

Historical Review

HISTORICAL REVIEW OF HODGKIN'S DISEASE

Hodgkin's disease is an uncommon but nowadays highly curable disorder accounting for only approximately 1% of cancers registered in developed countries each year. The disease is named after Thomas Hodgkin whose historical paper (Fig 1) entitled 'On Some Morbid Appearances of the Absorbent Glands and Spleen' was read before the Medical–Chirurgical Society on the 10th and 24th of January 1832 (Hodgkin, 1832).

Brief history of Thomas Hodgkin and his work

Thomas Hodgkin was born 17 August 1798 to a family of staunch Quakers and he maintained the standards of this sect in his life and daily activities. After a brief period as an apothecary's apprentice, Thomas Hodgkin chose a career in medicine and enrolled as a pupil at Guy's Hospital in London. Being a Quaker, however, he could not enter the English universities of Oxford and Cambridge and decided to follow the medical courses at Edinburgh. At that times, Aristotelian and Hippocratic medicine were greatly influencing British physicians. Hodgkin, still a medical student, wrote a paper 'On the Uses of the Spleen' where he reported his beliefs on the purposes of the spleen: to regulate fluid volume, clean impurities from the body, supply expandability to the portal system. The subject was a presage of the disease that bears his name.

Hodgkin interrupted his studies at Edinburgh to spend a year in Paris where he met many people who had a great influence in his life and future activities. Among them, were Laennec (Hodgkin played an important role in bringing the stethoscope to Great Britain); Baron von Humboldt who introduced Hodgkin to the field of anthropology; Baron Cuvier, a distinguished anatomist and palaeontologist; and Thomas A. Bowditch, whose expeditions to Africa had a great impact on Hodgkin's future activities.

In 1825, Thomas Hodgkin returned to London to join the staff at Guy's Hospital, and in 1826 he was made 'Inspector of the Dead' and 'Curator of the Museum of Morbid Anatomy'. In developing the museum he had accumulated, by 1829, over 1600 specimens demonstrating the effects of disease. The correlation of clinical disease to pathological material was quite new: from analyses of pathological specimens Hodgkin was able to describe appendicitis with perforation and peritonitis, the local spread of cancer to draining lymph nodes, noting that the tumour had similar characteristics at both sides, and features of other diseases. In addition, in 1829 he reported 'On the Retroversion of the

Valves of the Aorta', clearly describing aortic insufficiency some years before Corrigan.

In his historic paper 'On Some Morbid Appearances of the Absorbent Glands and Spleen' (Hodgkin, 1832), he briefly described the clinical histories and gross postmortem findings on six patients from the experience at Guy's Hospital and included another case sent to him in a detailed drawing by his friend Carswell (Fig 2). In the very first paragraph he wrote: 'The morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection'. He was correct in believing that other anatomists had observed similar conditions and, in fact, David Craigie in 1828 in his *Elements of General and Pathologic Anatomy* reported on the enlargement of glands and mentioned a case described by Cruickshank in 1786. However, Craigie failed to recognize the distinctive nature of this disease process and rather ascribed it to some secondary response to an obscure inflammatory condition. By contrast, Hodgkin's studies had convinced him that he was dealing with a primary disease of the absorbent (lymphatic) glands. 'This enlargement of the glands appeared to be a primitive affection of those bodies, rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed texture.... Unless the word inflammation be allowed to have a more indefinite and loose meaning, this affection... can hardly be attributed to that cause' was stated on pages 85 and 86 of his 1832 paper. Hodgkin also mentioned that the first reference that he could find to this or similar disease was in fact by Malpighi in 1666.

Hodgkin's 1832 article, however, was not widely recognized, although in 1838 Richard Bright, a consulting physician at Guy's Hospital, reported some of the original Hodgkin's contribution. In 1856, Sir Samuel Wilks wrote a paper on what he termed 'lardaceous disease', describing 10 cases, including three of the original cases of Thomas Hodgkin. Nine years later, Wilks (1865) described the disease in further detail and, made aware by Bright that the first observations were done by Hodgkin, linked his name permanently to this new entity in a paper entitled 'Cases of Enlargement of the Lymphatic Glands and Spleen (or Hodgkin's Disease) with Remarks' (Fig 3).

In 1837 Thomas Hodgkin was the outstanding candidate for the position of Assistant Physician at Guy's Hospital in succession to Thomas Addison who had been promoted to Physician. After 10 years spent as Inspector of the Dead, he had published a great deal, including a two-volume work entitled *The Morbid Anatomy of Serous and Mucous Membrane*.

Correspondence: G. Bonadonna, Istituto Nazionale Tumori, Via Venezian 1, 20133 Milano, Italy. E-mail: bonadonna@istitutotumori.mi.it

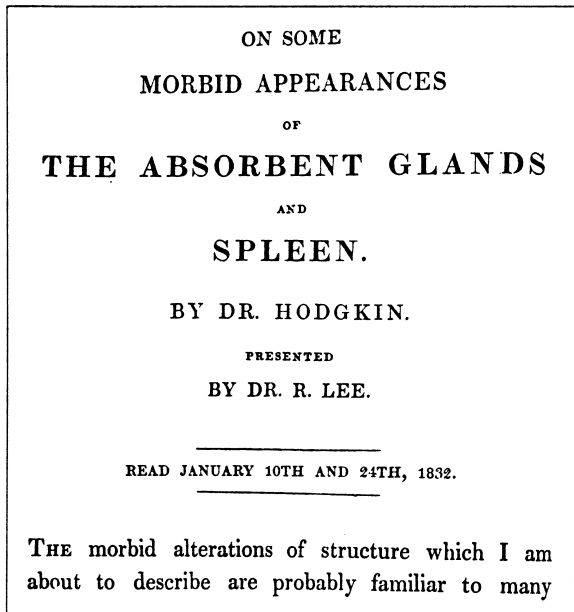


Fig. 1. Cover page of the historical 1832 paper by Thomas Hodgkin.

He was a Fellow of the Royal College of Physicians and had been invited by the Home Secretary to serve on the Senate of the new University of London.

However, in September 1837, it was not Thomas Hodgkin who received this appointment. The decision had nothing to do with medicine, even though his activities in this field were well recognized. Another passion of his life, the protection of aboriginal tribe people against their ruthless exploitation by European traders, caused him to have some differences with Benjamin Harrison, the wealthy Treasurer of Guy's Hospital. Harrison was, unfortunately, also the Deputy Governor of the Hudson Bay Company, and some years before Hodgkin, acting in his other capacity, had sent him a report on the terrible consequences to the native Indians of monopoly trading and on the inhuman treatment they received from officials of the Company. Hodgkin, naïvely, expected his support, but instead Harrison was affronted by this report and, when the opportunity to appoint an Assistant Physician occurred, Harrison exercised an autocratic rule over the hospital and presided at the appointment made by the General Court. Thomas Hodgkin did not get the job and the next day he resigned all his appointments at Guy's Hospital.

Social medicine, medical problems associated with



Fig 2. Painting of a patient seen by Robert Carswell at postmortem examination. This was the seventh case reported by Thomas Hodgkin in his 1832 article.

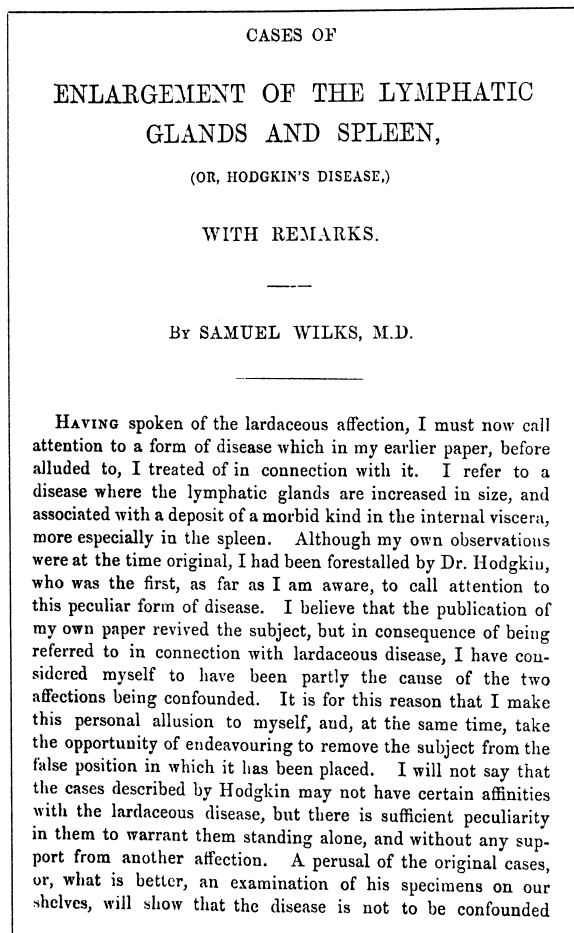


Fig. 3. Cover page of the 1865 paper by Sir Samuel Wilks. This article linked, for the first time, the name of Hodgkin to the disease he described in 1832.

poverty, antislavery, concern for underprivileged groups such as American Indians and Africans, as well as a strong sense of responsibility defined his life after this separation.

On 4 April 1866, during one of his trips outside Great Britain for his ethnological interests and concerns for the welfare of indigenous civilizations, Thomas Hodgkin died of an unknown but lengthy illness and was buried in Jaffa.

The history of Hodgkin's disease

Beginning in the 1860s, many European investigators recognized and described one, sometimes two, varieties of 'large cells, containing two or three nuclei', as noted by Tuckwell when in 1870 he performed an autopsy on a 49-year-old woman with a huge spleen and enlarged abdominal nodes. These pathognomonic giant cells of Hodgkin's disease were clearly recognized by Greenfield who, in 1878, contributed the first drawing of such cells seen at low magnification in a lymph node.

However, Sternberg (1898) and Reed (1902) are generally credited with the first definitive and thorough descriptions of the histopathology of Hodgkin's disease. Based on the

findings observed in her case series, Dorothy Reed concluded 'We believe then, from the descriptions in the literature and the findings in 8 cases examined, that Hodgkin's disease has a peculiar and typical histological picture and could thus rightly be considered a histopathological disease entity'.

Fox (1926) examined microscopic sections that he was able to prepare from gross specimens preserved in the Guy's Hospital Museum using the histological criteria described by Reed (1902). Almost a century later, the microanatomy was remarkably preserved and Fox was able to confirm Hodgkin's disease in three of the original cases of Thomas Hodgkin, but classified one case as non-Hodgkin's lymphoma, and the two remaining cases as tuberculosis and syphilis.

During the successive decades, pathologists began to describe a broader spectrum of histological features. However, it was Jackson and Parker who, in scientific papers and in their well-known book *Hodgkin's Disease and Allied Disorders* (Jackson & Parker, 1947), presented the first serious effort at a histopathological classification. They assigned the name 'Hodgkin's granuloma' to the main body of typical cases. A much more malignant variant, usually characterized by a great abundance of pleomorphic and anaplastic Reed–Sternberg cells and seen in a relatively small number of cases was named 'Hodgkin's sarcoma'. A third, similarly infrequent, variant characterized by an extremely slow clinical evolution, a relative paucity of Reed–Sternberg cells and a great abundance of lymphocytes was termed 'Hodgkin's paragranuloma'. It was only approximately 20 years later that Lukes & Butler (1966) reported a characteristic subtype of the heterogeneous 'granuloma' category, to which they assigned the name 'nodular sclerosis'. They also proposed a new histopathological classification, still in use to date, with an appreciably greater prognostic relevance and usefulness than the previous Jackson–Parker classification.

The nature, aetiology and pathogenesis of Hodgkin's disease have been the subject of controversy for over a century. Hodgkin himself considered it to be a kind of 'hypertrophy of the lymphatic system'. Proponents of the infectious nature of the disease were impressed with the frequency of its association with tuberculosis. Sternberg himself, finding that eight of his 13 patients had coexistent tuberculosis, argued that Hodgkin's disease was a peculiar form of tuberculosis. Among other investigators, Dorothy Reed, however, refuted this thesis and concluded that Hodgkin's disease was an independent entity, sometimes associated with tuberculosis. A search for an infectious agent other than the tubercle bacillus continued for many years: in 1915 Bunting and Yates centred their interest on diphtheroid bacteria, Parsons and Poston proposed a possible role of *Brucella* in 1940, and Jackson & Parker (1947) were for a time interested in an aerobic gas-forming bacillus that they isolated from some of their autopsies. Gordon, after discovering in 1932 that the extracts from involved lymph nodes could induce an acute encephalitis in rabbits, initiated a period in which viruses were strongly suspected of being the aetiological agents of Hodgkin's disease. Definitive evidence that Hodgkin's disease is a

malignant neoplasm came only in the 1960s when cytogenetic studies demonstrated that the giant cells satisfy two of the fundamental attributes of neoplastic cells: aneuploidy and clonal derivation.

Hodgkin presented only a cursory description of the clinical history and physical findings of his cases, but Wilks clearly observed anaemia in his patients and called attention to intermittent fever in at least one patient. It was, however, in 1887 that Pel and Ebstein first carefully described that this fever, which bear their names, had peculiar cyclic bouts. It was again Dorothy Reed that, at the beginning of the 1900s reported a high frequency of anergy to tuberculin, but it was only in 1956 that Schier and coworkers demonstrated that the relative anergy of patients with Hodgkin's disease was also evident with a number of other natural antigens capable of eliciting delayed cutaneous hypersensitivity reactions.

Despite efforts in describing clinical features of Hodgkin's disease, it was only in the mid-20th century that diagnostic evaluation and systematic analysis of the anatomical extent of involvement began to receive attention, thank to the adoption, by several specialized centres, of the lower extremity lymphography first developed by Kinmonth (1952). This new diagnostic method, by revealing that many patients had unsuspected lymph node involvement in the retroperitoneal space, increased tremendously the knowledge of the extent of lymphoma at diagnosis and enabled the determination of the orderly progression in the spread of Hodgkin's disease. Nevertheless, the spleen, splenic hilar nodes and liver remained silent areas until 1969 when laparotomy was used, initially on a selective basis, at the Stanford University Medical Center (Glatstein *et al.*, 1969). This surgical staging, which today has been replaced by more modern, less invasive techniques capable of determining the appropriate details on the extent of disease, became rapidly popular in many research centres and shed more light on the fact that, in the majority of patients, Hodgkin's disease spreads non-randomly and predictably via lymphatic channels to contiguous lymph node chains and other lymphatic structures.

The new ideas about the nature, epidemiology, aetiology, modes of spread and treatment were extensively discussed by people working in many different disciplines in a series of small international meetings held in Paris and Rye during 1965, Ann Arbor in 1971, Palo Alto in 1973 and the Cotswolds in 1988. These meetings served to concentrate effort, disseminate information, agree on classification and staging, secure uniformity of histological reporting and emphasize the importance of prospective clinical trials, and the concept that Hodgkin's disease is indeed a curable disease began to receive adequate attention.

The history of treatment of Hodgkin's disease

Throughout the nineteenth century, therapy of Hodgkin's disease was essentially symptomatic. Pusey (1902) was apparently the first to treat the lymphomas with the X-rays newly discovered by Roentgen in 1896. It was probably the start of non-surgical anticancer treatment and the history of therapy of Hodgkin's disease (Table I), which largely

influenced the history of cancer therapy. Starting on 2 September 1901, Pusey treated five cases of lymphoma, two of whom presented with Hodgkin's disease. The first case was a boy with bilateral cervical involvement who had received surgical resection on the right side. Under X-ray exposure the swelling rapidly subsided and Pusey reported that in 2 months the glands were 'reduced to the size of an almond'. The other patient was a 50-year-old man with right axillary and epithroclear adenopathy unresponsive to arsenic treatment. The epithroclear nodes were treated first and achieved a prompt response. Then X-rays were delivered to the axillary nodes, which decreased in size and firmness, and the patient achieved improved mobility of the arm.

The second report on the use of X-ray therapy in the treatment of Hodgkin's disease appeared in a paper published in 1903 by Senn, Professor of Surgery at Rush Medical College in Chicago. In his article, Senn described dramatic responses in two male patients that he referred for Roentgen therapy.

However, modern radiotherapy for Hodgkin's disease really began in 1925 with the Swiss radiation therapist Gilbert. He was in fact the first radiation therapist to emphasize the fundamental principle of treatment, i.e. the destruction of 'all granulomatous lesions' in the first course of irradiation (Gilbert, 1925). Gilbert also stressed the formulation of a systemic plan of irradiation in each case after careful clinical and radiological evaluation of all detectable sites of involvement. Based on clinical observations about 'recurrence developing in the immediate vicinity of a field too narrowly treated', he advocated the concentration of the therapeutic effort first on lymph node-bearing regions clinically involved by the disease and then extending the field of treatment to encompass the apparently uninvolved regions 'which experience shows are frequently invaded by the process'. By utilizing the strategy of segmental irradiation, Gilbert and Babaïantz were able to report the first patients with prolonged survival: 4.3 years for the entire group and 6.5 years for the living patients.

Widespread interest in the curative potentialities of radiation therapy arose, however, only after the publication of two classical papers: Peters (1950) and Peters & Middlemiss (1958). Important from many points of view were the initial publications by Peters, who, with Gordon Richards, between 1928 to 1953, used a treatment plan very similar to that of Gilbert. First, she reported treatment results according to a three-stage clinical classification, which also included the presence or the absence of systemic symptoms. By doing this, she started the new era of rational emphasis on diagnostic evaluation and treatment reporting based on the anatomic extent of involvement. The survival results of her case series (51% at 5 years and 25% at 10 years for all stages) included impressive figures for stage I (88% at 5 years) and stage II disease (72% at 5 years). The doses employed ranged from 18 to 50 Gy, depending on the site and extent of lymphoma. Most importantly, the prolonged survival was ascribed to the extent of radiotherapy, which included in many patients 'prophylactic' irradiation of adjacent lymph node-bearing regions clinically uninvolved, with doses ranging from 4 to 8 Gy. In a

Table I. Chronological flow of major concepts and events influencing the evolution of the treatment of Hodgkin's disease.

Year	Investigator(s)	Concept
1925	Gilbert	Concept of destruction of all lesions in the first course of radiotherapy; segmental irradiation to encompass suspected microscopic disease
1943	Goodman and Gilman	Striking, but temporary dissolution of tumour masses by single-agent nitrogen mustard
1950	Peters	Improved 5- and 10-year survival by prophylactic irradiation of adjacent lymphoid areas; first three-stage clinical classification
1952	Kinmonth	Lower extremity lymphangiography
1963	Lukes	Relationship of histological features to clinical stages and prognosis
1962	Kaplan	Development of wide-field technique with irradiation in continuity of multiple node chains (mantle, inverted Y, and total lymphoid radiotherapy); identification of tumoricidal dose levels
1965	Rosenberg and Kaplan	Evidence for an orderly progression in the spread
1966	Frei	Efficacy of a cyclical four-drug combination (MOPP)
1969	Kaplan and Glatstein	Staging laparotomy and further studies on the pattern of anatomic distribution
1970	De Vita	Concept of high cure rate by MOPP chemotherapy
1971	De Vita	Staging laparoscopy
1973	Young	No real advantage of maintenance chemotherapy in pathological complete responders
1968	Rosenberg	Trials with combined radiotherapy and chemotherapy, especially MOPP
1973	Bonadonna	Development of non-cross-resistant chemotherapy (ABVD) and of alternating regimens (MOPP/ABVD)

subsequent publication, Peters noticed that the long-term survival was not significantly related to the initial site of presentation but rather was influenced by the presence or the absence of systemic symptoms, age below or over 40 years, and sex. Thus, the work of her group in Toronto with 'complementary' irradiation represented the first systematic application of the principles advocated by Gilbert and a treatment plan based on technical factors as well as on natural spread of the disease.

At the end of the 1950s and the beginning of the 1960s, megavoltage irradiation made a major impact on the evolution of treatment for Hodgkin's disease. The high-energy beams generated by new megavoltage devices induced some research centres in England and the United States to adapt 'supervoltage' irradiation to medical radiotherapeutic use. Cobalt teletherapy units as well as new electronic devices, such as the betatron and the linear accelerator, provided apparatus capable of yielding beams of very high energy while operating at quite nominal voltages. The physical advantages of megavoltage equipment have greatly increased the versatility and precision of modern radiation therapy and have opened the way to entirely new treatment approaches for Hodgkin's disease and other malignant lymphomas. Since 1956, using the Stanford 5 MV linear accelerator, Henry Kaplan (Kaplan, 1962) was able to introduce the wide-field technique of radiotherapy for stage I and II Hodgkin's disease, and this represented the major event in the development of the more successful radiotherapy techniques of today. The studies of the Stanford group, by identifying the tumoricidal dose levels, established one of the milestones for definitive treatment

and provided confidence in the capacity of radiotherapists to eradicate tumours in irradiated areas that were involved by Hodgkin's disease. Kaplan's strategy was aimed from the beginning at treating multiple lymph node chains in continuity with as few fields as possible (Kaplan & Rosenberg, 1966). The development of optimal field size and shape led to the classical 'mantle' and the 'inverted Y' fields for the irradiation of all the major lymph node chains above and below the diaphragm respectively; hence the concept of total lymphoid (TLI) or total nodal irradiation (TNI) when both fields were utilized. Total lymphoid megavoltage irradiation proved to be remarkably well tolerated and not as dangerous as feared. Subsequent studies have further defined the optimal selection of dose levels and the dose fractionation patterns.

Chemotherapy for lymphomas was mentioned in the first edition of Osler's textbook of medicine (Osler, 1894). In this case it was Fowler's solution, an arsenic-containing medicinal, that was considered the standard of the day and used to treat a number of cancers. The first use of alkylating agents in humans actually resulted from the development of the United States war gas programme. An explosion in the harbour in Bari, Italy, during World War II exposed servicemen to the lethal toxic effects of mustard gases. Profound marrow and lymphoid aplasia were noted, and, as a consequence, a derivative of mustard gas, nitrogen mustard, was submitted for testing in humans to Goodman and Gilman at Yale in 1943. A group of six patients with Hodgkin's disease and lymphosarcoma were treated in the same year the compounds were submitted, 1943, in what has to be considered the first phase I/II cancer clinical trial

on record. Because of the secrecy surrounding the war gas programme, the results were not published until 3 years later (Goodman *et al.*, 1946). Striking, but temporary dissolution of tumour masses occurred in these patients with both Hodgkin's disease and lymphosarcoma after intermittent dosing with nitrogen mustard.

Despite this important achievement, the first study to have an impact on the management of patients with Hodgkin's disease was published by Scott, 1963. Eighty-nine patients with advanced Hodgkin's disease received a conventional induction course of nitrogen mustard (0.4 mg/kg), of which 40 patients with satisfactory response were randomized to receive either no further treatment or continuous treatment with the newly developed oral alkylating agent chlorambucil. For the 16 patients who received chlorambucil, time to relapse averaged 35 weeks (range 4–84 weeks) compared with 11.7 weeks (range 4–51 weeks) without further treatment. This highly significant difference in the duration of a satisfactory remission provided the first useful information on alternatives in the management of patients with Hodgkin's disease.

It is also worth remembering that one of the first survival curves reported in the modern chemotherapy era was published in 1969 by Jacobs and coworkers. Nitrogen mustard and cyclophosphamide treatment in patients with advanced Hodgkin's disease was associated with a median survival of less than 2 years, with only 5% living beyond 4 years, all with evidence of disease.

The next major advance in the chemotherapy of the lymphomas came with the identification of the plant-derived natural products called the vinca alkaloids. The availability of two apparently non-cross-resistant classes of antitumour agents and the conceptual separation of induction and maintenance therapy gave impetus to a large study initiated through the combined effort of two clinical co-operative groups supported by the National Cancer Institute in United States (Acute Leukaemia Group B and the Eastern Solid Tumor Group). In this important early study (Carbone *et al.*, 1968), which provided the foundation for the future studies on combination chemotherapy that were to prove so effective, 342 patients were randomized by disease and prior therapy to remission induction with cyclophosphamide or one of the vinca alkaloids. Vinblastine was used in Hodgkin's disease and vincristine in non-Hodgkin's lymphomas, known then as lymphosarcoma and reticulum cell sarcoma. The objectives of this study were to compare the effectiveness of the vinca alkaloids to an alkylating agent in remission induction in lymphomas. The results established the superiority of vinblastine over cyclophosphamide for remission induction in patients with advanced Hodgkin's disease.

The first intensive programme designed to test the new principles of combination chemotherapy in advanced Hodgkin's disease began in 1963 and utilized the combination of cyclophosphamide, vincristine, methotrexate, and prednisone (MOMP) given for only 2.5 months. The aim of this protocol was to test the safety of combination chemotherapy in advanced Hodgkin's disease. Only 14 patients were studied, and all were hospitalized and kept in

reverse isolation. This approach was shown to be safe, and a high complete remission rate was attained.

As experience accrued with procarbazine, the MOMP programme was modified in several ways in 1964. Because of the data on the low-growth fractions for human tumours, duration of treatment was increased to 6 months and procarbazine, by the time an agent known to be active in Hodgkin's disease, was substituted for the antifol methotrexate for which there was less evidence of clinical utility. This new programme was the well-known MOPP regimen (De Vita *et al.*, 1970). The clinical results were impressive: of 198 patients with advanced stages treated between 1964 and 1975, 80% attained complete remission, a fourfold increase over that achievable with single agents. Furthermore, 68% of patients who attained complete remission were continuously progression-free 5 years from the end of all treatment. The contrast to the results using single agents in the past trials was quite striking, as less than 10% of patients treated with a single agent survived 5 years and even fewer survived free of tumour.

Although the MOPP studies revolutionized the treatment of advanced Hodgkin's disease, 15–30% of patients did not achieve complete remission after MOPP and 20–30% of complete responders eventually relapsed. This indicated selective drug resistance in patients with treatment failure or early disease recurrence. Thus, at the beginning of the 1970s, these limits of MOPP or MOPP-derived combinations, as well as the availability of new compounds induced many investigators to design and test new chemotherapeutic regimens to be delivered first in MOPP-resistant patients and then to potentially substitute for or complement the four drugs used in the MOPP combination.

The ABVD programme developed at the Milan Cancer Institute was the first and most effective. This four-drug regimen included adriamycin, a new anticancer antibiotic available for clinical use in the summer of 1968, bleomycin, vinblastine and dacarbazine. A pilot study activated in 1973 showed that ABVD chemotherapy was at least as effective as MOPP in inducing durable remissions in advanced Hodgkin's disease (Bonadonna *et al.*, 1975; Bonadonna, 1982). Later, a larger randomized study, which also included radiation therapy, proved that ABVD was able to improve long-term treatment outcome compared to MOPP (Bonadonna, 1982). The higher therapeutic activity of ABVD, which is easy to administer, devoid of severe side-effects and well tolerated by the patients, was confirmed in many other studies and this regimen today is considered the gold standard in Hodgkin's disease. More importantly, salvage treatment with ABVD in patients failing during or soon after MOPP yielded higher complete remission rates (46%), compared with the opposite sequence, i.e. salvage MOPP in ABVD-resistant patients. Based on these observations, investigators at the Milan Cancer Institute empirically designed what was called the alternating MOPP and ABVD regimen. The early findings demonstrated a superiority of the alternating regimen over MOPP alone in the achievement of complete remission (89% vs. 74%), and this superiority was evident in those subsets known to be less affected by MOPP chemotherapy. The 18-year results from

the Milan study, remain consistent: 47% of the patients in the MOPP alone group died because of disease progression as compared with 23% of the patients given the alternating regimen.

The consequence of cure: the decline in mortality

MOPP chemotherapy of advanced Hodgkin's disease demonstrated that combination chemotherapy could cure a high proportion of patients with an advanced adult malignancy, using well-defined therapeutic principles. The most reliable indicator of the effectiveness of MOPP chemotherapy in the management of Hodgkin's disease is the decrease in the national mortality rate from Hodgkin's disease in the United States by over 60% once this regimen was extensively utilized in clinical practice.

The principles behind MOPP went beyond the treatment of Hodgkin's disease. The modern approach of intermittent (cyclical) combination chemotherapy with a full-dose regimen, as well as the concept of different dose attenuation schedules in the presence of various types and degrees of toxicity, and the importance of the delivered dose intensity were all derived from the initial trials with MOPP.

Most of the controversy about the treatment of Hodgkin's disease today centres on which approach to combination chemotherapy is the most effective and the impact of dose reductions; whether or not radiotherapy is beneficial in advanced disease as an adjunct to chemotherapy; and whether chemotherapy alone can be sufficient for the treatment of early stage disease to avoid what has become a frightening incidence of solid tumours secondary to radiotherapy, especially breast cancers. New combination regimens devised by American and European research institutions require additional follow-up time to document their real benefit as compared to conventional regimens. Actual choices in practice today, outside of a clinical trial, remain one of the standard four-drug programmes and, in some cases, a programme that combines two of the standard programmes in an alternating or hybrid fashion.

Today, almost one-third of patients with Hodgkin's disease die without evidence of lymphoma at autopsy. A significant number of patients, however, die from complications of therapy, both non-malignant and malignant. This has led to the focus of new treatment programmes on morbidity and the cost of delivery of treatment. Relatively few new programmes evaluate the use of either chemotherapy or radiotherapy alone compared with combined approaches in all stages of disease.

The history of Hodgkin's disease is one of the most fascinating adventures in medicine. Still to date, clinical investigations in Hodgkin's disease represent a model for many other cancers. In the early 1970s, increase in survival was achieved by associating several chemical agents and by using a multidisciplinary approach. At that time, it was believed that the success of a therapeutic strategy could be assessed by the analysis of the 5-year survival. We know today, and Hodgkin's disease has been instrumental in this, that only a prolonged follow-up of 20–25 years is mandatory because it enables the assessment

of the long-term effects of a treatment, including its delayed consequences on the normal tissues.

Hodgkin's disease, with its complex treatment strategy, was instrumental in showing the need for continuing medical education, the necessity of prospective controlled clinical trials with quality assurance and proper statistical analyses.

The total conquest of Hodgkin's disease does not appear to be a too distant goal. Its achievement requires new treatment studies for high-risk groups as well as more consideration of overt and relatively occult treatment morbidity. Patients with Hodgkin's disease should continue to be referred to major research institutions where efforts in accurate diagnosis, proper staging, the discipline of controlled trials, and identification of complications will remain the essential ingredients of progress.

*Istituto Nazionale Tumori
Via Venezian 1
20133 Milano, Italy*

GIANNI BONADONNA

ACKNOWLEDGMENTS

The author wishes to acknowledge the University College London Library and the editor of *JAMA* for their kind permission to reproduce the painting by Robert Carswell (Carswell papers, University College London Library; also published in an article in *JAMA* entitled 'Archives of internal medicine', 121: 288–290, 1968, by P. J. Dawson, copyrighted 1968, American Medical Association).

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Keywords: Hodgkin's disease, history, radiotherapy, chemotherapy.

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