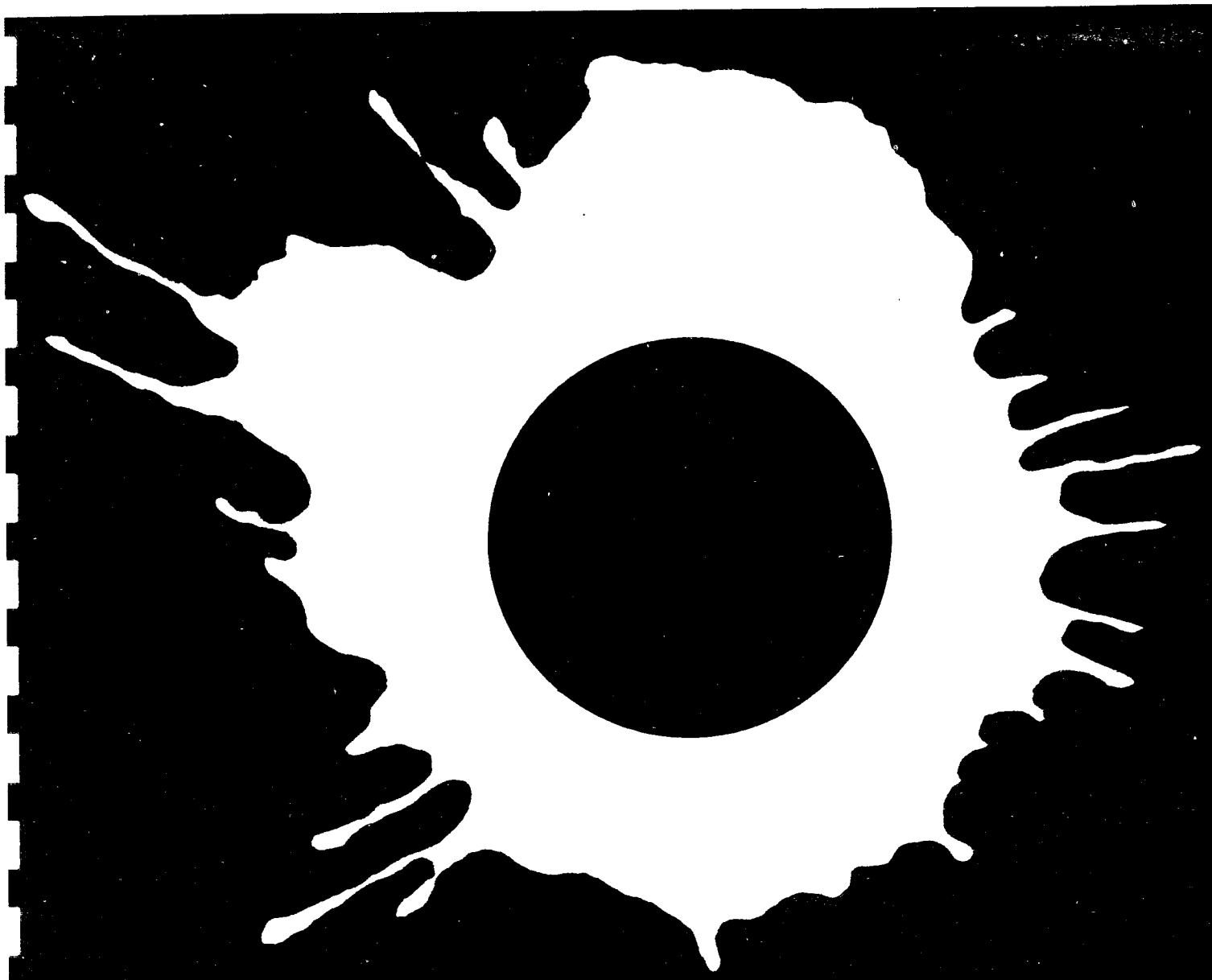
ABSTRACTS

POSTER PRESENTATIONS



TICARPEN

Ticarcillin

Das parenterale Antibiotikum gegen gramnegative Problemkeime

BEECHAM RESEARCH LABORATORIES
Erfinder der halbsynthetischen Penicilline

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

P 1 DETECTION OF COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN (CALLA) IN THE SERUM OF LEUKEMIA PATIENTS.

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CALLA was characterized as a single glycosylated polypeptide with a molecular weight of 100 KD which is expressed on the surface of lymphoblasts from patients with common acute lymphoblastic leukemia (c-ALL) and from some patients with malignant lymphoma. We developed a radioimmunoassay (RIA) for the detection of CALLA in biological fluids and found that this antigen was released in vitro into the medium of cultured human leukemia cell lines and in vivo into the serum of patients with c-ALL. The CALLA RIA was based on the inhibition of binding of ^{125}I-labelled monoclonal anti-CALLA antibody (termed A12) to glutaraldehyde fixed CALLA-positive NALM-1 cells. The binding of ^{125}I-labelled A12 antibody was inhibited up to 100% and to 70% by concentrated NALM-1 and DAUDI cell line supernatants, respectively. Culture fluids from various CALLA-negative lines gave background inhibition values of 12 to 20%. 34 out of 42 serum samples from untreated patients with c-ALL displayed an inhibition from 40 to 100% (median 70%), whereas serum samples from normal volunteers (n=43), from patients with acute myeloblastic leukemia (n=26) and with acute T-cell leukemia gave less than 30% inhibition (medians = 15%, 12% and 20%, respectively).
6 patients with c-ALL having CALLA-positive sera at presentation were tested again after remission and found to have markedly decreased circulating CALLA levels. Centrifugation of positive sera and culture fluids at 100'000 x g led to the recovery of almost all antigenic activity in the pellet. We found that the pellet also contained 100% of membrane bound 5'-nucleotidase activity suggesting that the CALLA circulating in the serum of c-ALL patients is associated with membrane fragments. Work is in progress to evaluate the value of circulating CALLA measurements to monitor remission or relapse in leukemia and lymphoma patients.

P 2 FOUR MONOCLONAL ANTIBODIES (LN-1 to -4) REACTIVE IN B5 FIXED, PARAFFIN EMBEDDED TISSUES WITH LYMPH NODE B-CELLS AND HISTIOCYTES AND DERIVED MALIGNANCIES.

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Three monoclonal antibodies (Mab) to B-cell related antigens (LN-1 to -3) and one Mab to histiocytes (LN-4) have been produced which are reactive in B5 fixed, paraffin embedded tissue sections. Specificity screens using indirect immunofluorescence methods with 36 human lymphoma and leukemia cell lines show that LN-1 and LN-2 stain cell lines of B-cell lineage but are unreactive with those of T-cell or, with one exception, myeloid derivation. CALLA+, HLA-Dr+ null cell ALL cell lines are LN-1$^-$, LN-2$^+$. The specificity of these reagents on B-cell neoplasms was confirmed on sections from over 100 B5 fixed, paraffin embedded human lymphoma biopsies using the avidin-biotin complex immunoperoxidase (IP) staining procedure. IP staining of B5 fixed, paraffin embedded human lymphoid tissues showed that LN-1 bound to the cell membrane and cytoplasm of germinal center cells while LN-2 stained the nuclear membrane and cytoplasm of germinal center and mantle zone B-cells as well as interfollicular histiocytes and thymic medullary dendritic cells. IP staining of 20 non-lymphoid human organs and tissues revealed that LN-1 reacted positively with RBC precursors of the bone marrow and a variety of epithelial cells from several organs. In contrast, LN-2 was unreactive with all human non-lymphoid organs including the bone marrow. Immunobiochemical studies have shown that LN-1 recognizes a cell surface sialoantigen while LN-2 is directed against a 35 kd nuclear membrane protein. LN-3 is an anti-HLA-Dr Mab, which, unlike all other reported HLA-Dr reagents is reactive in B5 fixed, paraffin embedded tissue sections where it stains the cell membrane of a subset of germinal center cells, mantle zone B-cells, and interfollicular histiocytes of reactive lymph nodes. IP staining with LN-3 showed that it was reactive with 47/55 HLA-Dr+ human lymphomas including two cases of T-cell derivation. LN-4 is a newly developed Mab that is reactive with dendritic histiocytes in the germinal centers and mantle zones of reactive lymph nodes. LN-4 is unreactive with nodular and diffuse lymphomas but prominantly stains dendritic cells which have markedly proliferated in the germinal centers of lymph nodes from patients with benign lymphoproliferative diseases such as AIDS and dermatopathic lymphadenopathy. Because of their high specificity and unique ability to stain B5 fixed, paraffin embedded tissue sections, LN-1 to LN-4 are exciting and useful reagents for the diagnosis and classification of the human lymphomas.

P 3 MONOCLONAL ANTIBODIES AGAINST B CELL DIFFERENTIATION ANTIGENS (HD 6, HD 28, HD 37, HD 39) - IMMUNODIAGNOSTIC REAGENTS FOR B CELL LEUKEMIAS AND LYMPHOMAS

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A series of monoclonal antibodies was raised against human B cell derived leukemias and lymphomas. In this report we describe four of these antibodies designated HD 6, HD 28, HD 37 and HD 39. The reactivity of antibodies to cell surface antigens was determined by immunofluorescence and immunoenzymatic staining tests on various human cells and tissues. HD 37 reacted with all B cell tumors, whereas tumors of T cell and myeloid origin were negative. This antibody also reacted with 14 out of 21 cases of acute lymphoblastic leukemia (ALL), this pattern of reactivity being in accordance with recent evidence that the majority of ALL belong to the B cell lineage. HD 28 also reacted exclusively with B cell tumors. The corresponding antigen however was not found on all B blast type lymphomas: only 5 out of 11 cases of (Non Burkitt) Lymphoblastic lymphomas were positive. Moreover, only 2 out of 15 cases of ALL were stained, suggesting that the HD 28 antigen is expressed later in B cell maturation. HD 6 and HD 39 were reactive only with certain types of B cell tumors: both reacted strongly with hairy cell leukemia (HCL) and prolymphocytic leukemia (B-PLL). HD 6 was negative in 20 of 24 chronic lymphocytic leukemias (B-CLL), HD 39 was negative in all 24 cases of B-CLL. B-CLL cells were studied with phorbol diester (TPA) known to promote cellular differentiation. TPA was capable of inducing the expression of the HD 6 and the HD 39 antigen. Both antibodies did not react with all 20 cases of ALL.

	ALL	B-CLL	B-PLL	HCL
HD 37	14/21	24/24	5/5	6/6
HD 28	2/20	24/24	5/5	6/6
HD 6	0/20	4/24	5/5	6/6
HD 39	0/20	0/24	5/5	6/6

Examination of normal cells in peripheral blood, bone marrow and tonsils showed that the corresponding antigens were exclusively expressed on subpopulations of B lymphocytes; T-cells, monocytes and myeloid cells were negative. It could be demonstrated that the antigens were distinct from conventional markers including surface immunoglobulin and Ia-like antigens. The different reaction patterns of the 4 antibodies suggest that the corresponding antigens are B cell differentiation antigens. HD 37 seems to be a marker for the entire B lineage, HD 28 shows a more restricted distribution and is expressed later in maturation. HD 6 and HD 39 may be related to the more mature stages of the B cell lineage. The 4 monoclonal antibodies may be useful for the study of normal B cell differentiation and for the characterization of the B cell neoplasias.

P 4 UTILIZATION OF MONOCLONAL ANTIBODIES FOR PHENOTYPING OF LYMPHOPROLIFERATIVE DISORDERS

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Lymphoproliferative disorders are heterogenous with respect to their morphological and clinical appearance and response to therapy. The use of monoclonal antibodies (mcAbs) directed against restricted antigenic determinants or epitopes renders it possible to define more precisely lymphocyte subsets and stages of lymphocyte differentiation and may represent a useful tool in the diagnosis of lymphoproliferative disorders.
In the present review, we summarize our data obtained from membrane marker studies in more than 400 cases of malignant non-Hodgkin's lymphomas and acute lymphoblastic leukemias using a large panel of mcAbs. These mcAbs, recognizing various differentiation-linked antigens of B- and T-lineage as well as certain non-lineage-restricted or HLA-derived antigens, permit the detection of the phenotypic heterogeneity of B- and T-cell-derived lymphoma/leukemia and their putative precursors.
It was possible to establish characteristic phenotypic patterns of the expression of different surface antigens for particular maturation and differentiation stages, which enabled us to classify thus defined lymphoma/leukemia entities into a sequence corresponding to the framework of the normal B- and T-cell ontogeny.
The clinical relevance and diagnostic utility of membrane marker phenotyping using mcAbs will be discussed and compared with data obtained by means of morphological examination (Kiel-classification, FAB-classification).

P 5 DETECTION OF SMALL AMOUNTS OF MONOCLONAL LYMPHOMA CELLS IN PERIPHERAL BLOOD BY FLOW CYTOMETRY.

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The non-Hodgkin's lymphomas (NHL) represent a monoclonal proliferation of malignant cells. In the great majority of cases in adults the malignant cell is derived from the B-cell line and thus bear immunoglobulins (Ig) on its surface or intracellularly. The Ig produced by a B-cell clone all contain the same light chain, K or L. In a quantitative analysis of the light chain distribution in a lymphocyte population the monoclonal cells will appear as a peak in the frequency distribution of either K or L. In patients with NHL of B-cell type a disturbed K/L distribution thus points to a spread of tumour cells in the circulation.

Material and Methods: 93 patients with different kinds of NHL, investigated, treated and followed at the Department of Oncology, University Hospital, Lund, Sweden, are included. At the time of analysis 52 patients had active lymphoma disease and 42 patients were clinically free from disease. The majority of the latter were off therapy.

Blood lymphocytes were isolated by standard gradient centrifugation. The harvested cells were incubated at 37°C for 30 min. to shed passively adsorbed Ig. They were then incubated at room temp. for 30 min. with commercially available FITC-conjugated antibodies ($F(ab)_2$ fragments) directed against human K and L light chains. The fluoresceinanalysis was performed in a flow cytometer (Ortho System 50-H). The frequency distributions of K and L was compared by superimposing the curves. If the distributions were not identical the sample was considered to contain lymphoma cells. The records of the patients were reviewed to estimate the extent of disease at the time for the immunological analyses. The patients were considered to be clinically leukemic if the blood smear contained clearly abnormal cells or the lymphocyte count was above the normal range.

Results: 36% of the patients with clinically active NHL showed abnormal K/L distribution although leukemia was not obvious with standard hematological methods. The majority of patients with immunological signs of circulating lymphoma cells had low grade malignant lymphomas. This is in agreement with today's knowledge of the behaviour of this type of lymphomas. In patients considered to be free of disease, the frequency of abnormal light chain distribution was 20%.

Conclusion: Analysis of the light chain distribution on peripheral blood lymphocytes with immunofluorescence technique is a sensitive method for detection of a monoclonal B-cell population. It might be a convenient test in staging, treatment monitoring and follow-up in patients with NHL. The prognostic importance of small amounts of circulating lymphoma cells in the blood is not yet determined.

P 6 THE MONOCLONAL ANTIBODY (MAB) Y 29/55 AS A TOOL FOR THE IMMUNOLOGICAL CHARACTERIZATION OF B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (B-CELL) AND LEUKEMIC NON-HODGKIN LYMPHOMA (NHL).

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Mab Y 29/55 recognizes an antigen on mature B lymphocytes, which does not cluster with other B cell antigens by serological analysis (1.International Workshop on Leukocyte Differentiation Antigens, Paris, 1982). Differences in marker expression between B-CLL and leukemic NHL B-lymphocytes have been described recently. The phenotype ofthe circulating malignant cells in B-CLL and leukemic NHL was therefore determined on 69 occasions with this mab and a panel of other immunological markers including mouse erythrocyte rosettes and indirect immunofluorescence with anti-human Ig, anti-kappa and anti-lambda. Generally, Y 29/55 positive cells were also positive for monoclonal kappa or lambda light chains, but correlated not significantly with mouse erythrocyte rosette formation ($r=0.28$, $p< 0.1$). Y 29/55 surface immunofluorescence on an arbitrary scale from + to ++++ was much stronger for B-CLL lymphocytes than for leukemic NHL cells. No reactivity of malignant lymphocytes with mab Y 29/55 was found in 20% of the patients with leukemic NHL, but only in 7% of B-CLL patients, indicating a lower differentiation stage in these cell populations. Serial determinations in 14 patients during the course of their disease demonstrated the clinical usefulness of mab Y 29/55 in the periodical evaluation of a clonal excess of the malignant cell population and in monitoring of cytostatic therapy effects.

P 7 B CELL LYMPHOMAS WITH INCREASED OKT 4 CELLS: UNUSUAL IMMUNOLOGICAL AND CLINICAL PRESENTATION

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The finding of immunologic abnormalities in the T cell compartment has been a general finding in patients with B cell chronic lymphocytic leukemia.A decrease in the ratio of helper/suppressor related T cells has been claimed to play a role in the origin of the immunocompetence failure of these subjects.

A total of 83 patients with B cell malignancies was evaluated in our laboratory with a panel of monoclonal antibodies. In 28 out of 31 patients evaluated for their peripheral blood status, a relative increase of the OKT 8 positive T cell subset was found, resulting in a OKT 4/OKT 8 ratio of 1.18 (control value 1.8). The remaining 3 patients presented with an unusually elevated ratio (3.5 ,6.5 and 3.7 as means of different bleedings). Two of them also had a marked lymphocytosis in their bone marrow aspirates: the infiltrating cells revealed predominantly the OKT 4 phenotype, B cells were in normal range, at this time evidencies for a lymphoproliferative disorder of the B lineage completely lacked. On the other side low percentages of T cells were found in the bone marrow of our third patient (but the immnunological study had been done late in disease stage, when malignant B cells accounted for more than 95% of marrow cells) and in other 56 patients with (48 cases) or without (8 cases) overt leukemic marrow involvement.Among the two cases with T lymphocytosis one patient developed later in the disease course a Bence Jones proteinuria, and beside a persisting 30% infiltration by T cells plasmacytoid appearing B cells progressively rose to 40% of marrow cellularity, until chemotherapy was begun. In the second case up to 50% of the marrow cells belonged to the T lineage, most expressed OKT 4, so that in fact a T cell malignancy was suspected. 6 months after the first observation however an immunocytoma of IgM-k-type was diagnosed in a lymph node biopsy, and one year later a highly malignant immunoblastic lymphoma was demonstrated in an inguinal node. A few weeks later the patient died of uncontrolled sepsis: his marrow and blood immunological findings had persisted unmodified throughout the entire follow-up.

While common evidencies suggest that blood T cell abnormalities (decreased helper/suppressor ratio) in B cell tumors are a secondary, may be reactive phenomenon, our finding of unusual T cell distribution in 3 patients support the possibility that immunoregulatory aberrancies may play a role in the control (if not in the origin) of the disease. In one of our cases, the disregulation of the T cell system has the appearance of a true lymphoproliferative disorder: if this really is the case remains open to discussion, this hypothesis should at least not be discarded.

P 8 RADIOIMMUNODETECTION OF HODGKIN TUMORS IN NUDE MICE WITH A MONOCLONAL ANTIBODY (Ki-1).

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The hybridoma derived mouse monoclonal antibody reacting with Hodgkin- and Sternberg Reed cells in culture and in frozen section of biopsy material was labelled with I-131 by lactoperoxidase method and administered intravenously into nude mice bearing transplanted tumors of Hodgkin (L 540), T-cell (Jurkat) and Burkitt lymphoma origin (BJAB Raji). Localization of radioactivity was determined with a gamma-scintilation camera 24, 48, 72 and 120 hours after the inoculation. Accumulation of radioactivity could be demonstrated in Hodgkin tumors only but not in BJAB, Raji or Jurkat tumors. Most distinct images of the tumor could be achieved at 48 hours after the administration of the labellet antibody. Activity ratios of 8:1 (tumor/muscle), 3:1 (tumor/live) and 3:1 (tumor/spleen) could be observed without using background substraction techniques. A radio labelled K-1 antibody might be of potential value in detecting Hodgkin tumors in man.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

P 9 Detection of a Sternberg-Reed- and Hodgkin cell specific antigen on atypical cells in lymphomatoid papulosis.

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Lymphomatoid papulosis(LyP) is a usually benign recurrent papular eruption of the skin with a histological appearance suggestive of malignant lymphoma. Ever since its first description as a distinct clinicopathological entity in 1968 this condition has posed considerable diagnostic problems to the histopathologist. A polymorphic cell infiltrate and the presence of large atypical lymphoid cells sometimes prevent a clearcut morphological distinction of LyP from malignant lymphoma. Cytochemical and immunohistochemical studies so far could not provide unequivocal evidence for an attribution of the atypical cells in LyP to the known lymphoid or myeloid differentiation lineages and thus supply additional diagnostic criteria. Morphologically a sometimes close resemblace to Sternberg-Reed (SR) cells was noted by several authors.

In the present study we investigated whether this morphological similarity would be parallelled by the expression of a surface determinant defined by the monoclonal antibody Ki 1. This antibody has been proved to react specifically with Hodgkin(H)- and SR cells and a recently detected small cell population in normal lymphnodes and bone marrow regarded as the normal counterpart of H- and SR cells. Ki 1 was however unreactive with non-Hodgkin-lymphomas. In addition reactivity of the atypical cells in LyP with a large panel of monoclonal antibodies was tested: Ki 24, Ki 27 (H-,SR cells,some non-Hodgkin lymphomas);RTO15 (B cells); T 28, Leu3a, Leu1, T102,(T-cells and T-cell subpopulations); Na1/34 (interdigitating reticulum cells) R 423 (dendritic reticulum cells) SHC 1/3 (macrophages) 3C4 (cells of granulopoetic origin); Ki 67 (proliferating cells). Cryostat sections of skin biopsies from 10 patients with LyP were studied using a multi-step immunoalkaline phospatase (AP)-anti-AP method.

In all lesions tested Ki 1^+ atypical cells were present,sometimes aggregations. In some cases Ki 1^+ cells were also stained by Ki 24 and Ki 27. Reactivity with Ki 67 was most pronounced in Ki 1^+ areas. All other antibodies did not constantly react with the atypical cells.

Our study demonstrates that the large atypical cells in LyP share a specific antigenic marker (Ki 1) with SR- and H cells. These cells have been supposed to arise from a recently described Ki 1^+ cell population in normal lymphoid tissue and bone marrow. Our results suggest that Ki 1^+ atypical cells in LyP are also derived from this cell population. The presence of Ki 1^+ cells seems to distinguish LyP from cutaneous lesions of other non-Hodgkin-lymphomas.

P 10 INDUCTION OF DIFFERENTIATION OF UNDIFFERENTIATED (BURKITT'S) LYMPHOMA CELLS WITH PHORBOL-ESTER (TPA) AND TELEOCIDIN (TCD)

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The observation that leukemic cells, which have the phenotype of pre-B or pre-T cells, can be induced to differentiate in vitro suggests that a failure to differentiate is a critical component of leukemogenesis. In an attempt to determine whether a similar defect in differentiation is of importance in the pathogenesis of childhood B-cell malignant lymphomas we have studied the effect on undifferentiated lymphoma cell lines of two agents (TPA and TCD) known to induce morphological and functional differentiation in normal and malignant hemopoietic cells in vitro. For comparative purposes, we have also studied 7 normal lymphoblastoid cell lines. Cell lines were examined for alterations in proliferative capacity, ultrastructure, immunoglobulin (Ig) secretion and Interleukin 2 (Il2) production. At concentrations in the range of 10^{-7}M to 10^{-8}M, TPA inhibited proliferation. The degree of inhibition was essentially total in the American lines, minimal in the normal lines and intermediate in African lines. 5 of 8 cell lines studied by electron microscopy showed maturational changes including development of extensive arrays of rough endoplasmic reticulum (RER), and an eccentric nucleus with a single prominent nucleolus and marginated heterochromatin. These changes varied in degree. At their most pronounced (2 of 5 lines), the cells were morphologically identical to malignant plasma cells. Both lines which were induced to undergo nearly complete plasmacytoid differentiation by TPA already possessed a small quantity of RER and secreted some IgM. The other 3 lines showed lesser plasmacytoid changes. In the remaining cell lines various morphologic changes were induced by TPA, but these were not indicative of plasmacytoid differentiation. In the cell lines in which maturational changes were demonstrated an increase in IgM secretion between 2 to 31 fold was observed. In cell lines in which RER was not induced, no alteration in IgM secretion was seen. TPA also caused increased IgM secretion in lymphoblastoid lines derived from patients with infectious mononucleosis and no change or decreased secretion in lymphoblastoid lines derived from cord blood lymphocytes. TCD was a more effective agent than TPA with regard to the induction of IgM secretion. This agent also induced secretion of Il2 in 7 of 8 EBV negative tumor cell lines, but none of 11 EBV positive tumor lines. Five normal lines, all of which were EBV associated, were also induced to secrete Il2 by TCD. Our findings indicate that the failure of B-cell lymphomas to differentiate is not irreversible, and raises the possibility that future therapeutic attempts may exploit the possibility of inducing neoplastic cells to undergo differentiation in vivo. This system may also be of use to examine oncogene expression in different states of differentiation.

P 11 DIAGNOSTIC RELEVANCE OF DETECTION OF SURFACE IMMUNOGLOBULIN (SIG) IN B-NON HODGKIN LYMPHOMA (B-NHL).

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The diagnostic relevance of cell suspension analysis for detection of sIg on tumor cells of B-NHL was investigated by comparison of the Direct Antiglobulin Rosetting Reaction (DARR) in suspension with a Direct Immuncfluorescence test (DIF) on frozen sections. We primarily focused on detection of light chain isotypes since a wide range for sμ, sδ, sγ, and sα positive cells in benign lymph nodes hampered determination of a monoclonal component by tests of heavy chains in B-NHL. In benign lymph nodes the κ/λ ratio by DARR tests ranged from 0.9 to 2.8 (mean ± 2SD; n=28). In 24 of 31 cases of B-NHL a monoclonal component was found in suspension. However, cytomorphological analysis of preparations made after rosetting (available in 14 of 31 cases) disclosed light chain restricted tumor cells in 2 more cases. Frozen sections revealed light chain restriction in 27/31 cases, while all were B_1 and HLA-DR positive . Heavy chain restriction was found in 14/26 cases studied in suspension, 10/14 studied on cytocentrifuge preparations and in 28/31 studied on frozen sections. In DARR tests most cases showed tumor cells with 2 or more heavy chain isotypes, an infrequent finding on frozen sections. We concluded that DARR tests may yield false negative results which can be corrected by cytomorphological analysis after rosetting. In our hands analysis of frozen sections by DIF was most distinctive in determination of monoclonality.

P 12 SPONTANEOUS T-CELL COLONIES IN PATIENTS WITH T-CELL MALIGNANCIES IN COMPLETE REMISSION.

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We have described that peripheral blood T-cell colony forming cells(T-CFC) from patients with T-cell malignancies(T-ALL and T-non Hodgkin's Lymphoma) in acute clinical phase can generate T-cell colonies in the absence of added growth factors.We studied a number of these patients in complete remission(CR) and found a spontaneous T-cell colony formation in 10 out of 17 cases.Three of the patients presented a significant colony growth in acute phase but not in CR.Colonies consisted of lymphocytes and/or lymphoblasts with cytochemical and immunological markers of the T-cell lineage.In some patients,spontaneous T-cell colonies were more differentiated in CR than in acute phase as demonstrated by the presence of the higher OKT_3 reactivity.However,in several cases,complete phenotypic study of colony cells revealed an abnormal differentiation(increased OKT_6^+ and/or OKT_8^+ and decreased E^+ and/or OKT_4^+ cells).

These results demonstrate an abnormal proliferation and differentiation of T-cells from patients with T-cell malignancies in CR,which were quite similar to that observed during the acute phase.Furthermore,in one patient,a proportion of cells from spontaneous T-cell colonies displayed chromosome abnormalities whereas the Karyotype of bone marrow cells was normal.This finding suggests the presence of,otherwise undetectable,residual malignant clonogenic cells during the complete clinical and hematological remission.

P 13 AN IMMUNOLOGICAL CLASSIFICATION OF 28 BURKITT CELL LINES BASED ON THEIR MEMBRANE ANTIGEN EXPRESSION

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From the first publication which identified Burkitt lymphoma (BL) as a B cell tumor, studies based on the expression of IgFc, complement and EBV receptors, showed immunological differences between EBNA- and EBNA+ cases or tempted to classify BL cells in a late stage of B cell differentiation, but very few were studied in regard to the membrane antigen expression. Monoclonal antibodies (MoAbs) which recognize B cell differentiation antigens are now available to characterize, in normal B cell lineage or in B malignant proliferations, populations of different degrees of maturation or activation, or even with different homings. Hence, we analyzed 28 Burkitt cell lines in immunofluorescence with seven of those MoAbs and heteroserums specific of human immunoglobulin determinants. Cell lines were established in IARC, 5 from BL of high incidence area (African cases), 9 from BL of intermediate incidence area (North African cases) and 13 from BL of low incidence area (Caucasian cases) ; 8 Caucasian BL were EBNA-. Y29/55, B_1 and BA_1 are pan B MoAbs : BA_1 is an earlier marker reacting with 50 % TDT+ cells in normal bone marrow (B.M.) and weakly expressed on germinal center cells. AL_2 recognizes the common acute lymphoblastic antigen P100 (C.ALLA) also expressed on germinal center cells, RFT_1 is a pan T monoclonal antibody expressed on follicular mantle cells, BL_{13} and $TÜ_1$ are two follicular specific markers, respectively of the germinal center and the follicule mantle.

26 out of the 28 cell lines expressed Y29/55 and B_1 ; none of them was stained by RFT_1. Hence, we classified the cell lines in three groups according to the expression of the four markers : CALLA, BA_1, BL_{13} and/or $TÜ_1$. Cell lines in groups I and II were characterized by the expression of specific follicular markers $TÜ_1$ and/or BL_{13} : their phenotypes were very similar to that of lymphomas defined as centroblastic in the Kiel classification for group I cell lines, and to centroblastic-centrocytic lymphomas for group II cell lines. Cell lines in group III lacked follicular marker expression and strongly reacted with CALLA and BA_1.

We will then discuss the possible duality of the BL cells origin : in groups I and II, cell lines could represent BL of lymphoid organ origin and, possibly, of germinal center origin ; group III cell lines could be established from malignant cells of B.M. origin. This classification may help to clarify clinical differences between BL since all cell lines established from BL of high incidence area belonged to group I, whereas cell lines from group III were all established from low incidence area BL.

P 14 PRECIPITABLE IMMUNE COMPLEXES IN SERA FROM PATIENTS WITH MALIGNANT LYMPHOMAS.

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We investigated 420 sera of 120 patients with malignant lymphomas for the presence of circulating immune complexes (CIC). Three techniques for the detection of CIC were applied: a modified 3% PEG precipitation technique (PEG-CIC) with subsequent quantitation of immunoglobulin and complement components by lasernephelometry, a new lasernephelometric Clq-binding assay (Clq-CIC) and a Conglutinin-EIA (Cg-CIC).

As compared to healthy controls (n=180), we did not find significant elevations of Clq-CIC or Cg-CIC in patients with malignant lymphomas. In contrast, elevated levels of PEG-CIC were nearly constantly found in patients with untreated Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHL). The amount of PEG-CIC correlated with disease stage and presence or absence of B-symptoms. Patients with high-grade NHL showed significantly ($p < 0.005$) higher amounts of PEG-CIC than patients with low-grade NHL (Kiel-classification). Main components of the precipitable material (60-70%) were C4, Clq, C3c and polyclonal IgM, IgG and IgA. Patients with complete remission for more than 2 years (n=15) showed PEG-CIC within the range of healthy controls, whereas relapsing disease was in all cases (n=11) accompanied with re-occurence of PEG-CIC. Constantly, quantitative predominance of IgM as compared to IgG was found in untreated HD patients with first occurence of the disease. In relapsing HD a reversal of the IgM/IgG-ratio with predominance of IgG was observed ($p < 0.005$). Normally, PEG-CIC were not observed in patients with paraproteinemias due to plasmocytoma. Few cases (n=3) of precipitable monoclonal IgM in some of the patients with IgM-secreting immunocytomas were observed. Patients with angioimmunoblastic lymphadenopathy (AIL) (n=8) had a distinctly differing profile of precipitable components: A high IgM/C4-quotient was found in AIL and was significantly contrasting with low IgM/C4-quotients in HD and NHL.

In conclusion, quantitation of PEG-CIC is suggested to be of clinical value for additional initial information concerning disease activity and in the long-term follow-up of patients with HD and high-grade NHL. Furthermore, the method might add some information to differential diagnosis of high-grade NHL versus AIL. The antigenic site of these complexes as well as their biological role in malignant lymphomas still remains to be clarified.

P 15 Abnormal helper and suppressor cell relationship in malignant Non Hodgkin's lymphomas revealed by immunomorphometric techniques

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Number and distribution of reactive T cells within 100 malignant B cell lymphomas were evaluated *in situ* by immunomorphometry using stereological methods. Findings were related to histological and clinical parameters. In malignant lymphomas 40 % of the T cell content of normal lymphatic tissues was found. When evaluating the different histological entities a correlation between number of helper T-cells, T-helper:T-suppressor (T_H:T_S) ratio and histological subgroups emerged particularly in Non-Hodgkin's lymphomas of low grade malignancy. The highest ratio was found in prognosticelly favourable subgroups, CLL (2.7 ± 0.3) and tumour areas of centroblastic/centrocytic lymphomas (2.9 ± 0.4). In contrast, a significantly lower ratio was found in centrocytic lymphomas (1.4 ± 0.3) corresponding well to the worst prognosis of this subgroup. The relationship between the number of helper T-cells in tumour tissues, T_H:T_S ratio and prognosis was confirmed and extended by the evaluation of clinical data. It could be shown that, independent of histological criteria, a close correlation exists between the number of T-cells, particularly T-helper cells within the tumour, T_H:T_S ratio and clinical course. Patients with a favourable course had 1.4×10^4 T-helper cells/µl tumour tissue compared to only 0.3×10^4 for patients with an unfavourable clinical course ($p < 0.01$), the T_H:T_S ratio was 2.8 for the favourable and 1.8 for the unfavourable group, respectively ($p < 0.04$). In contrast, neither treatment nor tumour stage had clear cut influence on the extent of T-cell infiltration.

P 16 SPONTANEOUS ACTIVATION OF T-CELL COLONY FORMING CELLS AND CONSTITUTIVE RELEASE OF GROWTH FACTORS BY LEUKEMIC CELLS IN HUMAN T-CELL MALIGNANCIES.

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We have shown that peripheral blood T-cell colony forming cells(T-CFC) from 17 of 21 patients with T-cell malignancies can generate T-cell colonies with self-renewal capacity in the absence of added growth factors.These colonies were composed of immature T cells and,in some cases,displayed the same chromosome abnormalities as fresh leukemic cells.Two groups of patients could be identified, according to high or low spontaneous plating efficiency(more or less than 100colonies/10^5PBL respectively).In the first group,added Interleukin 2(IL2)-containing conditioned media(PHA-LCM) or semi-purified IL2 could not enhance colony growth.In the second group,both PHA-LCM and IL2 without prior lectin stimulation,were able to increase significantly the number of T-cell colonies.

IL2 coud be produced by patients' PBL either spontaneously (in 2 of 15 cases) or after PHA-stimulation(in 12 of 15 cases).However,7 of 10 IL2-free conditioned media from unstimulated PBL of patients contained a T-cell colony promoting activity(T-CPA)demonstrable on normal T-CFC.

This T-CPA induced T-cell colony formation,in the absence of PHA or IL2,from mature(E+) and,occasionally, immature(E OKT_3^-) normal T-CFC.T-CPA could also *in vitro* expression of HLA-DR receptors on normal E+ cells and T-cell differentiation of immature T-CFC.

These results suggest that spontaneous activation of T-CFC and release of T-cell growth factors(both IL2 and/or T-CPA) may play an important role in the pathophysiology of human T-cell malignancies.

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P 17 FACTORS RELEASED BY HUMAN LEUKEMIC T CELLS INDUCE IN VITRO THE PROLIFERATION OF NORMAL T LYMPHOCYTES.

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Peripheral blood T-cell colony forming cells (T-CFC) from patients with T-cell malignancies can generate T-cell colonies in methylcellulose in the absence of added growth factors. In some patients, conditioned media from unstimulated leukemic cells (LCM-L) are able to induce T-cell colony formation from normal T-CFC without PHA stimulation (T-cell colony promoting activity; T-CPA). We studied the capacity of LCM-L to induce in vitro proliferation of normal T-lymphocytes in 48h liquid culture, using the thymidine incorporation technique. LCM-L from 4 of 17 and 3 of 10 patients showed a proliferative activity on normal PBL and E^+ cells respectively. The phenotype of proliferating cells was that of mature T lymphocytes after 48h cultures. PHA and/or semi-purified Interleukin 2 (IL2) enhanced this activity on E^+ cells. One and 2 of these active LCM-L contained IL1 and IL2 respectively. The kinetics of production of this activity was variable from patient to patient. All of the T-lymphocyte proliferating activity-containing conditioned media were able to induce in vitro T-cell colony formation from normal T-CFC but several T-CPA containing LCM-L did not display a proliferative activity. These results suggest that 1° T-leukemic cells constitutively release factors able to trigger into active DNA synthesis normal E^+ cells; 2° these factors are different from IL1 and IL2; 3° T-cell proliferative activity is not identical to T-CPA.

P 18 IMMUNOLOGICAL STUDY OF BURKITT'S LYMPHOMA CELL LINES ; CORRELATION WITH CYTOGENETIC, VIROLOGIC (EBV) DATA AND WITH GEOGRAPHIC ORIGINS

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50 Burkitt's lymphoma (BL) cell lines obtained from 50 patients at the international agency for research on cancer were studied : 15 from high incidence area and 35 from low incidence area. cytogenetic analysis of 44 BL lines was available and all the cell lines were tested for the presence of EBV genoma.

Immunological study consisted in detection of surface (SIg) and cytoplasmic (CIg) immunoglobulins, of surface antigens reacting with monoclonal antibodies specific (B1, BL13, BL14) or non specific (BA1, OKT9, OKT10, OKM1, T101, J5, P5, BL2) for B cells and of receptors for mouse red blood cells (MRBC). For 33 cells lines Ig classes excretion was measured in the supernatant of 2 and 5 days cultures using a sensitive ELISA technique.

From this study BL appears to cover a broad rang of the B cell differenciation since the following Ig phenotypes were observed : null cells (SIg^-, CIg^-), pre-B cells, non secreting B cells (SIg^+CIg^-) and secreting B cells (SIg^+CIg^+). In SIg^+ cell lines different classes of Ig were found : IgM, IgM+IgD, IgG, IgA. Among the different monoclonal antibodies used, none was associated with a precise stage of maturation.

No significative correlation was observed as we compared stages of maturation with characteristic chromosome translocations observed in BL and with the presence of EBV genoma. As regards geographic origins, immunological differences exist : - all but one cells lines with pre-B cell phenotype were obtained from patients of high incidence area ; however cell lines from high incidence area showed the same phenotypic heterogeneity as cell lines from low incidence area and, in some cases, were able to secrete large quantities of Ig -reactivity with BA-1, J5 and BL 13 was strongly linked with geographic origin.

This study lead us to suggest the peripheral origin of BL cell because of reactivity with markers absent of bone marrow B cells (BL13, MRBC). The phenotype profiles realized in BL and comparison with other B cell malignancies are evidence for divergence from a single linear pathway of B cell developpment resulting of Ig phenotype analyse.

P 19 TRANSFERRIN RECEPTOR AND B-LYMPHOBLAST ANTIGEN - THEIR RELATIONSHIP TO DNA SYNTHESIS, HISTOLOGY AND SURVIVAL IN B CELL LYMPHOMAS

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The reactivity of two monoclonal antibodies identifying antigens related to B-cell activation, B3/25 (the transferrin receptor) and BB-1 (the B-lymphoblast-1-antigen), was examined on cell suspensions from 75 cases of monoclonal B-cell lymphomas.

The expression of B3/25 antigen was correlated to DNA synthesis as measured by spontaneous ^{3}H-thymidine incorporation ($p = 0.0003$) and histopathologically high grade malignancy ($p = 0.00003$). Furthermore, B3/25 expression was associated with survival since the patients with B3/25 negative tumors survived longer than those with B3/25 positive tumors ($p = 0.018$). B3/25 expression also defined a larger group of patients with shorter survival than histopathology alone, 28 cases versus 16 cases, respectively.

On the other hand, the BB-1 antigen did not reveal an association with DNA synthesis, high grade malignancy or survival. However, the findings indicated that BB-1 may be related to B-cell maturation/differentiation.

P 20 LATENT C1 ESTERASE INHIBITOR (C1SINH) DEFICIENCY IN A PROSPECTIVE STUDY OF 100 PATIENTS WITH LYMPHOPROLIFERATIVE SYNDROMES.

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A prospective study of 100 patients with lympho-proliferative syndromes was carried out to better understand acquired angioneurotic edema (AE) previously described in these syndromes.

Patients included 64 males and 36 females aged 43 to 87 years (m=65,7) with chronic lymphoid leukemia (CLL, n = 54), non Hodgkin lymphoma (NHL, n = 25) or Waldenström's disease (WD, n = 21). None of the patients had symptoms or a family history of AE. Lab tests for all patients included = total complement (CH50) by immunohemolysis on sera stored at 4°C for 18 hr (normal range : 100 ± 40 % of control serum) and three complement fractions by radial immunodiffusion = C4 (normal range = 0,14 - 0,70 g/l), C3 (0,70 - 1,80 g/l) and C3PA (0,10 - 0,45 g/l). When abnormal levels were found C1q ($100\ \% \pm 30$ % of control serum) and C1SINH (0,10 - 0,45 g/l) were also determinated by radial immuno-diffusion.

Three patients (2 LNH, 1 LLC) presented strongly suggestive complement levels (low CH50, C4, C1q levels and normal C3 and C3 PA levels) and assays confirmed low C1SINH levels. In these three patients complement levels paralleled disease evolution.

It was concluded that careful analysis of the complement system in patients with lymphoproliferative syndromes can reveal latent C1SINH deficiency, a deficiency related to exagereted C1 activation. Despite the low frequency (3 %) such findings require close clinical monitoring in order to initiate androgen treatment at the first signs of AE and repeated assays should be made as complement abnormalities may mark disease evolution.

P 21 ENZYMATIC AND ULTRASTRUCTURAL ORGANIZATION OF PLASMA MEMBRANE IN HUMAN LEUKEMIC CELL LINES.

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Enzymatic and ultrastructural properties of plasma membrane have been studied on human leukemic cell lines expressing surface immunologic markers related to the B lineage. Subcellular fractions obtained by sucrose gradient centrifugation (d=1.05/1.30) from homogenates of REH-6 (T^-/B^-), Nalm-1 (pre-B) and Raji (B transformed) cell lines, were assessed for their relative membrane distributions by recording activities of the marker enzymes γ-Glutamyltranspeptidase (γ-GLUPase), 5'Nucleotidase (5'AMPase), (Na-K)-Mg total and ouabain dependent Adenosine triphosphatase ((Na-K)-Mg ATPase), Alkaline phosphatase (PNPase) Alkaline phosphodiesterase (PDAase), Glucose-6-phosphatase (G-6-Pase), and β-N-Acetylglucosaminidase (β-NAGase). REH-6 membrane fractions of intermediate density (d=1.15/1.20/1.25) presented measurable 5'Nucleotidase and total and ouabain dependent Adenosine triphosphatase activities, while most of the activity of Alkaline phosphatase, Glucose-6-phosphatase and β-N-Acetylglucosaminidase was measured in the heavy fractions (d=1.20/1.25). However γ-Glutamyltranspeptidase and Alkaline phosphodiesterase were not measurable. γ-Glutamyltranspeptidase activity was found in the light fractions (d=1.10/1.15/1.20) of Nalm-1, while 5'Nucleotidase and Alkaline phosphatase high activities were recorded in the heavy fractions (d=1.20/1.25/1.30). Intermediate density fractions (d=1.20/1.25) showed Adenosine triphosphatase activity, whereas the Alkaline phosphodiesterase activity was still lacking. On the contrary Raji cells displayed measurable activities for all ectoenzymes investigated and revealed similar enzymatic profiles within the various fractions. The ultrastructural topography was investigated on freeze-fracture preparations of intact cells by evaluating the density ($\alpha = Np/\mu m^2$) and the distribution of intramembranous particles. Particles density distributions appeared similar on protoplasmic face (PF) and external face (EF) of plasma (PM) and nuclear (N) membranes in all cell lines, with a particle density significantly different only in the plasma membrane (PF) of the Nalm-1. In conclusion, the enzymatic data seem to correlate with the stage of differentiation, as supported by the enrichment of the enzymatic equipment of the plasma membrane and the trend toward homogeneous profile distributions of the marker enzymes. On the contrary the ultrastructural topography does not correlate : indeed, no particle density distribution was found characteristic of the various cell lines.

P 22 ENZYME ACTIVITIES IN HUMAN LYMPHOMAS.

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Several enzymatic activities were examined in bioptic specimens of human non-neoplastic and malignant lymph nodes. The diagnostic role of terminal deoxynucleotidyl transferase (TdT) and adenosine deaminase (ADA) was evaluated on more than 100 cases. We defined as TdT positive the specimens with a content above 0.5 U/mg of protein, and as ADA rich those with an enzymatic value of more than 350 U/mg of protein. All the non-lymphoblastic histological types were TdT negative and ADA poor. Among the 11 lymphoblastic lymphomas (LL) tested, 6 were TdT positive and ADA rich, 2 were TdT positive and ADA poor, 3 were TdT negative and ADA rich. Therefore with both TdT and ADA determinations we were able to isolate the lymphoblastic cases from all the other types of lymphoma. Other enzymatic activities (DNA polymerase alpha, lactate dehydrogenase, thymidine and uridine kinases and poly(A) polymerase) did not have a diagnostic role, but their levels were higher in high-grade than in low-grade malignant non-Hodgkin's lymphomas (NHL). The most interesting findings were obtained with DNA polymerase alpha and LDH. DNA polymerase alpha was tested on 24 high-grade and 31 low-grade NHL; LDH was tested on 13 high-grade and 19 low-grade NHL; in both cases the p value was less than 0.01. Therefore, it is possible than the determination of some enzymes represent a useful internal marker of malignancy that could contribute to the definition of the prognosis of NHL. (Contribution n.8 of the program "Biochemical and immunological characterization of human lymphomas".)

P 23 THE IMPORTANCE OF THE ASSAY METHOD FOR ECTO-5'NUCLEOTIDASE DETERMINATION

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It is now well established that the ecto-5'nucleotidase activity of lymphoid cells displaying immaturity characters is lower than that of mature lymphocytes. Most often the substrate used to determine this enzymatic activity is 5'AMP labeled on the adenosine moiety (either 5'[8-^{3}H]-AMP or 5'[8-^{14}C]-AMP); excess nucleotide is generally removed from the radioactive adenosine produced by precipitation with $ZnSO_4$ and $Ba(OH)_2$. We show here that this method has led to underestimated ecto-5'nucleotidase values, as compared to those obtained with 5'[^{32}P]-AMP as substrate.

These differences arise from further transformation of radiolabeled adenosine, resulting from 5'AMP hydrolysis by ecto-5'nucleotidase, by adenosine metabolizing enzymes into metabolites which are not taken into account for the enzyme activity determination: i) in the case of intact cells, 5'AMP-derived adenosine enters the cell and is transformed mainly into radiolabeled nucleotides which are precipitated with the excess substrate; ii) in the case of cell homogenates, radiolabeled inosine produced from adenosine by adenosine deaminase coprecipitates with the starting nucleotide.

The use of adenosine-labeled 5'AMP may also lead to wrong interpretations of the experimental results, as in a recent paper by Sun *et al* (Biochim. Biophys. Acta 762, 577, 1983) who claimed the presence of a ecto-5'nucleotidase inhibitor in human leukemic cells: these authors did not take into account the adenosine deaminase activity of their cells and made a confusion between this enzyme and what they called a *proteic inhibitor*.

In order to avoid such problems, the best assay method for ecto-5'nucleotidase determination is the use of 5'[^{32}P]-AMP as substrate. ^{32}Pi (inorganic phosphate), produced during the enzymatic reaction, does not enter the cell and is separated from all organic materials by activated charcoal treatment. Under these conditions the metabolism of unlabeled adenosine does not affect the enzyme determination.

P 24 In-vitro induction of differentiation of human B cell lymphoma can result in cells with hairy cell phenotype.

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Phorbolester treatment of tumor cells can induce differentiation and thus can be used to analyze the genetic program of the malignant cell. We have treated leukemic cells from 10 patients with chronic lymphocytic leukemia (CLL), 4 patients with immunocytoma (IC) and 4 patients with prolymphocytic leukemia (PLL) with 12-O-tetradecanoylphorbol-13 acetate (TPA) at 160 nM for 3-5 days in-vitro. In Pappenheim stains, in many samples the enlarged cells exhibited an excentric nucleus, basophilic cytoplasm and, in addition, multiple fine projections. Cytoplasmic immunoglobulin could be induced in most CLL and IC. Cytochemical analysis revealed the appearance of acid phosphatase in all samples but one. The enzyme was found tartrate resistant in all instances tested.
Two monoclonal antibodies unreactive with plasma cells were applied to this system: Leu-1 (T65) which binds to T cells and to B-lymphoma cells and HD6 which is found on some types of B lymphoma cells, most strongly on hairy cell leukemia (HCL). Using both fluorescence microscopy and FACS TPA was found to induce HD6 staining in HD6 negative CLL samples and to increase HD6 staining in HD6 positive CLL, IC and PLL. Further, all Leu-1 positive leukemias with one exception, showed increased Leu-1 staining after TPA. While this unexpected finding does not fit into any current concept of B cell maturation, the majority of data is compatible with the concept that B cell lymphomas can differentiate towards hairy cells.

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P 25 IMMUNOHISTOLOGICAL ANALYSIS OF NEOPLASTIC AND REACTIVE CELLS IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

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A detailed multiparameter immunological analysis was carried out in patients affected by B-cell chronic lymphocytic leukaemia (B-CLL). The techniques employed in this study included immunohistochemical analysis of frozen tissue samples (lymph nodes -4 cases, bone marrow trephine biopsies -20 samples) and cell suspension analysis of peripheral blood and bone marrow by mouse and sheep erythrocytes rosetting and membrane phenotyping by double-staining immunofluorescence (43 cases). The heteroantisera and monoclonal antibodies used were espeCially selected in order to characterize the neoplastic cells (SIg, T1-antigen and HLA-DR-antigen expression) and the "reactive" and accessory cell population (antibodies to T cells and their subsets and to follicular dendritic cells -FDC-). The results can be summarized as follows:

1) the neoplastic B lymphocytes exhibited in all cases an identical phenotype in all tissues examined: peripheral blood, bone marrow and lymph nodes (when available).

2) T cells were more numerous than expected and both in lymph nodes and bone marrow the "helper" ($T4^+$) phenotype was dominant. This was in contrast with the finding in the peripheral blood where there was an increase of "suppressor" ($T8^+$) T cells. These findings suggest a T cell subsets redistribution in B-CLL.

3) FDC were clearly demonstrable in the bone marrow biopsies in 6/12 cases with a nodular pattern of involvement within the neoplastic nodules. On the contrary, FDC were not found in samples with diffuse neoplastic infiltration.

These data provide new elements to better understand the biological and clinical behaviour of B-CLL.

P 26 Q-LACKING TRANSFER RNA IN MALIGNANT LYMPHOMAS.

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Transfer ribonucleic acids (tRNAS) are the most complex of all biomacromolecules in both structure and function. They not only function as adaptor molecules in protein synthesis, but are also involved besides many other cellular processes in regulation of gene expression. To elucidate the significance of tRNA modification for human lymphoid maturation and malignant transformation the amount of tRNAS having guanosine (G) in place of queuine (Q) in the "wobble" position of the anticodon [(Q-)tRNA] was determined in several human lymphomas by exchange of G with 3H guanine, a reaction catalized by a specific tRNA transglycosylase from E.coli. The amount of (Q-)tRNA in high grad lymphomas (mean ± S.D. 38.64 ± 22.81 pmoles /A260) is substantially greater than that observed in germinal center cell lymphomas and CLL in favourable prognostic stage (6.65 ± 3.21) and non-neoplastic lymphoid tissue (6.83 ± 2.55). In CLL lymphocytes it increases significantly from stage A to C of the Binet classification [5.65 ± 0.5 (A); 9.25 ± 1.45 (B); 30.3 ± 4.5 (C)]. In representatives of late B-cell differentiation also increasing values were observed (HCL 14.8 ± 0.4; plasmacytic lymphomas 23.8 ± 4.05). By electrophoresis a pattern of undermodified tRNA species were found characteristic for the neoplastic cell type. These observations indicate the Q/G modification of tRNA may be important for proliferation and maturation in human lymphomas. The implications of Q/G modification for control of gene expression and treatment of lymphomas will be discussed.

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P 27 CYTOGENETIC AND IMMUNHISTOLOGIC PATTERNS IN LYMPHOGRANULOMATOSIS X (LGRX)/ANGIOIMMUNOBLASTIC LYMPHADENOPATHY.

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Seven cases with the histologic diagnosis of LgrX/AILD were studied by morphology and with cytogenetic as well as immunologic techniques.

Chromosome analyses with Q- and R-banding on unstimulated lymph node derived cells showed normal karyotypes in three cases. The other four cases had abnormal mitoses with structural as well as numerical aberrations beside cytogenetically normal cells. The structural abnormalities concerned chromosomes no. 2,3,4,5,9,13,16 and 20; there were no 14q+markers. The most frequent abnormality was trisomy 3, complete in two cases and partial in one. In concordance with reports of the literature on cytogenetic patterns in AILD and malignant lymphomas the four cases with chromosomal abnormalities are considered as neoplastic proliferations while in the other three the normal chromosomal patterns would also be in agreement with 'non-malignant' proliferations.

Beside the chromosome analyses immunhistochemical studies with a panel of 20 different monoclonal antibodies were done. Independently from the cytogenetic studies it was attempted to divide the seven cases studied according to their immunhistologic features into neoplastic and 'non-neoplastic' proliferations. This division was based primarily on the number of proliferating cells (Ki 67) as well as their phenotype and on the distribution pattern of dendritic reticulum cells (Ki-M4b). Three of the four cases with chromosomal abnormalities were considered neoplastic while the fourth one was considered 'non-neoplastic'. The three cases with normal karyotypes appeared also as 'non-neoplastic' proliferations.

On the basis of these findings it might be concluded that LgrX/AILD is a heterogeneous group of lymphoproliferative diseases. There appear to be primarily neoplastic (T-cell) proliferations beside primarily 'non-neoplastic' proliferations that might develope to B-immunoblastic lymphomas. Implications of these findings will be discussed with regard to the role of chromosomal abnormalities in LgrX/AILD.

P 28 Use of In Situ Hybridisation in the Classification of Malignant Lymphoma

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Malignant lymphomas are heterogeneous with regard to cellular phenotype, lymph node architecture, response to therapy and duration of survival. In an attempt to understand this heterogeneity and to improve upon the inherently subjective nature of descriptive pathology, emphasis has been placed upon the development of objective methods for characterising the origin and function of lymphoma cells. One such approach has been the development of monoclonal antibodies (MAb) that distinguish various classes of T and B cells. Such distinctions have proven useful in the management of acute lymphoblastic leukemia, and the use of this approach in the management of patients with lymphoma is now being investigated. Though promising there are a number of factors that limit the usefulness of MAbs. First, MAbs work best on fresh specimens as opposed to fixed material. Secondly cell sorter analysis of tumour cells, though rapid, results in loss of lymph node architecture and makes it difficult to distinguish the normal from the malignant cell. This problem has in part been overcome by applying MAb to frozen sections of lymph nodes. One method for circumventing both these difficulties is the use of in situ hybridisation to cellular mRNA with molecular probes.

This technique may be applied to fresh, formalin, acetone, or B fixed paraffin embedded specimens. The application of the technique requires: 1) high retention of cells on the slide; 2) the ability t permeabilise the cells to the probe; 3) the availability of highly sensitive detection techniques; 4) the availability of specific molecular probes that can distinguish various types of cells.

Probes against the immunoglobulin genes are readily available. Recently one of us (TM) has constructed a cDNA library using mRNA from a human T cell leukemia cell line. Using differential hybridisation with T cell and B cell mRNA several T cell specific clones were identified; one of these is the putative T cell receptor.

We have now established the conditions for in situ hybridisatio to paraffin embedded sections and are beginning to employ this technique to characterise patient lymphoma cells. In two patients studied a constant region probe and a T cell specific probe, as identified above, labelled with P^{32} were used. The phenotype of th patients' cells is shown.

	Calla	Ia	T101	Heavy Chain Rearrangement	μH.C. mRNA	T Cell Specific mRNA
Pt. 1	+	+	+	+	+	-
Pt. 2	+	+	+	-	+	+

This study demonstrates the ability to detect specific mRNA within lymphoma cells. The significance of these findings will require the study of a large group of patients and the development ar use of other probes, however this approach is feasible and has the advantage that fixed tissue sections are amenable to study.

P 29 QUANTIFICATION OF THE cμ CODING mRNA AS AN INDEX OF THE ACTIVATION OF THE IgM GENE IN NORMAL AND NEOPLASTIC LYMPHOID CELLS.

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Cells from two normal donors, two B-CLL's, a T-CLL, a T-ALL, and a CALLA-positive ALL were investigated for their cμ mRNA content and their IgM expression simultaneously. For this purpose individual cells were in situ hybridized with cloned rhodamine-labeled DNA and stained with fluorescein-labeled anti-IgM and measured for both labels microfluorimetrically.

It could be shown that the cμ mRNA content was correlated with IgM expression in individual normal B-cells, in cells of a μ-positive B-CLL; μ mRNA was lacking in cells of a κ-positive B-CLL and the T-CLL. High amounts of cμ mRNA could, however, be traced in a fraction of IgM-negative peripheral blood lymphocytes of a IgM negative T-ALL and in all cells of a common ALL.

The presented method provides a tool for the determination of the extend of IgM DNA activation in individual cells and allows to compare it to the realization of IgM in and on the cell. Thus it will help to analyze and classify normal and neoplastic lymphoid cells.

P 30 CHROMOSOME ABNORMALITIES IN NON-HODGKIN LYMPHOMAS:CORRELATION WITH IMMUNOLOGICAL PHENOTYPES AND CLINICAL EVOLUTION. I.

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Cytogenetic studies in malignant lymphomas have shown that some of the abnormalities observed are not at random. However, there are only few reports which correlate karyotypes with their immunological phenotypes and median survival. In this study, chromosome analysis was performed in 32 non-Hodgkin's lymphoma (NHL) cases and in 22 of them the immunological phenotype was done simultaneously. Lymph nodes were classified as: low grade (13), intermediate grade (12) and high grade (7) of malignancy, according to Working Formulation. For cytogenetic study, lymph nodes were cultured in medium F-10 with 15% fetal calf serum. Chromosome analysis with G-banding technique was performed and chromosome identification followed the International System for Human Nomenclature (ISCN). The following lymphocyte markers were determined: receptor for sheep erythrocytes, C_3, mouse erythrocytes and presence of surface and cytoplasmic immunoglobulins. Surface antigens were investigated using monoclonal antibodies of the OK series: T_1, T_3, T_4, T_6, T_8, T_9, T_{10}, T_{11}, Ia_1 and M_1. All karyotypes were abnormal. Clones were found in 83.4% of the patients, of which 81.5% had marker chromosomes and the remaining 18.5% had numerical abnormalities. Chromosome #1 and #14 were involved rather frequently in our cases (31.2% and 34.4%, respectively). Seventy percent of the patients with abnormalities of chromosome #1 showed a duplication of part of its long arm. Marker chromosomes 4p-,3q+,2q+,6q-,11q-, i(11q) and i(21q) were also found. With respect to surface marker, 10 (45.4%) nodes were of B-cell type, 10 (45.4%) were of T-cell type and 2 (9.2%) were of null-cell type. Forty percent of those of B-cell type expressed λ light chain, of which 75% were associated to duplication of part of 1q. Two cases of del(4)(p15) and 1 case of del(6)(q21) expressed T-cell type, the remaining 2 patients with del(4)(p13) had B-cell type, one associated with λ light chain and the other one with κ light chain. The patients were divided into 2 groups: those who only presented cells with abnormal karyotypes (AA) and those in which cells with abnormal and normal karyotypes (AN) were found and their actuarial survivals were compared by the Logrank test. The (AA) group had a median survival (15 months) significantly shorter ($P < 0.02$) than that of the (AN) group (52 months). The multiple chromosome abnormalities observed in NHL make it very difficult for them to be correlated with the immunological phenotype. However, in our study we have found an association between λ light chain and the duplication of part of 1q. As regards the median survival of the patients, our data indicate the importance of the presence of normal karyotypes (AN) in the clinical evolution.

P 31 DENDRITIC RETICULUM CELL; A GIANT CELL?

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Dendritic reticulum cells (DRC) have been described in cell suspensions of lymphoid tissue as multinucleated giant cells. In tissue sections however, a large proportion of DRC appears to be binucleated. This difference in appearance prompted us to study the three dimensional morphology of DRC.

DRC could be recognized in touch imprints of tonsils on basis of the morphology and typical doublet arrangement of their nuclei. In cytocentrifuge preparations of enzymatically prepared cell suspensions binucleated DRC-like cells were present free or in complexes with lymphoid cells. Larger complexes contained one or more pairs of nuclei apparantly belonging to DRC. The staining pattern of DRC-like cells for ecto-5-nucleotidase, alpha-naphthyl acetate esterase and acid phosphatase differed from that of macrophages. A number of DRC-like cells stained positive for alkaline phosphatase; whereas macrophages were negative for this enzyme.

Ultrastructurally,isolated DRC-like cells had a striking similarity with DRC present in germinal centres. In smaller complexes the cell body of DRC partially enclosed centrocytes and centroblasts with broad cytoplasmic protrusions leaving openings at one pole of the complex. Remarkably, lymphocytes were observed, adhering at the surface of the complex. Larger complexes of DRC and lymphoid cells were composed of more than one DRC cell body, indicated by the presence of desmosomes and of plasmamembranes separating the nuclei.

From these results it may be concluded that DRC are mostly binucleated cells. Their giant cell appearance in cell suspension is the result of complex formation with other DRC and with germinal centre cells. Membrane contacts between DRC and germinal centre cells may contribute to this complex formation. The close connection between these cells of different origin suggests that DRC influence the B-cell differentiation within the germinal centre by direct cell contact.

P 32 MACROPHAGE-HISTIOCYTES IN HODGKIN'S DISEASE: THE RELATION OF PNA-BINDING MACROPHAGE-HISTIOCYTES TO CLINICO-PATHOLOGIC PRESENTATION AND COURSE OF DISEASE

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We studied the occurrence of PNA binding cells in paraffin embedded specimens of 145 patients with Hodgkin's disease. The staining reaction of lymphocytes was consistently negative. A positive staining reaction was observed in two types of cells: macrophage-histiocytes (M-H), and Reed-Sternberg cells and their variants. Diffuse or globular cytoplasmic staining was found in M-H, which was easily distinguished from a unique "cell surface and cytoplasmic" staining pattern of Reed-Sternberg and related cells.* M-H, thus defined, were numerous in lymphocyte depletion and mixed cellularity, less common in lymphocyte predominance and least frequent in the nodular sclerosis type. Numerous M-H correlated with B-symptoms and a poor response to therapy. Among the asymptomatic patients with localized disease at presentation, the presence of M-H in large numbers was associated with a high incidence of relapse within two years of therapy. These findings suggest that the number of M-H, defined by a diffuse or globular cytoplasmic staining pattern of PNA, may be an important determinant in the clinical presentation and course of Hodgkin's disease. PNA staining may be useful for the detection of M-H in the routine diagnosis and classification of Hodgkin's disease, which has not been feasible by conventional methods.

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* Ree HJ and Kadin ME: Distinctive PNA-binding patterns of neoplastic cells in Hodgkin's disease: Comparison with non-Hodgkin's lymphomas and reactive lymph nodes. (Submitted for publication).

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P 33 MALIGNANT LYMPHOMA, SMALL LYMPHOCYTIC TYPE (WELL DIFFERENTIATED LYMPHOCYTIC LYMPHOMA), WITH MACROPHAGE-HISTIOCYTES

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We studied the occurrence of Ricinus communis agglutinin (RCA)-binding macrophage-histiocytes in paraffin embedded tumor tissue of 38 patients with malignant lymphoma, small lymphocytic type, a tumor of low grade malignancy. Thirty-one patients (82%) had an indolent clinical course and were free of disease for a minimum follow-up period of 24 months. However, seven patients (18%) died of rapidly progressive disease within 24 months of biopsy. Histologically, the tumors of these short-term survivors were indistinguishable from those of the long-term survivors. RCA staining of paraffin embedded tumor tissue of the 38 cases revealed three groups of tumors: 1) tumors with numerous (>10/HPF) stromal macrophage-histiocytes (4 patients); 2) tumors with a moderate number (4-9/HPF) of macrophage-histiocytes (5); 3) tumors with rare or no (0-3/HPF) macrophage-histiocytes, or only thin, anuclear variants (29). Of the seven short-term survivors, four had numerous macrophage-histiocytes in their tumor and three had a moderate number, while in 29 of the 31 patients who had an indolent clinical course, RCA-binding macrophage-histiocytes were either rare or absent, or were anuclear variants. These observations suggest that in malignant lymphoma, small lymphocytic type, there is a subgroup characterized by aggressive behavior of the tumor and an increased number of stromal macrophage-histiocytes. Tumors of this subgroup can be detected by RCA staining.

P 34 NON-HODGKIN'S LYMPHOMAS ASSOCIATED WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME.

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Persistent lymphadenitis in homosexual men preceding or associated with the acquired immune deficiency syndrome has been previously reported. Within the past 3 years we have studied in our department 54 such cases. During this time we observed 8 cases of non-Hodgkin's lymphoma in the same population of homosexual men. The mean age of patients with lymphoma was 44, ranging between 38 and 48 years as compared with a range of 20 to 44 and a mean of 32.9 years in those with lymphadenitis. All patients had histories of multiple sexually transmissible infections, as well as some of the infections associated with AIDS. At least 5 of 8 patients had preceding or concomittant lymphadenitis. The non-Hodgkin's lymphomas were primarily located in peripheral lymph nodes in 2 cases, visceral lymph nodes in 1 case, small intestine in 3 cases, bone marrow and pericardium in one case each. Four lymphomas were of diffuse, large, cleaved cell type,one of diffuse, large, non-cleaved cell type, one of diffuse small cleaved cell type, one of small plasmacytoid cell type and one of undifferentiated Burkitt's cell type. Mitoses were numerous and necrosis was common. Five lymphomas showed monoclonal immunoglobulin labeling. Bone marrow involvement was present in two cases, peripheral blood and liver in none. Excepting the cardiac lymphoma which was fatal, all others showed an initial response to chemotherapy.

P 35 NEOPLASTIC-APPEARING LYMPHOID CELLS WITH CLONAL ROSETTES IN PRISON-ACQUIRED LYMPHOPROLIFERATIVE SYNDROME (PALS).

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Previous reports describe the clinical, cytogenetic and immunologic data on ten cases of generalized lymphadenopathy in PALS (Han et al: Blood 62; Abst. 345-6, 1983). Seven prisoners were intravenous drug users but only one was homosexual. Leu-2a$^+$/OKT8$^+$ suppressor/cytotoxic cells were increased in lymph node frozen sections of 5 of 5 cases tested and human T-cell leukemia/lymphoma virus (HTLV) proteins or anti-HTLV antibodies were detected in 5 of 6 patients tested. Two of 5 cases had clonal chromosome abnormalities, i.e. +11q- and -11, respectively, and another had multiple non-clonal chromosome changes, including t(2p-; 3q+), 6q-, +12,14q+. Since these chromosome changes are often found in malignant lymphomas, a detailed histologic and cytologic study was made in order to ascertain whether associated morphologic abnormalities could be found. Ultrastructural studies were available in two cases. The ten lymph node biopsies showed a benign-appearing lymphoid hyperplasia with florid reaction center formation in nine. Varying degrees of plasmacytic, eosinophilic and endothelial cell hyperplasia were also noted. Two cases had a prominent focal epithelial histiocytic reaction and 4 cases had focal proteinaceous deposits. Of special note were the presence of sparse and subtle abnormalities in the interfollicular (T-zone) areas, including atypical cleaved cells and immunoblasts and three cases showed rare, previously unnoted, clonal clusters of neoplastic-appearing lymphoid cells which were arranged occasionally in rosettes. In addition, imprints of 6 of 8 cases showed small numbers of abnormal to bizarre lymphoid cells with polyploid, lobulated, serrated, fragmented or shattered nuclei. The clonal rosettes and abnormal lymphocytes may represent HTLV-transformed cells with chromosomal abnormalities.

P 36 DOMINANTLEY INHERITED IMMUNODEFICIENCY SYNDROME ASSOCIATED WITH NON-HODGKIN'S LYMPHOMA AND DEFICIENT NATURAL KILLER CELL ACTIVITY.

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Immunodeficiency states which are associated with an increased incidence of lymphoma usually have an x-linked recessive form of inheritance. The x-linked lymphoproliferative syndrome is the most intensively studied and demonstrates a variable phenotypic expression of immunodeficiency and lymphoid proliferation coupled with a defect of natural killer cell activity. In the present report a kinship is described in which the immunodeficient state follows a dominant inheritance with father and three sons affected. The sons are triplets (one non-identical). The two identical triplets developed a classical pattern of common variable immunodeficiency during the third decade. Both subjects demonstrate a marked reduction of immunoglobulin subclasses and both are Coombs positive. Other autoantibodies are not expressed. Both demonstrate B lymphocyte numbers towards the lower limit of normal and also reduction in absolute numbers of T cells with disturbance of OKT4:OKT8 ratio. Assessment on the same two individuals in vitro using PHA, Con A, poke weed mitogen and PPD stimulation indicate variations in response between the two individuals, with one subject showing marked impairment to poke weed mitogen and another showing PHA response defects. Both subjects demonstrated gross impairment of NK activity against K562 target cells and ADCC activity was similarly impaired against Chang liver cells. The non-identical triplet in 1979 demonstrated normal levels of immunoglobulin and was Coombs negative. In 1982 he presented with anaemia having become Coombs positive and also at this time demonstrated reduction of all immunoglobulins. This presentation coincided with the development of a rapidly progressive lymphoblastic lymphoma. NK cell activity in this subject was impaired, but ADCC activity relatively well preserved. The father in the family has been known to be prone to infections throughout his life and to have splenomegaly for several years. This subject has a normal haemoglobin and platelet count but is markedly granulocytopenic with a total white count of 0.9 x 10^9/l. NK and ADCC activity are markedly reduced in this subject. Mother and two other sibs within the family are immunologically normal in every respect.

This kinship represents striking similarities to the findings seen in x-linked lymphoproliferative syndrome but represents a variant of this form of immunodeficiency having a dominant inheritance pattern.

P 37 WALDEYER'S RING LYMPHOMAS- A STUDY OF 83 CASES FROM THE MIDDLE EAST.

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Eighty three cases of lymphoma involving the Waldeyer's ring (WR) at presentation were diagnosed at the AUBMC during the period 1955-1983 and were retrospectively studied. Median age was 45 years. Male/female ratio was 1.9/1. The most frequent sites of involvement were the palatine tonsils (63%) and the nasopharynx (26%). Involvement of palate and base of tongue occurred in 8% and 3% respectively. Gastro-intestinal involvement at presentation was described in 2 out of 11 patients who had radiological work-up. Of 11 other patients who had a long term follow-up, 5 developed gastro-intestinal involvement at a later point in the course of the disease. Thirty seven patients were adequately staged including lymphangiography and bone marrow biopsy. Of these, 28% were stage I (limited to WR); 33% stage II (involvement of neck nodes); 8% stage III and 31% stage IV. Bone marrow biopsy was negative in all patients who had apparently clinical stage I and II. Lymphangiography and/or ultrasound of abdomen and pelvis were positive in 11% of such patients. All patients had non-Hodgkin's lymphoma except one who had Hodgkin's. According to Rappaport's classification, diffuse histiocytic lymphoma (DHL) occurred in the majority of cases (72%). 8% of patients had undifferentiated lymphoma and all had stage IV at presentation. 80% of adequately staged patients with DHL had stage I or II at diagnosis. One patient who is not included in this study developed WR lymphoma 28 months after an initial diagnosis of gastric lymphoma was made. Tissues from both sites revealed similar histopathological features (DHL). In conclusion, the overwhelming majority of our patients with Waldeyer's ring lymphoma had a potentially curable disease (DHL).

P 38 PERIPHERAL T LYMPHOMAS: CLINICAL, MORPHOLOGICAL, AND IMMUNOLOGICAL DIVERSITY IN 24 CASES.

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24 patients with nonlymphoblastic, nonepidermotrophic T-lymphoma were encountered in 4 years among 200 patients with lymphomas (85 were not studied immunologically). In all cases, the T origin was proved by monoclonal sera, either on cell suspensions, or by electron microscopic study.

The initial presentation was: peripheral adenomegaly (12), mediastinal tumor (3), abdominal tumor (5), cutaneous localisation (3), pulmonary mass (2). The bone marow was pathologic in 7 cases, and the blood in 3 cases. In 15 patients, it existed symptoms. All the lymphomas were diffuse and classified as intermediate or aggressive in the Working Formulation: diffuse small cells: 3, diffuse mixte, polymorphous: 3, diffuse mixte + epitelioid cells: 3, large cells: 5, immunoblastic: 4, LAI-like: 6. In 15 out of 15 patients studied there were E-rosettes with pathological cells. 23 patients were T3 +, but only 18 were T8 +. One patient was T4 +.

2 patients presented a transformation of a Sezary syndrome, and three were treated initially as an angio-immunoblastic lymphadenopathy. 15 patients were treated by the sequential chemotherapy protocol "CHOP-Bleo" as the first treatment: 4 failure, 3 death due to toxicity of the chemotherapy, and 9 complete remission with only 1 relapse (median follow-up 16 months). 7 patients were treated with other chemotherapy: 6 failure, and 1 complete remission. 3 patients were not treated: 2 rapidly died.

Nonlymphoblastic peripheral T lymphomas are emerging types of malignant lymphomas with characterstics different of those encountered in B lymphomas. These T lymphomas necessitate large studies to describe their evolutivity, and the treatment(s).

P 39 LIGHT CHAIN ISOTYPE ASSOCIATED SUPPRESSION OF SURFACE IMMUNOGLOBULIN EXPRESSION ON PERIPHERAL BLOOD LYMPHOCYTES IN MYELOMA DURING PLATEAU PHASE

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The aim of this study was to determine immunoglobulin light chain isotype expression of peripheral blood B lymphocytes in patients with myeloma in plateau phase (defined as 6 months of clinical and laboratory stability). Twenty patients with myeloma in plateau phase were monitored over a period of 6 months for the expression of either the kappa or lambda light chains on the surface of peripheral blood lymphocytes using monoclonal anti-kappa and anti-lambda antibodies. Accurate numerical quantitation of these cells was obtained by using an Ortho Spectrum III Flow Cytometer. Ninety-six normal blood donors were used to determine the normal range of kappa and lambda ratios and absolute number of kappa and lambda cells. Of the 20 patients with myeloma in plateau phase who were studied, six were still on maintenance therapy. Kappa/lambda ratios of normal blood donors was found to lie between 0.5 and 4 (mean 1.55 ± S.D. 1.5). Thirteen patients had kappa myeloma and 7 had lambda myeloma. There was a mixture of both IgG and IgA heavy chain paraproteins, but none had IgM heavy chains. There was a significant difference in the kappa/lambda ratios of the control group to both types of myeloma. The ratios, however, remained stable during plateau phase. Kappa myelomas had a lower kappa/lambda ratio (mean 0.76 ± 0.40) and lambda myelomas a higher kappa/lambda ratios (mean 4.1 ± 2.7) than controls. These findings were similar to the observations of Leonard et al 1979, i.e. that there seems to be selective suppression of the light chain isotype coincident with the malignant paraprotein in myeloma. This finding, however, does not occur in active myelomatous disease. We have monitored patients with unstable myeloma who have demonstrated with increasing disease progression, changing light chain changes of those of stable myeloma to predominance of lymphocytes bearing the malignant light chain isotype. Four patients with monoclonal gammopathies of uncertain significance have also been studied, 3 were found to have normal kappa/lambda ratios and have remained indolent. One with a kappa/lambda ratio of 0.15 at presentation subsequently developed kappa myeloma within nine months.

The main finding of this study has been the presence of relative suppression of the light chain isotype on peripheral blood lymphocytes in patients with myeloma. This may reflect homeostatic control of myeloma in plateau phase at the differentiation stage of B cell development prior to the development of plasma cells. The development of new antibodies which recognise plasma cell and B cell differentiation antigens e.g. the K-1-1, antibody (Boux et al 1983) will allow further investigations of putative control mechanisms.

References
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P 40 MONOCLONAL GAMMOPATHY: CLINICOPATHOLOGIC AND CYTOGENETIC FINDINGS.

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Thirty-seven patients with monoclonal gammopathy have been followed for periods ranging from 18 to 139 months. Using the International Formulation there were 27 Low Grade lymphomas (1 small lymphocytic, 15 chronic lymphocytic leukemia - CLL, 6 plasmacytoid small lymphocytic, 5 follicular small cleaved cell), 9 Intermediate Grade lymphomas (3 diffuse small cleaved, 3 diffuse mixed cell lymphomas with epithelioid cells, 3 diffuse large non-cleaved cell) and 1 High Grade lymphoma (large cell, immunoblastic, plasmacytoid). Death rates for the CLL and plasmacytoid small lymphocytic lymphomas at 3 yrs. (20% vs. 17%) or 5 yrs. (38% vs. 33%) did not differ significantly. The 3-year death rates for Low Grade follicular and Intermediate Grade diffuse lymphomas were 25% and 44%, respectively; the corresponding values at 5 yrs. were 50% and 78%, respectively. Ten patients had serum immunoglobulin IgG type and 20 had IgM type. Their 3-yr. death rates were 0% and 35%, respectively; the corresponding 5-yr. values, however, were 67% and 43%, respectively. In nine patients the serum light chain immunoglobulin was of λ type and in 22 of κ type. Their 3-yr. death rates were 0% and 35%, respectively, and their corresponding 5-yr. death rates 34% and 57%, respectively. The above findings suggest that lymphoproliferative disorders associated with secreted heavy-chain-bound λ light chains in the serum may have a relatively favorable course. However, we reported earlier in CLL patients (Gajera et al, ASCO Proc., 2: 176, 1983, Abstr.) an absence of correlation between lymphocyte membrane-bound Ig light chain type and survival. In contrast, other reports in CLL (Hamblin and Hough, Brit. J. Haemat. 36: 359, 1977; Mellstedt et al, Acta Med. Scand. 204: 485, 1978) suggest that the expression of cell surface λ may be less favorable than κ light chains.

Two of our patients had a biclonal IgG and IgA gammopathy: one is alive at 20+ mos. and the other is dead at 34 mos. Two patients with γ-heavy chain disease died at 56 mos. and 132 mos., respectively, and one patient with α-heavy chain disease died at 28 mos. Two patients had free immunoglobulin light chains in the serum in the absence of demonstrable heavy chains; the one with λ died at 32 mos. and the one with κ at 129 mos. A report in patients with multiple myeloma (ALGB, Arch Int. Med. 135: 46, 1975) indicated also that λ-Bence-Jones protein production was associated with a less favorable course.

Nine of our 11 (82%) patients with CLL and 4 of 8 (50%) patients with malignant lymphoma had chromosomal abnormalities. Trisomy 12 was noted in 7 of 9 (78%) CLL cases, with or without other abnormalities. It was previously reported (Han et al Blood 62: No. 5, Suppl., 1983, Abstr.) that trisomy 12 (single abnormality) in CLL is not associated with a poor prognosis but that other abnormal karyotypes could be unfavorable prognostic indicators.

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P 41 IMMUNOBLASTIC LYMPHOMA: A CLINICOPATHOLOGIC STUDY ON 46 ADULT PATIENTS.

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A study was done on 46 previously untreated adult patients affected with immunoblastic lymphoma (IBL), to further analyze the clinicopathologic features, the response to therapy and survival. The diagnosis was done at the Institute of Pathology, University of Pavia, on lymph nodes (28 cases), tonsils (10), spleen (2), bone marrow (2), gastrointestinal tract (2), thyroid (1) and liver (1). IBL amounted to 12% of all cases of non-Hodgkin's lymphomas in our series (46 out of 369), classified according to the Kiel classification. The median follow-up was 12 mos (range 3-90+). Males were 32, females 14; the median age was 57 yrs; systemic symptoms were present in 39% of cases. Bone marrow involvement was evaluated by marrow aspiration and core biopsy; laparotomy was done in 5 cases with clinical stage I without systemic symptoms. The most frequent sites of initial extranodal involvement were: liver (41% of cases), spleen (37%), bone marrow (23%) and Waldeyer ring (20%). Initial stages (I-II) were 28%. Nine cases had limited extranodal disease: Waldeyer (6), GI tract (2), thyroid (1). Eight patients (17%) had a prior history of chronic infections (5 tbc, 2 toxoplasmosis, 1 malaria), 6 (13%) of immunological diseases (2 AIL, 2 rheumathoid arthritis, 1 thyroiditis, 1 Castleman disease) and 5 (11%) of prior lymphoproliferative neoplasias (3 chronic lymphocytic leukemia, 1 Waldenström's disease: 1 Hodgkin's disease). In 3 cases (7%) a shift from polymorphic lymphoplasmacytoid lymphoma was documented. Initial stages were treated with extended field radiotherapy (RT) and adjuvant chemotherapy (CVP for 6 cycles) while advanced stages with chemotherapy (CT) alone (BACOP regimen, NCI). No CNS prophylaxis was done. Forty-two patients were evaluable for therapy (I-II: 12; III-IV: 30). Overall complete remission (CR) rate was 36% (15 out of 42 cases); initial stages achieved CR in 67%, while advanced stages in 23% of cases ($p<0.01$). Nine out of 15 remitters have been treated with RT + adjuvant CT (8 were initial stages) and 6 with CT alone. Patients with disease limited to the Waldeyer ring achieved CR in 83% of cases after extended fields RT alone. The median survival for the whole group was 12.2 mos, but is not reached at 48 mos for remitters; all non-responders died within 30 mos from diagnosis. Median relapse-free survival is not reached at 48 mos and all 5 relapses occurred within the first year after CR. Patients with systemic symptoms fared significantly worse ($p<0.05$). Neurological involvement was seen in 4 cases (8%): epidural mass with paraparesis (1), posterior cerebral and cerebellular invasion (1), sympathic Bernard-Horner syndrome (1) and leukemic meningitis (1). In conclusion: a) an high percent of IBL (41%) had a previous history of chronic infections, immunological diseases, or prior lymphoproliferative neoplasias; b) in 7% of cases the IBL transformed from an original diffuse polymorphous lymphoplasmacytoid lymphoma (cytological shift); c) limited disease in the Waldeyer ring had a good prognosis when treated with extended fields RT and adjuvant CT; d) advanced stages had a very poor prognosis; e) all relapses occurred within 12 mos since CR; f) neurological involvement was infrequent and CNS prophylaxis does not seem necessary.

P 42 CLINICAL FEATURES OF THE HTLV-RETROVIUS ASSOCIATED ADULT T-CELL LYMPHOMAS IN THE UNITED STATES:

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The clinical course of 14 patients with adult T cell lymphomas associated with the human T cell lymphoma virus was reviewed. All patients had serum antibodies specific for HTLV, additionally virus was isolated from cultured cells of 8 patients. The majority of patients were young (median age 40 years), black (10 patients), and born in the Southeastern United States (8 patients). All patients presented with skin lesions, hypercalcemia, or both. The onset of symptoms was abrupt in all but two patients; these 2 also had a more indolent course. Skin and lymph node biopsies revealed diffuse large cell, mixed or poorly differentiated small cell lymphoma in all patients. Malignant cells had phenotypic characteristics of mature activated helper T cells (T11+, T1+, T4+, T8-, anti-Tac+, Tdt-). All patients had stage IV disease with involvement in the following sites: peripheral lymph nodes (1/14), retroperitoneal lymph nodes (6/10), mediastinal lymph nodes (1/14), skin (9/14) gastrointestinal tract (4/14), central nervous system (4/14), lung (5/14), bone (4/14), and bone marrow (6/14). Hypercalcemia was present in 12; these 12 had metabolic bone abnormalities and 4 had lytic bone lesions as well. The 2 patients without hypercalcemia were the 2 with a more indolent course. A unique syndrome of bone resorption with increased bone tumor, and abnormal bone scintigraphy presumably caused by an osteoclast stimulating lymphokine was present in the 12 hypercalcemic patients. Perpheral blood involvement was present in 12 patients with a median white blood cell count of 20,000/ul and a range of 6,800 to 145,000/ul. Opportunistic fungal, viral or parasitic infections were documented in 8 patients while neutrophil counts were normal. Metabolic complications of high cell turnover and hypercalcemia including dehydration, hyperuricemia and renal failure were common. All patients were treated with combination chemotherapy including 8 who received the PROMACE/MOPP regimen. Rapid tumor shrinkage was noted in 12/14 patients, but only 7 patients achieved a pathologically documented complete response (3 after PROMACE/MOPP) and all but one relapsed subsequently. The central nervous system, the lungs and other sites of initial disease were the most frequent relapse sites. Secondary therapies with chemotherapy or monoclonal antibodies were unsuccessful except in the 2 patients with a more indolent course. The actuarial median survival was 13 months with 4 patients alive at 3,12,48 and 92 months. We conclude that prompt recognition of this high grade lymphoma is important, so that supportive and cytotoxic therapies are instituted promptly. Prophylaxis of the central nervous system is indicated as are new experimental treatment approaches.

P 43 PRIMARY HISTIOCYTIC LYMPHOMA OF SKIN AND SUBCUTANEOUS TISSUES.

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During the years 1970-1982, of 406 previously untreated patients (pts) with non-Hodgkin's lymphoma (NHL) who were referred to the Northern Israel Oncology Center, 15 pts (3.7%) presented with primary histiocytic lymphoma (or reticulum cell sarcoma) of the skin or subcutaneous tissues (HLS). The primary lesions were localized to the skin in 13 pts, to subcutaneous tissue in 1 pt, and to the buccal mucosal membrane in 1 pt. The skin lesions were either solitary (9 pts), 2 lesions in the same anatomical site (2 pts), or a few lesions in 2 or more anatomical sites (4 pts). In 6 pts the color was either red or purple-red. The morphology of the primary lesions was either a nodule (6 pts) or an ulcerated nodule (2 pts), tumors (2 pts) or ulcerated tumors (2 pts), or plaques (3 pts). HLS patient characteristics were compared to those of 391 pts with other NHL (ONHL). The mean age of HLS pts was higher, 60.1±16.2 y as compared to 50.3±22.7 y for ONHL ($p=0.1$, NS). The male/female ratio was 0.7:1 as compared to 1.3:1 for ONHL ($p=0.1$, NS). HLS tended to be either localized (40%) or widespread (53%). 314 pts of ONHL were classified according to Rappaport. 26.1% had diffuse histiocytic lymphoma, and 5.1% had diffuse mixed lymphoma. The HLS pts were treated by surgery followed by either radiation therapy to localized lesions or combined chemotherapy (mostly of CHOP regimen) for systemic disease. The complete response rate of evaluable HLS was 61.5% as compared to 72.8% of evaluable ONHL. The 2-year survival of the HLS complete responders was 100%, and 22.5% for the nonresponders. The corresponding figures for ONHL were 87.3% and 32.1% respectively. In our experience solitary HLS can be controlled by biopsy or excisional biopsy followed by radiation therapy. Widespread disease is fatal and should be treated by aggressive chemotherapy.

P 44 CLINICO-PATHOLOGICAL STUDY OF PEDIATRIC NON-HODGKINS LYMPHOMA IN EGYPT ACCORDING TO THE WORKING FORMULATION.

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Lymphomas; Hodgkins and non-Hodgkins (NHL) comprise about one half of pediatric malignancies presenting to NCI Cairo. This is a clinico-pathological study of the NHL cases of the year 1983. They were 47 cases; 33 males, and 14 females, a ratio of 2.35:1. Age ranged from 1.5-16, average 8 years. According to the working formulation, histopathology was as follows:

Low grade: -diffuse small lymphocytic 3

Intermediate grade:

-diffuse small cleaved 3 -diffuse mixed small and large 2

-diffuse large cleaved 3 -diffuse large non-cleaved 3

High grade:

Immunoblastic 4 Burkitts 23 lymphoblastic 6

All cases were of the diffuse type, with marked preponderance of the Burkitt type contrary to what was published before. Two of the lymphoblastic cases underwent leukemic transformation.

Primary extra-nodal presentation was encountered in 28 cases, while primary nodal was encountered in 19 cases. The extra-nodal involvement was: ileum and ileo-cecal 21, colon 1, ovary 1, parotid 1, testis 1, and jaw 6. Both jaw and abdominal were encountered in 5 cases. Staging (Murphy) revealed: stage I, 9 cases, stage II, 21 cases, stage III, 8 cases, and stage IV, 9 cases.

Management was by chemotherapy using the COMP therapy vincristine, cyclophosphamide, methotrexate, and steroids in stages I, and II, and adding adriamycin in stages III, and IV. Responders to induction therapy were given cranial prophylaxis followed by maintenance therpy. All abdominal lesions were surgically removed: ileal resection, hemi-colectomy, removal of the ovary, and testis. Two cases received abdominal irradiation post-operatively, followed by chemotherapy. Three patients died during induction therapy, and one patient died after CNS invovement, the other patients responded and are still receiving their treatment. Their results will be presented during the meeting.

P 45 CLINICOPATHOLOGIC AND IMMUNOLOGIC CHARACTERISTICS OF NON-HODGKIN'S LYMPHOMAS PRESENTING IN THE ORBIT: A REPORT OF EIGHT CASES.

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Several points concerning the pathogenesis and the natural history of ocular adnexal lymphoid neoplasms are still a matter of debate, namely the nature of the lymphocyte subsets involved, the histopathologic features of tumor and its relationship to nodal lymphomas. In addition, the basic question of whether or not orbital lymphoid tumors may originate primarily in the orbit or whether they represent localized manifestation of a subclinical systemic disease is not conclusively answered. We report the clinicopathologic and immunologic features of 8 cases of non-Hodgkin's lymphomas (NHL) presenting in the orbit. These patients are part of a series of 325 consecutive cases of NHL classified according to the Kiel system and staged using the Ann Arbor classification. The incidence of orbital presentation was 2.4% (8/325) and appeared to be confined to the low-grade malignant lymphomas as defined by the original Kiel classification: 7 cases of lymphoplasmacytic/lymphoplasmacytoid lymphoma (LP immunocytoma) and 1 case of centrocytic lymphoma. The clinicopathologic and immunologic analysis ot the eight patients revealed characteristic biologic features: 1. Seven of the 8 cases exhibited lymphoplasmacytic/lymphoplasmacytoid features, suggesting a preferential association of orbital involvement and plasmacytoid differentiation. 2. A thorough initial evaluation of the 8 patients provided evidence of systemic, although clinically silent, disease. Indeed, bone marrow involvement was detected by trephine biopsies in all cases. 3. Serum protein studies at the time of orbital presentation demonstrated a concomitant serum paraproteinemia in 5 of the 7 cases with plasmacytoid features. The serum paraprotein was invariably a mixed type II cryoglobulin with a monoclonal IgM possessing antibody activity towards polyclonal IgG. In addition, the monoclonal IgM had the same light chain of the corresponding lymphoma cells studied by immunohistochemical methods. 4. Four of the 7 cases of LP immunocytoma and the single case of centrocytic lymphoma showed skin infiltration by tumor. In conclusion, our data lend further support to the hypotesis that most orbital lymphomas, although apparently isolated, represent one focus of an already systemic process. In addition this study confirms that a remarkable proportion of orbital lymphomas share peculiar clinicopathologic characteristics, suggesting an origin from a minor B cell subset immunologically equipped to home preferentially to orbital tissues and subcutis. The identification of this variant of malignant lymphomas has clinical, diagnostic and therapeutic relevance.

P 46 PERIPHERAL T-8 LYMPHOMA IN CHILDREN: EVIDENCE FOR A DISTINCT CLINICO-PATHOLOGIC ENTITY

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We report the clinico-pathologic features observed in two female patients aging 5 and 16 who were affected by a T cell lymphoma apparently different from T lymphoblastic lymphoma. Both patients displayed fever, pancytopenia, hepato-splenomegaly and moderate multinodal enlargements; mediastinal involvement was not observed. The bone marrow biopsy revealed severe cellular depletion in one patient and maturation arrest of hemopoiesis in the other. The lymph node histology was highly reminiscent of a peripheral T cell lymphoma. The normal lymph node architecture was obliterated by a neoplastic cell population with high mitotic activity which spared only few lymphoid follicles located in the subcapsular zone. The majority of the neoplastic lymphocytes were small-medium sized and presented an irregular nucleus surrounded by a thin rim of pyroninophilic cytoplasm; few immunoblast like cells and occasional binucleated cells were present. Nuclear convolutions and dot-spot staining for acid-phosphatase were not present. A rich histiocytic component, some polyclonal plasmacells, few eosinophils and numerous capillary vessels were also part of the tumor. The immunological characterization revealed that 70-80% of the cells were T lymphocytes having the $E^+/T\text{-}11^+/T\text{-}3^+/T\text{-}8^+$ phenotype. The ultrastructural features of most of the lymphoid cells were reminiscent of cytotoxic T lymphocyte-NK cells since they contained a well developed Golgi apparatus and numerous electron-opaque granules; these cells however, failed to exert NK activity in vitro and did not react with Leu-7 and B-73 monoclonal antibodies which are supposed to be specific for NK cells. In one patient, a subsequent lymph node biopsy taken 6 months later revealed the existence of a T immunoblastic lymphoma in which $T\text{-}11^+/T\text{-}3^+/T\text{-}8^+$ lymphocytes were still the prevailing cell-type. Finally, $T\text{-}8^+$ lymphocytes of possible neoplastic origin were identified in the peripheral blood and in the bone marrow aspirates from both the patients. All these findings indicate the existence of neoplastic proliferations of granular $T\text{-}8^+$ lymphocytes in children presenting with a malignant histiocytosis-like syndrome. This entity may share some similarities with the T-γ lymphoma and with some "truly" neoplastic T-8 Chronic Lymphocytic Leukemia of the adult.

P 47 ROLE OF RESTAGING LAPAROSCOPY IN MALIGNANT LYMPHOMAS.

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From June 1973 to December 1978, 1237 staging laparoscopies with spleen and/or liver biopsies were performed in patients with malignant lymphomas (Br. Med. J., 4, 554, 1975; Am. J. Roentgenol. 127, 501, 1976). During the same interval 70 restaging laparoscopies (RL) were performed in patients with initial liver and/or spleen involvement after achieving clinical and radiological complete remission (Hodgkin's disease or HD 23 cases; non Hodgkin's lymphomas or NHL 47 cases). The data obtained are reported below:

No of CR_s with involvement of	HD No	HD %	NHL No	NHL %
Spleen (restaging/total)	0/14	-	4/11	(36.5)
Liver (restaging/total)	0/2	-	3/19	(15.5)
Spleen + liver (restaging/total)	0/7	-	3/17	(17.5)
TOTAL	0/23		10/47	(21.5)

In 8/10 NHL with residual disease at RL a subsequent laparoscopy, performed after 6 to 10 additional cycles of polychemotherapy, detected occult residual disease only in 3/8 cases (38.5%).
The data obtained seem to indicate: a) the high incidence of occult residual disease at RL (21.5%) indicates that RL is of high prognostic and therapeutic importance in patients with NHL, with initial spleen and/or liver involvement. In fact, the detection of residual disease avoids the risk of a too early discontinuation of effective therapy. b) RL is not mandatory in HD. In fact no residual disease was detected in all 23 patients evaluated, probably for the high incidence of complete response (about 80-90%) achieved in HD with conventional combination chemotherapy. However, this observation must be confirmed on a larger series of patients.

P 48 IMPACT OF TREATMENT ON THE PROGNOSTIC VALUE OF HLA PHENOTYPES IN HODGKIN'S DISEASE.

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In a previous study of 79 patients with Hodgkin's disease the compound HLA marker AW19 was found to be an additional risk factor in patients already in a poor prognosis category (age 40, or mixed cellularity or lymphocyte depletion histology, or stage III or IV disease) (Cancer 46:1825, 1980). The increased risk of dying was confined largely to marker-positive patients with Stage IIIA disease, all of whom had been treated with radiation only and all of whom died within 3 years of diagnosis. In an attempt to confirm these results, a group of 143 patients had HLA phenotypes determined between 1974 and 1978. Patients who were in the poor prognosis category and who had the AW19 marker were found to be at only a slightly increased risk of death by 3 years of diagnosis, the risk not being significant at the 0.05 level (P=0.15). However, since 1974, the compound marker AW19 has been split into the specificities A29, AW30, AW31 and AW32. Of the patients with these specificities who died all were noted to have only the specificities A29 or AW30 and not AW31 or AW32. When the results were reanalyzed and only the 10 patients with the specificities A29 and AW30 are considered, their risk of dying within 3 years of diagnosis (0.50) was significantly increased as compared to the risk in 72 patients not having these specificities (0.19) (P=0.03). In Stage IIIA disease only 1 of 4 patients having either A29 or AW30 died, whereas it was expected from the previous study that all should have died. The explanation for this discrepancy is a major difference in the treatment given to patients with Stage IIIA disease in the two studies. In the confirmatory study all the Stage IIIA patients received treatment with both radiation and chemotherapy, whereas in the previous study they had received radiation only. We conclude that the specificities A29 and AW30 give additional prognostic information in a subgroup of patients with Hodgkin's disease having other known poor prognosis variables. However, appropriate treatment can improve survival despite the presence of adverse HLA prognostic factors. The latter observation is analogous to other observations showing that improvements in therapy have reduced the impact of such adverse prognostic factors as stage and histology.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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EPIDEMIOLOGY OF HODGKIN'S DISEASE IN NORTHERN ISRAEL, 1971-1980. Y. Cohen, N. Haim, M. Ben Shachar, R. Epelbaum, Y. Ben Arie, E. Robinson. The Northern Israel Oncology Center and Department of Pathology, Rambam Medical Center, Technion Faculty of Medicine, Haifa, Israel.

During the period 1971-1980, 139 previously untreated patients (pts) with Hodgkin's disease (HD), were referred to the Northern Israel Oncology Center (NIOC) for evaluation and treatment. The NIOC referral area is populated by one million, one third of whom are Arabs. The patients were grouped to three ethnic groups: Ashkenazi Jews (AJ), mostly European born Jews and their descendants, Non-Ashkenazi Jews (NAJ), Jews who were born in Islamic countries and North Africa and their descendants, and Arabs (Muslims, Christians and Druze (A). 133 pts were considered eligible for this study, 123 of them were histologically classified according to Lukes. There were 63 AJ (47.4%), 29 NAJ (21.8%) and 41 A (30.8%). The male/female ratio was 1.25:1, 1:1 and 1.7:1 for AJ, NAJ and A respectively (NS). The mean age for AJ, NAJ and A was 39±20.1, 27.4±11.8 and 26.9±17.1 years respectively (AJ vs NAJ or A p=0.01). The final stage of disease of the patients was: Stage I 17%, II 38%, III 30.5% and IV 14.5%. There was no difference in stage distribution among the different ethnic groups. 23 pts (18.7%) had lymphocytic predominance (LP), 42 pts (34.1%) had nodular sclerosis (NS), 50 pts (40.7%) had mixed cellularity (MC) and 8 pts (6.5%) had lymphocyte depletion (LD). The MC/NS was 1:1 for AJ, 1.3:1 for NAJ and 2:1 for A (NS).
In the age group 0-15 y, Arabs had twice the incidence of HD as compared to Jews. However, in the 15-20 y age group the reverse was observed. The highest incidence of HD in Jews was between 15y and 30y; in Arabs the peak lagged 5 years. There was no second peak of incidence for either Jews or Arabs. The pattern of subtypes was similar in the different groups, although LP was less common in the age group 0-35y. The 5y actuarial survival according to Stage was I-95.8%, II-83.7%, III-68% and IV-35.8%. The 5y survival for the whole group was 74.7%. For patients diagnosed in the years 1971-75 it was 66.5%,and 80.7% for those who were diagnosed and treated in the years 1976-80 (p<0.1). There was no significant difference in survival of the various ethnic groups. Histologic subtype did not affect survival (for LD, numbers were too small). Children under 16y of age survived best (100% at 5y). In the age group 16-50 it was 77.8% but only 40.9% for pts ≥40 years (p<0.001). In Non-Hodgkin's lymphoma we indicated a significant difference of age, sex, histologic subtype distribution, extranodal localization and survival among the various ethnic groups in Northern Israel. This observation was not found in HD - although some differences emerged.

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LYMPHOCITE-DEPLETION HODGKIN'S DISEASE - Report on 41 cases.

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Clinical features and post-treatment course of 41 patients referred with Hodgkin's disease of the lymphocyte depletion type (LDHD) between 1960 and 1980, were retrospectively analysed.
The male/female ratio was 0.95; mean age was 35 yrs; 5 patients were aged less than 15 yrs; constitutional symptoms were present in 23 (56%); a mediastinal adenopathy was present in 26 (63%) and out of them 15 had a large mediastinal mass; a contiguous extralymphatic involvement was found in 9 (3 in the lung, 3 in the bone, 3 in the skin). Distribution according to the clinical stage was as follows: 10 in stage I & II A, 11 in stage I & II B, 6 in stage III A, 6 in stage III B, 8 in stage IV. Subclassification in reticular (R) and diffuse (D) fibrosis was possible in 32; a higher number of patients presented an advanced stage (III & IV) in the group with the R subtype (10/15) than in the group with the D subtype (5/17); a similar distribution was found for the other clinical features.
After the primary treatment a complete remission was achieved in only 21 patients; 2 presented an incomplete remission; 17 showed a progression of disease and 15 out of them died shortly within 12 months after treatment. Fourteen patients were alive with no evidence of disease (NED) after a minimum follow up of 3 yrs. The NED figures were 9/21 for patients in stage I & II, 2/6 for patients in stage III A, 2/6 for patients in stage III B, 1/8 for patients in stage IV.
Clinical presentation features and survival of this LDHD group were compared to those of the patients with HD of the other hystologic types treated in the corresponding period. Comparison demonstrated that patients with the LD hystologic type had more often an advanced stage, unfavourable signs as the presence of constitutional symptoms, of a large mediastinal mass, of extralymphatic involvement and that they had an overall worse prognosis. Furthermore LDHD patients were more likely not to achieve a complete response after the primary treatment and to present an unusually rapid and fatal course.

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HODGKIN'S DISEASE: IMPROVED RISK FACTOR PROFILE ANALYSIS FOR OPTIMAL PATIENT MANAGEMENT. Guy B. Faguet and Harry C. Davis, Medical College of Georgia and VA Medical Center, Augusta, GA, USA

The management of Hodgkin's disease (HD) traditionally calls for selection of treatment modality and intensity depending on a stage-based clinical triad including histopathology and symptoms; in general, patients with early stages (I/II) are given radiotherapy; those with late stages (III/IV) received chemotherapy. While the latter was, early on, thought to be mostly palliative, it is now demonstrably curative in over 50% of cases so treated (V. DeVita, et al. Ann. Int. Med. 92:595, 1980), and has been suggested to be as effective as radiotherapy in early stages (C.L.M. Olweny, et al. Cancer 42:787, 1978). Thus, aggressive staging might be less crucial than once thought for optimally managing these patients. Furthermore, we recently demonstrated that risk factors uncovered by regression analysis of HD data exhibit greater discriminant power than stage in predicting outcome (Blood, 59:938, 1982). The current study was undertaken for cross-validation purposes and to generate a panel of discriminant models as an alternative to the stage-based clinical triad. We examined the correlation of 47 variables with the dependent variables; complete remission, survival and cure rates, (unmaintained remission > 6 years) in 87 previously untreated patients with HD. Patients were predominantly white (72%), males (52%), with symptomatic (62%) nodular sclerosing or mixed type (87%) disease in stages III/IV (65%) , the latter established according to accepted staging criteria including lymphography (64%) and laparotomy (49%). Treatment according to accepted guidelines led to complete remission in 72% of patients. Fifty-eight percent are alive (mean survival 87 months) and 42% died (37% of or with HD, and 5% without, all but one confirmed at autopsy). Twenty-seven variables found to correlate with survival, remission or cure rates were used to generate several hundred discriminant models. Of these, 28 are retained because of their highest correlation coefficients (R) and their greatest generalizability to future Hodgkin's populations. Ten models (10-14 variables each) correlated with complete remission (R=.59-.63) and showed correct case classification (CCC) of 79%-82%. Ten models (8-12 variables each) correlated with survival (R=.56-.62) with correct case classification CCC of 71%-78%. Eight models (8-11 variables each) predicted cures (R=.64-.68) with CCC of 76%-84%. Addition of stage did not affect (p > .05) the R value or the CCC of any of the predictive models. In contrast, the stage-based clinical triad showed lower correlations with remission, survival, and cure rates (R=.21, .44, and .38, respectively), and lower CCC (74%, 66%, and 68%, respectively). Our data show that these highly discriminant models generate improved risk factor profiles for each individual patient. With this information, adjustments in the amount and intensity of treatment can be made in each case to avoid overtreating and undertreating patients, predicted to have good and poor prognosis, respectively. Fewer complications and further improvements in cure rates would result.

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SYMPTOMATIC BONE INVOLVEMENT AS PRESENTATION OF STAGE IV HODGKIN'S DISEASE (HD).

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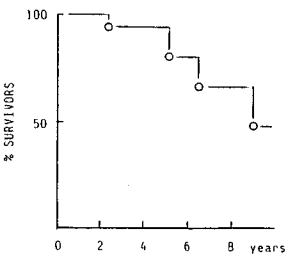
Bone involvement during first staging for HD is not unusual. However a symptomatic bone disease due to HD as initial presentation is rather rare. From Jan.1970 to Dec.1983 14 patients (pts) were referred to our institution from medical or ortopedics dep.ts because of symptomatic cancerous bone disease, which was then diagnosed as HD (in the same period total HD cases were 1107). Sex was: 9 males, 5 females. Age ranged from 14 to 69 years (median (m) 30, $\bar{x}$ 32). Localized bone pain was present in 10/14 pts; painful neurological (sciatic) compression in 2/14 pts; bone pain and soft tissues swelling in 2/14 pts. 10/14 pts were classified stage IV on the only basis of the presenting site; 4 other pts had also liver or lung or bone-marrow involvement. Histology was m.c. in 10, n.s. in 3, and l.d. in 1. Site of bone lesion: dorsal (5) and lumbar (5) spine, skull (1), sternum (1), iliac crest (4), clavicula (1), rib (1), homerus (1) (5/14 pts had multiple bone deposits). Rx features included in single bones osteolyis (22 instances), radiologic densities (1), mixed (1), vertebral collapse (1). Therapy: 6/14 pts received poly-CT, 8/14 poly-CT + RT. Period at risk for survival ranged from 26 to 115 months ($\bar{x}$ 67, m 67); 4/14 pts (29%) have died after 26 to 108 months (m 69); 10/14 (81%) are alive after 25 to 115 months (m 61). Serum phosphorus, calcium, magnesium, platelet count, WBC, were within normal range; ESR, serum copper, fibrinogen, alk. phosph., were consistently elevated over normal range; serum Fe was markedly reduced in all pts.



Stage IV HD with a painful bone disease as initial presentation is unfrequent (1.3% of 1107 pts); prognosis after poly-CT (MOPP ± ABVD) and RT (mainly on bulk disease) is not different from the average stage IV HD population.

P 53 HODGKIN'S DISEASE - RESULTS OF 3 PROTOCOLS WITH A FOLLOW-UP FROM 12 TO 15 YEARS.

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From 1965 to 1969, 88 patients (pts) stage I and 90 pts stage II of Hodgkin's disease (HD) were treated by H1 protocol (H1) : nitrogen mustard (6 mg/sqm2/day x 5 days) followed by extended field irradiation (EFI) and maintenance by Vinblastin (VBL 6 mg/m2 every month x 3 years). Complete remission (CR) was obtained in 148 pts (83 %) and partial remission (PR) in 25 pts (14 %). With 15 years of follow-up, the DFI is levelling off at 58 % and survival at 60 %. From 1969 to 1972, in 102 pts stage I and 93 stage II the induction was randomised between EFI alone (H9RT) and 3 MOPP followed by EFT (H9CH). Maintenance was randomised between VLB (as in H1) alone (H9V1) or associed by 1 MOPP every 3 months for 1 year even every 6 months for 2 years (H9V2). CR or PR was obtained in 95 % for H9CH and 97 % for H9RT. The DFI is levelling off at 90 % for H9CH and 58 % for H9RT with a 12 years follow up. MOPP reinductions do not change the prognosis. Between 1965 and 1972, 302 pts stages III+IV were treated by 6 MOPP followed by either VBL as in H9V1 or MOPP as in H9V2 or VBL plus EFI. CR + PR level is 81 % (for stages IV 67 %, for involved bone marrow (IVBM) : 73 %). DFI at 15 years is 52 % for VBL alone, 70 % for VBL + MOPP reinductions, 76 % for VBL + EFI and survivals are respectively 62 %, 82 % and 84 %. Prognosis factor for the 3 protocols is the age (>50 years), clinical and biological signs are prognosis only in protocol without MOPP ; for every protocol clinical staging and histological types have no prognosis value. In stage III and IV, positive lymphograms (extension and pathologic patterns) have a prognosis value in remission level and DFI. We observed 8 post-therapeutic leukemia (5 in relapsed HD treated by intensive chemotherapy). Results and prognosis of these 3 protocols are detailed and compared with litterature data.

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P 54 HEAVY VERSUS LIGHTER TREATMENT OF HODGKIN'S DISEASE CS I + II ON THE BASIS OF PROGNOSTIC INDICATORS. PRELIMINARY REPORT OF THE THIRD EORTC HODGKIN TRIAL (1977-1981).

E.M. Noordijk, on behalf of the EORTC Radiotherapy-Chemotherapy Group.

In the first and second clinical trial in Hodgkin's disease multivariate analysis identified several poor prognostic indicators: histology MC or LP, age ≥ 40 years, ESR ≥ 70 mm and stage II without mediastinal involvement. In the third trial these factors were used to form two subgroups, one with "favorable" and one with "unfavorable" patients. In both subgroups a relatively heavy treatment (with a higher chance for cure, but with certain risks) was compared to a lightertreatment (with the possibility of second treatment with curative intent in case of relapse).
In the "good" group all patients with PS I + II after staging-laparotomy were randomized between mantlefield irradiation (M) and mantle field + para-aortic irradiation (M+PA). The "poor" prognostic patients (that did not have a laparotomy) and the "good" patients with a positive laparotomy (PS IIIA) were randomized between total nodal irradiation (TNI) and 6 MOPP courses + mantle field (MOPP). Expected cure rates for M, M+PA, TNI and MOPP were at least 70-80%, 80-90%, 70% and 70-90% respectively. Treatment of first relapse was standardized.
Of 480 included patients (favorable 189, unfavorable 252, positive laparotomy 39) 172 have a follow-up of more than 4 years and 31 have died. Relapse-free and actuarial survival at 4 years are: M 84-97%, M+PA 81-96%, TNI 75-90% and MOPP 88-94% respectively. Both treatments within the favorable group produce acceptable relapse-free survival rates with good potential of curative salvage chemotherapy. In the unfavorable group total nodal irradiation is doing slightly worse than chemotherapy + mantle irradiation while the risk of sterility and second malignancy could prove to be lower after longer follow-up.

P 55 RADIOTHERAPY VERSUS CHEMOTHERAPY IN PATIENTS WITH EARLY STAGE HODGKIN'S DISEASE (H.D.) (PATH. STAGE I AND II, A) - PRELIMINARY REPORT.

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The use of intensive and more effective treatment programs - full radiotherapy plus chemotherapy - in the therapy of H.D. has improved results but increased damage, chiefly acute non lymphatic leukemia. Therefore the AA disagree with the current use of this intensive treatment (RT plus CHT) in the early stages (I or II path. st.), and basing on the extremely good results obtained in late stages (III and IV) treated by CHT alone, the AA have started a trial: RT versus CHT.
AIM: 1) to identify the therapy that, alone, gives the best results with less complications; 2) if chemotherapy will give equal or better results as radiotherapy, it will be used with less facilities: e.g. no more laparosplenectomies, therapy available everywhere.

DESIGN: I-II A (Clin)→Lap. → I-II path. st. - random: RT (Mantle + LA bar) versus CHT (6 MOPP)
III path. st.: out of the trial

MATERIAL: The trial was started in Dec. 1979 and was closed in Jan. 1983. Fifty patients were randomized in the RT group, 47 out of those were evaluable. Forty-eight patients were randomized in the CHT group, 44 out of those were evaluable. No differences as far as concerns the sex, age, hystology, number and size ("large masses" > 5 cm Ø superficial nodes, or mediast., on chest XRay AP, > 10 cm) of initially involved areas, or values of blood samples.
RESULTS: 6/47 patients in the RT group relapsed; 12/44 patients in the CHT group relapsed. No differences in the response to the therapy (RT or CHT) as far as concerns sex, age, hystology, number of initially involved areas. The only thing that up to date seems to be inequivocal is that "large masses" seem to respond to the CHT less than normal (in size) pathological tissue: 8/16 relapsed versus 4/28. The AA will present up to date results at the moment of the Conference.

P 56 COMBINED MODALITY THERAPY (CHEMOTHERAY PLUS RADIOTHERAPY) FOR HODGKIN'S DISEASE, CS IA TO IIIB.

I.- RESULTS OF THE H72 TRIAL (1972-1976) J.M. Andrieu*, M. Dana, C. Jacquillat, J. Briere, C. Julien, P. Casassus, N. Tea. * Hematology, Hospital Laennec 75340 Paris, France.

From april 1972 to december 1976, 334 patients (pts) suffering from Hodgkin's disease (HD), clinical stages (CS) IA to IIIB were prospectively treated at hospital Saint-Louis (Paris). The initial characteristics of the pts wsere : - sex : male 190, female 144 ; - CS : IA 92, IIA 123, IB IIB 82, IIIA 12, IIIB 25 ; - age : 5 to 63 years, median 28.7 ; histological type : I 9, II 268, III 43, IV 4, unclassif. 10. All pts received 3 or 6 cycles of MOPP followed by supra and/or infradiaphragmatic irradiations (40 Gy) according to two prospective trials (the H7201 trial for the 166 CS IA and IIₛA and the randomized H7202 trial for the 168 pts with more advanced stages). At completion of therapy 317 pts (94.9%) were in complete remission (CR). Twenty six pts relapsed (in situ or marginal: 8, non irradiated lymph node areas:15, visceral areas:3) after 4 to 58 months of CR (median: 17); 13 pts reached a second permanent CR. Forty three pts died (initial failure: 9; iatrogenic deaths under treatment: 8; relapsing pts:13 ; deaths in first CR : 11 (including 5 acute leukemias and 1 lung cancer) ; deaths non related to disease or treatment : 2). In september 1982, the median follow-up was 90 months (min :69, max :128). Actuarial probabilities (10 years) of survival (calculated from the beginning of treatment) and freedom from relapse (calculated from the completion of therapy) of all patients are 85.2% and 91.4% respectively (IA: 94.3% and 95.2%, IIA: 85.2% and 91.9%, IIIA: 83.3% and 100%, IB,IIB: 81.4% and 89.2%, IIIB: 67.8% and 73.7%). Survival is significantly lower in pts over 40 years of age (P=0.002), with constitutional symptoms (P=0.002), and with CS III (P=0.009); freedom from relapse rate is lower solely for pts with constitutional symptoms P=0.018).

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P 57 CHEMOTHERAPY(MOPP vs. MOPP/ABVD)+RADIOTHERAPY APPROACH IN ADVANCED STAGES HODGKIN'S DISEASE (HD).

Comella P., Scoppa G., Bruni G., Villari P., Comella G., Pergola M., Coucourde F., Zarrilli D. Tumor Institute, Naples - Italy

In Dec.'80 we started two randomized trials in order to compare the combination chemotherapy MOPP with the alternating chemotherapy MOPP/ABVD in advanced stages HD. In one trial, pts with stage IIB and III A&B were randomized to receive either 6 cycles of MOPP or 3 cycles of MOPP alternated with 3 cycles of ABVD. In both groups of patients, chemotherapy was combined with subtotal or total nodal radiotherapy (according to the extent of disease) with a "ping-pong" technique (i.e., 2 courses of chemotherapy were given before each field of irradiation) with a mean dose of 33 Gy. In another trial, pts with stage IV or relapsed after a CR obtained with chemotherapy and/or radiotherapy were randomized to receive either 8 cycles of MOPP or 4 cycles of MOPP alternated with 4 cycles of ABVD. Up to Dec.'83, 30 pts are evaluable for response. Results may be summarized as follows:

CHARACTERISTICS	MOPP GROUP No.CR/No.pts	MOPP/ABVD GROUP No.CR/No.pts	T O T A L No.CR/No.pts
All patients	14/16	13/14	27/30
age > 40 years	5/5	4/4	9/9
males	4/4	6/6	10/10
females	10/12	7/8	17/20
histology NS	5/6	5/6	10/12
" MC	7/8	6/6	13/14
" LP	2/2	2/2	4/4
Previously untreated	10/11	11/12	21/23
stage IIB	4/5	3/4	7/9
stage IIIA&B	3/3	8/8	11/11
stage IVA&B	3/3	-	3/3
Relapsed patients	4/5	2/2	6/7

No difference in hematologic toxicity was observed between the two regimens of chemotherapy. After 36 months of follow-up, the probability of survival for all patients is 75% (MOPP group=67%, MOPP/ABVD group=85%), and 5 patients (MOPP group=2, MOPP/ABVD group=3) relapsed after 9-17 months of CR. To date, we confirm the feasibility of our trials that yielded a high CR rate. There is a trend in favour of the MOPP/ABVD regimen in term of CR rate and overall survival of pts. We need further evaluation to better define the cost/benefit ratio of this approach of therapy.

P 58 HODGKIN DISEASE IN ADULTS. A PROSPECTIVE, RANDOMISED PHASE-III-THERAPY-STUDY. First results of the Protocolls HD 1-3 after 2 years.

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The treatment modalities of Hodgkin patients with risk-factors or in advanced stages remain a big problem. There is no standardised scheme showing the most effective results. Although combined modality-treatment (Radiation and Chemotherapy) is potentiating the risk of second-neoplasia-induction, this combination seems to be most effective, but until now has not been controlled in a randomised study. Therefore we started a prospective, randomised trial for the evaluation of these problems. Qualification for the three different protocols is given as follows: HD 1: stage I-III A with risk-factors large mediastinal tumormass, and/or growing p. continuitatem, and/or E-stage, and/or massive involvement of the spleen. Evaluation: combined modality-treatment with different radiotherapeutic dosis. HD 2: stage III_1 and III_2 A; radiation only against combined modality. HD 3: stage III B, IV A,B; evaluation of radiotherapy against Chemotherapy for all those pts. who came in CR after Chemotherapy only. Chemotherapy: the trial started with the COPP combination alone. The protocol has been changed after the results from Santoro et al, who demonstrated very impressive results with MOPP alternating with ABVD. Preliminary results: Between 1/82 and 2/84 132 qualified (of 239 registered) previously untreated pts. from 24 clinics in Germany were enclosed into the cooperative study (98 pts. were treated with the COPP regimen, 34 pts. with the alternating treatment program COPP and ABVD). Due to incomplete data 1,3 % were not included, 56,9 % of the pts. were males, 41,8 % females. Nodular sclerosis represented the most frequent histologic subgroup with 46,4 %, followed by mixed cellularity subtyp 36,4 %. 49 pts. entered the HD 1 - protocol, 16 pts. the HD 2 - protocol and 67 pts. the HD 3 - protocol. Treatment-results till now are very preliminary: HD 1: CR 21 pts., PR 1 pts. and PRO 3 pts., HD 2: CR 8 pts., PR 1 pts. HD 3: CR 19 pts., PR 5 pts., PRO 4 pts.

P 59 MOPP/ABV(HYBRID) IN TREATMENT OF ADVANCED OR RECURRENT HODGKIN'S DISEASE (PROGRESS REPORT).

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To test the Goldie-Coldman model which predicts superior outcome if active chemotherapeutic agents are used alternately rather than sequentially, MOPP and ABVD were split and the individual halves linked to form a new combination, MOPP/ABV (Hybrid). In the hope to further optimize treatment tolerance and results, DTIC was deleted, the dose of Adriamycin was increased by 10 mg/m^2 and prednisone was given with each cycle of therapy. Cycles of treatment were repeated every 28 days.

Day 1	Day 8
Nitrogen Mustard 6 mg/m^{2}i.v.	Adriamycin 35 mg/m^{2}iv
Vincristine 1.4 mg/m^2(max 2 mg) i.v.	Bleomycin 10 mg/m^{2}i.v
Procarbazine 100 mg/m^2/day x 7 p.o.	Vinblastine 6 mg/m^{2}iv
Prednisone 40 mg/m^2/day x 14 p.o.	

Since Sept. 1980, we have treated 49 new cases (1°), (4 stage IIAEE, 7 IIB bulky disease ±E, 9 IIIA (spleen+)±E, 18 IIIB, 3 IVA, and 8 IVB); 24 cases in first relapse (2°); 7 after radiation only (2°R), 10 after radiation plus chemotherapy (2°: C+R); 7 after more than 1 relapse (3°). In the new cases group, 21 patients were more than 40 years old, 33 had B symptoms and 27 had aggressive histology. In the first relapse category, only 3 patients were more than 40, 7 had B symptoms and 15 had nodular sclerosing histology. No specific pattern applied to the multiple relapses group.

Patients received 8 cycles of Hybrid, 4 patients received involved field radiation to consolidate residual abnormality involving lymph node sites. 61 patients have completed treatment and 56 are evaluable. The median follow up time off treatment is 12.months; 16 patients are off therapy for more than 18 months.

Results:

	Total	Evaluable	NR/PD	PR	CR	Relapse from CR
1°	37	33	1	0	32	0/32
2° R	7	7	0	0	7	0/7
C + R	10	10	0	0	10	3/10
3°	7	6	1	0	5	2/5

There have been no relapses in the categories of new cases or those originally treated with radiation only (39 patients). There were 3 cases of recurrence in the first relapse category treated previously by chemotherapy and radiotherapy and two cases of recurrence in the category of multiple relapses. Compared to other reported regimens, Hybrid is shorter and less toxic but at least as effective for remission induction, and, with up to three years off treatment follow up, remission durability.

P 60 CHANGES IN PITUITARY-GONADAL FUNCTION DURING AND FOLLOWING TREATMENT FOR HODGKIN'S DISEASE IN CHILDREN AND ADOLESCENTS - A LONGITUDINAL STUDY.

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Gonadal dysfunction is a major complication of treatment in patients with Hodgkin's disease. Longitudinal data are scarce that relate the onset of these complications to the different therapeutic modalities or to the period after therapy.

In 19 boys and 9 girls, age 4.25 - 16.0 years prior to therapy, pituitary-gonadal function was evaluated prospectively and longitudinally starting before, during, at the end of or at yearly intervals after combined chemo- and radiotherapy in 27 pts and irradiation alone in 1 pt. A standardized intravenous LHRH-test with 0.025 mg LHRH was performed. Estradiol/testosterone, basal and stimulated values of LH and FSH were measured. Results were compared to a control group with the same stage of puberty.

Normal results were obtained in 3 boys prior to therapy. Following intensive chemotherapy, but prior to irradiation, the pituitary-gonadal axis showed no changes in 4 boys (2 prepubertal, 2 pubertal). On the other hand, basal as well as stimulated LH- and FSH-values were increased up to 30 fold above control values in 2 pubertal girls and were normal in 1 prepubertal girl. Short term follow-up at the end of irradiation (excluding the inverted Y-field) showed, thus far, no major improvement.

An additional 15 boys and 3 girls were evaluated at the end of therapy. Abnormal LHRH-tests were found in 1 boy and 2 girls. The yearly follow-up revealed development of gonadal dysfunction in 2 more boys with previously normal LHRH-test 1 and 2 years after therapy. The overall incidence of hormonal changes, including those patients examined for the first time some years after therapy, was more frequent in girls than in boys (6/9 girls vs. 6/19 boys). Whereas puberty progressed normally, changes in the hormonal secretory pattern indicate the possibility of later infertility and/or premature gonadal failure in some of these patients.

We conclude that gonadal dysfunction is already present in some patients during or at the end of therapy while others develop it some years after treatment.

P 61 NON-HODGKIN'S LYMPHOMA ASSOCIATED WITH PREGNANCY: CLINICAL CHARACTERISTICS AND TREATMENT STRATEGY.

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Six patients with non-Hodgkin's lymphoma (NHL) diagnosed during late pregnancy or shortly thereafter are reported. Three patients had high grade lymphoma (2-undifferentiated, 1-diffuse large cell, immunoblastic type) and 3 intermediate grade histology (1-diffuse large cell, 1 diffuse small cleaved cell, 1 diffuse mixed large and small cell). Five of the 6 patients were in stage 4 and one was stage 1A. In three patients the lymphoma showed a striking progression shortly after time of delivery, while the other 3 patients showed widespread disease at diagnosis. In one patient a huge abdominal mass was found, and in two patients extensive involvement of the GI tract and ovaries was encountered. Five patients had full term natural deliveries with normal offspring. A single patient had a premature delivery with a Caesarean section in the 29th week because of abruptio placenta probably due to lymphoma of the uterine wall. The disease in this patient also involved the kidneys, adrenals, lungs, thyroid and most of the GI tract and the outcome was fatal for both patient and fetus. The other 5 patients were treated soon after delivery. Four patients received M-BACOD (Methotrexate, Bleomycin, Adriamycin, Cyclophosphamide, Vincristine, Dexamethasone) chemotherapy alone and 1 patient radiotherapy and CHOP (Cyclophosphamide, Adriamycin, Vincristine, Prednisone). All had a significant response (3-complete remissions, and 2 partial remissions). Our patients demonstrate that NHL associated with pregnancy is an aggressive disease with possible acceleration during late pregnancy or after delivery. As all cases were close to full term at the time of diagnosis, intensive chemotherapy was started after delivery. NHL associated with pregnancy has rarely been reported and in 22 isolated case reports collected from the literature different treatment modalities were employed and in general poor results were obtained. Current more aggressive chemotherapy regimens promise a better outlook for patients with NHL associated with an apparent poor prognostic factor-pregnancy.

P 62 Incidence, symptoms and course of central nervous system involvement in patients with lymphoproliferative disease

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The medical records of 26 patients with Non Hodgkin's lymphoma (NHL), of 4 patients with acute lymphocytic leukemia (ALL) and of 1 patient with chronic lymphatic leukemia (CLL) who presented with central nervous system involvment (CNSI) were retrospectivly analysed. CNSI was diagnosed in 7,8% of NHL and in 31% of adult ALL patients from 1979-1982. CNSI was frequently seen in NHL patients with stage IV disease, bone marrow involvment, extensive retroperitoneal tumor masses and diffuse histiocytic subtype. 8 NHL patients had unrecognised lymphomatous meningitis discovered at postmortem.
At diagnosis of CNSI, 71% of our NHL patients had active systemic disease, 26% were in remission, 3% had CNSI only. 10% showed CNSI at initial presentation of their NHL.
The main clinical symptoms of the whole group were cranial nerve palsies (48%), paresthesias (35%), palsies of peripheral nerves (32%), behavior changes (29%) and headaches (26%). 10% had no symptoms at all.
On their first lumbar puncture, 52% of the patients had a positive cytology and 91% had elevated protein levels. Of 22 computed tomography brain scans (CT), 56% were positive, 38% negative and 6% unconclusive. Follow up CT in unclear or negative cases did not provide additional information.

Therapy of CNSI included intrathecal applications of methotrexate and/or Cytosine Arabinoside as well as radiation therapy. Patients with NHL in remission and CNSI survived longer (median survival: 11 months) than patients with CNSI and progressive systemic disease (median survival: 3 months).
In summary, advanced disease, extensive retroperitoneal masses, histiocytic subtyp and progressiv systemic disease were associated with CNSI in NHL patients. Patterns of clinical symptoms varied, 10% were completly asymptomatic. Most of our patients had elevated protein levels, only half of them had a positive cytology on first lumbar puncture. Half of the CT scans were positive. Survival after therapy was longer in patients in remission of their NHL than in those with active disease.

P 63 PATTERNS OF DISEASE IN EXTRANODAL NON-HODGKIN'S LYMPHOMA - INDIRECT EVIDENCE SUPPORTING 'HOMING'.

M.K. GOSPODAROWICZ, S. SUTCLIFFE, R.S. BUSH, T.C. BROWN

There is in-vitro and in-vivo precedent for the belief that site of origin within lymphoid tissue is an important determinant of lymphocyte migration patterns. Additional evidence suggests that lymphocyte migration from gut-associated lymphoid tissue (G.A.L.T.) differs from that of axial lymphoid tissue. Our own experience confirms that of others in the demonstration of a clinical association between lymphomas of Waldeyer's rings and the gastrointestinal tract (G.I. tract).

To test whether such migration patterns affect clinical patterns of disease in non-Hodgkin's lymphoma, survival and relapse characteristics for 496 patients with Stage I and II NHL treated with loco-regional XRT alone at the PMH between 1967-78 were examined. The patient population comprised 139 patients with G.A.L.T lymphoma (defined as lymphoid tissue arising in association with primitive gut and thereby including Waldeyers' ring, thyroid and gastrointestinal lymphomas), 270 patients with axial nodal lymphoma (N.L.), and 87 patients with other extranodal non-gut associated lymphoma (E.N.-L.). Survival and relapse have been analyzed in multifactorial analysis to correct for other prognostic variables (eg. tumour bulk, stage and symptoms, age and histology).

G.A.L.T. lymphomas (G.A.L.T.-L) have a survival advantage compared to other E.N.-L. ($p=0.017$), however no advantage was present in comparison with N.L. There was a difference in distant relapse (D.R.) rate between G.A.L.T.-L. other E.N.-L. ($p=0.0002$), and between G.A.L.T.-L. and N.L. ($p=0.005$). There was no significant difference in D.R. rate for E.N.-L. and N.L. Local relapse rates were similar for all three groups.

If a genuine difference in the behaviour of G.A.L.T.-L were apparent, this should be most obvious in patients without nodal spread ie. Stage IE disease. Distant relapse rate for Stage IAE G.A.L.T.-L. is 11% and for E.N.-L. 55% over 10 year period. The relative risk of D.R. is 0.38 for G.A.L.T.-L and 1.62 for E.N.-L., the difference being significant at $p=0.0001$ level. Those differences whilst also significant are less apparent when nodal spread has occurred (IIE).

There is no difference in relapse rates between G.I. lymphomas and other G.A.L.T.-L.

Site of involvement of localized N.H.L. is therefore also an independent determinant of outcome. The above findings are compatible with the hypothesis that the clinical expression of malignant lymphomas reflects the origin and migration patterns of the malignant lymphocyte.

P 64 A RETROSPECTIVE REVIEW OF PROGNOSTIC FACTORS IN NON-HODGKIN'S LYMPHOMA, 1974-1980.

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A retrospective analysis was performed on 462 patients biopsied from 1974 to 1980 and presenting to the OCTRF London Clinic or one of the three teaching hospitals. Thirty-five point five percent of patients were age 70 and over. The most frequent pathologic diagnoses by the Rappaport classification were diffuse histiocytic (36.2%) and diffuse, poorly differentiated, lymphocytic (20.1%). There was fairly equal distribution by clinical stage (I, 20.3, II, 24.7, III, 21.2, IV, 32.3). Combined radiotherapy and chemotherapy was frequently given to stage I and II patients; overall, and unfavourable histology subgroups. Chemotherapy alone was most frequently used for stage III and IV.

Survivors were followed a median of 48.4 months (mean 51.3, range 12-100). Actuarial survival was influenced, significantly and favourably, by lower stage, nodular pathology, better tumour differentiation, age less than 70, absence of systemic symptoms, absence of lymphoma cells on peripheral smear, present of bone marrow involvement in stage IV patients, by absence of bulky disease and lymphocytic histology. There was no difference in outcome between sexes; nodal versus extranodal sites and year of entry. Survival curves were similar for stage II and III patients overall and in all subgroups suggesting that stage II is not early disease and calling into question the primary use of local therapy. Cox regression analysis showed cell type was not significant, and in the 1979-80 subgroup, tumour bulkiness did not contribute to the prediction of lymphoma deaths.

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P 65 CLINICOPATHOLOGIC RELATIONS IN THE EORTC TRIAL (20751) ON NON HODGKIN LYMPHOMAS.

For the EORTC Radiotherapy/Chemotherapy group : C. De Wolf-Peeters, B. Caillou, J. Diebold, P. van Heerde, J.A.M. van Unnik, J.J. van den Oord, M. Van Glabbekke and R. Somers

The EORTC has organised a non-Hodgkin lymphoma trial (EORTC trial 20751) during the years 1975-1980. Patients with nodal presentation and in all stages of the disease were included. One of the objectives of the trial was an investigation on the correlation between histopathology and prognosis.

612 patients were included in the trial. Paraffin sections from a tumoral lymph node taken before therapy from 402 of these patients, were available for this study. For various reasons 33 cases were omitted. The remaining 369 cases were independently studied by 6 pathologists and subdivided according to various classifications. Only those results which were obtained with a consensus of at least 4 of the 6 pathologists were used for further analysis.

Most cases (92%) could be classified on the growth pattern of the tumor. Dividing non-Hodgkin lymphomas in nodular and in diffuse, the prognostic of survival is statistically different. In 30% of the cases a further subclassification according to Rappaport revealed no agreement.

108 out of 109 cases with a nodular growth pattern could be classified in the Kiel classification. On the contrary, in half of the cases with a diffuse growth pattern no consensus was reached in that same classification. The prognostic of survival of cases recognized as low grade malignant and those recognized as high grade malignant, again is statistically different. However, analyzing both groups according to the growth pattern, it is demonstrated that the latter subdivision is of primary prognostic significance.

66% of the cases included in the study were classified according to the International Working Formulation. Cases recognized as low grade malignant have a prognostic of survival which statistically differs from cases recognized as intermediate grade malignant and those diagnosed as high grade malignant. The latter two groups do not have a significant difference in prognostic of survival.

This study illustrates that non-Hodgkin lymphomas are most easily and confidentally subdivided according to their growth pattern. Moreover this subdivision turns out to be of primary prognostic significance.

As the nodular lymphomas were supposed to be of follicle center cell origine and as in half of the diffuse cases no agreement was obtained, one can speculate that other classifications of non-Hodgkin lymphomas will become more important as prognostic of survival, with a more precise identification of the tumoral cell type e.g. supported by immunophenotyping.

P 66 PROGNOSTIC FACTORS IN NON-HODGHKIN'S LYMPHOMA.

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To evaluate the factors affecting the survival(s.), two hundred twenty seven patients(pts) with non-Hodgkin's lymphoma seen from 1973-1982 were studied. Histological diagnosis was made according to the Working Formulation. Actuarial 5 year s. for all pts was 46%. By histology, 5 year s. was 86% for 22 pts with low grade;54% for 150 pts with intermediate grade;and 26% for 54 pts with high grade . 5 year s. according to the range of LDH was 74% for 102 pts with $<$ 250U, 51% for 42 pts with 250-349U and 14% for 44 pts with $>$350U. Pts with higher LDH had apparently poorer survival even in the same stage and same histology. Albumin also was a prognostic factor;5 year s. was;64% $\geq$ 4.5g/dl(93pts), 54% 4.4-3.5g/dl(66pts) and 33% $<$ 3.5g/dl (42pts). Though the pts with alkaline phosphatase $>$20U was few(10/189. 5%), their 5 year s. was 20% in comp. with 59% for 151 pts with alk. phos. $<$10.0U. 5 year s. for 55 pts with pos. PPD was 83% and for 85 pts with neg. PPD was 44%. Hb affected the 5 year s.; $\geq$13.0g/dl(121pts) 61%, 12.9-12.0g/dl(40pts)39% and $<$12.0g/dl(38pts) 37%. ESR ($>$ 50mm/hr), leucocytosis($>$5.000/mm^3), lymphocytopenia ($<$ 1.000/mm^3) also were important prognostic factors. These factors had a good correlation with clinical stage and some of them with histopathology. Pts ages $<$19 had poor s. because of the high percentage of the pts with lymphoblastic type. No difference was observed between the pts ages $<$69 and $>$70 in stage I and II disease, but in stages III and IV disease difference was observed caused by the difficulty in continuing the intensive chemotherapy. There was no difference in s. between male(139 pts) and female(88pts).

P 67 The prognostic significance of the Lukes and Collins classification of non-Hodgkin's lymphomas.

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In a retrospective study of 301 non-Hodgkin's lymphoma patients the clinical and prognostic value of the classification of Lukes and Collins was studied.

Two prognostically different subgroups were discerned. The more favourable group consisted of the small cleaved follicular center cell (FCC) type (five year relative survival 74 %), the small lymphocytic type (62 %) and the plasmacytoid-lymphocytic type (51 %). The small non-cleaved FCC type, the large non-cleaved FCC type and immunoblastic sarcoma formed the other group with a less favourable prognosis. Mortality due to these types manifested itself to a level of 65 % in the course of the first two years.

The Bayesian multivariate statistical method was applied to determine the relative strength and optimal combination of 17 variables in predicting survival of 151 patients with non-Hodgkin's lymphomas assigned as non-cleaved FCC and immunoblastic sarcoma types. Considering all the factors simultaneously, the analysis showed that the combination of stage, haemoglobin level and localization of the lymphoma was included in the best predictive model at each survival time studied. Of the histologic variables, only the growth pattern and mitotic ratio remained significant.

Reference:

Aine R. et al. Acta Path Microbiol Immunol Scand Sect A (1982) 90: 251-256.

P 68 Chronic lymphocytic leukemia of B-cell type (B-CLL) and LP immunocytoma (LP-IC): Non-Hodgkin lymphomas (NHL) of low-grade malignancy with different prognosis.

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In a prospective trial performed from 1975 to 1980 by the Kiel Lymphoma Study Group, 221 patients with B-CLL and 213 patients with LP-IC were observed. Histopathologic diagnosis was made at the Kiel Institute of Pathology by three of us (K.L., A.C.F., E.-W. Sch.). In the majority of cases diagnosis was established by lymph node biopsy. Although most initial symptoms and signs of both entities were similar it was shown that rapid lymph node enlargement and initial B symptoms were associated with a poor prognosis in LP-IC but not in B-CLL. At diagnosis all but one patients with B-CLL but only 86 % of LP-IC patients revealed bone marrow involvement. Inspite of a frequent nodular pattern of tissue infiltration overall prognosis of LP-IC was worse compared to B-CLL, as demonstrated by a significant difference ($p <$ 0,01) of actuarial survival between the two disorders. In B-CLL median actuarial survival was not reached after 75 months of follow-up whereas in LP-IC it was only about 50 months. Several poor risk factors, e.g. male sex, initial Karnofsky index below 70 %, elevated serum LDH activity, were identified. Monoclonal gammopathy was found in 28 % of patients with LP-IC but only in single cases of B-CLL. However, it does not represent a poor risk factor as survival of LP-IC patients with monoclonal gammopathy was not different from that of patients lacking this feature. Prognostic difference between B-CLL and LP-IC may necessitate future differentiation of therapeutic approaches.

P 69 CLINICAL ANALYSIS OF 322 CASES OF NON-HODGKIN'S LYMPHOMA.

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Clinical pretreatment data of 322 patients (pts) with Non-Hodgkin's Lymphoma (from Jan 1980 to Apr 1983) that were included in different treatment protocols are presented. There were 172 males and 150 females (M:F ratio 1:0.87). Mean age was 53.4 years (ys) and median age 55 ys (range 16-99). Pts with less than 16 ys are attended in other hospitals and are not presented here. 143 pts (44.4%) belonged to low socioeconomical level, 147 (46.2%) to medium level and 28 (8.8%) to high level. 71 pts (22%) referred familial background of cancer. A second neoplastic disease was associated in 6 pts (1.8%). The initial symptoms were as follows: lymphadenopathy in 109 (33.9%) (head and neck lymph nodes 79.8%, axilar 5.5%, inguinal 14.6%); extranodal tumors 38 pts (11.8%):(head and neck 36.8%, limbs 31.5%, abdominal 24% and miscellaneous 7.8%); pain in 86 pts (26.8%):(head and neck 25.6% thoracic 2.3%, limbs 7%, abdominal and lumbopelvic 59.3% and miscellaneous 5.8%); constitutional B symptoms 21 pts (6.5%):(1 symptom 76.1% and 3 symptoms 23.9%) and miscellaneous 67 pts (20.8%):(general symptoms 7.4%, G.I. tract 25.3%, respiratory tract 35.8%, hemorrhagic 4.5% and others 22.3%). Staging: 39 pts (12.1%) I (A 56.4%, B 43.5%); II 53 pts (16.5%)(A 32%, B 68%); 32 pts (10%) III (A 25%, B 75%) and 196 pts (61.3%) IV (A 27%, B 73%); there were 2 non-staged pts. 220 pts (68.8%) had constitutional symptoms when the diagnosis was made: 45% had one symptom (most frequently weight loss), 26.3% had 2 symptoms (most frequently weight loss and diaphoresis followed by weight loss and fever) and 28.7% had 3 symptoms. Of the whole group, 54 pts (16.7%) had exclusively nodal involvement, 35.1% supradiaphragmatic (one site 21%, 2 or more sites 79%); 14.8% infradiaphragmatic (one site 62.5% and 2 or more 37.5%) and 50% had nodal involvement of both siedes of the diaphragm. 170 (52.7%) had either lymph node involvement only or lymph nodes plus other localisations; in this group the most common localisations were intra-abdominal and cervical lymph nodes followed by axillary and inguinal, less commonly at Waldeyer's ring, spleen, mediastimum and others. 168 pts (52.1%) had extranodal involvement, with or without lymphadenopathy; the most common localisation was bone marrow (19.3% had leukemic infiltrate), followed by liver, connective tissue, nasal cavity, paranasal sinuses, nasopharynx, G.I. tract (mainly stomach), skin and others. 52 pts (16.1%) had eclusively extranodal involvement; of these 22 were stage IE (42.3%) and the remaining (57.7%) stage IV. The more common localisetions were nasal cavity, paranasal sinuses and nasopharynx (42.3%), bone (23%), G.I. tract (13.4%), CNS (7.6%) and others. Clinical data have been well documented in other countries but not in Mexico; this is the first document of its kind in our country and shows some interesting differences with other casuisties, mainly a high incidence of paranasal sinuses lymphomas. Histological review with clinical correlation is being currently done.

P 70 CLINICAL RESULTS OF LOW STAGE DIFFUSE HISTIOCYTIC LYMPHOMA (DHL) TREATED BY RADIOTHERAPY ONLY.

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DHL is a common generic subtype of lymphoma which often presents with low stage (I, II) localized disease that may be extranodal. Radiotherapy to doses of 4000 to 6000 rad can control most local disease with few infield relapses. Chemotherapy can be curative in about 50% of advanced stage patients. Chemotherapy with or without radiotherapy can also be curative in low stage patients. However, chemotherapy has significant systemic morbidity. We are studying a population of patients treated with radiotherapy alone in an attempt to determine what factors influence prognosis and whether a subpopulation of patients exists which can optimally be treated with local radiotherapy alone. Amongst our patient population, we have reviewed 42 patients with clinical stage I, II DHL with disease presenting above the diaphragm, who were treated with radiotherapy alone. The predominant site of presentation was nodal or extranodal disease in the head and neck region. Only one patient had B symptoms. Staging methods included 60% by lymphangiogram, 29% by bone marrow biopsy, 52% by IVP, 10% by CT scan and only 5% by laparotomy. Forty-eight percent of the patients (20) had no relapse and died free of disease or are alive free of disease with a minimum 4 year followup. Of the 52% who relapsed, the mean disease free survival was 22 months with a median of 9 months and the mean overall survival was 33 months with a median of 17 months. The relapse rate and survival did not differ by stage (I vs II). Most of the relapses were distant and occurred within one year, probably because of inadequate staging. Only 21% of patients had good staging methods for occult advanced disease but 78% of these patients are free of disease. Most other patients with more recent, good, staging methods (bone marrow, lymphangiogram, CT scan, laparotomy) either were atuomatically given chemotherapy (+/- radiotherapy), or have too short a followup to be included in our data. Pathological review is being done on all patients with analysis by new International subclassifications. Further analysis of the patients include factors of bulk disease, specific site of disease, and radiotherapy factors. We think that there is a subpopulation of patients with localized DHL patients who can have adequate long-term control with radiotherapy alone, and this includes well staged patients, with stage I or II-A disease, above the diaphragm, and without bulk disease (<5-7 cm).

P 71 TREATMENT RESULTS WITH RADIOTHERAPY ALONE OF DIFFUSE HISTIOCYTIC LYMPHOMA LOCALIZED IN THE HEAD AND NECK

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Some recent results for patients with localized diffuse histiocytic lymphoma treated by chemotherapy alone or combined modality therapy are superior to those obtained with radiation therapy alone. However, patients who have Waldeyer's ring primaries have a relatively favorable prognosis with radiation therapy alone.

Between 1971 and 1981, 81 patients (CS I:38; CS II:43) of diffuse histiocytic lymphoma localized in the head and neck were treated with radiation. Of these, 52 cases had Waldeyer's ring disease (CS I:13; CS II:39), 14 cases had nodal disease (CS I:13; CS II:1), and 15 had extranodal disease (CS I:12, CS II:3).

All of 13 stage I Waldeyer cases achieved complete remission after 40 to 60 Gy of radiation therapy. All cases except one were disease-free at 2 to 11 years after treatment. One has relapsed in ileocecal region at 3 years after treatment. Of 39 stage II Waldeyer's lesion with cervical lymph node involvements, only one (3 %) has failured to achieve complete remission and 2 cases (6 %) had recurrence in the irradiated cervical lymph nodes, at 14 and 32 months after treatment, respectively. Another 11 cases (28 %) have relapsed in distant site (5:stomach; 1:duodenum; 2:paraaortic nodes; 2:inguinal nodes; 1:skin), at 3 to 80 months after treatment (median 16 months). 5-year disease-free rates were 91 % in stage I and 71 % in stage II after radiation therapy alone.

Of 13 stage I cases with cervical lymph node involvement, all cases achieved complete remission, but 7 cases (54 %) have relapsed in distant site (4:paraaortic nodes; 2:inguinal nodes; 1:skin), at 2 to 13 months after treatment. 5-year disease-free rate was 58 %. Of 12 stage I cases with extranodal involvement (6:maxillary sinus; 2:nasal cavity; 2:lower jaw; 2:thyroid) all cases achieved complete remission, but 7 cases (58 %) have relapsed in distant sites (2:skin; 2:breast; 1:mediastinum; 1:spleen; 1:CNS; 1:cervical lymph nodes) at 1 to 18 months after treatment. 5-year disease-free rate was 33 %.

The results in this study reveals that the patients with clinical stage I disease of Waldeyer's ring have favorable prognosis with regional radiation therapy alone. However, those with stage II disease the addition of chemotherapy to radiation therapy may be required. The patients with other nodal or extranodal stage I disease initial combined modality therapy may be essential.

P 72 A PROSPECTIVE STUDY OF THE TREATMENT OF HIGH GRADE HISTOLOGY NON-HODGKIN'S LYMPHOMA (NHL) OF THE GASTRO-INTESTINAL TRACT.

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35 previously untreated patients presenting with NHL of high grade histology primarily involving the gastro-intestinal (GI)tract were entered into a prospective study of treatment with surgery followed by chemotherapy using Vincristine, Adriamycin and Prednisolone (VAP). Those patients with stage II disease subsequently received abdominal radiotherapy. The histologies have been re-reviewed, stained with histiocytic markers, where relevant, and classified according to the Rappaport and Kiel systems with the addition of a true histiocytic subgroup.

16 patients had stage II, 1 patient, stage III and 18 patients, stage IV disease. Primary sites of involvement were stomach (16 patients), small intestine (14 patients) and large intestine (5 patients). Eight patients (23%) had true histiocytic, 13 patients (37%) follicle centre cell, 4 patients (11%) immunoblastic, 4 patients (11%) lymphoblastic and 6 patients (18%) unclassified lymphomas Breakdown in the Rappaport system was - diffuse histiocytic, 21 patients (60%), diffuse poorly differentiated lymphocytic, 11 patients (31%), unclassified, 3 patients (9%).
Median follow up was 64 months.

Overall complete response (CR) rate was 57%. 62% of patients with true histiocytic and 67% of patients with diffuse histiocytic NHL achieved a CR.

The median survival was 10 months and the five year survival 36%. For patients with stage II disease, the five year survival was 63%.

No difference in survival or relapse-free survival (RFS) was seen according to subdivisions by Kiel classification or by site of involvement. Patients with diffuse histiocytic NHL had a significantly longer survival ($p = 0.01$) and RFS ($p = 0.03$) than other histologies using the Rappaport classification.

The importance of adequate surgery followed by effective chemotherapy and achievement of a CR is stressed.

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Thirty-seven patients with non-Hodgkin's lymphoma of the stomach were treated with curative intent from 1958 to 1979. Twenty-two patients presented with Stage IE and 15 patients with Stage IIE disease (Ann Arbor staging). All the patients except three had exploratory laparotomy. The surgery-alone (S) group (N=11) consisted of patients with Stage IE disease who were treated with subtotal or total gastrectomy. The radiation-alone (R) group (N=8) consisted of patients who were medically inoperable (3) or unresectable (5) at the time of laparotomy and were treated to doses of 4000-4500 rad encompassing stomach and para-aortic area. The surgery and radiation (S+R) group (N=12) consisted of patients who were treated with gastrectomy and radiation to the entire abdomen or stomach and para-aortic area with doses ranging from 2200-4600 rad. Patients in the surgery + radiation + chemotherapy (S+R+C) group (N=6) were treated with gastrectomy followed by radiation to the gastric bed and para-aortic area and chemotherapy (mostly COP).

Tumor failure vs. treatment method and stage is shown in Table 1. Failure sites were: Primary (Four patients), inguinofemoral nodes (2) and distant metastases (6). Tumor failure vs. histology and extent of disease will also be presented. Of 29 patients who underwent gastrectomy, three died of surgical complications and six had severe dumping syndrome. Radiation caused no major complications. Most patients had transient nausea/vomiting. Thirteen patients were treated with R ± chemotherapy, nine for cure and four for palliation (these four patients had massive stomach involvement with Stage IV disease and are not included in failure or survival analysis). None of these thirteen patients developed any evidence of gastric perforation or hemorrhage. Two of 37 patients had gastric perforation at the time of initial presentation and underwent gastrectomy.

Five-year absolute NED survival for all 37 patients is 61%; for Stage IE 57%; for Stage IIE, 67%; for S group, 45%; for the R group, 37%; for the S+R group 74%; and for the S+R+C, 100%. Survival was significantly higher ($p = < .05$) for females and for patients receiving adjuvant radiation and chemotherapy than for patients treated with R or S alone.

TABLE 1 Failures According to Treatment Method and Stage

Stage	Treatment Method S		R		S+R		S+R+C		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
IE	3/8*	(38)	2/3	(67)	1/6	(17)	0/2	(0)	6/19	(32)
IIE	-	-	2/5	(40)	3/6	(50)	1/4	(25)	6/15	(40)
Total	3/8	(38)	4/8	(50)	4/12	(33)	1/6	(17)	12/34	(35)

* Three patients excluded because they died of surgical complications.

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A COMPARISON OF TOTAL BODY IRRADIATION TO COMBINATION CHEMOTHERAPY IN THE TREATMENT OF LYMPHOPROLIFERATIVE DISORDERS

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Lymphoproliferative disorders defined to include chronic lymphocytic leukaemia and the indolent or low-grade malignant lymphocytic lymphomas are known to be responsive to both total body irradiation and to chemotherapy. Although complete remission (CR) may be obtained, in which there is resolution of organ enlargement and return of blood count and bone marrow morphology to normal, therapy has primarily been palliative and aimed at improving the duration of good quality survival. This study was undertaken to compare these two forms of treatment. 106 consecutive patients were biologically stratified into chronic lymphocytic leukaemia (CLL) (n=41), stage III and IV follicular lymphoma including all cell types (n=45), and stage III and IV diffuse malignant lymphocytic lymphoma of the small cell type (n=20). Within each of these strata patients were prospectively and randomly assigned to receive chemotherapy with chlorambucil and prednisone (CP) or 15 rads total body irradiation (TBI) twice a week to a total of 150 rads. The CR for the entire chemotherapy group (n=53) was 58% and that for the TBI (n=53) was 57%: at 60 months survival for CP was 61% and for TBI was 48% and disease-free survivals were respectively 62% and 33%. In the 41 patients with CLL the CR for chemotherapy (n=17) was 47% and for radiotherapy (n=24) was 58%: survival at 60 months was 80% and 60% and disease-free survival 83% and 63% respectively. For the 45 patients with follicular lymphoma the CR for chemotherapy (n=22) was 72% and for radiotherapy (n=23) was 52%: survival at 60 months was 62% and 42% and disease-free survival 46% and 20% respectively. In the 20 patients with diffuse lymphocytic lymphoma the CR for chemotherapy (n=14) was 50% and for radiotherapy (n=6) was 67%: survival at 60 months was 45% and 82% and disease-free survivals 67% and 0% respectively. Disease-free survival was calculated as a percentage of patients achieving complete remission. None of these differences are statistically significant (p 0.05). It is concluded that in these lymphoproliferative disorders CP and TBI are equally effective forms of therapy when the endpoint is survival. The longer disease-free periods in the chemotherapy arm may be related to the continuous schedule of therapy but confirs no significant treatment advantage.

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THERAPEUTIC RESULTS IN MALIGNANT LYMPHOMA (ML) PATIENTS (PTS) TREATED WITH CHOP FOLLOWED BY "ICEBERG" IRRADIATION (RT).

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33 consecutive evaluable pts with proved diagnosis of non-Hodgkin's ML (20 males and 13 females; median age: 48 years, range: 19-69; 13 stage II, 10 stage III, and 10 stage IV) were treated with 6-8 cycles of CHOP at 21-day intervals, followed by RT 40 Gy on sites known to contain lymphoma at the onset of chemotherapy ("iceberg" irradiation). 26 pts (79%) achieved complete remission (CR) with CHOP therapy. No further CRs were obtained with RT. Relapse from CR was observed in 11 of 26 complete responders (5 to 46 months after CR, median: 17 months), in each case in sites not initially known to be involved by ML. 15 pts remain in CR for 8+ to 72+ months (expected relapse rates were 40% at 3 years, and 44% at 5 years respectively). Within pretreatment characteristics (i.e. sex, age, stage, symptom status, histological subtype, nodularity, site of involvement, serum lactate dehydrogenase (LDH), serum copper level (SCL), serum Hb level), the only ones that influenced the duration of remission (shorter disease-free survival) were: increased values of LDH ($P < 0.005$) and SCL ($P < 0.025$), and Hb < 12 g/100 ml ($P < 0.01$). Age < 40 years seems also to be associated with a shorter remission, although significance has not been reached. The actuarial 3-year survival of the evaluable pts is 63% (59% at 5 years; median duration of follow-up of surviving pts: 64 months); the length of survival is significantly related to the response: complete responders have a 3-year survival of 72% versus 28% of nonresponders ($P < 0.01$). Pretreatment LDH ($P < 0.005$), SCL ($P < 0.05$) and Hb ($P < 0.001$) levels, and age < 40 years ($P < 0.025$) were again found to be important factors for predicting survival. The small number of pts within each histological subgroup did not allow evaluation of the prognostic significance of this pretreatment characteristic; the same can be said regarding symptom status (only 3/33 pts with generalized symptoms).

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PROGNOSTIC AT 9 YEARS OF 181 PATIENTS WITH THE DIFFERENT NON HODGKIN'S LYMPHOMA (NHL) TYPES SUBMITTED TO THE SAME PROTOCOL: AVmCP-ICEBERG RADIOTHERAPY-IMMUNOTHERAPY.

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Between 1973 and 1978, 181 patients with NHL referred to our Service were submitted to the same protocol comprising: a) a maximal remission chemotherapy induction with 8 cycles of adriamycin (ADM), teniposide (Vm-26), cyclophosphamide (CPM) and prednisone (PDN); b) a possible radiotherapy applied only to complete a partial remission, hence on persisting lesions; c) an adjuvant chemotherapy with vincristine (VCR), CPM and PDN for one year; d) a randomized BCG immunotherapy. The rate of CR was 79% for the lymphoblastic type, 33% for the immunoblastic type, 79% for the small and mixed centrofollicular cell types, and 64% for the large-cell type. The median duration of DFS was 16 months for the lymphoblastic, 3 years for the small and mixed centrofollicular cell type, and one year for the large centrofollicular cell type. The median duration of survival was 15 months for the lymphoblastic, 11 months for the immunoblastic, 2 years for the large-cell type, and it was not achieved for the small and mixed cell types. Since 1978, treatment policies have been adapted to all types according to the WHO classification. Centrofollicular lymphomas whether nodular or diffuse were still treated with the above described protocol: today there are 169 patients with a 9-year follow up. CR was attained by 85% in the small plus mixed cell group and 70% in the large-cell group. The median DFS was 4 years in the small plus mixed cell group and 2.5 years in the large-cell group. The median of survival curves was 7.5 years for the small plus mixed cell type and 3 years for the large-cell type. Seven patients with T lymphoblastic non leukemic lymphoma (OKT4+ or OKT8+) were treated with a new protocol designed for high-risk ALL (CR induction with ADM, VCR, ASP and PDN, and maintenance with MTX, 6-MP, VDS): a 85% CR rate with a median duration of survival of one year. Twelve patients with B immunoblastic lymphoma were treated with a new protocol consisting in an intensive biphasic chemotherapeutic regimen (ADM, PTC, VDS, CCNU, PDN, PCZ)-(N2H, Ara-C, VCR, ASP, BLM, PDN) given over one year. Of these patients, 7 are in first CR (off treatment). The median of DFS for these 7 patients who achieved CR is not yet reached. The median of survival for all patients is 8 months.

P 77 E.O.R.T.C. NON-HODGKIN LYMPHOMA TRIAL 20751: AN UPDATE ANALYSIS

For the E.O.R.T.C. Radiotherapy/Chemotherapy Group:
J.M.V. Burgers

From 1975 to 1980 612 patients of all stages with a non-Hodgkin lymphoma starting in lymphnodes have been registered. For stage I the trial continued to 1983 (143 patients). Treatment consisted of regional radiotherapy (reg. RX) to 40 Gy alone or followed by chemotherapy consisting of either Vincristin 1.4 mg/m^2 day 1, Cyclophosphamide 4 x 300 mg/m^2 day 1-4, Prednisone 5 x 40 mg/m^2, day 1-5 (CVP) or the same dosages of Vincristin at day 1, of Cyclophosphamide day 2-5 and Prednisone day 2-6 (VCP). Courses were repeated day 29 for 12 courses in 1 year. Survival (S) is 90% at 4 years independent of maintenance chemotherapy. For supradiafragmatic presentations after laparotomy or infradiafragmatic presentations S = 95% S; for supradiafragmatic presentations staged without laparotomy (> 60 years) S = 75%.

Stage II patients (76) after reg. RX were randomized to receive either no further RX or reg. RX to nodes at the other side of the diafragm (ext. RT). All received maintenance treatment with CVP or VCP. Survival was highly dependent on histology: 4 yr S = 90% for follicular pattern, 20% for diffuse high grade according to Kiel and intermediate for the remaining group. Ext. RT seemed helpful for follicular cases, but patient numbers are too small for conclusions.

In stage III and IV all patients (393) received induction chemotherapy, either Adriamycine 50 mg/m^2 day 1, VM26 60 mg/m^2 day 1, Cyclophosphamide 600 mg/m^2 day 1 and Prednisone 5 x 40 mg/m^2 day 1-5 (CHVP) repeated day 22 for 8 cycles; or the same dosage Adriamycine and VM26 day 1, Cyclophosphamide 2 x 300 mg/m^2 day 3 and 4, Prednisone day 3-7 (CICS), repeated day 25 for 8 courses. Iceberg RX to 25 Gy was given to each lymphnode area bearing nodes ⩾ 5 cm initially or not in complete remission after 3 courses. Thereafter followed 1 year of maintenance chemotherapy, CVP or VCP. Stage III 4 yr S = 62%, stage IV S = 48%. CVHP gave better relapsefree survival (RFS) for follicular cases and CICS better RFS for diffuse cases, but both not significant.

From the registered patients about 20% were found inevaluable, these are omitted from the survival data. Pathology review was done for 360 cases for cell pattern, Kiel classification and International Working Formulation. For the follicular group all stages 4 yr S = 78%, for the intermediate group, i.e. non follicular low grade Kiel: all stages 4 yr S = 53% and for the high grade group according to Kiel classification all stages 4 yr S = 35%). Part of the diffuse cases could not yet be coded for Kiel's classification. Correlations between pathological group, clinical presentation and survival will be given.

P 78 A NATIONAL CANCER CARE PROGRAM FOR NON-HODGKIN'S LYMPHOMA IN SWEDEN - PART I. ADJUVANT CHEMOTHERAPY AFTER RADIOTHERAPY FOR LOCALIZED NON-HODGKIN'S LYMPHOMA.

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Within a cancer care program for non-Hodgkin's lymphoma (NHL) in Sweden the effect of adjuvant chemotherapy given to non-laparotomized patients in remission after radiotherapy for NHL stage I and II was studied in a randomized trial. Locally extended field radiotherapy was given to a target absorbed dose of 40 Gy in 20 fractions. Between 1975-1982, 173 adult patients in CR after radiotherapy entered the study. 91 patients were randomized to no further therapy (group A) and 82 patients to adjuvant chemotherapy with 9 cycles of CVP (Cyclophosphamide+Vincristine+Prednisone) (group B). In group B 13 pats declined chemotherapy and these are analyzed separately.

Results: Patients in group A had an actuarial RFS at 75 months of 44% while the corresponding figure for group B was 61% (p=0.008). Survival for these pats was 67% and 80% respectively (n.s.). When stage I pats (no. 105) were analyzed separately no differences were found. Both treatment arms had a RFS of 60% and a survival of 80%. With stage II disease (55 pats) only 25% of the untreated pats remained in first CR at 75 months compared to 50% for CVP-treated pats. Corresponding figures for survival were 51% (group A) and 78% (group B). These differences did however not reach statistical significance. A total of 58 pats have relapsed within the observation period. 5 pats got recurrence only within the radiation target volume while 53 relapsed with extensions.

Conclusions: Adequately delivered radiotherapy to a target absorbed dose of 40 Gy/20 fractions gives an excellent local control (>95%) for NHL stage I-II. For stage I pats adjuvant chemotherapy with CVP may postpone the relapse but has no influence on survival. For stage II, 3 out of 4 pats will relapse within 75 months after radiotherapy only, indicating disseminated disease from the beginning. These patients might do better with chemotherapy as the main treatment modality.

Participating clinics: Depts of Oncology in Umeå, Uppsala, Radiumhemmet Stockholm, Karlstad, Örebro, Linköping, Göteborg, Lund and Malmö,
Depts of Internal Medicine in Akademiska sjukhuset Uppsala, Samaritenhemmet Uppsala, Huddinge, Danderyd, Halmstad, Växjö, Karlskrona, Karlshamn, Kristianstad, Helsingborg, Lund and Malmö.

P 79 TEN YEARS EXPERIENCE WITH CHOP IN THE MANAGEMENT OF GENERALISED GRADE II NON-HODGKIN'S LYMPHOMA. EARLY RECOGNITION OF CASES WITH A POOR PROGNOSIS.

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During the past 10 years the British National Lymphoma Investigation (BNLI) has used a combination of Cyclophosphamide, Rubidomycin, Vincristine and Prednisone (CHOP) as the standard therapeutic arm in controlled studies of the treatment of Grade II generalised Non-Hodgkin's lymphoma in unselected patients over the age of 15. The BNLI experience with CHOP is similar to that in other centres using drug combinations in that a certain number of patients achieve Complete Remission (CR) and can be cured. All other cases prove incurable with routine combination chemotherapy and must be considered for much more aggressive therapy often including autologous marrow infusion. Between January, 1974 and January, 1984 308 patients received initial treatment with CHOP achieving a 5 year survival rate of 30.5%.

Because with some patients the results of treatment are so bad 229 cases have been analysed in detail to allow the earliest possible recognition of those non-responders who might benefit from more aggressive treatment. The most important factor is early CR the probability of which is usually apparent after completing two courses of CHOP. Of patients achieving CR, 60% remain alive free of disease at 5 years. The extent of disease is important: Stage III cases have a 4 year survival rate of 50% as opposed to 27% survival of Stage IV cases. Marrow involvement, (25% of cases) does not affect the prognosis. This difference in survival rate is therefore related to involvement of other organs. The difference in 5 year survival between patients with (22.2%) or without (38.5%) 'B' symptoms is also significant.

Age and sex have little influence in survival and at this point in time the BNLI cases show no difference between the different morphological subgroups. A significant difference may be detectable following analysis of all the 308 patients, some of whom have not yet been followed for long enough to justify inclusion at the time of preparation of this report. The BNLI have also investigated the use of maintenance chemotherapy. In patients achieving CR with CHOP, 51 were randomised for no maintenance or for maintenance using Chlorambucil, Vincristine, Cytosine Arabinoside and Prednisone (LOAP) for 6 courses. There was no detectable difference in survival of the two groups.

The BNLI conclude that at present the most important indications of a possibly good prognosis are the absence of extranodal involvement (excluding marrow) and 'B' symptoms, and the rapidity and completeness of the initial response.

P 80 LONG TERM RESULTS AND RISK FACTOR ANALYSIS FOR STAGE IV DIFFUSE LARGE CELL LYMPHOMA (DLCL) TREATED WITH CHOP-BLEO.

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Sixty-one consecutive previously untreated adult patients with Stage IV DLCL were treated at M.D.A.H. between 1974 and 1981 with CHOP BLEO followed by COP for a total of 1 year. There were 32 males and 29 females. The median age was 56 years (21-78 years). The median duration of follow up of patients alive at the time of analysis was 53 months (22-98 months). Twenty-nine patients had "B" symptoms. Thirteen patients had mediastinal involvement and 37 patients had extensive abdominal involvement. Also 28 patients had only 1 site of extranodal disease while 33 patients had 2 or more sites. The more common extranodal sites of involvement were bone marrow, bone, lung, pleura and skin. Bone marrow involvement was present in 21 patients. LDH was elevated in 41 patients. Three patients were further categorized as having immunoblastic lymphoma (High Grade). The 5 year survival rate for the entire group was 49%. There were 2 early deaths and 3 additional patients were lost to follow up. Among the 56 evaluable patients for remission, 41 achieved CR (73%), 9 achieved PR and another 6 did not respond. Five year survival was significantly better for patients achieving CR (72%). All 15 patients who did not achieve CR died within 26 months. Six risk factors were identified to be significantly related to overall survival time. These were age, constitutional symptoms, serum LDH level, mediastinal enlargement, bone marrow involvement with large cell, and number of extranodal sites of disease. The proportional hazards model, however, identified that only age and number of extranodal sites of disease were significant independent prognostic factors for survival. There were direct correlations between these independent factors and other risk factors. Eleven relapses had occurred among the 41 patients who achieved CR. Presence of "B" symptom and/or elevated LDH at diagnosis were important predictors for relapse. All patients with normal LDH had not relapsed whereas half of the patients with elevated LDH or "B" symptom had relapsed. A subset of 17 patients younger than 56 years with low tumor burden had an excellent probability of survival (86%) at 5 years. However for the rest of the patients the 5 year survival was less than 40%, which indicates the need for chemotherapy intensification for this group of patients. This analysis must be considered for designing new clinical trials and evaluation of their results.

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HIGH DOSE ADRIAMYCIN COMBINATION CHEMOTHERAPY FOR NON-HODGKIN'S LYMPHOMAS OF UNFAVORABLE HISTOLOGY. L Dabich, WD Ensminger, and B Schnitzer, University of Michigan, MK Liepman, University of Massachusetts, KS Zuckerman, RH Wheeler and AF LoBuglio, University of Alabama.

Intensive experimental drug regimens have improved the prognosis for patients (pts) with some of the non-Hodgkin's lymphomas of unfavorable histology. We have treated 41 of these patients including 22 with large cell (histiocytic) lymphoma, 3 with diffuse poorly differentiated lymphocytic lymphoma, 5 with undifferentiated lymphoma (3 Burkitt's and 2 non-Burkitt's), 4 with diffuse mixed lymphoma and 6 with diffuse T-cell lymphoblastic lymphoma according to a protocol which includes 3 courses of adriamycin 120 mg/M^2 IV on Day (D) 1, vincristine 2 mg IV on D 1 and prednisone 50 mg po TID Ds 1-5, administered at 21 day intervals and 3 courses of cyclophosphamide 800 mg/M^2 IV D 1 and cytosine arabinoside 3000 mg/M^2 IV over 2 hours on Ds 1 and 8, administered at 21 day intervals or when bone marrow recovery was evident. No maintenance therapy was used. The 22 pts with large cell lymphoma include 9 women and 13 men with a median age of 52 (20-65). The Ann Arbor stages were II-A 6, III-A 3, IV-A 3, IV-A 8 and IV-B 5. 15 of 15 patients who completed the full course of chemotherapy entered a complete remission (CR). 2 other pts, 1 of whom died of treatment related sepsis after 2 courses, and 1 of whom died of a myocardial infarction after 5 courses, had no clinically detectable lymphoma at the time of death. It is too early to evaluate the 5 other pts. There has been a systemic relapse at 12 1/2 mos in a woman whose IVA disease was bone. There have been two intracerebral relapses. 1 after 9 mos was treated only with cranial radiation and intrathecal methotrexate and the patient is in CR at 44 mos. The second occurred at 16 mos. The only death in the CR group was a man who died of metastatic prostatic carcinoma after 21 mos. Disease free survivals for the other patients are 59, 47, 46, 36, 34, 34, 30, 27, 21, 14 and 11 mos. Pts with the other B cell disorders have also done well. In contradistinction is the experience with the 6 patients with T-cell lymphoblastic lymphoma: 5 men and 1 woman (22 - 39) whose median age was 21. Their stages were II-B 1, III-A 1, IV-A 4. With one exception they either failed to reach or sustain a remission. Despite the small sample size, the study suggests that these patients do not benefit from this program and that consideration may need to be given to separating out patients with T cell disorders in designing future studies.

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TREATMENT RESULTS WITH A MODIFIED CHOP/BLEO PROGRAM IN NON-HODGKIN'S LYMPHOMA (NHL) OF UNFAVORABLE HISTOLOGY (UH). J.C. Díaz Maqueo, E.L. García de Díaz, B. López Ariza, Leticia Rodríguez M., Sergio Loera F. and Enrique Arechavala Servicio de Hematología. Hospital de Oncología, CMN. IMSS. MEXICO.

63 previously untreated patients (pts) with NHL of UH received CHOP/Bleo (cyclophosphamide 600 mg/M2, adriamycin 50mg/M2, vincristine 2 mg, bleomycin 15 mg I.V. day 1 and prednisone 60mg/M2 P.O. 5 days) with the addition of methotrexate (20mg/M2) alternating with cytosine arabinoside (80mg) on day 14th of each cycle. There were 28 males and 35 females with a median age of 53 years (range 16-86). ECOG performance status (EPS) was 0-3, 54 pts and 4, 9 pts. The original histological diagnosis were: 25 Diffuse predominantly large cell, 11 Diffuse mixed, 7 Diffuse small cleaved cell, 4 immunoblastic, 1 signet ring cell and 12 unclassified lymphomas. 32 pts belonged to low socio-cultural level, 28 to medium level and 3 to high level. 7 pts were stage I (5, IE), 9 IIE, 5 III (3, IIIE) and 34 IV, but all had unfevorable prognostic factors. Of 63 pts, 9 were not evaluable, there were 36 (66.6%) complete responses (CR) and 12 (22.2%) partial responses (PR). The median duration of disease free interval (DFI) and total survival (TS) for the CR group were $>$ 21 months (ms) (range 2-29) and $>$26 ms (range 7-35) respectively. Major factors affecting response rate are: dosage, EPS, socio-cultural level, stage, age and histology; multifactorial analysis will be presented on the Conference but concrete percentages are presented in this abstract. 87.5% of pts who received complete doses had CR and 36.4% of pts who received half doses had CR. 72.3% of EPS 0-3 pts had CR and 28.5% of EPS 4 pts had CR. 81.4% of pts with medium socio-cultural level had CR and 54% of low sociocultural level had CR. 80% of stage I-III pts had CR and 56.7% of stage IV pts had CR, however, stage IV pts who received complete doses had a CR rate of 93.3% indicating that their lower response rate is related to intolerance rather than unresponsiveness. 31 to 60 years pts had better responses (62.5-75%) than younger and older groups (53 and 57.1% respectively), nevertheless, evaluable pts 71 years or older had a 100% CR, indicating than intolerance can be the major cause of failure in elderly groups and histologic unresponsive subtypes in younger groups. Not important differences were observed in relation to histology except for immunoblastic lymphoma that had 33% CR. We consider that the addition of methotrexate and cytosine arabinoside to CHOP/Bleo increases the response rate, the mean DFI and the TS in a significative way. This is an excellent program when administered in complete doses to pts with intermediate degree of malignancy lymphomas whose EPS and sociocultural level are adequate.

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INTENSIVE SEQUENTIAL COMBINATION CHEMOTHERAPY (ISCC) WITH F-MACHOP IN NON-HODGKIN'S LYMPHOMA (NHL). Guglielmi C., Amadori S., Anselmo A.P., Cimino G., Marzullo A., Papa G., Baroni C.D. and Mandelli F.. Dipartimento di Biopatologia Umana, Università Studi, Roma.

During the years 1980-82, 54 consecutive pts with NHL were treated by ISCC with the F-MACHOP regimen. Eligibility criteria included: diagnosis of intermediate grade (IG) or high grade (HG) NHL (Working Formulation), age 15-70 yrs, no previous treatment and no clinical contraindications for ISCC. F-MACHOP consists of vincristine(0.5mg/m^2 i.v. hr 0 and 12), 5-fluorouracil(15mg/Kg c.i. hr 36-42), cytarabine(1g/m^2 c.i. hr 42-48) adriamycin(60mg/m^2 i.v. hr 48), methotrexate(500mg/m^2 c.i. hr 60-66) and prednisone(60mg/m^2 p.o. days 1-14). Folinic acid rescue(20mg/m^2 q.12hr x 4) was started at hr 84. Courses of therapy were administered every 3-4 wks for a total of 6. CNS prophylaxis was carried out by 6 monthly injections with MAIT or by cranial irradiation only in selected pts (BM inv. or HG-NHL). Responsewas evaluated by a careful clinical restaging 1 mo. after the 6th course and no further treatment was given to those found to be in complete remission (CR). The CR rate in all study pts, including 3 early deaths), was 73%. There was no significant difference in CR between 14 IG-NHL(71%) and 40 HG-NHL(72%). Highly significant was the difference in CR between 25 pts with bulky disease and 29 pts without it (48% vs 93%, p$<$0.01). Some other clinical features were found to be associated with a lower CR rate (male sex, lymphoblastic histology, primary mediastinal disease, stage III-IV, B-symptoms and age 30yrs) but none of these was found to be a significant predictor of response. The median follow-up time in CR pts is 24+mo. and a total of 6/39 (15%) of them have relapsed, all within the first 18 mo. 83% of CR pts is therefore projected alive and disease-free 42 mo. after cessation of treatment. CNS involvement occurred in 1/12 (8.3%) of non-responders and in 1/39 (2.5%) of CR pts. Toxicity included transitory myelodepression in most pts with a return to normal counts before day 21 in the majority of them. However 3 pts(5%) died from septicemia while severely granulocytopenic No pt suffered of severe dose-limiting cardiac or neurologic toxicity. In conclusion, F-MACHOP is an effective regimen for pts with non-bulky NHL with acceptable toxicity.

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AGGRESSIVE NON-HODGKIN'S LYMPHOMA TREATED WITH INTENSIVE SEQUENTIAL CHEMOTHERAPY. B Coiffier, PA Bryon, D Fière, M Ffrench, H VuVan, D Guyotat, F Berger, JJ Viala. Département d'hématologie, hopital E-Herriot, 69374 LYON FRANCE.

83 patients with aggressive malignant lymphoma (diffuse mixed: 18, diffuse large cells: 18, small noncleaved cells: 14, immunoblastic: 12, lymphoblastic: 5, other nonepidermotropic T-lymphomas: 11, and other: 5) were treated with intensive sequential chemotherapy during 9 months: (doses for 1 m2)

months 1 - 2		month 3		months 8 - 9	
cyclophosphamide	1200	aracytine 100/dx4d x3		cyclophosphamide	1200
adriamycine	75			aracytine	200/d x4
vindesine	3	month 4		VM 26	60
bleomycine	5	methotrexate 3000 x2		bleomycine	5
prednisone	60			prednisone	60
IT methotrexate	10	month 5			
x 3 or 4		asparaginase 60000 x3		x 2	

Complete remission (CR) was achieved in 75 patients (90 %): 4 patients died in the induction phase from complications due to the treatment, 4 patients did not responde. Among the patients with CR, there was 13 (17 %) relapses. 3 patients died from unrelated disease while in CR.

Blood toxicity was tolerable (neutropenia 1.000 in 50 patients, but only 14 of them presenting a documented infection; thrombocytopenia 50.000 in 11 patients without severe hemorrhagia) and treatment could be realized without problems in most cases. 10 out of 26 patients with immunoblastic or small non cleaved lymphomas presenteed an acute lysis syndrome after the first course of chemotherapy (2 died).

The median survival cannot be reached with a 28 months median follow-up, but the survival rate seems to plateau at 70 %. The only three prognostic factors identified were poor general condition, high serum lactate deshydrogenase level, and anemia.

P 85 CHEMOTHERAPY OF NON-HODGKIN'S LYMPHOMA WITH ALTERNATING NON-CROSS COMBINATION REGIMENS (AVCP/EMLP)

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In an attempt to increase the complete response (CR) rate and survival of patients (pts) with non-Hodgkin's lymphoma, induction chemotherapy of alternating non-cross combination regimens (AVCP/EMLP) was administered to 18 pts since January 1981. The chemotherapeutic regimens were as follows: AVCP (adriamycin 40 mg/m2 d1, vincristine 1.4 mg/m2 d1 weekly, cyclophosphamide 500 mg/m2 iv d1, prednisolone 40 mg/m2 po d1-5, q 3 wks), and EMLP (VP-16 200 mg/day po d 1-5, methotrexate 200 mg/day iv d1-5 with leucovorin, L-asparaginase 5.000 u/day iv d2-8, prednisolone 40 mg/m2 po d1-5, q 3 wks). The treatment was started with two courses of AVCP regimen, and then was switched to two courses of EMLP regimen, regardless of the response of AVCP regimen. Thereafter, treatment was chosen to use one of better regimen or alternatingly. Treatment for CR pts was continued for 2 years after the achievement of CR. Median age of pts was 53 years, and male:female ratio was 5:1. Clinical stages were II 4, III 2 and IV 12 pts, and extranodal sites of 16 pts were bone marrow 7, tonsil 3, pleura 2, liver 2, GI tract 2, nasal cavity 1 and bone 1. Pathological classification by Rappaport was DH 12, DPDL 3, DM 2 and NPDL 1. Three pts had previous chemotherapy and 5 pts irradiation. Seventeen pts were evaluable for responses. Four pts achieved a CR (24%), 12 pts partial response (PR, 71%), and one non-response (NR). The median duration of response was 6.5+ mos for CR and 4+ mos for PR. Median survival times from the start of the treatment were 6.9+ mos for all pts, 10.3+ mos for CR and 5.5+ mos for PR. Toxicity was acceptable. Although this treatment produced a high rate of overall response (94%) the CR rate was low (24%). The reason of the low CR rate seems that there were pts with poor prognostic factors (7 bone marrow involvement, one bulky abdominal mass, and 5 T-cell marker among 8 pts). Pts with 2 PRs and 3 NRs after two courses of AVCP regimen, achieved 2 CRs and 3 PRs. Further study is needed to define the activity of this chemotherapy.

P 86 TREATMENT OF ADVANCED HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL) WITH CHOP AND INTERMEDIATE DOSE MID-CYCLE METHOTREXATE COMBINATION CHEMOTHERAPY (MACOP).

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Cyclical combination chemotherapy (maximun 6 cycles) comprising i/v adriamycin 50mg/m², cyclophosphamide 1Gm/m², vincristine 2mg, and intrathecal methotrexate 12.5 mg on day 1, oral prednisolone 100mg/m² days 1-5,i/v methotrexate 300mg/m² day 10 (followed by folinic acid rescue 24 hours later) was given at 3 weekly intervals to 51 consecutive, previously untreated adults with high grade (Kiel classification) NHL (age range 17-76, mean 49, median 54 years; stage IV, 36, stage III, 9 and bulky stage II, 6). Twenty-six were very ill (Karnofsky grade less than 70) and 28 had bulky disease. Thirty-one (62%) achieved complete or good partial (minimal radiological abnormalities on restaging) remission; 6 failed to respond (including 1 partial response) and 14 patients (28%) died during therapy (12 during the first 6 weeks). The latter patients were older (mean age 62 years) andmost had bulky disease; 8 died of sepsis, 3 of heart failure and 1 each of renal failure, gastrointestinal bleeding and oesophageal rupture. Ten patients have relapsed, all within 4 months of completing therapy. Twenty-one (42% overall, 68% of responders) continue infirst remission between 3 months and 2½ years (median follow up 18 months). None achieved remission with less than 3 cycles of treatment; 19 received 3-5 cycles and only 20 (40%) completed 6 cycles. The frequency of remission and survival were adversely affected by advanced age and stage.

Severe toxicity included mucositis (56%), fever requiring antibiotic therapy (62%), neutropenia (82%), thrombocytopenia (40%) and anaemia requiring blood transfusion (40%). Alopecia, nausea and vomiting were universal. Reversible renal impairment occurred in 4 patients.

In conclusion this treatment approach resulted in remission being achieved in the majority of younger patients for whom the treatment related morbidity and mortality was low. However, early relapse has already occurred in 10/31 (32%) remitters, demonstrating this approach to be less than adequate.

P 87 ADRIAMYCIN, VINCRISTINE, AND ARA-C FOR POOR PROGNOSIS LYMPHOMA

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Aggressive chemotherapy leads to cure of many patients (pts) with diffuse large cell lymphoma (DHL) who achieve complete remission (CR). However, some pts either fail to achieve CR or later relapse. Factors associated with a poor prognosis include: GI, bone marrow, or CNS disease; tumor mass > 10 cm; and clonal evolution from a lower grade lymphoma. We undertook to evaluate a very intensive regimen, modelled on regimens for acute leukemia, in patients with these adverse prognostic factors.

Ara-C and Adriamycin are active in treating DHL, as well as lymphoblastic lymphoma. To test the combination of these agents against poor prognosis subcategories of non-Hodgkin's lymphoma, 7 pts were treated with Adriamycin 25 mg/M² IV qd X3, Vincristine 2 mg IV d. 1 + 8, and Ara-C 100 mg/M² continuous IV qd X5. Restaging was done after three 21-28 d. courses, and CR surgically confirmed after a fourth course. 4 pts had DHL (International Working Formulation category G or H; 1 with marrow invasion, 1 previously treated for lower grade histology, 2 with > 10 cm mass), 2 LBL (category I), and one D-PDLL (category E; with total marrow replacement). 6/7 were previously untreated; 5/7 completed 4 courses each (2 required dose reduction, 3 required treatment delay). 5/7 (71%) achieved CR, of whom 3 subsequently relapsed after mean remission duration of 164 days (range 117-222); 1/7 achieved partial remission and entered CR after 3 cycles of Cytoxan, Vincristine and Prednisone (CVP). 4 pts are alive (all with DHL), and 3 pts (including the one who entered CR after CVP) now have unmaintained CR of 12+, 14+ and 20+ months. Toxicities included: all pts had WBC < 1,000 and plts < 25,000 for all courses; 6 pts had 7 infectious episodes during 24 courses of treatment, including 4 life-threatening infections; 3/7 had severe hepatic toxicity (SGOT > 10X nl), developing after multiple courses; 3/7 had severe mucositis (requiring enteral or parenteral alimentation); and 3/7 had severe neurological toxicity, including 2 pts who became unable to walk for several weeks. Interestingly, the 3 pts who remain in CR had significantly less acute and overall toxicity than the other 4 pts.

All 4 patients with DHL ultimately achieved CR, including 3 durable CRs, indicating activity for the regimen in this disease. However, the excessive toxicity seen with this dose and schedule appears to preclude any advantage for it over previously described regimens.

P 88 A NATIONAL CANCER CARE PROGRAM FOR NON-HODGKIN'S LYMPHOMA IN SWEDEN - PART II. PREDNIMUSTINE VERSUS CVP IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA VITH FAVOURABLE HISTOPATHOLOGY.

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Within a nationwide cancer care program for non-Hodgkin's lymphomas in Sweden a prospective randomized trial of NHL with favourable histopathology (NLPD, NM, DLWD and DLPD according to Rappaport), comparing the treatment results of Prednimustine with the CVP regimen has been carried out. From Jan. 1, 1979 to May 30, 1982, 226 patients were randomized and by March 1983, 206 patients (103 in each arm) were evaluable.

Prednimustine was given orally in a daily dose of 200 mg (if body surface ≥1.8 m²) or 150 mg (<1.8 m²) five consecutive days every two weeks. When a complete remission was obtained the cycle was prolonged with two weeks for every third cycle. The total time of therapy was two years after a complete remission was achieved.

The CVP regimen consisted of Cyclophosphamide 800 mg/m² i.v. bolus and Vincristine 1.4 mg/m² bolus i.v. injection on day 1 and Prednisolone orally 25 mg x 3 for five days. The length of the cycle was three weeks. When a complete remission was assessed the length of cycle could successively be prolonged with two weeks every third cycle. The total treatment time was two years after a complete remission was documented.

Results: The overall response rate was 64% (66/103, CR 40%, PR 24%) for the Prednimustine regimen and 69% (71/103, CR 34%, PR 35%) for the CVP regimen. The relapsefree survival was significantly longer in the Prednimustine arm compared with the CVP arm (p=0.02). The overall survival for CVP regimen was however significantly longer (p=0.03) and the median survival is in excess of 40 months compared to 32 months for the Prednimustine regimen. However, the overall survival in the responding patients did not differ.

The patients were in retrospect reclassified according to Kiel, and if patients having a high grade malignant lymphoma according to this classification are excluded, the significant difference in overall survival disappears.

Treatment with Prednimustine was less toxic and better tolerated than CVP. Dose reduction due to toxicity had to be performed in 28% of Prednimustine patients and 62% of CVP patients. Since Prednimustine is a more agreeable treatment for the patients and consume less hospital care resources, it was concluded that Prednimustine was the therapy of choice for low grade malignant non-Hodgkin's lymphomas.

Participating clinics: see part I.

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P 89 ETOPOSIDE, METHOTREXATE/CITROVORUM, AND CYTOSINE ARABINOSIDE (EMC^2) FOR RECURRENT NON-HODGKIN'S LYMPHOMAS. Richard S. Kaplan for the Mid-Atlantic Oncology Program (MAOP).

Despite advances in the primary therapy of the diffuse or aggressive non-Hodgkin's lymphomas (NHL), patients with recurrences are not presently curable and many groups are investigating the activity of non-cross resistant combinations which might be alternated with standard initial chemotherapy. We are evaluating Etoposide (VP-16) 100 mg/m^2 days 1,3,5 q3 weeks with methotrexate/citrovorum (MTX/C) and cytosine arabinoside (ara-C) given on days 8 & 15 (120 mg/m^2 MTX & 200 mg/m^2 ara-C) in a manner similar to the use of these drugs in "COMLA". All 3 agents have demonstrated activity in NHL, and we elected to study the combination in all types of NHL resistant to standard types of chemotherapy.

MAOP investigators have entered 18 patients (pts) in the first 3 months of accrual and preliminary data are available for 16. All had far advanced NHL and 9/16 had documented bone marrow involvement by lymphoma. Distribution of histologic types according to Rappaport and International Working Formulation (IWF) systems and objective responses to the initial cycles of therapy are as follows:

Rappaport	IWF	#	Response	
DWDL	A	1	0/1	(stable)
NPDL	B	2	0/2	(both stable)
NM	C	2	1/2	(1 stable)
DPDL	E	5	1/5	(2 stable; 2 prog.)
DM	F	2	1/2	(1 stable)
DHL	G	4	1/4	(2 prog.; 1 TETE)

The 4 responses were all PR's (3 abdominal masses and 1 pelvic lymph node mass) and have lasted 4-12+ weeks thus far. Hematologic toxicity has been significant. Pts without known marrow invasion had M WBC nadir of 2.0 (day 15) (range 0.2-10) and platelet nadir of 90K (day 15) (10-200). Those with positive marrow biopsies had M WBC nadir 1.2 (0-7.0) and plt nadir of 20 K (9-180). Pts with 3rd-space fluid had marked myelosuppression even with negative marrow biopsy. Non-hematologic toxicity was minimal.

Updated results on a larger series will be presented.

P 90 CIS-PLATINUM (CPDD), VENIPOSIDE (VM-26) AND HEXAMETHYLMELAMINE (HMM) VERSUS CIS-PLATINUM AND VINDESINE (VDS) FOR REFRACTORY NON HODGKIN LYMPHOMAS (NHL) AND HODGKIN'S DISEASE (HD).

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31 cases of refractory to conventional chemotherapy NHL and HD were randomised to two chemotherapeutic schemes:Scheme A:Day 1 CPDD 60 mg/m^2 days 2-8 HMM 6mg/kgr/day P.O. and day 8 VM-26 100 mg/m^2. Scheme B:Day 1 CPDD 60 mg/m^2 and days 1, 8, 15 and 22 VDS 4 mg/m^2. Treatment was repeated every 4 weeks. Switch over to the other scheme was scheduled for cases not responding or relapsing. Most patients were heavily pretreated and in poor condition. 17 patients (12 NHL and 5 HD) were randomised to scheme A and 14 patients (11 NHL and 3 HD) to scheme B. 6 patients were switched over to scheme A from scheme B and 4 to scheme B from scheme A. Scheme A produced 2 complete remissions (CR) and 2 partial remissions (PR) in NHL and 5 PR in HD. Scheme B produced 1 CR and 3 PR in NHL and no remission in HD. The mean duration of response was short in both schemes (3,4 months). Toxicity was acceptable considering the patients' condition and prior chemotherapy. Both schemes seem active in NHL. All 5 patients with HD who were randomised to scheme A responded.

P 91 CHEMOTHERAPY WITH VINDESINE, IPHOSPHAMIDE AND PREDNISONE (VIP) AS TREATMENT FOR REFRACTORY NON-HODGKIN'S LYMPHOMA (NHL). W F Jungi, Th Kroner, J P Obrecht, K Bürki, W Berchtold, F Cavalli for Swiss Group for Cancer Research (SAKK).

In a prospective study 25 patients (pts) with advanced NHL were treated with Iphosphamide (1.2 g/m^2 iv d 1-5), Vindesine (3 mg/m^2 iv d 1) and Prednisone (60 mg/m^2 po d 1-5). Courses were repeated every 3 weeks. In order to prevent Iphosphamide-induced urothelial toxicity Mesna (2-mercaptopurine sulfonate sodium) was given in addition. Treatment was usually ambulatory. 21 NHL pts are evaluable for response and toxicity. All pts were pretreated with a median of 5 (range 3-11) cytotoxic agents in various combinations. A total of 117 VIP courses were given (median 4 courses/pt, range 1-20). Nausea, alopecia and dose-limiting neutropenia were the most prominent side effects. Urothelial toxicity was virtually absent, no CNS-toxicity and no toxic death were observed. Overall response rate was 57% (95% confid.interval: 34-78%): CR 2/21 pts (duration 2 and 16+ months), PR 10/21 pts (median duration 5.7 months, range 1.5-11.5 months). All responding pts had been pretreated with cyclophosphamide and all but one with vincristine, they were considered resistant to these agents. Responsiveness to prior chemotherapy proved to be a more important prognostic factor than histology at time of diagnosis. Our data suggest that VIP is an effective regime for some pts with advanced NHL. It possibly lacks cross-resistance to conventionally dosed cyclophosphamide.

P 92 A PHASE II TRIAL OF TENIPOSIDE (VM 26) IN ADVANCED NON-HODGKIN'S LYMPHOMA (NHL), WITH EMPHASIS ON THE TREATMENT OF ELDERLY PATIENTS (PTS). U.Tirelli°, A.Carbone‡, D.Crivellari°, G.Franchin°,A.Veronesi°,E.Galligioni°,M.G.Trovò°,R.Volpe°,S.Tumolo° and E. Grigoletto°. °Radioter.& Medical Oncol.,General Hospital,Pordenone; ‡Dept.Pathology,Ist.Naz.Ricerca sul Cancro,Genova, Italy.

54 pts had entered a phase II trial of VM 26 in stage III (35 pts) and stage IV (19 pts) NHL classified according to modified Rappaport system. The median age was 71 years (19-85). 32 pts were previously treated with chemotherapy and radiotherapy, whereas 22 were elderly (70-85 years) untreated pts with a median Karnofsky of 70. VM 26 was given by i.v. infusion at 100 mg/m^2 weekly for at least 3 doses in unfavourable suptypes and for at least 6-9 doses in favourable subtypes, prior to the evaluation of response. The overall objective response rate was 43% in the 51 evaluable pts. The median duration of the 12 CRs was 7+ months (26+ to 2). According to the histology, VM 26 was very effective in the 6 pts with diffuse"histiocytic" (DH) subtype (4 CRs, 1 PR), and in the 8 pts with mycosis fungoides (MF) (2 CRs, 2 PRs). Diffuse lymphocytic poorly differentiated and lymphoblastic NHL were less sensitive subtypes to VM 26. Among the 20 evaluable elderly pts a 50% objective response rate was obtained with 5 CRs. 4 CRs and 1 PR were obtained in the 5 pts with DH subtype; no response was obtained in the only pt with MF. Toxicity, usually hematologic, was mild, even in elderly pts; neurotoxicity occurred in 4 instances.

VM 26 seems to be an effective and well tolerated drug in advanced NHL; this drug should be further evaluated as first-line chemotherapy in elderly (≥ 70 years) previously untreated pts with poor general conditions and DH histology.

93 PHASE II TRIALS WITH AMSACRINE (M-AMSA), AZIRIDINYLBENZOQUINONE (AZQ), ACLACINOMYCIN (ACM) IN LYMPHOMA. D.C. Case, Jr. and D.M. Hayes, Maine Medical Center, Portland, ME.

Clinical trials with three investigational drugs have been conducted in patients with advanced lymphoma. Patients failing or relapsing after initial combination chemotherapy were eligible for these phase II studies. Represented histologies included nodular poorly-differentiated lymphocytic lymphoma (NPDL), nodular mixed (NM), diffuse well-differentiated lymphocytic (DWDL), diffuse poorly-differentiated lymphocytic (DPDL), diffuse mixed (DM), diffuse histiocytic (DHL), lymphoblastic lymphoma (LL), and Hodgkin's disease (HD). Each drug was administered as a single IV dose given at 21-day intervals. M-AMSA, an acridine dye derivative, was used in 25 patients at a dose of 120 mg/M^2. Ten responses were seen (8PR and 2CR). Responses were seen only in DHL (5/9) and NPDL (5/9). All responses were <6 months duration except for one CR (14+ mo). Median nadir WBC during first cycle of therapy was 2300/mm^3. Significant thrombocytopenia was not observed. One patient appeared to have suffered a fatal cardiac arrhythmia one half hour after therapy with M-AMSA. Autopsy was negative for any cardiac or cerebral thromboembolic disease or lymphoma. AZQ, a synthetic benzoquinone, has been utilized in 35 patients at a dose of 30 mg/M^2. Eight responses have been noted, 5 CR (2,3,3,14+,14+) and 3 PR (2,2,7). Six of the responses were seen in diffuse histologies (4DHL, 1DPDL, and 1DM). Only one of eight patients with NPDL responded. One patient with CNS lymphoma responded completely to IV AZQ. Median nadir WBC was 2100/mm^3 and platelet count 80,000/mm^3. Cumulative thrombocytopenia, requiring dose adjustment in one-half of patients, was seen and was not related to prior nitrosourea. In two patients receiving 12 cycles of AZQ, thrombocytopenia has persisted for more than 3 months after treatment has been discontinued. Bone marrow during the period of thrombocytopenia revealed reduced megakaryocytes. ACM, an anthracycline antibiotic, has been utilized at a dose of 100 mg/M^2 in 22 patients. Two partial responses have been seen. Median nadir WBC was 2500/mm^3 and platelet count 126,000/mm^3. Nausea/vomiting was seen in the majority of patients. Significant responses have been seen with M-AMSA and AZQ in these studies in lymphoma. Further exploration of the dose and scheduling of ACM may be required to determine the potential utility of this agent. Acute arrhythmias may affect M-AMSA use; serum potassium should be monitored. Cumulative thrombocytopenia may complicate long-term use or combination chemotherapy with AZQ. (Supported by a grant from the Maine Cancer Research and Education Foundation)

P 94 MITOXANTRONE IN REFRACTORY NON-HODGKIN'S LYMPHOMA: C.A. Coltman, Jr., T.M. Coltman, S.P. Balcerzak, F.S. Morrison, and D.D. Von Hoff for the Southwest Oncology Group. San Antonio, Texas, 78229.

A Phase II study of mitoxantrone in non-Hodgkin's lymphoma using an every three week schedule, was conducted by the Southwest Oncology Group between July 1981 and May 1982. The study involved 37 patients with histologically proven non-Hodgkin's lymphoma, not eligible for higher priority protocols, and with clearly measurable disease. Patients received 12mg/M^2 at three week intervals with a 10% increase in dose in the absence of myelosuppression and a 17% reduction for a WBC <2,000/μL or a platelet count of <50,000/μL. The median number of prior regimens was 3(1-5). Prior Adriamycin, in a median dose of 242mg/M^2 (12-650), was given to 34 of 37 patients. Thirty-one of the lymphomas (84%) were reviewed by the Pathology Panel for Lymphoma Clinical Studies.

International Working Formulation	N	CR	PR
Low Grade			
A. Diffuse, Small Lymphocyte	6	0	2
B. Follicular, Small Cleaved Cell	10	2	2
C. Follicular, Mixed Cell	2	0	0
Intermediate Grade			
D. Follicular, Large Cell	2	0	0
E. Diffuse, Small Cleaved Cell	2	0	1
F. Diffuse, Mixed Cell	0	0	0
G. Diffuse, Large Cell	9	0	1
High Grade			
H. Large Cell, Immunoblastic	0	0	0
I. Lymphoblastic	2	0	0
J. Small Non-Cleaved	0	0	0
Unclassified	4	0	1
TOTALS:	37	2	7

The 4 of 10 responses in follicular, small cleaved cell lymphoma contrast with the 1 of 9 responses in diffuse, large cell lymphoma. The median duration of response was 231 days. A median of two doses of mitoxantrone was given, with a range of from 1 to 18. The median WBC nadir following the first dose of mitoxantrone was 5,100/μL (0.4-9.4) and the median lowest WBC for all doses was 2,400/μL (0.8-16.0). Among 17 patients with a first nadir WBC <3000/μL there were 3 PR's compared to 9 patients with WBC >3000/μL in which there were 4 responses (1-CR, 3-PR). There were 7 responses (1-CR, 6-PR) among 23 patients with ≤3 prior regimens and 2 responses (1-CR, 1-PR) among 14 with >3 prior regimens. The response rate was independent of the dose of prior Adriamycin with 5/23 responses (1-CR, 4-PR) with a total dose of less than 300mg/M^2 and 4/14 responses (1-CR, 3-PR) at total doses more than 300mg/M^2. These data are compatible with the hypotheses that mitoxantrone alone is active in previously treated low grade lymphomas; that the response rate is twice as high among those who had received three or less prior regimens; that response rate is independent of the total dose of prior Adriamycin, and that response rate is independent of the degree of myelosuppression. Mitoxantrone may be non-cross resistant with Adriamycin.

P 95 PHASE II AND CLINICAL PHARMACOLOGY STUDIES WITH ORALLY ADMINISTERED VINZOLIDINE. W. Kreis, D.R. Budman, J. Freeman, A. Greist*, R.L. Nelson*, P. Schulman, M. Marks, L. Kevill, V. Vinciguerra, T. Degnan. Dept. of Medicine, North Shore University Hospital and Cornell University Medical College, Manhasset, New York 11030 and Lilly Research Laboratories, Indianapolis, Indiana 46202.

Vinzolidine (VZL), a new semi-synthetic Vinca alkaloid with substantial oral bioavailability, was evaluated in 22 patients with non-small cell lung cancer (5 pts), chronic lymphocytic leukemia (3) and lymphomas (14). The treatment consisted in 3 portions given p.o. q 6-8 hrs every 2 weeks starting at total doses of 30 mg/m^2 in PS=1 (CALGB) and 25 mg/m^2 in PS=2 or heavily pretreated patients. Partial responses were seen in 1 patient with adeno-ca of the lung and patients with diffuse large cell lymphoma, mycosis fungoides, nodular well differentiated lymphoma and nodular sclerosing HD. Some of these patients responded despite prior exposure to Vinca alkaloids. Toxicities were neutropenia, anorexia and diarrhea. None of these toxicities resulted in discontinuance of the drug. Dose limiting toxicity was neutropenia. Patients have been continued on VZL as long as 11+ months without evidence of cumulative toxicity. Clinical pharmacology studies in 4 patients using ^{3}H-VZL, revealed rapid absorption after p.o. administration, with peak time of 4 hrs. Biphasic decay of total tritium revealed an initial half life of 8.4 hrs and a terminal one of 170 hrs, fitting well a two compartment open model with first order absorption. These pharmacokinetic values are similar to the ones reported earlier (R. Nelson, Proc. ASCO, 2, 19, 1983). Recovery of radioactivity over 14 days was 4% in urine and 55% in feces. Qualitative analysis by HPLC revealed predominance of unchanged VZL and one to four metabolites with varying elution times in plasma, urine and feces. In the latter, the four radioactive peaks observed (besides the unchanged ^{3}H-VZL), presently analyzed for their chemical structure, might be partly responsible for the toxicity pattern, which is different from the one of Vincristine but similar to the one of Vinblastine. Whether the metabolites found in feces are primary (due to the action of pH and/or intestinal flora) or secondary (due to metabolism in the liver), cannot be decided on the grounds of these studies. Rapid absorption, long retention in plasma and metabolism are the pharmacokinetics of Vinzolidine.

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P 96 PHASE II TRIAL OF MITOXANTRONE IN NON-HODGKIN'S LYMPHOMA. D.C. Case, Jr., R.S. Stein, R.A. Gams, J. Steinberg, and L. Posner. Maine Medical Center, Portland, ME 04102, Vanderbilt Univ, Nashville, TN 37232, Univ Alabama in Birmingham, Birmingham, AL 35294, and Lederle Laboratories, Pearl River, NY 10965.

Mitoxantrone, an anthracenedione derivative, has been utilized in a multi-center phase II study in adult patients with advanced non-Hodgkin's lymphoma. Eligibility requirements included: 1) one of the following histologies - nodular poorly differentiated lymphocytic (NPDL), nodular mixed (NM), nodular histiocytic (NH), diffuse poorly differentiated lymphocytic (DPDL), diffuse mixed (DM), and diffuse histiocytic (DHL); 2) prior treatment to have included only prior chemotherapy regimen; 3) performance status of 0-3; and 4) prior anthracycline 450 mg/m^2 and normal ejection fraction as measured by radionucleotide angiography. Patients have received mitoxantrone as a single IV dose every three weeks with an initial dose of 14 mg/m^2 with dose modifications to 16 mg/m^2 or 10-12 mg/m^2 according to degree and duration of hematologic toxicity (granulocytopenia). To date, 71 patients have been enrolled on this study. Twenty-eight patients are now evaluable to determine response. Fifteen patients have responded (54%) (2 CR& 13PR). Responses by histology include NPDL (1.5, 1.5, 2+, 6.5+, 8 mo), NM (1,1+), DM (1,1+,1+), DPDL (4+), and DHL (1+,1+, 1.5+, 3). Prior adriamycin therapy did not adversely affect response rate. Seven of the responses were seen in patients who received an anthracycline and nine responses were in patients who did not receive prior anthracycline. The major dose-limiting toxicity was granulocytopenia. Median nadir WBC was 2300/mm^3 (range 500-9700/mm^3) with granulocytes 1000/mm^3 (range 40-5335/mm^3). Non-hematologic toxicity has been infrequent and mild. Follow-up is too limited to assess the incidence of cardiac toxicity. Mitoxantrone appears to have significant activity in patients with non-Hodgkin's lymphoma who have received only one prior combination chemotherapy regimen. Neutropenia was acceptable with the present dose and schedule.

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A PHASE II STUDY OF PREDNIMUSTINE THERAPY IN REFRACTORY NON-HODGKIN'S LYMPHOMA: D. Gandara, J. Redmond, M. Kohler, B. Lewis. Northern California Oncology Group, Palo Alto, California 94304.

Prednimustine is a combination steroid cytotoxic agent structurally consisting of a prednisolone ester of chlorambucil. Early studies have reported a wide spectrum of antitumor activity. The therapeutic advantage of this agent is reported to be mild toxicity characterized by a low degree of myelosuppression and minor steroid-related side effects. To better define the effectiveness of this agent, 38 patients with refractory non-Hodgkin's lymphoma were treated with a pulse regimen of 100 mg/m^2/day for 3 consecutive days every two weeks. The mean age for all patients is 60.9 years. All patients were heavily pretreated, in all instances being refractory to prior combination chemotherapy. All patients had stage III or stage IV disease. Histologic subtyping demonstrated 19 patients with favorable histology lymphoma and 19 patients with an unfavorable histology. There were 3 early deaths in the unfavorable histology subgroup and 2 additional patients are nonevaluable due to protocol violation. The response rate in 33 evaluable patients is as follows: for 19 favorable histology patients, the complete response rate is 1/19 (5%) and the total response rate (CR+PR) is 7/19 (37%). For unfavorable histology patients the complete response rate is 2/14 (14%) and the total response rate is 3/14 (21%). Remissions have generally been of short duration, with a median time to progression of approximately 4 months. In 2 patients with diffuse histiocytic lymphoma, however, the duration of CR has been 9 and 18+ months. Treatment has been well tolerated with moderate leukopenia and thrombocytopenia each observed in 5% of patients. No infectious complications or hemorrhagic events have occurred. Nonhematologic toxicities have been mild. Preliminary conclusions in this ongoing study are as follows: 1) Prednimustine has activity in refractory non-Hodgkin's lymphoma, particularly in patients with favorable histology. 2) This study confirms the mild degree of toxicity of prednimustine given in an intermittent pulse regimen. 3) These data suggest that prednimustine is an appropriate agent to test in primary combination chemotherapy regimens for non-Hodgkin's lymphoma.

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ASPARAGINASE (ASP) IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA (NHL). D.Y.R.Pendharkar, R.A.Abdyldaev and G.V.Kruglova. Oncology Research Centre, Moscow 115478, USSR.

ASP was used as treatment modality in 55 patients (pts) of NHL (32 -lymphoblastic type, 13 -prolymphocytic, 4 -immunoblastic and 6 -unclassified). Most of the pts (77.4%) had received prior chemotherapy and were being treated for relapse or progression. In 90.6% of cases stage IV disease was recorded with 37.5% having bone marrow involvement. ASP was administered in dose of 300 IU/kg daily till maximum effect was evident or dose-limiting toxicity developed. Overall dosage varied between 180000 and 410000 IU. Only 50 pts were considered evaluable for response as 5 pts died within 4-8 days of the initiation of therapy.

Owerall response rate was 50% with 8% complete remission (CR) and 42% partial remission (PR). Response was most often evident in the first week of therapy. Response was better in previously untreated pts (80%) as compared to previously treated pts (32.5%), CR rate was 10% and 7.5% resp. The CR were recorded in lymphoblastic histology only, while in other histologic types only PR were seen. Median disease free survival was 7 weeks. Following side effects were observed -mild leukopenia 17%, thrombocytopenia 5.7%, abnormal liver function and pancreatic tests 31,1%, nausea and vomiting 50.9%.

In conclusion, relatively high doses of ASP may be succesfully used in the treatment of generalized NHL in relapse especially lymphoblastic type. High doses of ASP may be very usefull, when immediate response is desirable and when due to low wbc or thrombocyte count or other reasons combination chemotherapy regimens can not be used. Role of these doses as a initial chemotherapy in non-Hodgkin's lymphoma and in combination chemotherapy needs to be evaluated.

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HUMAN α2 INTERFERON (Schering-Plough 30500) (IFN) IN THE NON-HODGKIN'S LYMPHOMAS (NHL). A REPORT OF TWO PHASE II STUDIES.

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Eighteen patients with centrally reviewed histologically confirmed stages III and IV low grade NHL (DWDL = 8, NM = 3, NPDL = 5) were treated with 2 x 10^6/m^2 IU IFN by subcutaneous injections three times per week for three months. Five patients were previously untreated. If the disease remained static or responded, treatment was continued for one year or until disease progression. The IFN was well tolerated with mild subjective toxicity (myalgia, malaise and tiredness). There was mild myelosuppression and no hepatic toxicity. Six patients are still on treatment. The median duration of treatment was three (0.25 - 12) months. One patient did achieve CR after four months treatment. She has stopped IFN after one year and remains disease-free two months later. Three others have achieved PRs of duration 6 weeks, 3 months+ and 10 months+. Three patients are static (one stopped, two continuing). This IFN seems to have activity in approximately 25% of this group of patients.

Seven patients with refractory high grade NHL (6 = DPDL, 1 = lymphoblastic) were treated with 250 x 10^6 IU IFN/m^2 as a 24 hour infusion at 3-4 weekly intervals. The median number of cycles given was three (range 2-5). Acute toxicity was severe with malaise, high fever, rigors, nausea and vomiting. More chronic toxicity consisting of malaise and lethargy lasted 4-7 days after therapy. There was rapid, mild myelosuppression and transient liver function abnormality. Four patients had a rapid reduction in their disease over the first week after therapy but all four began to recur prior to the next cycle. Two patients qualified as PR. This suggests that very high dose IFN is active in this disease but that the more continuous scheduling which is required in order to prevent mid-cycle progression may be intolerable.

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MASSIVE THERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION AS RESCUE STRATEGY IN NON HODGKIN'S MALIGNANT LYMPHOMA. T. Philip, P. Biron, D. Maraninchi, J.A. Gastaut, P. Hervé, Y. Flesh, A.H. Goldstone, B. Souhami. Centre Léon Bérard - Lyon - France and the GRAFT Cooperative Study Group France and U.K.

We report a retrospective study of the GRAFT study group in 42 cases of NHML who received massive therapy and autologous bone marrow transplantation. 16 patients, all having received adriamycin, had truly resistant or progressive disease to all regimes. 11/16 responded significantly to massive therapy but the duration of complete remission (CR) was short (median 104 days) and only one patient out of the 16 is alive and in CR at more than one year post ABMT. Another 19 patients were in relapse but still responding to rescue protocols and 16/19 had relapsed whilst on therapy which had included adriamycin. 3/19 had relapsed whilst off therapy which had included adriamycin in the past. 9/19 of these patients are still alive apparently free of disease with a median observation time of 300 days (range 73-962). A further 7 patients were partial responders to conventional adriamycin containing induction therapy (median time from diagnosis to ABMT 4 months). 6/7 achieved CR after massive chemotherapy and are still alive and in CR 39-1230 days after ABMT (median 230). Our conclusions are as follows : ① Massive therapy with ABMT is effective in resistant NHL which is a new demonstration in vivo of a dose effect relationship in end-stage disease. However, the median length of CR is short and in end-stage disease less than 10 % long term survivors can be expected. ② When the patient is in relapse but still responding to conventional chemotherapy, massive therapy and ABMT produces 9/19 long term survivors. The group of 16/19 relapsing on therapy represents a group of patients with exceptionally bad prognosis on conventional regimes and ABMT might be the best treatment available for this group. ③ In the small group of patients given ABMT in partial remission (PR) 6/7 were converted to CR and remain alive and in CR. This seems to be an excellent result in this group of patients compared to conventional regimes. ④ Massive therapy with ABMT is associated with 31 % severe morbidity and 14 % therapy related deaths. These figures are comparable to morbidity by aggressive conventional chemotherapy. ⑤ Massive therapy and ABMT should, at the present time, be reserved for patients still responding to chemotherapy when in PR or in relapse. It seems likely that for the future massive therapy and ABMT might be considered in NHL as an early form of rescue when first line conventional chemotherapy has failed.

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AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR CHILDHOOD NON-HODGKIN'S LYMPHOMA (NHL): LIMITATIONS BY ACUTE EXTRA-MEDULLARY TOXICITY.

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Childhood NHL of B-cell or Burkitt's type in advanced stage or after relapse are known to require aggressive cytoreductive regimens. At our institution 16 children with NHL (15 with abdominal and one with cervical primary, 13 in first and 3 in second remission) have undergone ABMT as consolidation after conventional remission induction. The pretransplant regimen included vincristine (2 mg/m^2) and adriamycin (60 mg/m^2) on day -7, cyclophosphamide (45 mg/kg) on days -6 to -3, and total body irradiation (600 rads) on day -1, followed by ABMT on day 0. In 6 children the bone marrow was decontaminated in vitro with the monoclonal antibody anti-Y 29/55 and complement (1,2). The usual side effects included stomatitis, vomiting, anorexia, abdominal pain, diarrhea and fever which usually resolved soon after recovery of blood cell counts. Excessive acute toxicity was observed in 8 patients. It involved the following problems:
- Liver: Massive ascites with minor or severe abnormalities of liver function in 2 patients.
- CNS: Severe polyneuropathy with prolonged anorexia in one case and convulsions under platelet and granulocyte substitution in another case.
- Kidneys and urinary tract: Renal failure (due to aminoglycoside therapy?) requiring peritoneal dialysis in one patient with liver damage; hemorrhagic cystitis (due to cyclophsophamide) in one patient; and bladder stones in one patient with previous bladder surgery.
- Infection: One patient had candida sepsis. Another patient had intestinal perforation (from tumor necrosis) resulting in a peritoneal abscess. Viral and bacterial infections were not a major problem.
One child died on day 2 after ABMT with generalized edema, intestinal obstruction and hemorrhage, and cardiac failure. The 6 other patients who died after ABMT succumbed to the tumor. Toxicity appeared to be more severe in patients receiving decontaminated marrow. From 13 patients with Murphy stage III and IV NHL transplanted in first remission 9 are alive and free of tumor (including all 5 patients of this group with decontaminated marrow). The median observation time is 26 (range 1-55) months after ABMT. Possible factors responsible for toxicity will be discussed.

Ref.: 1. Forster H.K. et al. Cancer Res 42: 1927-1934, 1982
2. Baumgartner C. et al. Exp Hematol 11 (suppl 13): 169, 1983.

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HIGH-DOSE CHEMOTHERAPY AND BONE MARROW TRANSPLANTATION IN POOR PROGNOSIS HODGKIN'S DISEASE. J.Dumont*, T.Philip, D.Maraninchi, N.C.Gorin, F.Teillet, M.Kuenz, J.L.Harousseau, M.Marty and P. Hervé : Groupe d'Etude Français sur l'Auto-greffe (F.A.G.) Centre Regional de Transfusion Sanguine, BP 1181, 25003 Besançon Cedex - France
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18 Hodgkin patients were treated with high-dose chemotherapy protocol followed by autologous bone marrow transplantation (ABMT). 11 patients were refractory from the onset of the disease (group 1), 6 patients had relapses (group 2) and 1 was treated at the initial period. Chemotherapy included high dose cyclophosphamide for all patients (50mg/kg/day IV for 4 days) and the most frequent association used was TACC or BACT protocol. 4 patients received additional TBI (10 Gys). In the first group, 5 patients achieved complete remission (CR) and 2 were considered as failure. 4 cases are not evaluable, due to an early death in 2 cases, and a too short follow-up in the 2 others. In the second group, 3 patients achieved CR, 2 cases are not evaluable (1 early death, 1 recent treatment) and there was 1 failure. The last patient treated as initial phase achieved CR but relapsed 2 months later. Among CR patients, 4 relapsed between the 2nd and the 5th month, but 3 patients remained in CR, off therapy, 6 +, 24 +, and 48 + months, respectively, after ABMT. The 8th patient died in CR at Day 80 due to cytomegalovirus septicemia. The toxicity included : fatal infections in 6 cases and cardiac failures in 2 cases, minor complications in 7 other cases. This excessive toxicity could probably be avoided if such treatment is given earlier in the evolution of the disease, before the accumulation of iatrogenic effects.

The high percentage of CR obtained in these refractory patients proves the validity of such therapeutic attempts in poor prognosis Hodgkin's disease.