treatment has been given or when relapse is suspected. The potential of immunoscintigrams using non-specific antiferritin polyclonal antibodies or specific monoclonal antibodies to the CD 30 determinant needs confirmatory studies.³⁹

New staging classification

Implicit to the Ann Arbor classification were the assumptions that early stages of Hodgkin's disease (determined by pathological staging through exploratory laparotomy) should be treated with radiotherapy and that chemotherapy should be reserved for the more advanced cases. The importance of laparotomy diminished with the appearance of newly recognised factors and with the increasing role of chemotherapy in early stage disease. Chemotherapy became more popular because of new, better tolerated regimens and its ability to improve the freedom from progression. Twenty years after formation of the original Ann Arbor classification committee a part of the committee took into account some of these considerations (table II)⁴⁰: hilar disease was separately categorised as a disease site and computed tomography, bulk of the tumour, and assessment of residual disease were included. However, although computed tomography may provide additional information, it cannot replace lymphangiography, and in large multivariate analysis studies there are no data to support the impact of tumour bulk or residual masses.²⁴ Furthermore, no objective biological test, although some have potential prognostic or follow up importance, has as yet been incorporated to the staging process.

TABLE II—Cotswolds revision⁴⁰ of Ann Arbor staging system

Staging*†	Ann Arbor system	Cotswolds revision
Stage I	1 nodal area or structure—(that is mediastinum=1; thymus=1; Waldeyer's=1; spleen=1)	Same
Stage II	2 or more nodal areas on the same side of the diaphragm	Right and left hilum=1 area each, independent of mediastinum; indicate the No of anatomical nodal areas affected by a subscript (for example, II ₃)
Stage III	At least 1 nodal area on each side of the diaphragm	III ₁ = Upper abdomen (splenic, coeliac, portal) III ₂ = Para-aortic and lower abdomen
Stage IV	Visceral disease	Same
B symptoms	Fever, drenching sweats, weight loss	Same
A	None	Same
E	Extranodal by contiguity, can be included in the nodal radiotherapy field	Same
X		Bulk=mediastinum >1/3 at T5/6; mass >10 cm
CR[u]		Unclear complete remission (residual radiological abnormality)

*Clinical staging without histological confirmation.

†Pathological staging by histological confirmation and eventually surgical exploration (usually laparotomy).

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Rio Diary: a fortnight at the earth summit

Fiona Godlee

Tuesday 2 June

At the conference centre 35 km south of the city we stood in line, delegates on one side, journalists on the other, waiting to be photographed. Beside me an American, an Austrian, and a Czech debated the futility of the summit. The treaties on climate change and biodiversity had been watered down so much as to make them meaningless, and the likelihood of reaching agreement on even the diluted texts was extremely slim. And then there was the distance, more than 30 km, between the main UN conference on environment and development (UNCED) and the fringe event, the Global Forum.

After two hours a rumour filtered down the queue that there was only one camera at the front. In the distance a man in torn jeans was painting the wire perimeter fence green.

Wednesday 3 June

In his opening speech to massed delegates in the plenary hall the UN secretary general, Boutros Boutros-Ghali, said that he was "inclined to optimism." Gro Harlem Brundtland, prime minister of Norway and author of the 1987 Brundtland report, struck a different note. This was, she said, "a crisis meeting on humanity's future."

I found the British delegation in a prefab booth in the exhibition hall. David Maclean, minister of state for the environment, was holding the fort until the secretary of state, Michael Howard, arrived. No, there had been no decision yet on whether Britain would sign the biodiversity treaty. Asked about the government's plans for reducing carbon dioxide emissions in line with the treaty on climate change, he came up with something on domestic insulation schemes. And did he

agree with the UK transport minister, who said recently that roads were good for the environment? He looked uncertain. "What transport minister is that?"

Thursday 4 June

The representative of the Holy See had spoken in the plenary hall. His speech held no surprises, but Werner Fornos, who runs the Population Institute, added it to his bundle of papers almost with satisfaction. "Five hundred million women in the world don't want any more children, and most of those didn't want the last one," he said. "The Vatican is abusing its nation status at this conference to the detriment of millions of non-Catholics throughout the world."

Behind closed doors work had begun on the text of Agenda 21, the 40 chapter action plan for improving the environment. Over the next 10 days negotiators would work through it chapter by chapter, trying to remove the brackets around disputed items. The most contentious of these formed a compendium of unenlightened self interest: the Vatican objected to family planning, the developing countries to discussions of population control, the Israelis to inclusion of rights of settlement, the Saudis to any mention of energy efficiency and reducing reliance on fossil fuels, and the Americans to all talk of over-consumption.

The British press gathered for the midday briefing. David Maclean looked nervous. There were more of us now, and the little room was getting unbearably hot. Apparently there was some problem with the air conditioning. "We're saving the ozone layer," quipped Maclean, so that we knew that he knew that air conditioning destroyed ozone. As we piled out into the corridor someone pointed out that the exhibition hall

Rocinha: slap in the middle of opulent Rio

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