

ABSTRACTS

ORAL PRESENTATIONS

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

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THE MALIGNANT LYMPHOMAS AS A HUMAN MODEL FOR THE STUDY OF NEOPLASIA
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The lymphomas illustrate the value of human models of human disease. Once therapy had a modicum of success in the treatment of Hodgkin's disease and the other lymphomas, subsequent progress was made in each case by detailed studies of the natural history of each disease subset to determine the reasons for treatment failure. The data provided from staging studies of Hodgkin's disease have supported a unifocal origin of the disease with contiguity of spread rather than a probabilistic pattern of lymph node involvement. In the non-Hodgkin's lymphomas, the patterns of spread follow the patterns of travel of the equivalent cell in the lymphatic system. The information led a path back to the laboratory to help unravel the lymphomas as a set of tumors of the immune system. In the non-Hodgkin's lymphomas, there is evidence that most adult lymphomas derive from B-lymphocytes and that the more indolent nodular lymphomas evolve to the more aggressive diffuse large cell types. These observations have had a profound impact on the decision of past and current treatment protocols.

Recently, spontaneous mutation towards phenotypic drug resistance has come to the forefront as a reason for drug treatment failure in all cancers and especially in the lymphomas (Cancer Treatment Reports, December 1979). The response of NPDL, DHL and Hodgkin's disease to single and combination chemotherapy currently provides the best evidence that this process is taking place at a clinical level. The best differentiated lymphomas (NPDL, a B-cell tumor) respond as well to single agent as to drug combinations (growth characteristics close to normal lymphatic tissue-therefore lower mutation rate and no need for a combination of drugs). The least differentiated tumor (DHL, also a B-cell tumor in most cases) is curable by drug combinations but not single agents. This differential response of a tumor derived from the same cell line suggests that the cell effectiveness of combination chemotherapy relates not to kinetic parameters but to its ability to cover resistant cell lines since mutation rates are higher for less differentiated tumors. Modelling of these data by Goldie and Coldman predicts that for two equally effective therapies alternating cycles of administration should prove superior to each combination used to exhaustion before switching. The only successful clinical model testing this hypothesis is in the treatment of Hodgkin's disease with alternating cycles of MOPP and ABVD. This experiment appears successful and is already serving as a model for future protocols. These concepts will be reviewed as they pertain to lymphomas in some detail.

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ADVANCES IN BASIC BIOLOGY RELEVANT TO A BETTER UNDERSTANDING OF HUMAN LYMPHOMAS.

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A historical review of the evaluation of treatment concepts will be presented.

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EVOLUTION OF CLASSIFICATION OF MALIGNANT LYMPHOMAS.

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Malignant lymphomas have traditionally been diagnosed and classified on purely morphologic grounds. For Hodgkin's disease, the subclassification of paragranuloma, granuloma, and sarcoma originally proposed by Jackson and Parker was superseded in the mid-1960's by the Lukes-Butler classification as modified at the Rye conference. Non-Hodgkin's lymphomas had been broadly divided into the categories of lymphosarcoma, reticulum cell sarcoma, and (giant) follicular lymphoma. In 1958 Rappaport and Call proposed a new classification, which was refined and widely disseminated with the publication in 1966 of Rappaport's AFIP fascicle on "Tumors of the Hematopoietic System." The term "reticulum cell" was abandoned in favor of the histiocyte and neoplasms of apparent lymphoid nature were subdivided morphologically according to presumed degrees of "differentiation." In the ensuing 15 years the Rappaport classification has been successfully applied to numerous clinicopathologic studies of non-Hodgkin's lymphomas.

At the same time, new immunological, cytochemical, and ultrastructural techniques have made possible a sophisticated characterization of normal cells of the T-lymphocyte, B-lymphocyte, and monocyte-macrophage series. Such studies have greatly enhanced current understanding of the compartmentalization, immunology, and function of the lymphoreticular system. Application of the same modern techniques in studies of the neoplastic cells of malignant lymphomas has established that such cells often bear markers similar or identical to those demonstrable on normal cells. Malignant lymphomas are tumors of the immune system and they often seem, both structurally and functionally, to be neoplastic caricatures of their normal benign counterparts. These advances have led to a series of recently proffered classifications, which can be related to each other through a new Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage.

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THE EVOLUTION IN THE TREATMENT STRATEGY OF MALIGNANT LYMPHOMAS. G. Bonadonna, Istituto Nazionale Tumori, Milan, Italy.

The evolution concerning treatment strategy for Hodgkin's disease indicates that the improvement in results is now being achieved in all stages at major research centers. Current achievements are based on solid advances, and represent the results of brilliant leadership in the rational development of therapeutic program. The fact that today no stage of the disease is beyond cure following the initial treatment program, and even after recurrence following primary irradiation, represents a dramatic improvement in the overall prognosis of a disease which only about twenty years ago was considered to be almost universally fatal. The first strategic concepts were first outlined from 1925 to 1939 by R. Gilbert of Geneva. He was the first to emphasize the fundamental principle of treatment, i.e. the destruction of all lesions in the first course of radiotherapy through segmental irradiation encompassing suspected microscopic disease. In the 1950's the publications of V. Peters and later of E. Easson arouse widespread interest in the curative potentialities of radiotherapy. Subsequently megavoltage irradiation made a major impact on the evolution of treatment. H. Kaplan at Stanford introduced the wide-field technique of radiotherapy and, through appropriate staging procedures (lymphography, laparotomy, bone marrow biopsy), he and other radiation therapists were able to cure 70-80% of patients with PS I-II. Chemotherapy was developed mainly during the 1960's and the advances in drug treatment culminated in the report of V. De Vita et al. in 1970 showing the impressive results of MOPP. During the 1970's combined modality treatment was extensively studied mainly through the prospective randomized trials of the Stanford Group led by S. Rosenberg. The concept of non-cross resistant chemotherapy and of alternating regimens (MOPP/ABVD) were developed in Milan since 1973. Today, combined modality treatment is being utilized in patients with PS IIIA as well as in PS IIA and IIB with massive mediastinal involvement while the MOPP/ABVD program was found to be more effective than MOPP in PS IV disease. At present, the only approach that appears to increase the cure rate of advanced Hodgkin's disease, either at diagnosis or at relapse following primary radiotherapy, is the cyclical use of non-cross resistant combinations. This approach could also decrease some of the acute and late effects associated to MOPP chemotherapy. Current strategies are aimed at refinement of available treatment programs to include more consideration to overt and occult treatment morbidity.

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T-CELL INHIBITOR IN THE SERA OF UNTREATED PATIENTS WITH HODGKIN'S DISEASE. Marcia M. Bieber and Henry S. Kaplan. Department of Radiology, Stanford, Ca., U.S.A.

Hodgkin's disease (HD) is associated with a selective defect of cell mediated immunity, manifested *in vivo*, even in patients with localized disease, by impaired delayed hypersensitivity responses to natural recall antigens and to chemical allergens such as 2,4-dinitrochlorobenzene (Eltringham and Kaplan, *NCI Monogr.* 36:107, 1973). Peripheral blood lymphocytes (PBL) from patients with untreated HD have deficient phytohemagglutinin (PHA) and E-rosette responses (Levy and Kaplan, *NEJM* 290:181, 1974; Bobrove et al., *Cancer* 36:169, 1975). Sera from patients with HD and low density extracts from HD spleens contain an inhibitor of these responses (Fuks, Strober, and Kaplan, *NEJM* 295:1273, 1976). This inhibitor has now been purified by sequential fractionation of HD vs. normal (N) sera on sucrose and KBr gradients, yielding the HD-SKL and N-SKL fractions, followed by thin layer chromatography (TLC), where the inhibitor migrates with the glycolipids. At 5% concentration, HD-SKL inhibited the PHA response of HD-PBL (mean of 10 individuals 19,086 cpm, vs. 37,827 cpm in absence of inhibitor) but not that of N-PBL. At 30%, both HD-PBL and N-PBL were inhibited. Elution of 4 bands from TLC of HD-SKL and N-SKL fractions revealed major inhibitory activity in band III eluate of HD-SKL which was absent in band III eluate of N-SKL. The chemical identity and *in vivo* source of the T-cell inhibitor are being studied.

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LONG TERM EFFECTS OF TOTAL LYMPHOID IRRADIATION ON THE IMMUNE SYSTEM AND ITS USE AS AN EXPERIMENTAL MODE OF IMMUNOSUPPRESSIVE THERAPY. Z. FUKS and S. SLAVIN, The Hebrew University-Hadassah Medical School, Kiryat Hadassah, Jerusalem, Israel 91 120.

Fractionated total lymphoid irradiation (TLI) such as used in the treatment of Hodgkin's disease, results in profound and prolonged immunosuppression in treated patients. Examination of peripheral blood after TLI reveals marked and persisting T lymphocytopenia and impairment of *in vitro* T cell mediated immune responses to lectins recall antigens and allogeneic cells. The allogeneic response to lymphocytes in the MLC reaction is virtually eliminated for approximately two years, although it gradually recovers and returns to normal levels thereafter. The elimination of the MLC response after TLI suggests that irradiated individuals may exhibit transplantation tolerance to tissue and organ allografts.

Experimental models of TLI treated mice showed a fivefold increase in the duration of skin allografts transplanted across major histocompatibility barriers when compared to unirradiated controls. Furthermore, transplantation of bone marrow cells from strongly histoincompatible donors into TLI treated recipient mice, produced a state of bilateral permanent tolerance of host versus graft and graft versus host without evidence of graft versus host disease (GVHD). The resultant stable chimeras showed indefinite survival of skin allografts taken from the marrow donor strain but rejected normal skin from third party unrelated donors. Specific and permanent transplantation tolerance was also induced experimentally after TLI and bone marrow transplantation in rats, dogs and monkeys. In all of these experimental models, survival of organ allografts was indefinite and the transplantation of the bone marrow did not result in GVHD.

Preliminary experience demonstrated that TLI may also have a clinical application as immunosuppressive therapy in organ allotransplantation and autoimmune diseases in the human. TLI induced significant clinical remissions in intractable progressive rheumatoid arthritis, and has been used to prepare patients for renal allotransplantation and for bone marrow transplantation in aplastic anemia. The possible future use of TLI to prepare patients for rescue replacement therapy with allogeneic bone marrow transplantation after treatment of advanced Hodgkin's disease and malignant lymphoma with superlethal doses of radiation and chemotherapy, will be discussed.

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IMMUNOLOGIC STUDIES IN HODGKIN'S DISEASE PRIOR TO THERAPY AND AFTER PROLONGED REMISSION. Richard I. Fisher, Christian Vanhaelen, Robert Young, and Vincent DeVita, Medicine Branch, National Cancer Institute, Bethesda, Maryland 20205

Initial studies demonstrated that untreated patients with Hodgkin's disease (HD) have impaired cell-mediated immunity including depressed delayed hypersensitivity, decreased E rosette formation and depressed proliferative responses to T cell mitogens or foreign antigens. However, neither skin test reactivity nor lymphocyte proliferation predicted long term survival (*Arch. Int. Med.*, March, 1973). More recent studies have attempted 1) to define the immunologic mechanisms responsible for these abnormalities and 2) to determine their relevance to the development or natural history of HD.

Significant reductions in E rosettes and mitogen-induced proliferation were observed in 47 long term survivors of HD who had been treated successfully with MOPP chemotherapy (*Ann. Int. Med.*, May, 1980). These assays did not return to normal with disease free intervals up to 11 years. Furthermore long term survivors with diffuse histiocytic lymphoma (DHL) who had been treated with similar combination chemotherapy have significantly greater numbers of E rosettes and totally normal mitogen-induced proliferation. In contrast, the long term survivors of HD have normal numbers of circulating B cells and cells with an Fc receptor as well as normal quantitative immunoglobulin levels.

Subsequent studies have demonstrated that T cells from untreated HD patients have increased sensitivity to normal monocyte suppressor cells that regulate mixed lymphocyte culture responses (*Blood*, May, 1981). The increased sensitivity to monocyte suppression is not reversed by the addition of indomethacin nor is it caused by plasma factors. Increased sensitivity of T cells to monocyte suppressor cells is detected in the long term survivors with HD but not those with DHL.

T cell proliferation in untreated HD patients is also more sensitive to the suppression mediated by another type of normal regulatory cell, the suppressor T cell (*J. Immunol.*, in press). Suppressor T cells can be induced by incubation with concanavalin A (ConA) and regulate allogeneic as well as autologous proliferation. ConA induced suppressor cells from HD patients exhibited normal regulatory control of the proliferative responses of normal T cells. However, responding T cells from HD patients were significantly more sensitive to the suppression mediated by the normal suppressor cells. In studies of long term survivors with HD, this increased sensitivity to suppressor T cells also persisted. These results demonstrate that T cell responses in HD may be suppressed because of increased sensitivity to a variety of normal immunoregulatory systems. These abnormalities may be 1) a persistent acquired consequence of HD, or 2) a genetic predisposition to the development of HD.

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CHARACTERISTICS OF HODGKIN-DERIVED CELL-LINES (L 428, L 439, L 538, L 540)
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We were able to establish four in vitro cell lines from various materials derived from patients with histologically proven Hodgkin's disease, which are now in culture from 12 up to 30 months.

The neoplastic nature of the culture cells is indicated by the demonstration of cytogenetic abnormalities (structural and numerical markers) associated with a monoclonal pattern of marker chromosomes.

The phenotypic characterisation of these cells showed the following features: 1. lack of EBV-genomes or EBV-associated antigens, 2. negativity for all cellular markers defining B- and T-lymphocytes, macrophages, monocytes or myeloid cells.

Positive reactivity was shown for Ia-like antigen, acid phosphatase and acid esterase, as well as receptors for human T-cells in two out of four lines.

Heterotransplantation in nude mice resulted in tumor-growth with all cell lines after intracranial inoculation, after subcutaneous/intramuscular transplantation, however, only under additional protective conditions (plasma clot). The morphology and the marker pattern of the established culture cells was identical with that of Hodgkin (H)- and Reed-Sternberg (RS) cells freshly obtained from biopsies.

In addition we produced a conventional antiserum in rabbits against the L 428 cells. After excessive absorption with human tissues the anti L 428 serum defined an antigen that was restricted in expression to the L 428 and the L 540 cells as well as H- and RS-cells in Hodgkin-biopsies from 12 patients with different histologies.

Further tests are in progress to define the cellular origin by application of monoclonal antibodies and induction of differentiation markers.

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PROGNOSTIC FACTORS AND SUBGROUPS IN HODGKIN'S DISEASE. S.A. Rosenberg, M.D., Stanford University, Stanford, California, U.S.A.

There are several well-known prognostic factors which influence the natural history of patients with Hodgkin's disease. The most obvious factors are the stage of the disease, utilizing the Ann Arbor system, and the histologic type, according to the Rye-Paris conference.

There are numerous other prognostic factors usually appreciated by clinicians experienced with the disease. These are:

- 1) Bulk of disease
- 2) Age
- 3) Sex
- 4) Number of sites
- 5) Site of involvement, i.e. spleen, bone marrow
- 6) Bone marrow function

Some of these prognostic factors are being lost or diminished by currently utilized successful treatment programs. For example, the histologic subtype is no longer a major prognostic variable, unless the patient fails to achieve cure of the disease. If cure is not achieved, then the natural history variable associated with the various histologic subtypes influences the survival after relapse.

Several of the prognostic variables are important in predicting the success of control of the disease by irradiation alone. Patients with large mediastinal masses ($> 1/3$ of the transverse chest diameter) and extensive splenic involvement (more than 4 nodules) are cured by irradiation alone in less than half of the cases. This suggests that combined modality therapy is indicated for these poor prognostic subtypes. Similarly, certain patients with Stage IV disease, such as those with bone marrow involvement, experience a high relapse rate after the usual course of 6 cycles of MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) chemotherapy. This subtype should be considered for alternative treatment programs which may be more successful, employing alternating non-cross-resistant combination chemotherapy or adjuvant irradiation.

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SEVERE PRURITUS : A "B" SYMPTOM IN HODGKIN'S DISEASE. P.G. Gobbi, G. Attardo Parrinello, G. Lattanzio, S.C. Rizzo, E. Ascari. Istituto di Patologia Medica I and Clinica Medica I, University of Pavia, Pavia 27100, Italy.

The Ann Arbor Conference stated that pruritus in Hodgkin's disease was no longer to be considered related to a poor prognosis (i.e., within the B category). Nevertheless, very few and conflicting reports are available on the true prognostic significance of this symptom.

Pruritus was estimated by us with respect to frequency, intensity and prognostic importance in 360 Hodgkin's patients observed between 1971 and 1979. For the discrimination of severe from mild pruritus the following requirements were necessary: a) ineffectiveness of local and systemic antipruritics, b) improvement with either radiotherapy or chemotherapy and c) presence of multiple excoriations. Ninety out of 360 patients (25%) had mild itching at admission and showed the same survival as the 249 non-itching cases; 21 patients (5.8%) presented with severe pruritus and showed a statistically shorter survival than that of mildly and non-itching cases. Such comparison was performed on groups of patients made homologous - according to the Hunkey and Myers adjusting procedure - with respect to sex, age, stage, histology and Ann Arbor A or B category. Thus the very poor survival related to severe pruritus appeared independent of the main prognostic parameters that are commonly taken into account in the management of the disease. This result may be important for treatment, when severe pruritus occurs in early stages or without other systemic symptoms.

The inclusion of severe pruritus among the Ann Arbor criteria for definition of the B clinical category is here proposed.

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AN ANALYSIS OF 528 SCANS USING ABDOMINAL COMPUTED TOMOGRAPHY (CT) IN PATIENTS WITH LYMPHOMA.

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Abdominal CT has been carried out on 105 patients with untreated Hodgkin's disease (HD) before staging laparotomy. Only 11 of 42 patients with a positive laparotomy correctly showed disease at the involved site(s). The main reason for this inaccuracy resulted from the inability to detect intra-splenic disease. There were two patients falsely diagnosed as having intra-abdominal disease. Comparison with abdominal lymphography indicated a higher detection rate using CT. Abdominal CT was performed in 48 patients with relapsing HD. Forty of these had evidence of intra-abdominal disease documented by CT. Of the 20 patients who had clinical relapse above the diaphragm only, CT showed infradiaphragmatic disease in 14. Additional unsuspected disease was found in 12 of 23 cases with infradiaphragmatic or generalised relapse. All 5 patients with B symptoms as the only clinical evidence of relapse had abnormalities below the diaphragm on CT.

Forty three patients with non-Hodgkin's lymphoma (NHL) of diffuse (high grade) pathology were scanned at a time of apparent complete remission (CR) using conventional restaging (but excluding lymphography). Of 21 patients with abnormal scans, 16 have relapsed or died compared with only one out of 22 patients with normal scans ($p = 0.00001$). The results were different in 39 patients with nodular lymphoma scanned at the time of CR. In this instance, the presence of an abnormal scan was not significantly associated with a poorer prognosis.

Fifty patients with NHL were scanned at a time of clinical relapse. Twice as many sites of involvement were detected using CT than by conventional restaging criteria. Of 50 unexpected lymph node areas shown to be enlarged on CT, lymphography would have been expected to detect only 23% of the abnormalities. All but three retrocrural abnormalities were unsuspected clinically. Coeliac and mesenteric lymphadenopathy was rarely suspected yet was present in 19 patients.

The advantage of CT over abdominal lymphography in the initial staging and follow up of patients with lymphoma will be discussed.

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UPDATE ON STAGING IN HODGKIN'S DISEASE (HD). J.E. Ultmann, S. Neely, H. Golomb, D. Sweet, E. Lester, University of Chicago Cancer Research Center, Chicago, IL 60637, USA

Curability of HD regardless of stage has been established using radiotherapy, chemotherapy, or both. It is now appropriate to examine approaches permitting further improvement in survival which at the same time reduce the risks which come with extensive treatment. Since it is possible to assure five year survival for 90% of patients regardless of stage, it becomes important to consider the price of treatment, and in particular, the incidence of second cancers, including leukemia, which occur in from 3-8% of patients. Any study design which reduces treatment must assure that the outcome in terms of curability is not diminished. A number of approaches are possible: delivery of minimal effective treatment followed by observation and salvage therapy for those who exacerbate; combined modality treatment measuring response rate and complication rate; or, carefully tailored treatment based upon detailed staging technology. We have concentrated on the third of these options. We will review newer staging technology and will elaborate on the special problems and significance of substaging abdominal disease.

From 1969-1979, 76 patients with biopsy proven HD were determined by extensive staging laparotomy to be in pathologic stage (PS) III. We have updated our follow-up through 1980. We have previously described the subclassification of PS III into III₁ or III₂. Twenty-five patients were III₁A; 8, III₁B; 26, III₂A; and 17, III₂B. Randomization to total nodal radiation (RT) or RT plus combination chemotherapy (CC) was prospective in the first five years; subsequently, either single (RT or CC only) or split modality (RT + CC + RT) therapy was instituted depending on substaging. Relapses were determined as to whether they were regional or disseminated. Of the 16 patients in PS III₁ receiving RT alone, 4 have shown regional recurrence and 1, dissemination; of the 17 patients who received CC with or without RT, three patients have shown regional relapses, and three, dissemination. Of the 20 patients in PS III₂ receiving RT alone, 1 has shown a regional relapse and 15 have disseminated; in contrast, of the 23 patients in PS III₂ receiving CC with or without radiotherapy, 2 have had regional relapse and 3 have had dissemination. These data demonstrate that patients with PS III₂ who have received RT alone, have a significantly increased risk of disseminated relapse compared to patients given CC after RT ($p = 0.001$). Actuarial data analyzing relapse-free survival, as well as survival for PS III₁ over a 10 year period indicate no difference in these parameters for RT only compared to RT + CC. This is in sharp contrast to actuarial relapse-free survival and survival for PS III₂ where patients treated with CC have similar results to PS III₁, but patients receiving RT alone have a highly significant incidence of relapse with dissemination in the first three years and significant mortality. Therapy results with RT alone for PS III₁ patients and with CC alone for PS III₂ patients are currently being evaluated.

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LOW DOSE RADIATION AND MOPP CHEMOTHERAPY FOR PEDIATRIC HODGKIN'S DISEASE. Henry S. Kaplan and S.S. Donaldson. Department of Radiology, Stanford University School of Medicine, Stanford, Ca. 94305, U.S.A.

A challenge in the treatment of children with Hodgkin's disease is to delineate a program yielding excellent probability of cure while minimizing risk of complication. In order to prevent the profound impairment of bone growth known to accompany high dose total lymphoid irradiation, 46 pathologically staged children, 14 years of age or less, have been treated with low dose radiotherapy and 6 cycles of MOPP chemotherapy. Doses were 1500 rad for bone age less than 6 years, 2000 rad for those 6-10 years, and 2500 rad for those 11-14 years, to involved or extended fields depending upon extent of disease. Pathologic stages were PS I (7), II (16), III (18), IV (5). Nine of 46 had systemic symptoms. Actuarial survival at 10 years is 96%, and freedom from relapse is 93%, with maximum follow-up of 10 years, median follow-up of 3.5 years. Two of 3 relapses occurred in children with stage IV marrow disease who failed to respond to chemotherapy; the third relapse occurred at 18 months in an irradiated neck node in a girl with stage III EE B disease. 150 of 151 (99.4%) involved lymph node sites have been controlled. Treatment has been well tolerated with no serious bacterial infections in children who have received prophylactic antibiotics. Thyroid dysfunction has occurred in only 17% of children. There have been no second malignant tumors. Follow-up interval is too short to ascertain impact on gonadal function in pre-pubertal patients. Follow-up growth curves (height/weight) are within one standard deviation of normal for these children. The combination of low dose radiation and MOPP is effective in achieving apparent cure without the known bone growth sequelae of high dose radiation.

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CONSERVATIVE MANAGEMENT OF CHILDHOOD HODGKIN'S DISEASE - CHEMOTHERAPY OF LOW TOXICITY, LIMITED RADIOOTHERAPY AND NO LAPAROTOMY.

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Thirty six children aged between 2 and 15 years have received treatment for Hodgkin's disease. Median follow-up time is 34 months with a range of 3 - 120 months. In ten children staging included laparotomy but for the past five years it has been our policy not to perform laparotomy but to stage clinically only and to treat with chemotherapy for all stages, followed by involved field radiotherapy in patients with Stage I and II disease. All patients with bulky mediastinal involvement have received radiotherapy to this site following chemotherapy.

Chemotherapy has been ChlVPP. This is less toxic than mustine containing combinations and is chlorambucil 8 mg/m² orally daily for 14 days, vinblastine 6 mg/m² on days 1 and 8, prednisolone 30 mg/m² orally daily for 14 days, procarbazine 100 mg/m² orally daily for 14 days. Courses were given on a 28 day cycle with a minimum of 6 courses and a maximum of 10 courses.

Ten patients received ChlVPP as their only treatment. Nine achieve complete remission. Twenty patients received chemotherapy followed by elective radiotherapy. Nineteen achieved complete remission. Three patients treated with ChlVPP on relapse from previous radiotherapy all achieved complete remission as did 2/3 who had relapsed following treatment with a mustine containing combination.

Side effects were mild and easily tolerable. Twelve patients vomit after the first injection of vinblastine, usually only once, 24 hours after the injection had been given. No patient vomited after the second injection.

Laparotomy was associated with a higher subsequent infection rate than that observed in non-laparotomised patients (3.75 : 1). Sixty percent of laparotomised patients developed Herpes zoster compared with twenty three percent on non-laparotomised patients.

Ninety three percent of children were in complete remission after chemotherapy or chemotherapy / irradiation. Ninety one percent of the whole group are alive at the time of follow-up.

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HODGKIN'S DISEASE IN CHILDREN. RESULTS IN CLINICALLY STAGED CHILDREN TREATED WITH MOPP AND MODERATE DOSE EXTENDED FIELD RADIATION (EF RT). Derek Jenkin, Helen Chan, Melvin Freedman, Mark Greenberg, Peter McClure, Frederick Saunders and Marilyn Sonley. The Princess Margaret Hospital and Hospital for Sick Children, Toronto.

During 1973-1977 41 children entered a study in which patients with clinical stage I disease were treated with involved field RT alone and all others were treated with 3 cycles of MOPP, EF RT and a final three cycles of MOPP. Radiation dose was reduced to 2-2500 rad in 20 fractions. A 1979 analysis (Jenkin and Berry, Seminars in Oncology 7:202-211, 1980) demonstrated that the 5 year relapse free survival and survival rates were 85% and 89% respectively. Only 1/32 patients in CS II-IVA relapsed. 4/9 CS IVB patients relapsed. Two viral infectious deaths in CR occurred.

This study has continued. Current results will be presented.

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HODGKIN DISEASE IN CHILDREN: STAGING AND TREATMENT OF 102 CASES.

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From 1971 to 1979, 102 consecutive untreated children with Hodgkin disease, aged 16 or less at the time of diagnosis, were referred to the Istituto Nazionale Tumori of Milan, Italy. Boys were 64 and girls 38, with a sex ratio of 1.7. The age ranged from 2.11 to 15.8 years. The clinical stage was determined in accordance with the Ann Arbor classification. After clinical staging procedures, 16 children were classified as stage IV disease because of bone marrow involvement or lung metastases. Pathologic stage was: stage I 26 patients, II 22, III 1, IIIS 36 and stage IV 17. Laparotomy with splenectomy and multiple biopsy was carried out in 72 patients. In 14 children laparoscopy was performed instead of laparotomy. Laparotomy modified the clinical stage in 30/72 children (42%): in 29 stage was increased and in 1 was decreased. Thirty-five of 72 children showed spleen involvement; in 28/35 spleen was not palpable. Laparoscopy has never changed the clinical stage.

Through the years, treatment program was modified, especially in terms of drug regimens. However, the treatment strategy was designed in order to treat stage I and II with radiotherapy alone (mantle or subtotal nodal irradiation with 40-45 Gy to involved areas and 35-40 Gy to uninvolved areas). Stage III and IIB were given combined chemotherapy (MOPP or MABOP or ABVD) and radiotherapy (subtotal nodal or total nodal irradiation at 35 Gy to involved areas and 30 Gy to uninvolved areas). In stage IV, radiotherapy was delivered after chemotherapy at 25 Gy to bulky tumor site(s). The 5-year relapse free survival was 80 %, 77 %, 81 %, 65 % for stage I, II, III and IV, respectively, while the actuarial 5-year total survival was 100 %, 95 %, 81 % and 85 %. Considering all the children staged as I, II and III disease, the 5-year relapse free survival and total survival were 79 % and 90 % respectively.

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THE GERMAN COOPERATIVE STUDY FOR THE TREATMENT OF HODGKIN'S DISEASE IN CHILDREN AND ADOLESCENTS: DESIGN AND PRELIMINARY RESULTS

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Between June 1978 and April 1981 134 children and adolescents with Hodgkin's disease of all stages were enrolled without any selection in this prospective and randomised study (age range from 2 5/12 - 18 8/12, 91 males, 43 females). 43 hospitals are participating (40 from FRG, 3 from Austria). Only newly diagnosed cases were admitted. Laparotomy and splenectomy are done in all patients older than 5 years except in patients with stage IV disease. The aim of the study is to investigate the outcome of the disease under a reduced radiotherapy when a combination of radiotherapy and chemotherapy is administered. Two courses of chemotherapy (Oncovin, Prednisone, Procarbazine, Adriamycin - OPPA) each lasting 15 days are given to all patients prior to radiation in order to reduce tumour mass and to destroy micrometastases. We randomised the radiotherapy in the following way: Group 1 - Radiation of the involved and extended field with 3600 - 4000 rad. Group 2 - Radiation of the involved field with the full dose of 3600-4000 rad, the extended field with 1800 - 2000 rad only. No further therapy for patients with stage IA, IB and IIA. Patients with more advanced stages receive 4 additional cycles of COPP (Cyclophosphamide, Oncovin, Prednisone, Procarbazine).

The two courses of chemotherapy prior to radiation achieved complete remission in 70% of the patients by clinical criteria including chest x-ray. After 34 months the over-all relapse free survival rate using life table analysis is 0,91 (S=0,03). 2 patients were non responders and died within months. 4 patients died due to intercurrent infections, 2 while in CCR. 1 patient died due to GVH-reaction following blood transfusion. 2 patients refused further therapy after the 1st 2 cycles of chemotherapy. Only 2 patients have relapsed so far. Thus 123 out of 132 evaluable patients (93%) are in CCR (medium remission time 16 months). The relapse free survival rate for patients with stage I - IIA is 0,96 (S=0,03) and for stage IIB - IV 0,87 (S=0,05). Group 1 and 2 did not show any statistically significant difference in their relapse free survival rates (0,92 - S=0,04 - versus 0,96 - S=0,03). Thus patients with a lower dose of radiation are doing as well as the other group.

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PRESENT STATUS OF PRIMARY CHEMOTHERAPY OF HODGKIN'S DISEASE (HD)

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Over half of all patients with advanced HD are now curable by combination chemotherapy. National mortality from HD in the U.S.A. has fallen significantly since its introduction in the mid-1960s. Single agent treatment provides no more than palliation and should be reserved in medical practice to situations where infirmity from cause other than HD dictate their use. The availability of curative drug programs set in motion a series of clinical trials that follow four main directions. The areas are: 1. The development of programs to prevent relapse after complete remission is attained with a drug combination (drug maintenance studies). Of 8 such programs completed worldwide, none has proven effective. Failure in these programs seems related to the invariable reduction of dose and dose rate of maintenance programs and development of resistance during and prior to induction treatment. 2. The development of modifications of the original MOPP program to ameliorate toxicity and/or improve results. Of over 12 such programs reported toxicity has been ameliorated in some cases but none has led to a significant therapeutic advance (such as a higher complete remission rate or more durable remissions). 3. The development of clinical trials to test the use of radiation as an adjuvant to chemotherapy in patients with advanced stages (III and IV) of HD. These have taken two forms, standard or low dose radiotherapy. In one study, standard dose radiation in addition to chemotherapy in Stage IIB and IV disease has not provided a significant advantage over chemotherapy alone. The two studies exploring low dose radiation may show some advantage for low dose x-ray plus drugs. In Stage IIIA, a debate still exists over the approach to treatment. As in early stages of HD, the second malignancy rate is a serious concern. 4. The development of non-cross resistant drug combinations. Non-cross resistant combinations (ABV, B-DOPA or SCAB) offer some hope of salvage of patients who relapse after treatment with the first drug combination. They also can be used in an alternating fashion with MOPP or MOPP-like programs as initial treatment. This latter approach offers the advantage of avoiding toxicity associated with combining radiotherapy with drugs while intensifying treatment. In the author's view this is the area of greatest promise to induce a greater number of more durable remissions in advanced HD. The results conform with recent thinking on how to effectively deal with the spontaneous development of resistance to drugs. Disease variables such as symptoms, histology and prior treatment (chemotherapy adversely, radiotherapy favorably) influence the outcome with all drug programs. Staging laparotomy has not been shown to aid in the delivery of adequate chemotherapy.

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RESULTS OF RADIOTHERAPY IN THE TREATMENT OF HODGKIN'S DISEASE

M. J. Peckham

The results of treatment with radiotherapy ± chemotherapy in PS I, II & III Hodgkin's disease at the Royal Marsden Hospital will be presented and compared with treatment results in clinically staged patients. Between 1970 and 1976, 110 patients with PS I & II disease received treatment. The actuarial five-year survival and disease-free survival rates were 90% and 68% respectively. The presence of systemic symptoms significantly influenced survival. Number of lymph node areas involved and bulk of disease significantly influenced disease-free survival. Sex and histology were not significant prognostic factors. Mediastinal node involvement was associated with a worse prognosis for survival and disease-free survival. Relapses occurred at 0-69 months after irradiation (median 10 months) with 25% occurring 2+ years after treatment. Mantle irradiation and mantle + para-aortic strip irradiation for supra-diaphragmatic PS I & II produced similar results.

Between 1970 and 1979, 125 patients with PS III disease were treated with radiotherapy ± chemotherapy. Actuarial survival and disease-free survival results at ten years were 74% and 50% respectively. The prognostic significance of factors including age, sex, ESR, histology, involvement of spleen, splenic hilar nodes and porta-hepatis nodes, symptoms, sub-staging based on upper and lower abdominal disease and volume of disease has been investigated and the results will be summarised. Second tumours have occurred in 5/185 (4%) of patients.

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Clinical trials in Hodgkin's disease (CS I + II) carried out by the E.O.R.T.C. Radiotherapy-Chemotherapy Group. M. Tubiana, M. Hayat, M. Henry-Amar on behalf of E.O.R.T.C. Radiotherapy-Chemotherapy Group.

Three clinical trials have been conducted. Their general aim was to find how to proportionate the aggressiveness of the treatment with the severity of the disease. The first in which 296 patients were included (1964-1970) compared regional radiotherapy solely versus the same radiotherapy plus adjuvant chemotherapy (one weekly injection of Vinblastine for 2 years). In the group having received adjuvant chemotherapy, the relapse free survival rate was significantly higher; the survival rate was improved but the difference was not statistically significant. The multivariate analysis of the study was able to identify several prognostic indicators. In the subgroup with poor prognostic indicators the survival rate was higher in the arm with adjuvant chemotherapy.

The aims of the second trial (1970-1975) in which 300 patients were included, were: 1) to compare splenectomy versus spleen irradiation: the survivals were identical in the two arms; 2) to assess the prognostic significance of the spleen involvement relapses in unirradiated lymph node areas and extra nodal relapses were more frequent in the group with spleen involvement; 3) to compare 2 types of adjuvant chemotherapy (VLB versus VLB + PCZ): no difference was observed.

The third trial (1976-1981), in which over 300 patients have been included, divided the patients in 2 groups. Those with good prognostic indicators were, after laparotomy, randomized between mantle field irradiation or mantle field + para aortic irradiation. Those with poor prognostic indicators were randomized between total nodal irradiation or 6 MOPP + irradiation. The preliminary results will be discussed.

It must be underlined that after a follow-up longer than 10 years, the incidence of secondary leukemia is very low (< 1%) in the group of patients treated by association of radiotherapy + VLB.

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CHEMOTHERAPY-RADIOTHERAPY IN STAGES IB, IIn A, IIB, III HODGKIN'S DISEASE. POSSIBILITY OF CHEMOTHERAPY REDUCTION : RESULTS OF 3 VERSUS 6 COURSES OF M.O.P.P. F. Teillet, Ch. Bayle, B. Asselain, Ph. Lelièvre, Ch. Ferme, M. Boiron, J. Bernard. Institut de recherches en hématologie et oncologie - Hôpital Saint Louis Paris, et Hôpital Louis Mourier Colombes - France.

We have used MOPP chemotherapy prior to radiotherapy in patients with Hodgkin's disease (clinical stages IB, IIn A, IIB and III). Efficiency of 3 versus 6 courses of MOPP was evaluated in terms of complete remission (C.R.), incomplete remission (I.R.), failure (F) according to two successive therapeutic trials : 1) From 1972 to 1977, 69 patients received 6 courses of MOPP chemotherapy followed, 1 month after completion, by clinical, radiological and biological examination and exploratory laparotomy with splenectomy and multiples biopsies for pathological restaging prior to extended-field irradiation 2) From 1977 to 1980, 47 patients were treated according to the same schedule except for MOPP chemotherapy which was reduced to 3 courses. There is no significant difference according to clinical stages as summarized in table.

	MOPP	CR (%)	IR (%)	F (%)	Total
Global	6	55 (80)	10 (14)	4 (6)	69
	3	38 (81)	7 (15)	2 (4)	47
IInA	6	13 (72)	4 (21)	1	18
	3	11 (100)	0	0	11
IB-IIB	6	29 (85)	4 (12)	1	34
	3	16 (76)	3 (14)	2	21
III	6	13 (76)	2 (12)	1	16
	3	11 (75)	4 (26)	0	15

Furthermore it must be pointed out that secondary post-chemotherapy laparotomy was negative in 100 % of clinical stages IInA and in 96 % of clinical stages IB, IIB and III patients in clinical, biological and radiological C.R. These data allow 1) To reduce MOPP chemotherapy in combined-modality therapy and consequently to improve the treatment tolerance as well to decrease the long term toxicity especially oncogenic risk 2) To avoid secondary exploratory laparotomy in patients in post-chemotherapy C.R., especially in stages IIn A.

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MOPP CHEMOTHERAPY-SELECTIVE NODAL IRRADIATION(RT) IN HODGKIN'S DISEASE (HD)-CLINICAL STAGES (CS) IA-IIIB. JM Andrieu, C Bayle, F Teillet, J Bernard. Institut de Recherches sur les Maladies du Sang, Hôpital Saint-Louis Paris 75010.

334 patients(pts) suffering from HD, CS IA-IIIB were prospectively treated between 1972 and 1976. The 166 CS IA,IIA pts (trial 7201) received 3 MOPP cycles plus mantle (M), mantle without mediastinum (MWM) or inverted Y (IY) RT according to presentation. The 168 CS II₃,A, IB IIB, IIIA IIIB pts were submitted to the randomized programs 7202 P and 7202C. The group 7202P (82 pts) was submitted to pathological staging (PS) : the 35 PSII₃,A, IB IIB pts (trial 7202P2) received 3 MOPP ; complete and partial responders (CR, PR) were submitted to M,MWM or IY RT ; the 47 PS IIIA IIIB (trial 7202P3) received 6 MOPP plus 4 monthly Vinblastine : 6 mg/m² (VBL) ; CR and PR received M or MWM and I Y or lumboaortic (L) RT according to initial extension. The group 7202C (86 pts) was clinically staged only; the 67 CS II₃,A, IB IIB pts (trial 7202C2) received 6 MOPP+ 4 VBL ; CR and PR were submitted to prophylactic splenectomy followed by M or MWM RT ; L RT was added for the 4 pts with positive splenectomy ; the 19 CS IIIA IIIB (trial 7202C3) receive 6 MOPP plus 4 VBL ; CR and PR had splenectomy followed by M or MWM and I Y or L RT. 40 pts died : 9 after MOPP failure, 12 after relapse; 8 from iatrogenic complications under treatment, 10 in complete remission (5 with acute leukemia) and 1 from a car accident. The overall survival (SV) at 8 years and disease free duration (DFD) are 85.8% and 91% . SV and DFD of the trial 7201 are 93.1% and 92.5% . There is a significant difference between the trials 7202C (C2+C3) and 7202P (P2+P3) for S (85.6% VS 74.6% , P = 0.04) as well as for DFD (94.8% VS 84.1% , P = 0.05).

We conclude that the sequence MOPP (3 or 6 cycles according to stage). prophylactic splenectomy (according to stage) - selective RT is an adequate treatment for HD CS IA-IIIB.

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EFFECTIVENESS OF NITROSOUREA (CCNU) CONTAINING 4-DRUG PROGRAMS FOR RADIATION THERAPY FAILURES IN ADVANCED HODGKIN'S DISEASE. Cooper, M.R., Pajak, T.F., Glicksman, A.S., Gottlieb, A.J., Bloomfield, C.D., Nissen, N.L., Spurr, C.L. For Cancer and Leukemia Group B, Scarsdale, N.Y., 10583

A study was designed to test the value of the substitution of CCNU for mechlorethamine and/or vinblastine for vincristine in the MOPP regimen for advanced Hodgkin's disease. Each treatment contained prednisone and procarbazine. Regimen I contained mechlorethamine and vincristine (MOPP); II contained mechlorethamine and vinblastine (MVPP); III contained CCNU and vincristine (COPP); and IV contained CCNU and vinblastine (CVPP). Mechlorethamine and vinca alkaloids were injected on day 1 and 8 of each 28 day cycle but CCNU was taken orally on day 1 of each cycle. Induction consisted of 6 cycles of therapy. Of 518 evaluable patients with stage III and IV Hodgkin's disease randomized to this study, 141 had relapsed following prior radiation treatment (RT) and are the basis for this report. 32% were \geq 40 years old, 58% stage IV, 78% "B" symptoms, and 59% male. 47% had received involved field (RT), 18% extended field (RT), and 35% total nodal (RT). After the first two cycles of induction chemotherapy, the CCNU patients received a greater proportion of each scheduled dosage cycle than the mechlorethamine group.

The complete remission (CR) frequencies were MOPP 64%, MVPP 70%, COPP 87%, and CVPP 84%. All (RT) relapses achieved a greater (CR) frequency with the CCNU containing treatments (86%) than those receiving mechlorethamine (67%) ($p = .01$). Stage III and IV patients with "B" disease had a higher (CR) frequency with the CCNU containing treatments than those receiving mechlorethamine (87% versus 69%) ($p = .03$). Similarly, CVPP showed an induction advantage over MOPP for stage IVA and B patients (88% versus 65%) ($p = .07$).

The frequency of severe neurological and gastrointestinal toxicity was greater for the mechlorethamine than the CCNU groups ($p = .01$). In patients with extensive prior (RT) and/or >60 years old, the vinblastine combinations were associated with greater hematological toxicity than those containing vincristine.

Radiation therapy failures attain a greater (CR) frequency with less toxicity when inducted with a CCNU containing treatment as compared to those containing mechlorethamine. The vinca alkaloid used in combination with CCNU should be based on the degree of prior (RT) and the patient's age.

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INFLUENCE OF MOPP DOSES AND TIMING ON TREATMENT OUTCOME IN ADVANCED HODGKIN'S DISEASE (HD). Carde, P., MacKintosh, F.R., Rosenberg, S.A. Stanford University Medical Center, Stanford CA.

Records of 132 protocol patients (pts) with HD treated with MOPP at Stanford as initial therapy (38 pts) or for relapse following radiotherapy (94 pts) were analyzed to assess whether chemotherapy (CHT) dose and timing influenced treatment outcome independent of other prognostic factors. Attainment of complete remission (CR) is best (multivariate logistic) for pts without B symptoms ($p = .001$) who have a higher mean rate of drug delivery in the first 3 cycles ($p = .01$). No other factor had significant additional impact on CR achievement although there is a trend ($p = .17$) toward lower CR rates with increasing number of extra nodal disease sites. Survival (Cox/Breslow) is better for younger pts ($p = .003$) without pleural involvement by HD ($p = .03$) and who received higher 6 cycles doses of nitrogen mustard ($p = .06$). Responses are more durable in CR patients without initial bone marrow ($p = .03$) or liver ($p = .12$) involvement and/or with lung involvement ($p = .05$). Clinical features at presentation (stage, bone marrow involvement, B symptoms, do not influence the drug delivery. The drug delivery is decreased in patients who received prior Total Nodal Irradiation (68 pts) or combined modality radiotherapy and chemotherapy (9 pts). However, outcome was related to drug delivery independent of previous Total Nodal Irradiation.

In Conclusion, higher CR rates are achieved in advanced HD, particularly in symptomatic pts, if higher doses can be given with minimal delay during the first 3 cycles of MOPP. CHT dose and timing analyses are of importance in directing decision making in HD and probably in other neoplasms as well. Such analyses must also be considered when comparing results from different instructions using same regimens.

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SECOND MALIGNANCIES IN PATIENTS TREATED FOR HODGKIN'S DISEASE. Robert C. Young, Eli J. Glatstein, Dan L. Longo, Richard I. Fisher, and Vincent T. DeVita, Jr., Medicine Branch and Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland 20205, U.S.A. Second malignancies are a well described, albeit, uncommon complication of Hodgkin's Disease treatment. They have developed only because the primary treatment of the underlying disease has been so successful that the majority of patients experience long survival and are now at risk for these late complications.

Our initial reports (New Engl. J. Med. 287: 1119, 1972) documented a 3.5 fold increased risk of second malignant tumors. The greatest risk (29 fold increase) was observed in patients who received intensive radiation therapy and intensive chemotherapy. Subsequent studies (Coleman et al, New Engl. J. Med. 297: 1249, 1977; Toland et al, Cancer Clin. Trials 1: 27, 1978; Valagussa et al, Brit. Med. J. Jan. 26, 1980) have confirmed this risk and emphasized that the risk is due to an increase in incidence of Acute Non-Lymphocytic Leukemia. The Stanford studies put the actuarial risk of leukemia for all treated patients at 2.0% at 7 years, and 4.0% for those receiving combined modality treatment. The acute leukemias usually develop from one to four years after completion of definitive therapy, and are preceded by a period of pancytopenia and/or sideroblastic anemia. Response to leukemic therapy has been poor.

Although the risk appears greatest for acute leukemia, increased risks for thyroid cancer, lung cancer, skin cancer, and Kaposi's sarcoma have also been described.

Recent attention has been drawn to the occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's Disease (Krikorian et al, New Engl. J. Med. 300: 452, 1979). These lymphomas are of the diffuse large cell variety and occur from 4-10 years after the initial Hodgkin's Disease diagnosis. The actuarial risk of non-Hodgkin's lymphoma developing in aggressively treated Hodgkin's Disease appears to be approximately 4.4% at 10 years.

Factors important in increasing the risk of second malignancies include combined modality treatment, prolonged and repeated treatment therapy or disease-related immunosuppression, and the use of chemotherapy regimens containing alkylating agents, nitrosoureas and/or Procarbazine. Initial reports of a reduced frequency of secondary leukemia with ABVD (Valagussa et al, Proc. AACR 22:197, 1981) are of interest but will require as long a followup as is now available with MOPP before a truly reduced incidence of second tumors can be documented.

Although risk of second malignancies is small, efforts of minimizing this risk should be of high priority. Areas of major focus include 1) Restoration of normal immune competence, 2) Restricted use of combined modality therapies to subsets of patients with demonstrated benefit, 3) Minimal use of intermittent reinduction therapies and 4) Prospective comparative trials of regimens with reduced leukemic induction risk.

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STERILITY AFTER TREATMENT FOR HODGKIN'S DISEASE

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Intermittent combination chemotherapy comprising cyclical Mustine, Vinblastine, Prednisolone and Procarbazine (MVPP) resulted in a complete clinical remission of advanced Hodgkin's disease (HD) being achieved in 120 out of 188 previously untreated men at St. Bartholomew's Hospital between 1968 and 1978. 73 of these men formed the basis of the study by Chapman et al reporting that oligospermia was present in one third of men prior to chemotherapy and azoospermia was inevitable after the first cycle. Subsequent long term follow up of 44 out of 86 men remaining in complete remission in 1980, up to 10 years from treatment, shows that limited recovery of spermatogenesis has only occurred in 3. All these were under the age of 30. Repeated high gonadotrophin levels support the initial interpretation that azoospermia is the consequence of testicular failure and has been confirmed by post treatment testicular biopsy. During the same period MVPP resulted in a complete remission in 69 out of 102 women with advanced HD. 41 of these women formed the basis of the second study by Chapman et al who reported ovarian failure in 20. This study has been followed up in all these females, normal menstruation being maintained in 12. Retention of menstruation bears a striking age relationship, being preserved in 50% of those women under 30 years. Preliminary data is presented as to the effectiveness of the oral contraceptive device in protecting against the effects of chemotherapy.

1. Chapman, R.M., Sutcliffe, S.B., Rees, L.H. and Edwards, C.R.W. cyclical combination chemotherapy and gonadal function. Lancet **i**:285-289, 1979.
2. Chapman, R.M., Sutcliffe, S.B. and Malpas, J.S. Cytotoxic induced ovarian failure in women with Hodgkin's disease. J.A.M.A. **242**:1877-1811, 1979.

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FERTILITY, PREGNANCY AND PROGENY IN PATIENTS TREATED FOR HODGKIN'S DISEASE. P.H. Konits, P.H. Wiernik, J. Aisner, C. Rulenz. Baltimore Cancer Research Program, DCT, NCI. Baltimore, Maryland 21201 U.S.A.

The improved survival in Hodgkin's disease has led to concern for long term sequelae of treatment including gonadal dysfunction. The fertility and pregnancy frequency and outcome were thus evaluated among 209 treated Hodgkin's disease patients in the reproductive ages (13-45 yrs). By questionnaire, 83 of 209 patients actively desired children after treatment and the remainder wished to delay and/or practiced contraception. Of the 83, 23/38 females and the spouses of 19/45 male patients had pregnancies. Nine of the 83 patients received combination chemotherapy alone, and 4 had pregnancies. Thirty-one of the 83 received radiation therapy alone and 19/31 had pregnancies (4/6 with pelvic irradiation). Forty-three of the 83 patients received combined modality therapy (radiation therapy and combination chemotherapy); 20 females and 23 males. Among these 43, pregnancy frequency in females 13/20 (65%) was greater than in spouses of male patients 6/23 (26%), $p=0.01$. The 2 females and 2/6 spouses of male patients treated with pelvic irradiation as part of combined modality therapy had pregnancies. For females 9/14 (64%) with radiation therapy alone and 13/21 (62%) with combined modality therapy had pregnancies ($p=N.S.$). For spouses of male patients 11/18 (61%) with radiation therapy alone and 7/24 (29%) with combined modality therapy had pregnancies ($p=0.04$). Analysis according to pelvic radiation therapy did not show any significant differences in the pregnancy frequency.

Forty of the 115 males had semen analysis. Overall 31/40 had low or absent sperm counts regardless of stage and treatment (radiation therapy, combined modality therapy or chemotherapy). One of the 10 males (none with normal analysis) who received pelvic irradiation (regardless of other treatment) had any evidence of spermatozoa and 14/30 (9 with normal analysis) without pelvic irradiation had spermatozoa ($p=0.03$).

There were 63 pregnancies in 42 patients (or spouses) resulting in 42 full term children, 8 current pregnancies, 2 spontaneous abortions, 10 elective abortions and one set of stillborn twins at 6 1/2 months gestation. Median age of the offspring is 4 years (range 1 month to 12 years). Birthweight and growth and development milestones were normal. There were no major and few minor birth defects including 1 case each of pes planus, hip dysplasia, and heart murmur of unknown etiology. One child died of neuroblastoma at age 2 1/2 years. There were no differences in the 42 patients (or spouses) in the rate of spontaneous abortions or anomalies compared to 131 pregnancies in 63 patients (or spouses) prior to treatment or to the general population.

The offspring rate in Hodgkin's disease patients after treatment is about 50% but males receiving combined modality therapy have a decreased fertility which may be due to disease, pelvic irradiation, or combination chemotherapy as part of combined modality therapy. This study indicates that a larger number of patients with Hodgkin's disease than previously appreciated remain fertile and can have normal children after treatment.

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IMPORTANCE OF BIOLOGIC MARKERS IN NON-HODGKIN'S LYMPHOMAS (NHL) FROM THE POINT OF VIEW OF THE PATHOLOGIST. Elaine S. Jaffe, M.D., and Jeffrey Cossman, M.D., NCI, NIH, Bethesda, Md., USA.

The NHL represent multiple diseases with diverse morphologic and clinical expressions. In some instances distinctive morphologic entities may be very closely related clinically and/or biologically, whereas other diseases that share morphologic similarities may be clinically and biologically quite distinct. The application of modern immunologic techniques and concepts has enabled us to develop a conceptual framework which we may use to decipher the morphologic diversity of these neoplasms. The NHL are fascinating and instructive models when viewed as neoplasms of the immune system. The spectrum of B cell lymphomas reflects the functional and anatomic heterogeneity of the normal humoral immune system. The neoplastic cells often retain the morphologic, functional and migratory characteristics of their normal counterparts. Likewise the functional heterogeneity seen in the T cell system is reflected in its malignant expressions, and indeed, malignant clonal expansions have been useful in the identification of normal cellular phenotypes not previously recognized.

Immunologic studies in addition have been instrumental in the definition of new clinico-pathologic entities. For example, lymphoblastic lymphoma (LBL) had formerly been included in the generic group of diffuse poorly differentiated lymphocytic lymphoma. Immunologic markers helped to define LBL, and illuminate its relationship in both children and adults to acute lymphocytic leukemia. However, now that this entity has been defined, it can in most cases be recognized on histologic grounds without need for specialized studies. Similarly, immunologic and functional studies are currently defining the clinical and pathologic spectrum of peripheral T cell lymphomas.

Immunologic studies have also helped to delineate problem areas in the classification of NHL. Diffuse large cell or "histiocytic" lymphomas, are clinically and biologically heterogeneous, exhibiting common morphologic features of transformed cells of diverse origins. As yet, distinctive clinico-pathologic subtypes have not been delineated and currently used morphologic criteria are predictive of immunotype in only 61% of cases. In a series of 29 cases although the large non-cleaved and small non-cleaved cell types of Lukes and Collins were consistently associated with B cell surface markers, other cytologic subtypes were not as consistently associated with a specific immunotype.

Immunologic surface markers can also be used as a practical tool for the pathologist in differential diagnosis. The following clinical situations are representative: 1) subclassification of acute leukemia; 2) differential diagnosis of peripheral blood lymphocytosis; 3) classification of diffuse lymphomas; 4) lymphoma vs. leukemia; and 5) staging of lymphoma or diagnosis

IMPORTANCE OF BIOLOGIC MARKERS IN NON-HODGKIN'S LYMPHOMAS (NHL) FROM THE POINT OF VIEW OF THE CLINICIAN. Clara D. Bloomfield, M.D., University of Minnesota, Minneapolis, MN 55455 USA.

The clinical utility of a number of types of tumor biologic markers is actively being studied in patients with non-Hodgkin's lymphomas at the University of Minnesota. Lymphoma cells are being studied for immunologic, cytogenetic and steroid receptor characteristics. The current and potential use of these characteristics in diagnosis, prognosis and therapeutics will be discussed.

Immunologic markers, including surface immunoglobulin, complement receptors, Fc receptors and sheep erythrocyte receptors, have been studied on lymphoma cells from over 200 adults. Immunologic classification using these markers results in groups of patients with differing prognoses. Immunologic phenotype is an independent prognostic variable and adds important therapeutic and prognostic information to both the Rappaport and the Lukes-Collins histologic classifications. Recently all lymphomas have also been studied by Dr. K. J. Gajl-Peczalska with a broad panel of monoclonal antibodies including BA-1, BA-2, 7.2, TA-1, J5, OKT3, OKT4, OKT8, OKT11. Results from the first 50 cases demonstrate marked heterogeneity among lymphomas. The clinical utility of these new markers requires further study.

Giemsa banded cytogenetic analysis has been performed in lymph nodes from over 50 patients with NHL. Lymph nodes were simultaneously studied for immunologic markers. Almost all cases showed clonal chromosome abnormalities. These abnormalities generally differed from those found in acute lymphoblastic leukemia (ALL) and may have diagnostic utility. Preliminary analysis suggests that karyotype may correlate with histology and immunologic phenotype. Karyotype has been proven to be an independent prognostic variable in ALL and may have similar utility in NHL.

Glucocorticoid receptors (GCD-R) have been studied in lymphoma cells from 47 newly diagnosed patients. All demonstrated glucocorticoid receptors. Thirty-five adults with B cell lymphomas were treated with dexamethasone alone. Patients who responded (>50% decrease in all tumors) had higher receptor levels (median 5681 receptor sites per cell) than patients with mixed responses (>50% decrease in lymph nodes, increase in circulating lymphoma cells) (median 4118 GCD-R) or no significant responses (median 2434 GCD-R). Our data suggest pretherapy *in vitro* glucocorticoid receptor assays may allow selection of those patients with NHL who should receive glucocorticoids.

KINETIC AND PLOIDY CHARACTERISTICS AND THEIR CLINICAL RELEVANCE IN NON-HODGKIN'S LYMPHOMAS. R. Silvestrini, A. Costa, G. Del Bino, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

Aside from the difficulties in morphologically classifying non-Hodgkin's lymphomas (NHL), histologic pattern and subtype as well as the anatomic extent of disease, which have represented up to now the conventional prognostic factors, still make the course of the disease unpredictable in many patients. In the last few years the immunologic, cytochemical, functional and electron microscopic aspects of the cells of lymphoproliferative diseases have been thoroughly investigated and have shown important implications for the advancement of the biologic understanding of these diseases. More recently, the kinetic aspect of the cell population has proved to be not only a feature for biologic characterization but also a discriminant of clinical relevance (JNCI 66:1,1981). In addition to the proliferative activity, in this study we also investigated the ploidy and heterogeneity of a tumor cell population. For the [³H]thymidine labeling index (LI), samples of 6 to 10 × 10⁶ viable cells obtained from fresh lymph node material were incubated at 37°C for 1 h in agitation with DNA labeled precursor. Smears were processed by autoradiography according to the stripping film technique. The LI was determined on at least 3000 cells per smear and three smears per patient. The overall median LI (4.1%) was used as cutoff value for low and high proliferating tumors in the analysis of clinical results. For DNA content, cellular suspensions were fixed in 70% ethanol at 4°C, treated with RNase and stained in propidium iodide. At least 10⁵ cells for each tumor were measured by a cytofluorograph, and nuclei isolated from chicken erythrocytes were used as an internal standard. The DNA content was expressed as the ratio between the G_{0/1} peak of the pathologic sample and that of chicken erythrocyte nuclei. The analysis of the different morphologic and biologic features shows that 79% of nodular NHL are slow proliferating tumors, whereas 63% of diffuse NHL are fast proliferating tumors. The frequencies of diploid and aneuploid NHL are respectively about 40% and 60% with an overall frequency of a heterogeneous cell population in 15% of the tumors. The prognostic relevance of cell kinetics, histologic pattern and different DNA characteristics alone or in association were comparatively analyzed. The prognostic relevance of LI (JNCI 66:1,1981) was confirmed on a larger series of patients (100 cases) with a longer follow-up (6 years), and the kinetic parameter as a discriminant of patients at low and high risk appeared superior in comparison to all the other biologic and morphologic aspects. The relevance of the different biologic features as predictors of clinical response to treatment was also investigated and, when possible, on homogeneously treated patients. The predictive value of proliferative activity on the achievement of complete remission, already observed from the overall analysis of patients differently treated, was more precisely defined according to the different types of treatment.

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CYTOKINETIC STUDIES IN THE NON-HODGKIN'S LYMPHOMAS. H. Hansen, D. Filippa, M. Andreeff, J. Valauri, B. Clarkson. Memorial Sloan-Kettering Cancer Center, New York, New York 10021.

Non-Hodgkin's lymphoma tumors display a wide range of proliferative behavior from patient to patient, which is reflected in the clinical course and response to therapy. In vivo tumor cell doubling times from 28 to 400 days, and growth fractions from 15 to 100% have been reported. Evidence suggests that these in vivo growth parameters can be estimated by measurements of the fraction of cells in S-phase in vitro in freshly obtained suspension of tumor cells.

We have studied flash ³H-thymidine labeling indices and S-phase fractions in over 200 cases of malignant lymphomas and correlated these measurements with cell surface markers, electronically determined cell volume analysis, histopathologic appearance, and clinical patient data.

These data will be presented, as well as a review of previous cell kinetic studies in the non-Hodgkin's lymphomas.

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ORAL PRESENTATION OF MALIGNANT LYMPHOMAS. F. Rilke. Istituto Nazionale Tumori, Milan, Italy.

Waldeyer's ring is not uncommonly the primary site of presentation of malignant lymphomas, although with variable geographical incidence. Non-Hodgkin malignant lymphomas (NHL) arising primarily in this area show peculiar features, such as the involvement of the base of the skull and the stomach, and definitely outnumber Hodgkin's disease (HD). Since the involvement of Waldeyer's ring is often apparently primary, complete staging procedures are always warranted. The natural history of these NHL is insufficiently known because of the small number of published series, which, in addition, have been treated heterogeneously. Herewith an account is given of the cases observed in the last decade with special reference to the newer staging procedures and therapeutic approaches and to the revision of the whole material according to the Kiel classification. A total of 182 patients was evaluated (M 118, F 64); median age was 52 years. The most frequent sites involved were the palatine tonsils (73%), the nasopharynx (30%) and the base of the tongue (8%). Gastric involvement at presentation was found in 7% and bulky tumor masses in 16%. Waldeyer's ring alone was found to be involved at presentation in 15 cases, the ring combined with the cervical nodes in 53, and the ring with other nodal and extranodal sites in 114 cases. There were 5 cases of HD and 163 of classifiable NHL: 97 (60%) were of low grade and 66 (40%) of high grade malignancy. Centroblastic and immunoblastic NHL were the most common types found to involve Waldeyer's ring alone whereas centrocytic NHL was the most frequent entity (23%). Centroblastic-centrocytic, follicular NHL were found in 12% of the cases. On the whole, 10% were stage I, 35% stage II, 20% stage III, and 35% stage IV. Fifty per cent of immunocytomas and 40% of centrocytic and centroblastic-centrocytic NHL were stage IV. In contrast, immunoblastic NHL were stage II in 40% of the cases. Immunoblastic and lymphoblastic NHL showed the worst prognosis with a median survival of 14 and 8 months, respectively. Median survival for centroblastic NHL was 50 months whereas immunocytomas and centrocytic NHL showed a median survival of 26 and 32 months, respectively. Centroblastic-centrocytic, follicular, NHL had a median survival of 68 months. Five-year survival for stage I was 78%, stage II 32%, stage III 22%, and stage IV 16%. Regardless of the type of treatment, all stage I patients, 89% of the stage II cases, and 60% of stage III and IV cases obtained complete remission. Five-year survival for patients with involvement of Waldeyer's ring only was 70%; for those with Waldeyer's ring and adjacent nodes it was 36%, and for those with Waldeyer's ring and other sites, 20%. Patients with response to therapy reaching complete remission had a 7-year actuarial survival of 33% versus 6% of nonresponders.

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Non-Hodgkin's Lymphoma of Waldeyer's Ring

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From 1961 through 1979, 331 patients with Stage I and II non-Hodgkin's lymphoma were treated with curative intent by radiation therapy at the Department of Radiology, Osaka University Hospital. Of these, 202 patients (61.0 %) represented with clinical involvement of Waldeyer's ring. In 44 patients disease was limited to Waldeyer's ring (Stage I), and 158 patients had involvements with Waldeyer's ring and neck nodes (Stage II), of which only six cases had axillary and/or mediastinal involvements. According to the Rappaport classification, diffuse histiocytic was the most common subtype, presenting almost 75 %, whereas diffuse lymphocytic, poorly differentiated (15 %) and diffuse lymphocytic, well differentiated (7 %) were infrequent. There were 118 males and 84 females and the age range was 6 to 81 years with a median 45 years. Irradiation was administered with 6 MV linear accelerator x-rays with dose ranged 40 - 50 Gy in 5 to 6 weeks. Treatment fields were opposing lateral fields to Waldeyer's ring and upper neck, and anterior field to mid and lower neck.

Relapse-free survivals at 5 years after radiation therapy were 74.4 % in Stage I, and 40.6 % in Stage II. In the patients treated after 1971, cumulative 5 year survival were improved to 86.4 % in Stage I, and 54.7 % in Stage II. Furthermore, in the patients to whom chemotherapy (1 or 2 cycles of COPP) had administered before radiation therapy, 5 year survival were much improved (76.3 %) in Stage II. The most common manifestation of relapse was in upper abdomen and the most of relapse (86 %) occurred within two years after radiation therapy

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PRIMARY MALIGNANT LYMPHOMA OF WALDEYER'S RING:
CLINICAL ANALYSIS OF 145 CASES

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From 1964 to 1972, 145 patients with primary malignant lymphoma of Waldeyer's ring, consisting of 85 reticulum cell sarcomas, 56 lymphosarcomas, 1 Hodgkin's disease and 3 unclassified, were treated at the Cancer Hospital of the Shanghai First Medical College. A tumor dose of 4000 to 6000 rads has been found effective for local control in most cases. The 5-yr survival rate was 48.3%, while the 10-yr survival rate was 45.8%. Abdominal lymph nodes were the common initial site of metastasis, and neck and inguinal lymph nodes were next. Liver and stomach were the most frequent sites of visceral involvement. Recurrence in the previously irradiated area was seen in 3 patients (1 nasopharynx and 2 tonsils). Of the relapsing 59 cases, 46 patients (78%) recurred within one year. Owing to their particular clinical characteristics and tendency to distant metastasis, it must be stressed that Primary malignant lymphomas of Waldeyer's ring should be considered as a special type of malignant lymphoma, hence accurate staging and proper are necessary.

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IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE - A NEW AND A DISTINCT FORM OF MALIGNANT LYMPHOMA . Philip Salem , Victor Nassar, Charles Allam, Samih Alami, Antoun Salem, Khaled Jabboury, Labib Hashimi and Maryse Khalyl . American University of Beirut Medical Center . Beirut , Lebanon .

38 cases of (Mediterranean Abdominal Lymphoma) or better known as Immunoproliferative Small Intestinal disease (IPSID) are studied at the American University of Beirut Medical Center. In this study IPSID is shown to be a distinct disease entity characterized by chronic diarrhea , malabsorption pattern on small bowel radiological work up , and diffuse involvement of small bowel mucosa and/or mesenteric lymph nodes by a lymphoplasma-cytic cellular infiltrate. Pathologically there is diffuse involvement of the whole length of the small bowel . The disease is also characterized by the presence of abnormal IgA globulin which is devoid of light chains and which is related to the Fc portion of the alpha heavy chain (AHCP) . AHCP could be found in the serum, intestinal fluid and/or involved tissues. The majority of patients are young and come from low socio-economical background . A new histopathological classification and a new staging system are proposed. The role of laparotomy in staging is emphasized . A pre-malignant phase (phase 0) which is clinically indistinguishable from the malignant one is described . Three cases were considered in stage 0. In contrast to the malignant phase which is associated with poor prognosis, the pre-malignant phase is totally reversible with antibiotics alone. Combination chemotherapy with Adriamycin, Cyclophosphamide, Vincristine and Prednisone has been shown to be effective in the treatment of the malignant phase .

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LONGITUDINAL STUDIES OF PERIPHERAL BLOOD LYMPHOCYTE (PBL)-FUNCTIONS IN NON-HODGKIN LYMPHOMAS (NHL). Christina Lindemalm, Bo Johansson, Håkan Mellstedt. Div. of Oncology, Karolinska Hospital, Stockholm, Sweden. Göran Holm. Div. of Immunology, Huddinge Hospital, Stockholm, Sweden. Magnus Björkholm. Dep. of Medicine, Danderyds Hospital, Stockholm, Sweden.

All consecutive previously untreated patients with NHL admitted to Radiumhemmet between Nov. 1977 - Apr. 1979 were studied by in vitro immunological tests. The aim of the investigation was to analyse the immune functions of PBL in NHL at diagnosis and its correlation to clinical stage, histopathology and the course of the disease.

68 patients, 30 men and 38 women, were studied. The median age was 59 years (range 20-87 years). 57 healthy persons age between 20 and 92 years were used as control donors. 23/68 patients were in addition studied in complete remission and 7/23 in relapse. Highly purified lymphocytes were analysed for T and B cells by surface markers. Spontaneous and mitogen induced lymphocyte DNA-synthesis was studied by ¹⁴C-thymidine incorporation. Initial antibody titers to EB virus was evaluated as well as delayed skin hypersensitivity to PPD antigen.

NHL patients were significantly lymphocytopenic and had significantly low numbers of E-lymphocytes compared to normals. Lymphocytes were poorly activated to DNA synthesis by T cell mitogens. No correlation to histology was found. In NHL patients younger than 60 the immune dysfunction was significantly more prominent in advanced stage. 18/34 had negative skin test to PPD and this was well correlated to the in vitro response to PPD. 25 % had circulating monoclonal B-lymphocytes at diagnosis more frequently associated with bone marrow involvement when compared to those patients without a circulating clone present. NHL patients had raised anti-VCA titers without correlation to defect cellular immunity.

NHL patients younger than 60 years normalized their DNA-synthesis in remission and returned to reduced values at relapse in 4/7 patients. Stage and histology as well as spontaneous DNA-synthesis in stage I and II had statistically significant prognostic implications to survival. In predicting complete remission stage alone and spontaneous DNA-synthesis in stage I and II were of statistically significant importance.

NHL patients exhibited a defect cellular immunity at diagnosis and relapse of the disease. A tendency to normalization of the immune dysfunction was noticed in complete remission. The pattern of anti-EB titers were similar to that in solid tumor but different from the pattern seen in Hodgkin's disease.

IMPLICATIONS OF STAGING AND RESTAGING OF PATIENTS WITH LYMPHOMA.
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Most non-Hodgkin's lymphomas are systemic at presentation and initial staging with procedures of limited invasiveness (e.g., bone marrow core biopsy, liver biopsy, lymphangiography, computed tomographic (CT) scanning and ultrasonography) usually provides adequate information for decisions regarding therapy. For patients with Hodgkin's disease (HD), about half of whom will have localized disease, an exploratory laparotomy with splenectomy is often performed after noninvasive staging, particularly if radiotherapy with curative intent is planned. With improved treatment programs for HD and NHL it has become increasingly more important to define complete remission (CR) prior to stopping therapy as CR is the first step to cure. Over several years we have evaluated the results of careful restaging of patients in apparent remission. Initially abnormal tests are repeated (e.g., lymphangiography, lung tomography), biopsies of suspicious or residual enlarged lymph nodes are performed and initially involved extranodal sites (bone marrow and liver) are rebiopsied. In 2 large series of patients in apparent remission from combination chemotherapy we found that 24% of 140 patients with NHL and 12% of 82 with HD harbored occult lymphoma detected by restaging. Most sites of involvement at restaging were sites originally involved by lymphoma. Several series have suggested that the subsequent risk of relapse is substantially reduced by careful restaging. More recently we have analyzed 26 patients with advanced HD who were selected to undergo surgical restaging after clinical restaging. Six (23%) of these patients had residual abdominal HD usually in the spleen. More importantly no relapses have been observed in 20 patients documented by surgical restaging to be free of HD compared to 48 relapses in 224 patients who underwent only clinical restaging ($p < 0.05$). This small series of patients suggests the usefulness of surgical staging at the completion of therapy rather than at the outset, particularly for patients with advanced disease who require initial chemotherapy. In summary, careful initial staging followed by thorough restaging upon completion of therapy is a necessary requirement for clinical research and appears to have prognostic importance for defining groups of patients at low risk of relapse after stopping therapy and for defining patients with residual disease who require further therapy (e.g., alternate noncross-resistant combinations).

NEWER COMBINATION CHEMOTHERAPIES IN NON-HODGKIN'S LYMPHOMA (NHL).
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Most USA programs assess effect of combination chemotherapies (CC) on NHL classified according to Rappaport. Newer classifications have been analyzed by many groups (Strauchen, Armitage, Warnke, Bloomfield, Sweet and others). Unfortunately, divergent conclusions have been reached, probably due to differences in interpretations of histology and in treatment regimens selected. A consensus is emerging that a conservative approach appears indicated with "favorable" NHL. There is diverse information regarding the NHLs of intermediate type, [nodular mixed cell (NMC) and nodular histiocytic (NH)], since evidence is emerging that treatment strategies designed for the cure of diffuse histiocytic lymphoma (DHL) might be applicable to NMC and NH. The data on aggressive treatment of patients with diffuse non-histiocytic NHL, particularly diffuse poorly differentiated lymphocytic (DPDL) and diffused mixed-cell lymphomas (DMC) appear to indicate that the incidence of complete remission (CR) induction is now at a significant level; there remain some questions regarding prolongation of life, even in the patients achieving CR. In contrast to these controversies there is consensus regarding the management of the DHLs. The agents that have been examined in recent years are large doses of cyclophosphamide (CTX), the use of adriamycin (ADM) and intermediate to high-dose methotrexate (MTX) with leucovorin (Leu) rescue. The resultant benefits appear to be approximately similar in all instances with CRs in 50-60% of patients. Approximately half of CR patients derive major benefit with reports of 5 and 10 year survivals. Various permutations of programs have been developed including COMLA [CTX, vincristine (VCR), MTX with Leu rescue, cytarabine (Ara-C)]; M-BAGOP [mustargen plus bleomycin, ADM, CTX, VCR, prednisone (P)]; CHOP/HOP (CTX, ADM, VCR, P/ADM, VCR, P); Ifos-MTX-VP-16 (Ifosophamide, MTX and VP-16); and ProMACE (CTX, ADM, VP-16, P, MTX, Leu). An additional problem that needs to be addressed, particularly in the DHLs is the occurrence of CNS involvement in patients at high risk (bone marrow and skin involvement). A number of the programs which have built-in high-dose MTX or Ara-C appear to act as prophylactic measures to prevent CNS complications. Many new drugs and new drug combinations are now being examined to discover unique agents or unique combinations which will further improve the results already obtained in the NHLs. Amongst the new agents are AMSA (4'-(9-acridinylamino)methanesulfonamide), Maytansine, VM-26, cisplatinum, high dose (HD) MTX (HiMTX), detorubicin and deoxycoformycin. Amongst the newer combinations are various permutations of old and new agents, including ProMACE-MOPP (ProMACE plus mustargen, VCR, procarbazine, P); CHOP with late intensification by OAP (VCR, Ara-C, P); CHOP with HiMTX; alternating programs of CVP (CTX, VCR, P) and ABP (ADM, bleomycin, P); CCNU-CHOP (lomustine plus CTX, ADM, VCR, P); and others. The presentation will summarize the most current status of these trials

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CONSERVATIVE MANAGEMENT OF FOLLICULAR LYMPHOMA

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Conservative treatment of follicular lymphoma at St. Bartholomew's Hospital, London, since 1972 has comprised of short term initial treatment with either Chlorambucil (CB) or Cyclophosphamide, Vincristine and Prednisolone (CVP). This has been stopped after an arbitrary period of time (4½ months intermittent CB or 6 cycles of CVP) regardless of whether residual lymphoma remains. All patients are subsequently observed at close intervals in the clinic and recurrences are confirmed whenever possible with repeat lymph node biopsy. The decision to re-institute therapy is based on the clinical stage of the patient, evidence of increasing lymphoma and the histological findings. Patients in whom the histological pattern remains unchanged receive CB; those with blastic transformation receive intensive therapy. Between 1972 and 1977, patients were allocated on an alternate basis to receive either CB or CVP at presentation. The overall response rate was the same for both groups of patients, as were the duration of response and survival. Since 1978, patients with symptoms and clearly advancing disease have all been treated at presentation; the remainder have been observed initially and the rate of progression observed prior to the institution of treatment. All have received CB in the same manner as those treated between 1972 and 1977. Since the overall response rate, remission duration and survival are not significantly different from the previous groups, they are all considered together. A total of 187 patients with advanced (Stage III and IV) non-Hodgkin's lymphoma of favourable histological type, including 70 follicular lymphoma, form the basis of this report of the results of this treatment policy. While complete or almost complete remission of lymphoma is usually achieved with infrequent admission to hospital and prolonged periods of normal life are the rule rather than the exception, the median survival of the whole group was only 4½ years with only 20% of the patients being in long continuous remission. Such results must be considered unacceptable in a population with a median age of approximately 55 years and alternate approaches must be sought urgently.

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MANAGEMENT WITH CHEMOTHERAPY ALONE OF CLINICAL STAGE I-II LYMPHOMAS OF AGGRESSIVE HISTOLOGICAL TYPE. Fernando Cabanillas, Luis T. Campos and Gerald P. Bodey. The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030.

The traditional management of stage I-II lymphomas has consisted of radiation therapy alone or in combination with chemotherapy. Since 1967, we have treated 37 such patients with combination chemotherapy alone. Histological types are: 33 histiocytic, 2 diffuse undifferentiated and 2 diffuse mixed. Treatment consisted of COP (6 patients), CHOP or CHOP-Bleo (14 patients) and most recently sequential chemotherapy and late intensification (17 patients). All patients were clinically staged and laparotomies were not performed. Staging procedures included the routine tests in addition to lymphangiogram, bone marrow aspiration and biopsy and recently CT scan of the abdomen. Eight patients were rendered disease free clinically after their diagnostic lymph node biopsy and thus could not be assessed for response to chemotherapy. Of the remaining 29 patients with evaluable disease, 25 (86%) had a complete response (CR). Of the 33 patients who achieved disease free status, only 6 have relapsed, and of these, 3 have died. Considering all 37 patients entered in this study, 30 (81%) remain alive (10/10 stage I and 20/27 stage II) at a median follow-up time of 51 months. The relapses took place at 3,7,18,64,99 and 117 months. It was possible to obtain a second CR in the 3 patients who relapsed after 18 months and they have continued free of disease. Four of these 6 patients had a repeat biopsy done at the time of relapse. The histopathology of the recurrent tumors changed to the less aggressive nodular poorly differentiated lymphocytic subtype in 3. The remaining patient still had diffuse histiocytic lymphoma. In 5 of these 6 patients, the relapses took place in sites distant to the original tumor, indicating that the addition of adjuvant radiotherapy would probably not have made any major impact on the treatment program. Of the regimens used, the one associated with the highest CR rate (16/17) as well as the lowest relapse rate (0/16) was the sequential chemotherapy and late intensification program. The CR rate and relapse rate for the COP regimens were 5/6 and 3/5, respectively. For the adriamycin combinations, these rates were 10/14 and 3/10. The results of chemotherapy alone in this study compare favorably with results of radiotherapy or radiotherapy and chemotherapy programs. An additional advantage is the fact that a staging laparotomy is not necessary.

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AGGRESSIVE" VERSUS "MODERATE" CHEMOTHERAPY VERSUS CHEMOIMMUNOTHERAPY FOR NON-HODGKIN'S LYMPHOMA (NHL). S.E. Jones for the Southwest Oncology Group (SWOG). University of Arizona Cancer Center, Tucson Arizona, 85724, U.S.A.

In 1974 we initiated a study evaluating 3 forms of chemotherapy for all types of NHL. The study involved careful restaging to document complete remission (CR) before stopping therapy and expert hematopathology review to accurately classify all cases. The study is now completed with sufficient time to assess the effectiveness of 3 quite different treatment programs in the more favorable follicular (nodular) lymphomas as well as in the less favorable diffuse lymphomas. The induction treatments included a well tolerated "moderate" program of COP+Bleomycin (a 14 day schedule repeated every 4 weeks) compared to an "aggressive" adriamycin-based CHOP+Bleomycin program. The third arm employed CHOP plus nonspecific immune stimulation with BCG administered by scarification on rotating sites on all extremities. The results of induction (CR rates) are given below for each major histologic subtype.

Subtype*	Total No.	No. Treated (%Complete Response)			Significance (p Value)
		CHOP+BCG	CHOP+Bleo	COP+Bleo	
NLPD	160	53 (74%)	48 (75%)	59 (73%)	NS
NM	42	13 (92%)	19 (74%)	10 (70%)	NS
NH	24	8 (88%)	8 (38%)	8 (63%)	0.12
TOTALS	226	74 (78%)	75 (72%)	77 (71%)	NS
DLWD	48	22 (32%)	18 (50%)	8 (63%)	NS
DLPD	32	7 (14%)	17 (47%)	8 (50%)	NS
DM	15	5 (40%)	4 (100%)	6 (83%)	NS
DH	147	57 (65%)	53 (49%)	37 (41%)	0.05
TOTALS	242	91 (51%)	92 (51%)	59 (49%)	NS

For the common NLPD lymphoma there was no evidence of a difference in CR rates by treatment and COP+Bleomycin was significantly better tolerated than the CHOP regimens. For patients with the potentially curable lymphomas (NM, NH and DH) there was evidence favoring CHOP+BCG over CHOP+Bleomycin ($p < 0.05$) or COP+Bleomycin ($p < 0.05$). Overall survival of patients with nodular lymphoma (all types) was significantly longer if the initial treatment was CHOP+BCG ($p=0.05$) but this effect was least apparent in patients with NLPD. Patients with NH, NM and DH survived significantly longer if treated with CHOP+BCG compared to the other 2 regimens. New approaches with curative intent are needed for patients with NLPD lymphoma.

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PRIMARY CHEMOTHERAPY FOR LOCALIZED DIFFUSE LYMPHOMA. S.E. Jones and T.P. Miller. University of Arizona Cancer Center, Tucson, Arizona, 85724, U.S.A.

Radiotherapy alone for localized lymphomas of unfavorable histologies has generally been curative for 40-70% of patients with the best results observed in patients with very limited disease (stage I or I_E). Immediate combination chemotherapy offers the potential for early systemic control in patients with these lymphomas and has already proven curative in about 40% of patients with advanced stages of disease (stage III, IV). Between 1972 and 1981 we treated 33 patients with stage I (8 cases) or Stage II or II_E (25 cases) of lymphoma with combination chemotherapy using the CHOP regimen. Twelve patients also received adjuvant radiotherapy to involved fields. Two patients were just begun on treatment. Thirty (97%) of 31 who were evaluable for response achieved a complete remission (CR). Median follow-up is in excess of 36 months and only 3 patients of 19 who received chemotherapy alone and none of 12 who received adjuvant radiotherapy have relapsed. Only 1 patient has died. Immediate combination chemotherapy with CHOP for localized lymphoma with or without radiotherapy avoids the necessity for extensive staging and is associated with overall more favorable results than most series employing radiotherapy alone.

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ROLE OF RADIATION THERAPY IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMAS. Eli Glatstein, National Cancer Institute, Bethesda, Maryland 20205

The treatment of non-Hodgkin's lymphomas is changing rapidly in response to our better understanding of the natural history of these diseases. Although the curative role of radiation therapy in early staged disease (Stage I and II) is clear, these patients represent a small minority of the overall population of patients afflicted with this group of diseases. Moreover, controversy exists over the optimal way to approach the early stage patients, either with radiation alone or combined modality therapy or even chemotherapy alone.

The vast majority of patients with non-Hodgkin's lymphomas have Stage III or IV disease. These patients can be crudely divided into those with indolent or nodular histologies and those who have aggressive or diffuse histologies. For those with nodular patterns, the curability with modern treatment is far from established. This is because the natural history of nodular lymphoma requires at least 15 years of followup before any meaningful conclusion can be reached concerning curability. Even so, for patients who have Stage III lymphoma wide-field, high dose total lymphoid irradiation has achieved 33% relapse-free survival at 10 years, a figure unmatched by any present chemotherapeutic approach. For Stage IV lymphoma of nodular type, the role of radiation therapy is more difficult to assess, because of an absence of well constructed clinical trials that carefully evaluate its role.

Similarly, there is a remarkable lack of information on combined modality therapy for advanced Stage III and IV non-Hodgkin's lymphoma of the diffuse types. Those data that are available suggest that there may be some benefit in carefully integrated radiation therapy in the management of these patients, although it is clear that the major thrust of treatment is still chemotherapy. Even so, the curability with chemotherapy alone that has clearly been established in advanced stage non-Hodgkin's lymphomas of the diffuse type is only approximately 40% of patients who have diffuse histiocytic lymphoma; evidence for the curability of the other major diffuse lymphomas is lacking.

Analysis of data that are available following primary radiotherapy in the treatment of non-Hodgkin's lymphomas, reveals that the most likely site of failure following primary radiotherapy is in untreated sites; likewise, data that are available concerning relapse following primary chemotherapy in the treatment of non-Hodgkin's lymphomas show that the most likely site of relapse will be sites of previous involvement, especially lymph nodes. Despite these obviously complementary facts, few studies have addressed the role of radiotherapy in the treatment of advanced non-Hodgkin's lymphomas. The reasons for this apparent paradox are not entirely clear, but they probably represent (1) euphoria concerning the initial success of curative chemotherapy in the treatment of diffuse histiocytic lymphoma, (2) major concern over the toxicity of combined modality treatment for patients with lymphoma, especially potential risks of leukemogenesis as noted for Hodgkin's disease, and (3) difficulty in achieving commonality of opinion in the management of these diseases.

Available data and studies will be reviewed to assess the role of radiation therapy in the treatment of advanced non-Hodgkin's lymphomas.

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CLINICAL TRIAL USING RADIOTHERAPY AND CHEMOTHERAPY IN NON-HODGKIN LYMPHOMA. E.O.R.T.C. Radio-chemotherapy Group: M. Hayat (chairman)

In the EORTC Radiotherapy/chemotherapy Group a prospective clinical trial was done for Non-Hodgkin lymphoma, all stages and histology forms. For histologic classification Kiel classification was used. Preliminary evaluation of 260 patients from which histology is reviewed gave the following repartition over the histologic subtypes: 6,8 % immunocytic-lymphocytic; 6,4 % centrocytic, 50,4 % centroblastic-centrocytic, 5,6 % centroblastic, 17 % immunoblastic and 13,2 % lymphoblastic. Thirtyfive percent being of high grade malignancy. Regarding cell pattern 27,8 % could be classified as follicular, 48,4 % as diffuse, 23,8 % was mixed follicular and diffuse.

Of 95 patients in stage I treated with radiotherapy with or without adjuvant chemotherapy 90 % survive at 5 year; it is too early to evaluate the role of adjuvant therapy. In stage II patients treated with radiotherapy, survival at 5 years is 35 %. In this group of patients, patients with a high grade malignant lymphoma do badly in comparison with low grade types.

It can be concluded that for stage II patients with high grade malignancy chemotherapy seems the treatment of choice.

For stage III and IV patients combination chemotherapy CHVP consisting of 8 cycles Adriamycin (50 mg/m² d 1), VM 26 (60 mg/m² d 1), Cytosin (600 mg/m² d 1), Prednisone (40 mg/m² d 1-5), was compared with an intermittent regimen (CICS) in which the Cytosin was given in two doses on day three and four.

After remission induction consolidation radiotherapy was given to bulky masses maintenance treatment consisted of Vincristine, Cytosin, Prednisone.

For all patients in stages III and IV 5 year survival was 45 %, with no difference between the two regimens. Survival for the follicular histologic types in stages III and IV at 5 year was 78 %, without a difference for the two induction regimens; diseasefree survival was 60 % for patients treated with CHVP, 42 % for patients treated with the intermittent regimen (N.S.). For all the patients in the diffuse histology group in stage III and IV, 5 year survival was 45 %; for CICS and CHVP induction treatment 62 % and 25 % respectively (N.S.). In this high grade malignant group diseasefree survival was 45 % with CICS, 24 % with CHVP (p = 0,5 %). Prognosis was furthermore related to celltype; the high grade celltypes (centroblastic, lymphoblastic, immunoblastic) having a worse prognosis in comparison with centroblastic, centroblastic-centrocytic (76 vs. 46 % 3 year survival). It can be concluded that Kiel classification gives a good prognostic indication; that the combination of Adriamycin VM 26, Cytosin, Prednisone forms an effective treatment for stages III and IV.

COMBINED MODALITY TREATMENT OF LYMPHOCYTIC AND HISTIOCYTIC LYMPHOMA - A CALGB STUDY. H.W. Grünwald, A.S. Glicksman, N.I. Nissen, A.J. Gottlieb & T.F. Pajak; Queens Hospital Ctr. Affil. of L.I. Jewish-Hillside Medical Ctr., Jamaica, N.Y. 11432; Rhode Island Hospital, Providence, R.I. 02902; Finsen Institute, Copenhagen, Denmark; SUNY Upstate Med. Ctr., Syracuse, N.Y. 13210 & CALGB Operations Office, Scarsdale, N.Y. 10583 USA.

Companion protocols for treatment of lymphocytic and histiocytic lymphoma were initiated in early 1976 to evaluate the effects of a consolidation with radiotherapy (or adriamycin for histiocytic lymphoma) following 6 weeks of induction with chemotherapy. All responding patients were given maintenance therapy with cyclophosphamide, vincristine and prednisone for 2 to 3 years. Although the entry qualifications by cell type differ significantly from the newly adopted International Formulation for Lymphomas, the treatment results can now be evaluated following central pathology review according to the grades proposed by this formulation. Seventy five patients with lymphocytic lymphoma and 36 patients with histiocytic lymphoma are considered evaluable for continued response on the basis of eligibility, central pathology review and protocol compliance. In patients with lymphocytic lymphoma, the relapse rate is lower for patients who received radiotherapy (RT) consolidation, and their survival curve, which initially was rather steep due to toxic deaths, has flattened out at the 73% level after 18 months. On the other hand, patients treated only with chemotherapy died at a slower initial rate, but continue to do so due to the continued rate of relapse characteristic of the disorder. In patients with histiocytic lymphoma, the relapse rate of patients not receiving either RT or adriamycin consolidation was 78% at 2½ years, whereas patients with a consolidation phase had lower relapse rates (42% at 2½ years for RT consolidation, 63% for adriamycin consolidation). The advantage of consolidation therapy in producing fewer relapses was not reflected in improved overall survival, perhaps due to the increased toxicity of the consolidation regimens. The previously reported deleterious effect of concurrent administration of vincristine and abdominal irradiation has been confirmed, and resulted in increased toxicity of patients entered into the RT consolidation regimens during the first 18 months. The dose of radiation given to these patients (up to 3500 rad) appears to be excessive, and contributed to the observed severe toxic manifestations. We conclude that there may be a potential beneficial effect of irradiation as an adjunct to chemotherapy, but the serious toxic effects of such combined modality treatment mandates a more conservative approach with regard to dose and timing of the radiation therapy than that employed in these studies. Patterns of relapse in the patients treated with chemotherapy alone and in those receiving combined modality therapy are being analyzed.

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AFRICAN AND AMERICAN BURKITT'S LYMPHOMA HAVE DIFFERENT CELLULAR ORIGINS: STUDIES WITH CELL LINES AND A SPECIFIC HETEROANTISERUM. I. Magrath, D. Benjamin, R. Parsons, H. Todd-Kulikowski, C. Janus, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD 20205 and Biological Markers Program, Frederick Cancer Research Center, Frederick, MD 21701. Partly supported by NCI contract #NO1CO-75380 with Litton Bionetics, Inc.

The diagnosis of Burkitt's lymphoma is based upon histological identity with the tumor originally described in Africa. In studies of over 200 African and 72 American patients, we have observed highly significant differences in the frequency of involvement of various sites at presentation and relapse, and differences in the relapse pattern. We have studied 23 cell lines derived from African and American undifferentiated lymphomas, (mostly Burkitt's lymphoma) in order to determine whether cells from African tumors differ phenotypically from those of American tumors. All except 2 of the cell lines, regardless of origin, contain 8;14 chromosomal translocations or a 14 q+ chromosome. 11 of 15 American lines lack the Epstein-Barr virus (EBV) genome, whereas it is present in 8 African lines, consistent with reported data on fresh tumors. We have previously reported that EBV positive and negative lines differ in a number of characteristics including their expression of EBV receptors and surface IgM. In addition, we have now studied immunoglobulin secretion by collection of radiolabelled immunoglobulins on protein-A coated beads and analysis in SDS polyacrylamide gels. Pentameric IgM (demonstrated by sephacryl chromatography) associated with J chains, was secreted in significantly greater amounts in American lines (range 300ng to >1µg) than African lines (0 to 200 ng), paralleling the expression of surface IgM. In 4 of the African lines, IgM secretion was undetectable.

An antiserum raised in a goat against a purified membrane preparation of one of the American cell lines (CA46) initially reacts with both American and African cell lines (detected by indirect immunofluorescence). After extensive absorption with 5 African cell lines until all reactivity against these is removed, the antiserum still reacts with all but one of the American cell lines. The absorbed antiserum fails to react with cell lines of normal origin (including transformed cord blood lymphocytes) and with normal human lymphocytes. Blocking studies with IgM and anti-µ, and treatment of the cells with papain have excluded the possibility that the antiserum reacts with surface IgM. To date we have been unable to immunoprecipitate a protein from detergent treated cell pellets with the absorbed antiserum. These data strongly suggest that African and American Burkitt's lymphoma are of different cellular origin. Further studies may reveal the degree of relatedness of these tumors, which are probably the neoplastic counterparts of B lymphocyte precursors at different (though probably adjacent) stages of differentiation.

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PRETREATMENT STRATIFICATION OF CHILDHOOD NON-HODGKIN'S LYMPHOMA (NHL) ACCORDING TO PRIMARY SITE, CLINICAL STAGE, AND IMMUNOPATHOLOGIC SUBTYPE: CURRENT RESULTS OF COMBINED MODALITY PROTOCOLS. S.B. Murphy, H.O. Hustu, G. Rivera, W.P. Bowman, G.V. Dahl, St. Jude Children's Research Hospital, Memphis, Tn. 38101, U.S.A.

Since 1978-79, we have assigned treatment regimens for children with NHL based on stage, location of primary tumor, and immunopathologic subtype. Using a staging system we have previously shown to be of prognostic importance (Cancer 45:630, 1980), patients with a good prognosis (Stage I-II) are readily recognized and currently treated on a regimen of comparatively lesser intensity, regardless of histologic subtype, in order to reduce acute and long-term side effects. With 3-drug induction and concurrent low-dose (2000r) involved field radiotherapy, 100% of our Stage I-II patients have achieved complete remission (CR) and 19 of 21 remain disease-free for periods from 4+ to 30+ months (median 10+) with two drug oral maintenance. Children with Stage III-IV NHL fall into two main subgroups, T- or B-cell, each requiring a different treatment strategy. Stage III-IV T-cell patients exhibit lymphoblastic histology, mediastinal, nodal primaries, and T-cell blast characteristics and are currently treated on the same protocol as our high-risk ALL patients, incorporating induction and pulse therapy with VM-26 and Ara-C along with conventional ALL therapy, including prednisone, vincristine, asparaginase, mercaptopurine and methotrexate, and prophylactic treatment of the central nervous system with intrathecal methotrexate and cranial radiation. Ten children with Stage III-IV mediastinal lymphoblastic lymphomas have been enrolled on this study, and 7 of 10 are disease-free, 6+ to 20+ months, one had a local recurrence, and two were removed from study due to toxicity (1 fatal). Stage III-IV B-cell (Sig+) NHL and the related B-cell leukemias of children have the worst prognosis and require a radical treatment strategy. Our current pilot approach, incorporating fractionated high-dose cyclophosphamide (1800 mg/m²) and superfractionated radiotherapy (2 fractions/day) is based on appreciation of rapid tumor growth kinetics and individualization of intervals between courses based on variable host recovery from toxicity. A total of 13 children with B-cell Burkitt-like malignancies have been treated, including 7 Stage III, 2 Stage IV, and 4 B-cell leukemias. Nine of the 13 achieved a CR, one is too early, and 3 exhibited a PR but early progressive disease. Results are preliminary and the protocol for the advanced B-cell patients with marrow involvement is currently being modified, but 7 of the 9 complete responders are currently disease-free, and 4 are off therapy 11+, 16+, 18+ and 21+ months from diagnosis. We conclude that differing strategies of therapy for major subgroups of childhood NHL permits a more rational approach, yielding results equal or superior to our historical experience.

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HISTOLOGY SPECIFIC TREATMENT OF CHILDHOOD NON-HODGKIN'S LYMPHOMA (NHL): Results of a randomized clinical trial. J. Anderson, D. Jenkin, R. Chilcote, P. Coccia, P. Exelby, J. Kersey, J. Kushner, A. Meadows, S. Seigel, J. Wilson, S. Leikin, and D. Hammond for the Children's Cancer Study Group (CCSG), Los Angeles, CA 90031

In April 1977, CCSG initiated a prospective randomized trial (CCG-551) of treatment for children with all forms of NHL. By October 1979, 238 eligible patients were entered on study. Two intensive systemic treatment programs were compared, a 4-drug regimen (COMP) (Meadows, Med. Ped. Onc. 8:15, 1980) and a 10-drug regimen (a modified LSA₂L₂) (Wollner, Med. Ped. Onc. 1:235, 1975). All patients received radiation to sites of bulk disease and maintenance IT methotrexate (MTX). Disease-free survival (DFS) for all patients is 65% at 12 months, 59% at 24 months; 75% are surviving at 12 months, 65% at 24 months. Patients with disseminated disease had markedly different disease-free survival which depended on histology and therapy. LSA₂L₂ was more effective for those with lymphoblastic disease (18 month DFS: LSA₂L₂ - 78%, COMP - 38%) while COMP was more effective for those with non-lymphoblastic disease (18 month DFS: COMP - 64% LSA₂L₂ - 24%). Both regimens were equally effective for localized lymphoma of all subtypes producing overall long term remission in 84%. Repeated doses of IT MTX satisfactorily controlled the development of CNS relapse. It is concluded that a single drug program should not be used to treat all forms of childhood NHL.

THE MILAN EXPERIENCE IN THE TREATMENT OF NON-HODGKIN LYMPHOMA(NHL) CHILDREN. M.Gasparini, F.Lombardi. Istituto Nazionale Tumori, Milan Italy.

A total of 161 patients less than 16 years old were admitted and treated because of NHL at the Istituto Nazionale Tumori of Milan from 1968 to 1980. According to the Kiel classification histologic grouping was as follows: lymphoblastic convoluted cell type 49 (30%), lymphoblastic non specified 37 (23%), Burkitt type 52 (33%), immunoblastic 12 (7%), others 2 (1%) and not classifiable 9 (6%). Before 1974 treatment was not uniform and only 4 (14%) of 29 children survived, all of them treated with intensive chemotherapy regimens. From 1974 to 1980 two consecutive treatment protocols were utilized, and a total of 108 children are evaluable. First protocol (1974-76) consisted of an induction phase including ADM, VCR, CTX and prednisone followed by a maintenance phase (6MP + MTX) with cyclical reinforcement (ADM + VCR + CTX + prednisone). Only 5 (17%) of 29 consecutive previously untreated children are alive, relapse-free. CNS prophylaxis (brain RT + i.t. MTX) administered to 30% of the patients did not reduce the incidence of primary CNS relapse. Second protocol (1976-1980) consisted of an induction phase where ADM + VCR + CTX + prednisone were weekly alternated to HDMTX, Bleo + Ara C + 6TG, VCR. RT to the bulky tumor site was administered after partial or complete remission was obtained; Burkitt type NHL received superfractionated CNS prophylaxis consisted of brain RT and i.t. MTX. In the maintenance phase 3 monthly cycles of 6MP + MTX and of 6TG + Ara C were alternated to cycles of ADM + VCR + CTX + prednisone. Bimonthly i.t. MTX was also administered in patients with Burkitt type NHL or having mediastinal and/or bone marrow involvement by NHL. Treatment was discontinued after 2 years of CCR. Seventy-nine children were treated. Twenty (59%) of 34 with Burkitt type NHL are alive for 8+ to 63+ months and 14 relapsed after less than 4 months. Thirty-six (80%) of 45 children with other histologic subtypes are alive, with a follow-up ranging from 7+ to 58+ months. As far as the histologic subgroup is concerned, 19/25 convoluted cell type lymphoblastic NHL and 4/6 lymphoblastic unspecified NHL are alive. Thirteen of 15 belonging to other histologic subgroups or with unclassifiable NHL are alive disease-free.

PROGNOSTIC FACTORS AND TREATMENT OF CNS LYMPHOMA IN ADULTS. Robert C. Young, Richard I. Fisher, Dan L. Longo and Vincent T. DeVita, Jr. Medicine Branch, National Cancer Institute, Bethesda, Maryland 20201 U.S.A.

Involvement of the central nervous system by malignant lymphoma has been a well described complication for at least 100 years. A series of studies have established that the overall incidence of this complication is approximately 5-10% and that the complication is most likely in patients with diffuse histologies, lymphoblastic cell type, bone marrow involvement and advanced disease. The NCI made a comprehensive study of 445 adult patients with non-Hodgkin's lymphoma (*Arch. J. Med.* 66: 435, 1979). The incidence of nervous system involvement was 8.5%. The most common symptoms were headache (39%), extremity weakness (39%) and disorders of mentation (34%). Spinal fluid examination was abnormal in 97% with the commonest abnormalities being elevated pressure (66%), leukocytosis (73%) and elevated protein (88%). Spinal fluid cytology was positive in only 66% (only 54% on the first spinal tap). CNS complications were seen almost exclusively in patients with diffuse histologies. The overall incidence in the 204 patients with nodular histologies was 3.4% and in virtually all of these patients, histologic conversion to diffuse patterns had occurred prior to CNS relapse. CNS involvement was most frequently seen in the setting of advanced uncontrolled systemic disease. Isolated CNS relapse, of the type seen in childhood ALL before prophylaxis, was rare. Only 15 patients of the 445 (3%) developed isolated relapse and died because of CNS complications. Comprehensive reviews of the SWOG experience (Herman et al, *Cancer* 43: 390, 1979); the Peter Bent Brigham Hospital (Levitt et al *Cancer* 45: 545, 1980); and the ECOG (Johnson et al, *Proc. AACR* 22: 195, 1981) have reached similar conclusions.

Therapy for established disease has been variable in most studies but radiation alone, intrathecal chemotherapy alone, and whole brain irradiation coupled with intrathecal chemotherapy have been used. Treatment produces clinical improvement in the majority of patients (87%). However, irradiation of CNS disease is uncommon. Of the patients with CNS involvement ante-mortem, who subsequently died of systemic lymphoma, 20/25 (80%) had evidence of residual CNS lymphoma. Nevertheless, the majority of patients die, not because of their CNS disease, but because of uncontrolled systemic lymphoma.

In the face of the relatively low risk of CNS disease in all patients with non-Hodgkin's lymphoma, the need for CNS prophylaxis is clearly confined to select subgroups of patients at relatively high risk. These include patients with advanced diffuse lymphoma who have bone marrow involvement initially and achieved complete remission of their systemic disease. The worth of any particular approach to CNS prophylaxis, such as cranial-spinal irradiation, intrathecal chemotherapy, or systemic high dose methotrexate must be analyzed in the high risk groups where a significant relapse rate would be expected.

J-CHAIN AS A MARKER OF B NON-HODGKIN MALIGNANT LYMPHOMAS.
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J-chain is a polypeptide produced by B-lymphocytes for dimerization of IgA and pentamerization of IgM (BRANDTZAEG P. - Nature 252: 418, 1974).

Isaacson in 1979 first suggested that it could be employed as an immunocytochemical marker of B non-Hodgkin lymphomas (NHL) (ISAACSON P. - J.Clin.Path. 32: 802). Until now only a few Authors have verified the reliability of this marker with variable results (ISAACSON P. - J.Histochem. Cytochem. 27: 1197, 1979 and 28: 761, 1980) (STEIN H. - J.Histochem. Cytochem. 28: 746, 1980).

Forty lymphnodal biopsies from the files of the Institute of Pathologic Anatomy - Bologna University were studied employing a very sensitive modified PAP-method (PILERI S. - Bas. Appl. Histochem. 24: 75, 1980). They corresponded to 34 NHL (1 mycosis fungoides, 1 T-zone lymphoma, 6 immunocytomas, 1 centrocytic lymphoma, 12 centroblastic-centrocytic lymphomas, 6 centroblastic lymphomas, 6 immunoblastic lymphomas), 1 malignant histiocytosis (MH) and 5 hyperimmune reactions (HR). Specific antisera anti-albumine, muramidase, J-chain, heavy- and light-chains were applied diluted 1:1000. Thirty-six cases (31 NHL and 5 HR) were positive for J-chain, while 4 were completely negative. The latter consisted of mycosis fungoides, T-zone lymphoma, MH and centrocytic lymphoma, which was negative for both light- and heavy-chains too.

It is noteworthy that one of the immunoblastic lymphomas showing plasmablastic differentiation, was positive only for J-chain. No correlations were observed between the types of heavy- and light-chains produced by lymphomatous cells and the presence of J-chain.

According to these results, the Authors think that J-chain can be usefully employed as a marker of B-NHL.

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Use of a B-cell specific monoclonal antibody and conventional immunologic markers for typing of malignant NHL

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Results of conventional marker analysis (rosette formation with sheep and mouse erythrocytes, sIg, Fc-receptor) of malignant Non-Hodgkin's lymphomas were compared with those using a B-specific monoclonal antibody in 32 patients. The monoclonal antibody, anti-Y29/55, was produced by fusion between a mouse myeloma cell line and splenocytes of a mouse immunized to peripheral blood lymphocytes (PBL) of a patient with untreated CLL. This antibody has been shown to react with normal sessile B-lymphocytes but not with non-neoplastic B-cells circulating in blood.

The conventional marker typing gave the following results: All 15 CLL's were of the B-cell type when PBL's were studied. 11 NHL were positive for B-markers including the following histologic groups according to RAPPAPORT: 5 poorly differentiated lymphocytic, 2 lympho-histiocytic, 3 histiocytic and 1 Burkitt's lymphoma. 4 patients were of the T-cell type (2 poorly differentiated lymphocytic, 1 lympho-histiocytic, 1 histiocytic). It was observed that 2 of the 4 T-lymphomas showed CNS involvement. 2 histiocytic lymphomas did neither express conventional B- nor T-markers.

The monoclonal antibody detected all B-cell lymphomas in blood and/or tissue. In addition, one of the histiocytic lymphomas which was negative using the conventional markers, reacted with anti-Y29/55. The antibody did not react with T-cell lymphomas.

In conclusion, the antibody recognizes B-lymphomas in general. In PBL preparations it specifically distinguished between malignant lymphoma cells and normal lymphocytes. For subclassification, however, it is necessary to include the conventional markers. Additional studies with establishment of further marking antibodies are undertaken to correlate marker expression with clinical course.

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CLINICOPATHOLOGICAL STUDY OF 22 PATIENTS WITH B-IMMUNO-BLASTIC SARCOMAS (B-IBS).

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B-IBS has been recently identified as a distinct histological entity. The clinical relevance of this pathological subtyping remains to be documented. In a review of pathological material from more than 200 patients with non-Hodgkin's lymphoma, 22 fulfilled histological criteria of B-IBS. These patients were staged and treated in different institutions. The series included 12 men and 10 women with a median age of 51 years (18-99 years) and 73 years (48-83 years) respectively. At presentation, 65% of the patients had clinical stage III or IV disease and 50% had systemic symptoms (fever, weight loss and/or night sweats). Twelve patients had initial invasion in extra-nodal sites (breast 3, skin 3, ENT 2, testicle 1, small bowel 1, thyroid 1, bone 1). Four patients had history of prior immune disease (2) or lymphoproliferative disorder (2). Hypergammaglobulinemia, mostly polyclonal, was noted in 66% of the patients. Elevated LDH levels (> 500 mU/ml; $N: 100-200$ mU/ml) were seen in 8/20 patients. Anemia (5 patients), hypogammaglobulinemia (5 patients), and lymphopenia (3 patients) were more rarely encountered. A majority of patients received 4-drug combination chemotherapy regimens. These treatments yielded complete response in 29% of the patients for 17+ months (5-44+ months). The median survival time in our entire series was 9 months (3-51 months) and only 30% of the patients survived longer than one year. Younger age (< 58 years), elevated LDH levels, hypogammaglobulinemia and lymphopenia were associated with particularly short survival (3-12 months). Extra-nodal presentation, extent of disease, and presence of systemic symptoms did not seem to affect survival. These findings are consistent with previously reported data indicating that B-IBS is clinically characterized by a high incidence of extra-nodal presentations, frequent immuno- and/or lymphoproliferative disorders, relative resistance to conventional combination chemotherapy and short survival. Clearer identification of prognostic variables would require additional documentation in larger groups of patients with uniform staging procedures and therapeutic options.

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RESULTS OF NON HODGKIN'S LYMPHOMAS TREATMENT ACCORDING TO THE MIXED W.H.O. HISTOCYTOLOGIC AND IMMUNE CATEGORISATION. G. Mathé, J.L. Misset, M. Delgado, B. Caillou, D. Machover, P. Ribaud, C. Jasmin, M. Musset, G. Lemaigre & G. Santel. Service des Maladies Sanguines et Tumorales et I.C.I.G. (INSERM U-50 et Centre Claude-Bernard) de l'Hôpital Paul-Brousse; et Service d'Anatomo-pathologie de l'Hôpital Paul-Brousse, 94804-Villejuif, France.

For 5 years, we have applied the W.H.O. classification of lymphosarcoma (non-Hodgkin's lymphomas), treating all the stage III and IV patients of all ages with the same protocol: a) a maximal regression chemotherapy; b) radiotherapy on the possible residual lesions; c) complementary chemotherapy; d) randomized immunotherapy.

The prognosis evaluated to-day, with regard to survival is correlated with the W.H.O. types: a) the best concern the small cell follicular type (plateau at 85%), which is significantly different ($p = 0.01$) from that of the large cell follicular type (plateau at 25%). The latter is significantly better than the immunoblastic type ($p < 0.05$). It is similar to that of the overall lymphoblastic types, the prognosis of which is also better than that of the immunoblastic type ($p = 0.03$). However, in the lymphoblastic type, the prognosis of the null subtype is significantly better ($p < 0.01$) than that of the T subtype, which is similar to that of the immunoblastic type. Other factors, such as the nodular or diffuse structure and the presence of immunoblasts in the follicular types, and their possible immunoblastic conversion, will be envisaged.

PROGNOSTIC RELEVANCE OF THE KIEL CLASSIFICATION OF NON-HODGKIN LYMPHOMAS

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After a retrospective study on 405 patients had suggested the clinical relevance of the Kiel classification of non-Hodgkin lymphomas (NHL), in 1975 the Kiel Lymphoma Study Group initiated a prospective multicenter study which more than 1,000 patients entered during a period of 5 years. Interim evaluation of this investigation shows that survival of the entire group of patients with NHL of low-grade malignancy is exceeding that of patients constituting the group of NHL of high-grade malignancy. With regard to survival of patients with the various lymphoma entities belonging to these main histopathological groups, NHL with good prognosis (lymphocytic, centroblastic-centrocytic lymphomas) can be differentiated from lymphomas with a poor outlook (lymphoblastic, immunoblastic lymphomas). In addition, the existence of a third group with an intermediate prognosis (centrocytic, centroblastic lymphomas and possibly also LP immunocytoma or a subgroup of this entity) could be established. However, different initial slope of survival curves before plateauing at nearly the same level demonstrates that this latter group is inhomogeneous with regard to prognosis. Histopathological reevaluation of lymph node biopsies according to the original Rappaport classification showed that certain lymphomas considered entities in this scheme such as diffuse histiocytic lymphoma are prognostically heterogeneous if diagnosed according to the Kiel classification. Thus, the Kiel classification accounts for the problems arising from the considerable prognostic diversity of NHL.

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THE INTERNATIONAL FORMULATION OF THE PATHOLOGIC CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS. C.W. BERARD, Division of Pathology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101, USA

Between September 1976 and June 1980, under the auspices of the United States' National Cancer Institute, an international study of the classification of non-Hodgkin's lymphomas was performed at four major institutions. Each of 1,175 cases with detailed clinical data was classified according to six systems by a panel of six "expert" pathologists and a counterpart group of six "control" pathologists. The six systems were: Rappaport System, Dorfman System, Kiel System, British System, World Health Organization System, and Lukes-Collins System. Detailed statistical analyses of the results have been completed and discussed by all participating clinicians and pathologists. Although each of the systems had merit, as applied by either the "expert" pathologists or the "control" pathologists, none was clearly superior to the others. As a result of this study, it was possible to generate a new Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage. It should be clearly understood that the Formulation is not intended to replace any of the currently employed classifications. Its purpose is to provide a mechanism for translation of terminology from one classification to another, making possible a comparison of clinical therapeutic trials utilizing different classifications. The Formulation categorizes non-Hodgkin's lymphomas into the following groups:

Low Grade: Malignant lymphoma, small lymphocytic
Malignant lymphoma, follicular, predominantly small cleaved cell
Malignant lymphoma, follicular, mixed small cleaved and large cell

Intermediate Grade: Malignant lymphoma, follicular, predominantly large cell
Malignant lymphoma, diffuse, small cleaved cell
Malignant lymphoma, diffuse, mixed small and large cell
Malignant lymphoma, diffuse, large cell

High Grade: Malignant lymphoma, large cell, immunoblastic
Malignant lymphoma, lymphoblastic
Malignant lymphoma, small non-cleaved cell

Miscellaneous: Composite malignant lymphoma
Mycosis fungoides
Extramedullary plasmacytoma
Unclassifiable
Other

LYMPHOBLASTIC LYMPHOMA AND OTHER CHILDHOOD LYMPHOMAS. H. Weinstein, R. Cassidy, and E. Frei III. Sidney Farber Cancer Institute and Harvard Medical School, Boston, MA 02115 U.S.A.

Prior to 1973, standard acute lymphocytic leukemia (ALL) protocols were applied by the Farber Institute to pediatric lymphoblastic lymphoma. The disease-free survival was in the range of 10%. Starting in 1973, the protocol was revised to involve adriamycin with vincristine and prednisone (VP) for remission induction, followed by central nervous system (CNS) prophylaxis and then six months of adriamycin plus VP + 6-mercaptopurine (MP), followed by nine months of prednisone, oncovin, methotrexate, and purinethol (POMP). This is known as the APO protocol. In 25 patients treated over the past 7 years, 60% by actuarial analysis survive disease-free at 5 years with no relapses after 2 years. In ALL, and prior to 1973 in lymphoblastic lymphoma, almost all failures occur in the bone marrow (with some in the CNS). With the above APO protocol, relapses in the bone marrow have been rare, and they have occurred primarily in the CNS, testis, and retroperitoneum. Eighty percent of the 25 patients had a mediastinal mass, and of the 15 patients who were phenotyped, all were T-cell positive, and most had a relatively mature T-cell neoplastic clone (OK T-4-to 8). This contrasts with T-cell ALL, where the clonal expansion involves an earlier differentiation step. Of the six patients who failed, four have died of their disease. One has responded, and is beyond 2 years, to an ara-C -- cyclophosphamide combination, and the second has been transplanted and is alive at 18 months.

Thus, the estimated cure rate is 60% with this program, whereas with this and related programs in T-cell ALL, the cure rate has been much lower. Differences could relate to the differing clonal origin of the two diseases, differing tumor burden, or other factors which will be discussed.

In the past 8 years, we have had 25 pediatric patients with diffuse histiocytic lymphoma who have also been treated with the above mentioned APO program. No radiotherapy was employed. Ninety-five percent entered complete remission, and only one has relapsed, with a disease-free survival actuarial curve at 5 years of 90%. The same program in advanced-stage Burkitt's lymphoma has been much less effective.

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THERAPY OF DIFFUSE HISTIOCYTIC (DH) AND UNDIFFERENTIATED (DU) LYMPHOMA WITH HIGH DOSE METHOTREXATE AND LEUCOVORIN FACTOR RESCUE (MTX/LF), BLEOMYCIN (B), ADRIAMYCIN (A), CYCLOPHOSPHAMIDE (C), ONCOVIN^R (O), AND DEACDRON (D) (M-BACOD). Arthur Skarin, David Rosenthal, George Canellos, Delvyn Case, John McIntyre, Geraldine Pinkus, William Moloney and Emil Frei, III. Sidney Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. 02115.

Intensive combination chemotherapy programs fail to result in a complete remission (CR) in 30-50% of patients (pts) with DH and DU lymphoma and a significant number of those achieving CR develop early relapse including CNS involvement. MTX/LF is active in DH and DU lymphoma, is non-myelosuppressive, and is effective in established CNS lymphoma (Skarin, et al, *Blood* 50: 1039, 1977). 91 pts. received M-BACOD: MTX/LF (3Gm/m² i.v. q 3 wks) cycled between B (4 mg/m² i.v.), A (45mg/m² i.v.), C (600mg/m² i.v.), O (1mg/m² i.v.) and D (6mg/m² p.o.qd x 5) q 3 wks x 10 cycles. 9 pts. are inevaluable owing to early death (myocardial infarction-1, pancreatitis-1, lung toxicity-1, and sepsis-3) or discontinuation of MTX/LF (3 pts). 82 evaluable pts. with DH (70) or DU (12) consisting of Stage I_E-2, II, III-15, and IV-54, have completed M-BACOD. A complete remission (CR) was achieved in 62 pts. or 76% (DH-74%, DU-83%) partial response (PR) in 11(13%) and no response (NR) in 9(11%) pts. The median duration of PR was 6 months and all but 2 PR and NR pts. have died. 12 of 62 (19%) CR pts. have relapsed, 11 with median time of 6 mo. (range 1-18 mo.) after completion of M-BACOD. Among 30 pts. follow-up for more than 18 mo. after completion of M-BACOD, 29 remain relapse free for a median of 28+ mo. (range 19+ -50+ mo.). CNS relapse occurred in only 3/62 (5%) CR pts. (1 of 12 pts with previously positive marrow or bone and 2 of 50 pts with negative marrow or bone PR and NR pts had a higher CNS involvement rate of 6/20 (30%). 7/6 (11%) CR pts have died from disease in a median time of 14 mo (range 10-36 mo) from the onset of M-BACOD. Median follow-up for all 82 pts is 27+ mo. (range 9+ -57+ mo.) from onset of therapy. Toxicity included reversible increase in creatinine in 3% of courses, bleomycin related pulmonary infiltrates in 8 (10%) pts, and fatal granulocytopenic sepsis in 3(3%) pts. M-BACOD has acceptable toxicity, results in a high and durable CR rate, and may reduce CNS relapse by greater systemic disease control and/or by direct eradication of occult CNS involvement. The effectiveness of this program may be due to the frequency of treatment and the ability to offer antitumor therapy during periods of myelosuppression.

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THE EPIPODOPHYLLOTOXIN VP16-213 AS AN EFFECTIVE AGENT IN THE TREATMENT OF PATIENTS WITH DIFFUSE LARGE CELL LYMPHOMA

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Stage III and IV lymphocytic lymphoma of the diffuse large cell histology was, until approximately ten years ago, a neoplasm that responded poorly to chemotherapy, was associated with low complete remission rate irrespective of the drugs used, a short median duration of survival and few long-term survivors. Our initial studies demonstrated a clear benefit of the epipodophyllotoxin VP16-213 in the treatment of patients with large cell lymphoma. To define further the efficacy of this agent a randomised prospective trial was initiated in 1976 comparing VP16-213 as a single agent (Group I : n=41) to combinations with either cyclophosphamide (Group II : n=36) or adriamycin (Group III : n=41). Patients in all three arms received equivalent quantities of the epipodophyllotoxin (60 mg/m² IVI daily for 5 days) with the addition of cyclophosphamide (500 mg/m² IVI on day 5) in Group II or with adriamycin (40 mg/m² IVI on day 5) in Group III. Following a 9 day rest period this two week induction regimen was repeated three times in responding patients. Failure to respond called for patients in Group I to be randomised to either Group II or Group III; failures in the latter two groups were cross-randomised. All patients achieving complete remission were treated for 6 further months on a maintenance regimen of oral VP16-213 (100 mg/m² twice a week) for 3 weeks and in the fourth week the induction programme was repeated. Of the 118 patients entered into the study 3 have been lost to follow-up. Included are 12 individuals who died within one month of diagnosis while still receiving induction chemotherapy. For the three groups remission rates were respectively 39%, 26% and 54%; additional partial remissions were obtained in 20%, 11% and 10%. Treatment failure was 34%, 49% and 26%, with early deaths being 7%, 14% and 10%. These data demonstrate a clear activity for the epipodophyllotoxin VP16-213 as a single agent (Group I). The poor results obtained when combined with cyclophosphamide (Group II) remains unexplained. Of special interest is the combination with adriamycin (Group III) which compares favourably with those reported for CHOP or BACOP. The use of two drugs as opposed to four or five drug regimens may be an advantage but the final position of this simple regimen awaits direct comparison to the four or five drug programmes; such a study is presently in progress.

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A RANDOMIZED TRIAL OF HIGH-DOSE CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE WITH OR WITHOUT ADRIAMYCIN (CVP vs CAVP) IN ADVANCED NON-HODGKIN'S LYMPHOMAS (NHL).

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Newly diagnosed patients with pathologically documented Stage III or IV NHL were stratified by nodularity and randomized to receive either high-dose CVP (cyclophosphamide 1.5 gm/m² IV d 1, vincristine 1.4 mg/m² d 1 & 8, and prednisone 40 mg/m² PO qd d 1-10) or CAVP (cyclophosphamide 1.0 gm/m² + adriamycin 45 mg/m² IV d 1, vinc. & pred. as above in CVP). Chemotherapy was repeated q 3 weeks for a minimum of 6 cycles or 2 cycles past clinical complete response (CR). CR was documented by re-biopsies, including laparotomy when necessary. Patients (pts) achieving CR received 3 courses of consolidation with CCNU, bleomycin and prednisone. All chemotherapy was then discontinued and pts followed for relapse.

Ninety-three pts were randomized (CAVP 51, CVP 42) with \bar{M} followup >2 years. The histologies of all pts have been reviewed and classified according to both the Rappaport classification and the International Formulation. Nine pts, inevaluable for response because of inadequate documentation, are included in all survival analyses.

Overall, the CR rate was identical (51%) in the 2 regimens; the CR + PR rates were not significantly different (CVP-68%, CAVP-83%). Remission duration and survival were also similar.

In DHL (diffuse histiocytic lymphoma, Rappaport), CAVP produced 60% CR (6/10) and CVP produced only 10% (1/10) CR (p=0.057). CR's were durable with 86% of CR's continuing free of disease for a \bar{M} 3.75 yrs. Thus, there was a survival advantage for CAVP therapy in DHL. In diffuse lymphocytic and all nodular histologies, no significant advantage was seen with either treatment, though in nodular poorly diff. lymphocytic (NPD) there is a trend in favor of CVP (5/5 CR) compared with CAVP (7/14 CR). For all nodular histologies, there is a trend toward increased survival with achievement of CR (p=0.09).

The International Formulation correlated well with the Rappaport Classification. The sequence of grades (low, intermediate, high) and of lettered categories (A-K) predicted for survival with 2 exceptions: pts in Category D (follicular, predominantly large cell-nod. histio. lymphomas in Rappaport) and Category G (diffuse large cell-most DHL's) had plateaus in their survival curves reflecting long-term disease-free survival. When analyzed separately in low, intermediate or high grade categories, there was no significant difference in survival attributable to CAVP vs CVP. However, in sub-category G the CR rate was higher with CAVP (6/9) than with CVP (1/10) and the survival was superior with CAVP (p=0.04).

CAVP was a superior regimen for NHL pts (Rappaport classification) and for category G pts (diffuse large cell, International Formulation). In other histologies, there was no significant difference between CVP

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Almost all conventional chemotherapeutic agents have shown activity in malignant lymphomas. This broad chemosensitivity has led to the concept that these diseases might serve as a clinical model to prescreen for anticancer agents. In this approach, lack of activity in malignant lymphomas would prevent introduction of inactive compounds into phase II trials in the standard panel of solid tumors. However, demonstration of activity in lymphomas has become increasingly difficult with new drugs, because current studies with investigational agents are essentially conducted in far-advanced disease extensively pretreated with multiple field radiotherapy and combination chemotherapy regimens. Under such circumstances, the probability of detecting activity may be markedly reduced, particularly if crossresistance with prior therapy is significant. Moreover, residual toxic effects, such as persisting bone marrow damages, may require lowered, suboptimal dosages or largely restrict patient selection for clinical studies with new drugs. Finally, the large number of histological subtypes, in all pathological classifications, adds to the complexity of designing phase II trials in this heterogeneous group of malignancies.

In a compilation of cancer therapy protocols prepared in 1980 by the International Cancer Research Data Bank, 83 ongoing study protocols for malignant lymphomas were abstracted and, of these, 20% were specifically designed to test second-line chemotherapy regimens. There were only 6 phase II trials for both Hodgkin's and non-Hodgkin's lymphomas with 4 new agents: m-AMSA, maytansine, rubidazone, and gallium nitrate. Other compounds of interest recently tested include pyrazofurin, vindesine, pepleomycin, methylGAG, and anthracenedione derivatives. This list points to the additional problem of selecting and developing analogs. Higher therapeutic indices relative to the parent compounds generally require unappealing large scale comparative trials to be demonstrated.

Experimental models of clinical relevance could help settle a number of these problems. Among these models, the human cloning assay proposed at the University of Arizona seems most promising although in vitro testing has obvious limitations for cytotoxic agents and clear documentation of the malignant nature of the clones growing in this system remains difficult to ascertain.