REVIEW ARTICLES

The lymphomas—current management

T. A. LISTER
M.D., F.R.C.P.

J. S. MALPAS
D.Phil., F.R.C.P.

Department of Medical Oncology, St Bartholomew's Hospital, London EC1A 7BE

Introduction

The malignant lymphomas are an heterogeneous group of diseases, manifest most frequently by the development of painless lymphadenopathy with or without splenomegaly and sometimes associated with constitutional symptoms. The natural history of these conditions is one of progressive increase in lymphadenopathy, both in terms of size and the number of sites, with death occurring from intercurrent infection or as a consequence of compression of a vital organ by lymph nodes. Spontaneous regression, although it has been reported, is very rare. The rate of progression, and the specific sites most frequently involved, vary with the specific subtype of lymphoma in question. Happily, the natural history is rarely observed nowadays since treatment is available which may cure a significant proportion of patients and be of very considerable palliative benefit to others. Their importance to the physician lies in the fact that, as a group, they are the seventh commonest malignancy in the United Kingdom, they afflict a relatively young population and have become potentially curable.

Diagnosis

The diagnosis of malignant lymphoma can only be made on the basis of a stained section of lymph node or occasionally an extranodal tumour mass or bone marrow. The importance of obtaining an adequate sample and having it expertly cut and stained in addition to being examined by a pathologist familiar with the appearance of malignant lymphoma cannot be over-emphasized. The practice of lymph node biopsies being performed at the end of operating lists by the house surgeon is to be deplored: this generally results in inadequate specimens arriving in the laboratory after working hours and greatly increases the risk of either an incorrect or inconclusive diagnosis being made and often results in the necessity for a further biopsy.

Generally speaking progress in the subclassification of Hodgkin's disease has been more orderly and less traumatic than in the unfortunately named non-Hodgkin's lymphomas. In 1944, Jackson and Parker (1944) divided Hodgkin's disease into paraganuloma, granuloma and sarcoma. This was accepted until the 1960's when the Lukes and Butler classification (Lukes and Butler, 1966), subsequently modified at the Rye conference, was introduced (Lukes *et al.*, 1966). It remains in current use and is universally accepted. In spite of this, our understanding of the basic nature of the disease, and specifically the pathognomic Sternberg Reed cell, remains minimal. Many unsuccessful attempts have been made to grow these cells in culture, but only recently has it been possible to achieve this (Diehl *et al.*, 1982), and only in very selected cases.

The heterogeneity of the non-Hodgkin's lymphoma is reflected in the number of classifications which have been applied to them over the years. Gall and Mallory (1942), basing their observations on material at the Massachusetts General Hospital, Boston, distinguished follicular lymphoma from the diffuse lymphomas and subdivided the latter according to the size, maturity, and presumed source of origin of the cells. The modification of this, by Rappaport (Rappaport, Winton and Hicks, 1956; Rappaport, 1966) became the popularly accepted 'prognostically accurate' basis for clinical trials, particularly in the United States. Suffering from biological inaccuracy, with particular reference to the histiocyte, it is being relegated to the history books, having been superseded by two main alternatives which are based on the functional capacity of the predominant cell (Lukes and Collins, 1974; Lennert, 1978). Most recently 'a working formulation' (National Cancer Institute, 1982) generated by an international panel of pathologists has been published in an attempt to provide a universal classification of the non-Hodgkin's lymphoma acceptable to all and appropriate to the twenty first century.

During the past 15 years progressively more sophisticated techniques have been developed for raising specific sera against the subpopulations of the lymphoid cell system. With such sera, phenotyping of the lymphoid cells from lymph nodes of patients with lymphoma, both in cell suspension and in section, has greatly increased understanding of the precise derivation of many of the different lymphoma cells. For example, it has been clearly demonstrated that follicular lymphomas are invariably of 'B' cell origin (Jaffe *et al.*, 1974), that the Sternberg sarcoma is of 'T' cell origin (Smith *et al.*, 1973), and that the majority of lymphomas previously designated as reticulum cell sarcoma or histiocytic lymphoma are most frequently immunoblastic lymphosarcomas of 'B' cell origin (Habeshaw and Stuart, 1975; Brouet, Preud'homme and Seligman, 1976). These techniques have contributed considerably to the formulation of the recent classification of the non-Hodgkin's lymphomas, particularly those of Lukes and Collins, and Lennert.

It is inevitable that there will be further modification to the classification of the non-Hodgkin's lymphomas as understanding of the aberrations of the lymphoid system increases. It would be unwise to assume that any immediate apparent clinical benefit will accrue from these newer classifications until treatment becomes less crude than at present. Any classification may be shown to be 'prognostically accurate' when the only parameters for prognosis are the frequency with which treatment produces a return to normality (complete remission), the length of time until recurrence occurs (duration of remission) and time until death (survival). All of the currently available classifications divided the non-Hodgkin's lymphomas into 2 broad groups, which may be expected to have either a relatively long or short natural history, no longer seen, or a clinical course modified by what was accepted as optimal treatment at the time when the study (or analysis) was conducted. The test of the newer classifications will be whether they teach us more of the problems occurring during the course of the disease, for example, the probability of recurrent infection, the probability of recurrent splenomegaly and whether they can teach us enough of the biology of the disease to enable us to develop more appropriate therapy.

Distribution of disease (staging)

Very considerable advances have been made in the past 20 years in the techniques available for determining the extent of involvement of nodal and extra nodal sites with lymphoma. Rigorous clinical studies employing these techniques have produced data from which it is possible to develop guidelines for those

investigating patients with malignant lymphoma. At the outset it must be emphasized that there are 2 reasons for conducting staging investigations. The first is to provide a rational basis for the planning of treatment for an individual patient, allowing him the minimal treatment compatible with the optimal outcome ('cure' under the most optimistic circumstances). The second is to increase understanding of the disease itself by gaining as much information as possible at the time of a treatment decision.

It cannot be emphasized too strongly that the staging of a patient with malignant lymphoma must begin with the taking of a full history followed by a complete clinical examination, with particular attention not only to the distribution of palpable lymphadenopathy and the spleen, but also to their size. It should never be forgotten that both the tonsils and the testes may be infiltrated with lymphoma.

Intra-thoracic lymphadenopathy and lung infiltration may be determined by plain chest radiography with penetrated views, laterals and postero-anterior and lateral tomograms. Evidence is also accumulating that computerized axial tomography (CT) is more accurate than these methods at delineating intra-thoracic involvement, particularly in the mediastinum, and it has been suggested that the investigation may influence the treatment in a significant proportion of cases (Gallagher *et al.*, 1982).

Intra-abdominal lymphadenopathy may be detected accurately either by bipedal lymphography (if only the para-aortic chain is of interest) or CT scanning. Both have been compared prospectively with the pathological findings at laparotomy and are highly accurate (Earl *et al.*, 1980). Lymphography has the advantages of revealing abnormalities in nodes of normal size, and permitting easy follow-up with repeat abdominal X-rays, but the disadvantage of not delineating nodes outside the para-aortic chain. CT scanning has the advantage of showing up enlarged nodes in all areas but not detecting abnormalities in normal sized nodes. Neither predict with any accuracy whether or not the spleen is involved. Thus, if it is essential for treatment to know whether splenic involvement is present, laparotomy with splenectomy must be performed.

The frequency with which laparotomy is being performed in the investigation of malignant lymphoma is steadily diminishing. It is rarely, if ever, conducted in patients with non-Hodgkin's lymphoma because the spleen is very rarely the sole site of intra-abdominal involvement. Also the patient population is older and does not tolerate the procedure very well. Most paediatricians argue strongly against this procedure in childhood because of the subsequent risk of infection (Chilcote, Baehner and Hammond, 1976). The only group of patients for whom it is recommended are those with Hodgkin's

disease in whom localized radiation is the preferred treatment of choice and for whom the 30% risk of splenic relapse is considered unacceptable in spite of the reported efficacy of 'salvage' therapy. As with lymph node biopsy, the overwhelming importance of the laparotomy being performed by a surgeon who frequently undertakes the operation must be stressed.

Involvement of the bone marrow is assessed by bone marrow biopsy and of the liver by palpation and biochemical tests of liver function. Various scanning techniques have been applied to the detection of hepatic, splenic and nodal involvement but for various reasons none of them have been universally accepted into the routine investigations of the lymphomas.

At the completion of the investigation, a final stage is ascribed to the patient according to the guidelines of the Ann Arbor Classification (Carbone *et al.*, 1971) (Table 1), being a clinical stage (CS) or pathological stage (PS) depending upon whether laparotomy was performed.

Until recently, treatment, at least for Hodgkin's disease and for the majority of patients with non-Hodgkin's lymphoma, was rigidly based on the Ann Arbor Stage. The experience gained during the past 10 years with this policy has drawn attention to its failure to describe the bulk of tumour at any one site, and the number of sites involved. These factors are now being taken into account in the planning of

treatment for individual patients. In children, the inadequacy of the Ann Arbor Staging classification has led to the introduction of the more satisfactory recommendation by Murphy (1980) in which the serious prognostic import of any evidence of disease in the chest or massive intra-abdominal disease is recognized (Table 2).

Treatment

General considerations

It is now possible to modify the natural history of the malignant lymphomas with treatment so that a high proportion of patients may expect to be cured, a further proportion to have an excellent quality of life for many years although probably dying eventually of the disease, and relatively few to gain no benefit at all from therapy. In spite of this, the majority of patients are justifiably extremely alarmed at hearing the diagnosis and further so on learning of the prospect of radiation or cytotoxic chemotherapy. The importance of both patient and relatives receiving a full explanation of the likely course of events is paramount.

The achievement of converting the malignant lymphoma from invariably fatal to potentially curable diseases has been attained as the result of the

TABLE 1. Ann Arbor Staging Classification*

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

*Adopted at the Workshop on the Staging of Hodgkin's Disease held at Ann Arbor, Michigan, in April 1971 (Carbone *et al.*, 1971).

TABLE 2. Staging of childhood non-Hodgkin's lymphoma, St Jude Children's Research Hospital (Murphy, 1980)

Stage	Definition
I	A single tumour (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen.
II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tract tumour, usually in the ileocaecal area, with or without involvement of associated mesenteric nodes only.
III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All the primary intrathoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease.
IV	Any of the above with initial central nervous system and/or bone marrow involvement.

progressive refinement of radiation techniques and the development of cytotoxic chemotherapy programmes. The role of the special referral centre has been central to this success. The diseases are not very common, and the advantages of large numbers of patients being followed closely after experimental therapy is obvious.

Specific treatment of Hodgkin's disease

(a) *Localized disease (Stages I and II)*. The current strategy for the treatment of Hodgkin's disease localized to one side of the diaphragm is based on the concept that it spreads contiguously (Rosenberg and Kaplan, 1966). Finzi first recommended, then Gilbert, Peters, Kaplan and others subsequently pioneered the use of extended field (megavoltage) radiotherapy for stage I and II disease (Finzi, 1913; Gilbert, 1939; Peters, 1950; Peters and Middlemiss, 1958; Kaplan, 1962; Easson and Russell, 1963). Improvements in both technique and equipment have made it possible to deliver a midplane dose of 3500 Cgray over 4 weeks to the mantle or inverted Y area with minimum side effects for the majority of patients. At some centres, notably Stanford, the field is even more extended in some circumstances and the midplane dose may be as high as 4500 Cgray.

Such treatment is undoubtedly adequate for the great majority of patients with stage I disease. Those in whom this had been confirmed with a staging laparotomy have a maximum probability of recurrence of 15% by 10 years, and an overall expectancy of survival at 10 years approaching 100%. Those in whom treatment was commenced on the basis of clinical rather than pathological staging have, as would be expected, a higher frequency of recurrence within the abdomen, but an overall survival at 10 years, also approaching 100%, because of the effectiveness of chemotherapy at relapse. Analysis of large numbers of patients treated at single centres suggest that it may not be necessary to give as much treatment as this to a small subset of patients, namely those with a single lymph node high in the neck replaced with lymphocyte predominant Hodgkin's disease. This is a rare group in adults but considerably larger in children in which the frequency of relapse has been found to be less than 10%.

The heterogeneity of presentation within the Ann Arbor Stage II makes it much more difficult to be dogmatic about the optimum management of patients within this group. Standard mantle or inverted Y irradiation induces prolonged first remissions with only 20% likely to have recurred by 10 years in those patients without 'B' symptoms, without many sites of involvement, and in whom the size of the mediastinal lymph nodes is less than one third of the maximum thoracic diameter. Those patients with these unfavourable features at presentation have a significant possibility of failing to enter complete remission, and a much higher likelihood of relapse, which increases with the size of the mediastinal tumour. As with stage I disease, the frequency of recurrence is significantly higher for patients in whom pathological staging was not undertaken. Trends in terms of survival, although not significant, exist in favour of patients with lesser amounts of disease treated in the first instance with standard mantle radiotherapy, with the overall survival of all patients with PS IIA being 80% at 10 years. In consequence, at many centres the initial treatment of 'unfavourable' stage II Hodgkin's disease has been increased to include chemotherapy in addition to radiation.

(b) *Generalized asymptomatic nodal disease (Stage IIIA)*. There is much debate about the management of this group of patients, which is small in itself, and has been subdivided into even smaller subsets. Both total nodal irradiation (TNI) and combined chemotherapy induce complete remission in the majority of patients with PS IIIA disease. There is some evidence to suggest that chemotherapy induces longer remissions than TNI, although it comes from non-randomized studies. Analysis of the results of radiotherapy in respect of the distribution of involvement below the diaphragm has indicated that those patients at highest risk of relapse are those with lower para-aortic node involvement (IIIA2). Another study has shown that the extent of splenic involvement, measured by the number of nodules, is of prognostic significance. As is the case with stage II disease it seems likely that a proportion of patients require more treatment than standard extended field radiation therapy. Whether the 'extra' treatment is more radiation or chemotherapy, or even chemotherapy with radiotherapy in selected cases may not be crucial in terms of curing patients, although the treatment of choice may be influenced by the potential side effects. At Stanford, for example, there was no prognostic difference between those patients with and without lower para-aortic lymph node involvement or extensive splenic involvement since the latter group received irradiation to the liver. Similarly at other centres, the proportion of patients with IIIA (PS) without recurrence after treatment with chemotherapy exceeds 80% regardless of the distribution of disease. Thus, the prognosis of stage IIIA (PS) provided adequate initial treatment is given is very good. Indeed, although the freedom from recurrence falls to approximately 60% after 5 years in those treated with TNI at first, the overall survival of this group is identical to that of those treated more aggressively (once again because of the efficacy of salvage therapy). Consequently 80–85% of all patients with IIIA regardless of the initial treatment may expect to be alive 10 years after presentation, a

prognosis not worse than that of 'localized' nodal disease.

(c) *Generalized disease with symptoms and/or 'extranodal spread' (IIIB, IVA, IVB)*. This situation is almost invariably treated with chemotherapy from the outset. The introduction of the quadruple drug combination of nitrogen mustard, vincristine, prednisolone and procarbazine (MOPP), given cyclically every 4 weeks revolutionized the prognosis of patients with advanced Hodgkin's disease. Complete remission is induced in the majority of patients, and provided a total of approximately 6 cycles are given to those in whom it is achieved there is a 50% probability of remaining without recurrence at 5 years, with relatively few relapses seen thereafter (Sutcliffe *et al.*, 1978; de Vita, 1981).

The chief determinants of prognosis are advancing age, advanced stage and possibly the histological subtype lymphocyte depletion which all carry a prognostic disadvantage. There appears to be no significant difference between the remission rates or duration of remission in groups of patients receiving either MOPP or any of the variants. There appears to be no advantage in persisting with treatment for longer than 6 months or at most a year, regardless of the number of drugs used in 'maintenance'. There is a continuous relapse pattern for at least the first 3 years regardless of the approach. A 'post treatment' laparotomy study, in which lymph node mapping and splenectomy were undertaken in patients in clinical remission following therapy suggested that this was at least in part (up to 30%) due to failure to eradicate the disease with the initial therapy. Bonnadonna *et al.* (1982) have attempted to improve the low remission rate in patients with stage IVB disease by introducing a non-cross resistant combination of adriamycin, vinblastine, bleomycin and DTIC (imidazole carboxamide) (ABVD), into a rotating programme with MOPP. The initial results are encouraging, and further follow-up will show whether the increase in the complete remission rate will be accompanied by a prolongation of the duration of remission and thereby an increased probability of cure.

Management of patients failing to respond to the initial therapy

This is generally unsatisfactory and associated with a very poor prognosis. The outlook is significantly better for those failing to enter complete remission following radiotherapy for localized disease than chemotherapy for advanced disease but is usually disappointing. Differences between the results reported from different series may reflect genuine differences in the efficacy of the treatment in question although most of the time they are probably

a reflection of the criteria applied to the definition of treatment failure, and the length of time allowed to elapse before second time therapy is initiated.

Broadly speaking, a proportion of patients may be 'pulled into' complete remission with chemotherapy after radiation has almost, but radiologically not quite, achieved this. Survival following this may be equivalent to that in the group entering complete remission with radiotherapy alone. In contrast, patients in whom lymphadenopathy increases during radiotherapy very rarely derive long term benefit from chemotherapy.

Similarly, a small proportion of patients almost in complete remission following chemotherapy may enter complete remission following subsequent radiotherapy to cover a single site of residual disease. Even smaller is the proportion of patients entering remission with second time chemotherapy following failure of the initial chemotherapy. In general, results obtained in this situation are appalling although at one centre spectacular results have been reported with ABVD (Bonnadonna *et al.*, 1982).

Management of patients relapsing after successful initial therapy

Relapse following radiotherapy for localized disease may be detected early provided there is close surveillance. It is usually possible to achieve a second remission with MOPP or MVPP (mustine, vinblastine, prednisolone, procarbazine) and such second remissions may be very long, and compatible with cure. Survival of the whole population relapsing from radiotherapy as initial treatment is of the order of 60% at 5 years, with death being due either to failure to induce a second remission (approximately 25%) or recurrent Hodgkin's disease (about 5%) or other causes, either second malignancy or atypical infection.

The achievement of second remission of Hodgkin's disease following relapse after chemotherapy for advanced disease is less impressive, the frequency of second complete remission being less than 50%. It is achieved with least difficulty in patients with long first remissions. Second and subsequent remissions tend to be of decreasing duration.

*The management of 'endstage' disease (Mead *et al.*, 1982)*

This is extremely difficult in terms of both the physical and mental state of the patient and demands considerable skills. Late stage Hodgkin's disease is usually manifest by systemic symptoms of weight loss and fever. Lymphadenopathy is often absent and extensive searching for objective evidence of disease is unrewarding. It is frequently difficult to distinguish active disease from chronic infection which may

occur as the result of the immune paresis which accompanies advanced Hodgkin's disease and its therapy. Since cure is impossible at this stage, all attention must be directed at compassionate palliation, using both radiation and chemotherapy as appropriate. Treatment at this time is always administered on an individual basis, and therefore the interpretation of the results of various approaches difficult. Many chemotherapy combinations have been tested, that of chlorambucil and nitrosourea CCNU often bringing relief of symptoms and allowing the patient to be managed at home.

Conclusions

It is now possible to advise with confidence the majority of patients with Hodgkin's disease that they will be fit and well 10 years on, and that most of them can expect to be cured. The minority remains significant, however, being perhaps 30% of the total. Carefully conducted studies from major centres have demonstrated those patients at greatest risk for whom 'standard therapy' is inadequate. These have been identified as those with bulky disease, particularly in the mediastinum, even if confined to stage II in the Ann Arbor System, and older patients and symptomatic patients with disseminated disease. Appropriate modification of the standard therapy, to include 'more radiation' or adding chemotherapy to radiotherapy may improve the outlook in bulky mediastinal disease. The use of combinations of chemotherapy may help in patients with symptomatic disseminated disease. Whether or not the frequency with which laparotomy is used at presentation will decline further and will depend on the philosophy of the physicians. If it is to be eliminated 2 alternatives present themselves. The first is to undertreat a proportion of patients i.e. give radiation for localized disease and be prepared to attempt salvage about one third, and accepting that this salvage will be unsuccessful in approximately one half of the patients, when both failure to eradicate Hodgkin's disease and death from other causes are taken into account. The second is to overtreat the majority by giving chemotherapy to patients with clinically localized disease and accept the attendant morbidity.

These questions must be addressed with urgency and involve meticulous attention to detail. At the same time it is to be hoped that the combined research into the biology of the disease will allow the development of biologically orientated therapy, then removing the necessity for the current cytotoxic approach.

Non-Hodgkin's lymphoma

The current treatment strategies for the non-Hodgkin's lymphomas (NHL) are based on observa-

tions of the natural history of the diseases and their modification by treatment in use in the late 1960's and early 1970's. These led to the subdivision of the NHL according to the predicted outcome in relation to histological subtype and stage. For practical purposes, regardless of the histological classification employed, the physicians treating the patients have grouped the diseases into 2 broad groups with either an expected favourable, or unfavourable, prognosis. In general, patients expected to have a poor prognosis have been treated more intensively than those with a good prognosis. As is the case with Hodgkin's disease, radiation has been the mainstay of treatment for localized disease and chemotherapy for generalized.

Localized disease

The majority of patients who have localized NHL after clinical staging receive radiotherapy as the primary treatment. Unlike Hodgkin's disease however, NHL does not spread contiguously, and therefore the radiation fields are usually confined to the involved area and the immediately adjacent nodes. There is considerable evidence to show that the radiation dose required to achieve local control differs for the individual histological types, the high grade (immunoblastic lymphoma or diffuse histiocytic lymphoma, reticulum cell sarcoma) requiring considerably higher doses than either follicular lymphoma or the lymphocytic lymphomas.

There is a reasonable consensus of opinion in the reported literature that, overall, the 5 year survival of patients with stage I and II NHL treated with radiation alone lies at about 50% with the subsequent death rate being low. Survival is greater for those with stage I than II disease, and for those with low grade than high grade lymphoma. The relapse pattern for the high grade lymphomas is different from the low grade, reflecting the differences in their natural history. While relapse in the high grade group, when it does occur, is early in the course of the disease, in low grade lymphomas there is a continuous relapse pattern for as long as 20 years.

Localized extranodal presentations are much more frequent in NHL than in Hodgkin's disease, are particularly common in children, and appear to respond as well as nodal sites to radiotherapy. The radiation technique differs greatly from site to site and considerable expertise is demanded from the therapist. The most difficult area from which to extrapolate data is the gastro-intestinal tract which probably requires a separate staging system of its own. Surgery alone may be curative for a high proportion of patients with NHL confined to the gastro-intestinal tract alone, although either radiation or additional chemotherapy is usually advisable

if there is any suggestion of spread outside the gastrointestinal tract.

There is considerable controversy about whether 'adjuvant' chemotherapy should be used in the treatment of clinically localized NHL. The lack of pathological staging, and the relapse pattern both locally and at distant sites, are arguments used in its favour. There is general agreement that it is appropriate for patients with multiple sites of stage II disease and much agreement that it should be used in all patients with stage II disease. Several studies have shown a trend towards an advantage for patients receiving adjuvant chemotherapy, but the advantage has been small. Data similar to those for Hodgkin's disease with regard to salvage are not easily derived, but that which is available is discouraging. It has been suggested that chemotherapy might be substituted altogether for the treatment of 'early stage' NHL of unfavourable histology, but this is not widely accepted.

The present position with regard to management is as follows. Stage I NHL of favourable histology (predominantly follicular lymphoma) responds very well to local irradiation and to demonstrate any survival advantage to additional therapy would be difficult. Stage II follicular lymphoma is more likely to recur sooner than stage I and consequently further therapy may be appropriate, although the probability of inducing further remission with chlorambucil is high provided transformation has not occurred. Early recurrence occurs significantly frequently after local radiation for high grade stage I and II NHL (of which local control may not be easy) and adjuvant chemotherapy is probably appropriate if the cure fraction is to be increased. Certain subcategories with bulky disease regardless of the Ann Arbor stage require chemotherapy as their initial management. Extracapsular localized presentations carry at least as good a prognosis as nodal presentation.

Generalized disease

(i) *Favourable histology.* Several studies have demonstrated that it is possible to induce clinically complete or near complete remission in this group of patients with relatively conservative therapy. There is no evidence that the use of intensive chemotherapy has improved the natural history of the diseases more than conservative therapy, nor that prolonged treatment has any advantage over short-term therapy. Patients in whom the histological pattern is follicular respond more frequently than those in whom it is diffuse (within the favourable group). The duration of remission tends to be longer, as does survival. The use of chlorambucil in short pulses over several months only yields responses in 75% of patients with

follicular lymphoma. The median duration of remission is between one and 2 years, and the proportion in prolonged remission approximately 20% at 10 years. It is usually possible to induce second and third remissions as early as first remissions provided the histological pattern is unchanged, and there is no difference between the duration of first, second and third remissions. These results, coupled with the well-known indolent natural history of the disease has encouraged many to observe asymptomatic patients without therapy from presentation and only treat when there is evidence of progression. There is no evidence that such selected patients are comprised in any way by this approach.

While there is no evidence that any of the approaches to the low grade lymphomas have been curative, the experience gained with conservative management has been very valuable. The judicious use of short pulses of single agents with minimal side effects, local irradiation and sometimes splenectomy has allowed the majority of patients with follicular lymphoma to continue a full, active, normal life for many years, interrupted only by brief visits to the outpatient clinic and occasional admission for lymph node biopsy. The pattern of disease for patients with diffuse low grade lymphomas is similar, although responsiveness rather less, and survival times shorter. In addition, infectious complications and recurrent splenomegaly may present more problems than they do in patients with follicular lymphoma. This conservative approach is almost certainly appropriate for older patients. The minority who do not respond or who relapse and die within 5 years is still considerable however, and it must be remembered that the median age of the patients is 50, making the need to explore alternative therapy urgent. New approaches employing the use of anti-idiotypic sera are now being investigated, as is interferon.

(ii) *Unfavourable histology.* It is within this group that the introduction of intensive combination chemotherapy has had a major impact. It is now possible to induce long term unmaintained remissions in a significant proportion of patients; paradoxically the unfavourable histology lymphomas may have a more favourable prognosis. The frequency with which complete remission may be induced correlates with the stage of disease at presentation (III or IV) and the age and general state of the patient. It is possible to achieve complete remission in the great majority of patients with nodal disease (stage III) whereas it is still rare to do so in more than half of those with stage IV. Older and sicker patients withstand the treatment less well than the younger and fitter and therefore prescribing adequate therapy to them is difficult, and carries a significant mortality. Children, virtually all of whom have disseminated 'poor prognosis' NHL, are now doing well with more

than 50% having long term survival and possible cure (Malpas, 1982).

The combination of cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) (McKelvey *et al.*, 1976) forms the basis of most combinations. Prescribed at approximately 3 weekly intervals, it is rare for it not to induce regression of lymphoma. The observation that the disease regressed but began to return between cycles led to the introduction of 'interval' methotrexate (Canellos *et al.*, 1981). Doses of between 200 mg and 7.5 g have been given on day 10 of the cycle, followed by folinic acid rescue for 48 hr. Reports of this approach in terms of the frequency of complete remission induction have been encouraging; further follow up is required to permit analysis of the long term benefit.

No studies have shown any advantage to prolonging therapy for more than a year, and many groups give a total of 6 to 8 cycles of CHOP and then stop. The median duration of remission in most studies for all cases is approximately one year, being significantly longer for those with stage III than stage IV disease. In sharp contrast with follicular lymphoma, relapse after 18 months is a very uncommon event, and it is to be expected that a high proportion of patients surviving in complete remission without relapse at 2 years will be cured.

Three particular areas are worthy of special attention. The first is that of Burkitt lymphoma of European type presenting in an advanced state. This is extremely difficult to treat. Rapid lysis of tumour can almost always be achieved, but eradication is very rare. Lysis of tumour may be associated with the 'phosphate shower' or tumour overkill syndrome in which life-threatening metabolic disturbance may occur, particularly hyperuricaemia. Scrupulous attention to hydration and management of fluid and electrolyte balance are essential.

Similar problems may occur with T cell lymphomata, frequently presenting with a mediastinal tumour. Previously called the Sternberg sarcoma this is well recognized as developing into acute lymphoblastic leukaemia if not rapidly treated. Without doubt a proportion of these patients are now cured. Major problems exist in the management. The first is the tumour overkill syndrome referred to above. The second is the treatment of the frequently residual abnormal mediastinal contour. It is customary to proceed to irradiation if the contour remains abnormal after chemotherapy, although the frequency with which this is necessary is unknown. In a trial of radiotherapy to the mediastinum in children, no benefit in producing longer survival has been shown in children randomized to receive mediastinal irradiation (Mott, 1982, personal communication).

The third problem is the third area to which attention must be paid overall, namely the manage-

ment of the central nervous system in all patients with unfavourable histology NHL. This may be manifest either by extradural deposits or basal meningitis. The latter rarely occurs in patients without bone marrow infiltration. Meningitis is rare at presentation and also uncommon as a site of first relapse, almost invariably occurring in association with systemic disease. It is almost uncommon for it to be the direct cause of death. Its potential importance may be masked by the inadequacy of systemic control in patients presenting with bone marrow infiltration. Both intrathecal therapy and cranial irradiation have been used as prophylaxis but in non-randomized studies. High dose methotrexate and more recently high dose cytosine arabinoside have been shown to give cytotoxic levels in the cerebrospinal fluid when used for systemic therapy. The treatment of established disease is usually with a combination of both intrathecal chemotherapy and whole neuraxis irradiation. The efficacy of these treatments which obviously have some effect is hard to assess because death so frequently occurs from systemic disease.

Until the present, only a minority of patients have shown very obvious benefit from intensive combination chemotherapy, but for them the benefit has been massive because it has been cure. Although this minority represents only about 30% of the total in adults and 50–70% in children presenting with advanced disease it is most encouraging, particularly since the natural history of the disease is of an inexorable progression towards death within months. There is hope that even with the treatment presently available, that this minority may be increased towards a majority. In addition, as with the 'low grade' lymphomas, experimental approaches involving the use of intensive chemotherapy with bone marrow transplantation after 'clean up' with specific anti-sera may alter the prognosis markedly.

Complications of therapy for lymphoma

The mortality from either radiotherapy or chemotherapy in lymphoma is low. Both treatments may most often be conducted on an outpatient basis. Radiotherapy, properly prescribed, is less toxic than chemotherapy, both in the short and long term. Fatigue is the major side effect, with mucosal reactions and some minor pulmonary fibrosis occurring in a relatively small proportion of patients. Biochemical and clinical evidence of hypothyroidism are well recorded. Infertility should not occur in men, nor in women provided that oophorectomy has been performed at laparotomy. There is a low incidence of second malignancy in patients treated with radiation alone. The most widely used chemotherapy, MOPP, almost invariably causes nausea and often severe

vomiting at least on the first day of the cycle. This may be prevented in many patients with judicious use of antiemetics, but in a few is intractable. The substitution of chlorambucil for mustine has reduced this side effect considerably and also reduced the possibility of local excoriation if the chemotherapy escapes from the vein. This has made it an attractive combination for the treatment of children (Dady *et al.*, 1982). All the alkylating agents containing combinations cause sterility in men, although some degree of recovery may occur after many years. A premature menopause is frequently induced in women, and appears to be irreversible. This is almost invariable in patients over the age of thirty: below this age about half the patients retain normal menses. Attempts are presently being made to 'turn off' the gonads during treatment to prevent damage to the germ cells. Chemotherapy itself, particularly combinations including alkylating agents and procarbazine, have an undoubted incidence of second malignancy. The alternative favoured combination ABVD has to date been shown by Bonnadonna *et al.* (1982) to be as effective as MOPP and to have a lower incidence of male infertility and second malignancy. It is unfortunately immediately more toxic, with severe vomiting and alopecia being frequent and myocardial damage a possibility. The combination of radiation and chemotherapy, especially separated by a period of time carries the highest incidence of second malignancy.

The alarming array of side effects for both Hodgkin's and non-Hodgkin's lymphoma must be considered within the context of the natural history of the diseases and the impact upon them which the skilful manipulation of the therapy has had. Hodgkin's disease untreated was invariably fatal; the majority of patients are now cured with current therapy.

The malignant lymphomas continue to present an exciting challenge to all concerned in their management. Understanding of their biology, enhanced by immunohistopathological techniques which have become available in the last 5 years, has increased enormously. Methods for detection of minimal lymphadenopathy at clinically impalpable sites have a greatly increased degree of resolution. Even now, with the crude treatment available, it is possible to cure many patients which was inconceivable until very recently. With these achievements in mind, an optimistic approach must be taken to the determination of new therapeutic methods.

Major References

- BLOOMFIELD, C.D., JONES, S.E. & PETERSON, B.A. (Eds) (1982) Proceedings of the Symposium on Contemporary Issues in Hodgkin's disease: Biology, staging and treatment. *Cancer Treatment Reports*, **66**, 4, 601.

- CANELLOS, G.P., LISTER, T.A. & SKARIN, A.T. (1978) Chemotherapy of non-Hodgkin's lymphoma. *Cancer*, **42**, 932.
 CANELLOS, G.P. (Ed) (1979) The Lymphomas. *Clinics in Hematology*, No. **8**, part 3. Saunders, London.
 COLTMAN, C.A. JR (Ed) (1980) Hodgkin's disease. *Seminars in Oncology*, **VII**, 2.
 JONES, S.E. & GODDEN, J. (1977) Proceedings of the Conference on non-Hodgkin's lymphomas. *Cancer Treatment Reports*, **61**, 6, 935.
 KAPLAN, H.S. (1974) *Hodgkin's Disease*. Harvard University Press, Cambridge, Mass, London, England.
 PECKHAM, M.J. (Ed) (1975) Symposium on non-Hodgkin's lymphoma. *British Journal of Cancer*, **31**, Suppl. II.
 SMITHERS, D.W. SIR (Ed) (1973) Modes of Spread. In: *Hodgkin's Disease*, p. 107. Churchill Livingstone, Edinburgh and London.
 ULTMAN, J. & STREULI, R. (1980) Non-Hodgkin's lymphomas. *Seminars in Oncology*, **VII**, 3.

General References

- BONNADONNA, G., SANTORO, A., BONFANTE, V. & VALAGUSSA, P. (1982) Cyclical delivery of MOPP and ABVD combinations in stage IV Hodgkin's disease: rationale, background studies and recent results. *Cancer Treatment Reports*, **66**, 4, 881.
 BROUET, J.C., PREUD'HOMME, J.L. & SELIGMANN, M. (1976) Membrane markers in 'histiocytic' lymphomas (reticulum cell sarcomas). *Journal of the National Cancer Institute*, **56**, 361.
 CANELLOS, G.P., SKARIN, A.T., ROSENTHAL, D.S., MOLONEY, W.C. & FREI, E. III. (1981) Methotrexate as a single agent and in combination chemotherapy for the treatment of non-Hodgkin's lymphoma of unfavourable histology. *Cancer Treatment Reports*, **65**, 1, 125.
 CARBONE, P.P., KAPLAN, H.S., MUSSHOF, K., SMITHERS, D.W. & TUBIANA, M. (1971) Report of the Committee on Hodgkin's disease Staging Classification. *Cancer Research*, **31**, 1860.
 CHILCOTE, R.R., BAEHNER, R.L. & HAMMOND, D. (1976) Septicaemia and meningitis in children splenectomised for Hodgkin's disease. *New England Journal of Medicine*, **295**, 798.
 DADY, P.J., MCELWAIN, T.J., AUSTIN, D.E., BARRETT, A. & PECKHAM, M.J. (1982) Five years' experience with ChlVPP. Effective low toxicity combination chemotherapy for treatment of Hodgkin's Disease. *British Journal of Cancer*, **45**, 851.
 DIEHL, V., KIRCHNER, H.H., BURRICHTER, H., STEIN, H., FON-ATSCH, C., GERDES, J., SCHAADT, H., HEIT, W., UCHANSKA-ZEIGLER, B., ZEIGLER, A., HEINTZ, F. & SVENO, K. (1982) Characteristics of Hodgkin's disease derived cell lines. *Cancer Treatment Reports*, **66**, 4, 615.
 EARL, H.M., SUTCLIFFE, S.B.J., FRY, I.K., TUCKER, A.K., YOUNG, J., HUSBAND, J., WRIGLEY, P.F.M. & MALPAS, J.S. (1980) Computerised tomographic (CT) abdominal scanning in Hodgkin's disease. *Clinical Radiology*, **31**, 149.
 EASSON, E.D. & RUSSELL, M.H. (1963) The cure of Hodgkin's disease. *British Medical Journal*, **1**, 1704.
 FINZI, N.S. (1913) *Radium Therapeutics*, p. 84. London, Oxford Medical Publications.
 GALL, E.A. & MALLORY, T.B. (1942) Malignant lymphoma: a re-evaluation of its position in the scheme of malignant lymphoma based on a survey of 253 cases. *Cancer*, **9**, 792.
 GALLAGHER, C.J., WHITE, F.E., TUCKER, A.K., KELSEY FRY, I., MALPAS, J.S. & LISTER, T.A. (1982) The role of computed tomography in the detection of intrathoracic lymphoma. (Submitted for publication.)
 GILBERT, R. (1939) Radiotherapy in Hodgkin's disease (malignant granulomatosis): anatomic and clinical foundations: governing principles: results. *American Journal of Roentgenology*, **41**, 198.
 HABESHAW, J.A. & STUART, E.A. (1975) Cell receptor studies on seven cases of diffuse histiocytic malignant lymphoma (reticulum cell sarcoma). *Journal of Clinical Pathology*, **28**, 289.
 JACKSON, H. JR. & PARKER, F. JR. (1944) Hodgkin's disease II pathology. *New England Journal of Medicine*, **231**, 35.
 JAFFE, E.S., SHEVACH, E.M., FRANK, M.M., BERARD, C.W. &

- GREEN, I. (1974) Nodular lymphoma: evidence for an origin from follicular B lymphocytes. *New England Journal of Medicine*, **290**, 813.
- KAPLAN, H.S. (1962) The radical radiotherapy of regionally localised Hodgkin's disease. *Radiology*, **78**, 553.
- LENNERT, K. (1978) *Malignant lymphomas other than Hodgkin's disease*. Springer-Verlag, New York, Berlin.
- LUKES, R.T. & BUTLER, J.J. (1966) The pathology and nomenclature of Hodgkin's disease. *Cancer Research*, **26**, 1063.
- LUKES, R.T., CARVER, L.F., HALL, T.C. & RAPPAPORT, H. (1966) Report of the nomenclature committee. *Cancer Research*, **26**, 1311.
- LUKES, R.J. & COLLINS, R.D. (1974) Immunological characteristics of human malignant lymphomas. *Cancer*, **34**, 1488.
- McKELVEY, E.M., GOTTLIEB, J.A., WILSON, H.E., HAUT, A., TALLEY, R.W., STEPHENS, R., LANE, M., GAMBLE, J.F., JONES, S.E., GROZA, P.N., GUTTERMAN, J., COLTMAN, C. JR. & MOON, T.E. (1976) Hydroxydaunorubicin (adriamycin) combination chemotherapy in malignant lymphoma. *Cancer*, **38**, 1484.
- MALPAS, J.S. (1982) Lymphomas in children. *Seminars in Hematology*, **19**, 301.
- MEAD, G.M., HARKER, W.G., KUSHLAN, P. & ROSENBERG, S.A. (1982) Single agent palliative chemotherapy for end stage Hodgkin's disease. *Cancer*, **50**, 5, 829.
- MURPHY, S.B. (1980) Classification staging, and end results of treatment of childhood non-Hodgkin's lymphomas. Dissimilarities from lymphomas in adults. *Seminars in Oncology*, **VII**, 332.
- NATIONAL CANCER INSTITUTE SPONSORED STUDY OF CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS (1982) The non-Hodgkin's lymphoma pathologic classification project. *Cancer*, **49**, 2112.
- PETERS, M.V. (1950) A study of survivals in Hodgkin's disease treated radiologically. *American Journal of Roentgenology*, **63**, 299.
- PETERS, M.V. & MIDDLEMISS, K.C.H. (1958) A Study of Hodgkin's disease treated by irradiation. *American Journal of Roentgenology*, **79**, 114.
- RAPPAPORT, H. (1966) Tumours of the haematopoietic system. *Atlas of Tumour Pathology*, Section III, Fascicle 8. Armed Forces Institute of Pathology, Washington DC.
- RAPPAPORT, H., WINTER, W.J. & HICKS, E.B. (1956) Follicular lymphoma: a re-evaluation of its position in the scheme of malignant lymphoma based on a survey of 253 cases. *Cancer*, **9**, 792.
- ROSENBERG, S.A. & KAPLAN, H.S. (1966) Evidence for an orderly progression in the spread of Hodgkin's disease. *Cancer Research*, **26**, 1225.
- SMITH, J.L., BARKER, C.R., CLEIN, G.P. & COLLINS, R.D. (1973) Characteristics of malignant mediastinal lymphoid neoplasm (Sternberg sarcoma) as thymic in origin. *Lancet*, **i**, 74.
- SUTCLIFFE, S.B.J., WRIGLEY, P.F.M., PETO, J., LISTER, T.A., STANSFELD, A.G., WHITEHOUSE, J.M.A., CROWTHER, D. & MALPAS, J.S. (1978) MVPP chemotherapy regimen for advanced Hodgkin's disease. *British Medical Journal*, **i**, 697.
- VITA, V.T. DE (1981) The consequences of treatment of Hodgkin's disease. *Cancer*, **47**, 1.

(Received 5 October 1982)