ABSTRACTS

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 1 INHERENT AFFINITY AND MALIGNANT LYMPHOMA
Stojimirović E., Milosavljević D., University Children's Hospital, Belgrade, Yugoslavia.

Virchow has been the first to talk of inherent affinity and malignant diseases and has pointed out that a person is born with affinity or resistence to malignant diseases. In the last two decades of this century there were reports regarding the importance of hereditary factors in the development of malignant diseases, namely the interest for the study of human cancer genetics has greatly increased.

The authors studied inherent affinity in children with malignant lymphoma.

Investigation involved 30 children with M.Hodgkin and 30 children with Non Hodgkin's lymphoma in whom the following analyses were made:

a) familial pedegree on the presence of malignant diseases in the family members of our patients,

b) minor body anomalies and major clinical syndromes, as well as the presence of other hereditary diseases were registered,

c) cytogenetic studies were made so as to assess constitutionally abnormal kariotype, and

d) cellular and humoral immunity were studied so as to confirm presence of hereditary immunodeficiency states.

The results show that a positive familial illness history on the presence of malignant diseases in the family members was discovered in 40% of the patients, while in two of these their fathers had a malignant disease at the same time (Ca pulmonum and ALL respectively). Two, three or more minor anomalies were present in 100% of the patients. Among the anomalies of oculo-facial region, in 11.1% it involved strabismus. Renal anomalies, assessed by intravenous pyelography, were frequent with double pelvis present in 11%. Cytogenetic investigation did not discover chromosomopathies. Immunologic studies discovered a child with a hereditary IgA immunodeficiency.

The authors concluded that these results show the importance of genetic studies in malignant diseases. The high frequency of 2, 3 and more minor abberations in 100% of our patients makes it possible for the authors to assume that tissue dysplasia (mesenchymal and haematopoietic), resulting from mutation in the developmental genetics, forms the basis of the inherent affinity in the development of malignant diseases to which oncogenesis will be induced later on by some environmental agent.

T 2 PERSISTENT LYMPHADENITIS AS A PRODROME OF ACQUIRED IMMUNE DEFICIENCY SYNDROME.
Harry L. Ioachim. Departments of Pathology of Lenox Hill Hospital and Columbia University, College of Physicians and Surgeons, New York, N.Y. 10021.

In the present epidemic of opportunistic infections associated with the acquired immune deficiency syndrome (AIDS), persistent, often generalized lymphadenopathies are frequently observed. We have studied the histopathology and immunopathology of 54 biopsied lymph nodes in male homosexual patients and correlated the findings with the clinical presentation and immunological data. Repeat biopsies were also performed and correlated with follow-up. The lesions most commonly seen consisted of extreme hyperplasia of germinal centers showing extensive cellular destruction and phagocytosis of nuclear debris. In addition, there were focal hemorrhages, aggregates of clear cells of monocytic origin and accumulations of neutrophiles. These lesions diagnosed as acute lymphadenitis preceded in most cases by 6 to 20 months the opportunistic infections AIDS, Kaposi sarcoma or non-Hodgkin's lymphoma while in some cases the lesions were concomittant. A minority of cases were characterized by lymphocyte depletion , vascular hyperplasia and fibrosis, possibly representing the late phase of lymphadenitis. It is suggested that the systemic, persistent lymphadenitis of homosexual males is produced by a lymphotropic virus, resulting in the destruction of a certain class of lymphocytes leading to the induction of the acquired immune deficiency syndrome.

T 3 Dendritic reticulum cells in reactive and neoplastic lymphoid follicles.
M. Alavaikko[1], A. Rinne[1], M. Järvinen[1], V.K. Hopsu-Havu[3], R. Aine[4], G. Blanco[2] and M. Apaja- Sarkkinen[1]. Department of [1]Pathology and [2]Oncology, University of Oulu, [3]Department of Dermatology, University of Turku, and [4]Department of Pathology, University Central Hospital of Tampere, Finland.

Immuno-reactive acid cysteine proteinase inhibitor (ACPI) has been shown to be a characteristic of human squamous epithelia. When other tissues were tested by immunodiffusion for the presence of ACPI, it appeared to be present in some but not all the lymph nodes tested and subsequent immunohistochemical studies showed the dendritic reticulum cells (DRC) in the lymph node and tonsillar germinal centres to possess strong ACPI immunoreactivity.

We have tested 40 follicular center cell (FCC) lymphomas immunohistochemically for the presence of ACPI. It appeared that ACPI-positive DRC in neoplastic follicles are reduced or vanish and the reaction product is weak. We also have observed morphological alterations of DRC in neoplastic follicles, mainly a diminution and shortening of the dendritic processes. Preliminary analysis of the survival data suggest a poorer prognosis for those patients in whose tumours ACPI reactive DRC are totally absent.

References:
Rinne A. et al. Virchows Arch (Cell Pathol) (1983) 43: 121-126.
Alavaikko M. et al. Acta Histochem (1984) In print.

T 4 IMMUNOBLASTIC LYMPHOSARCOMA: A CLINICO-IMMUNOLOGIC STUDY
K.A. El-Ghamrawi, S. El-Ashmawi, A. Khalil, W. El-Metnawi and M. Haggag, Kasr Eini Centre of Radiation Oncology & Nuclear Medicine. Faculty of Medicine, Cairo University, Cairo, Egypt.

Seventy seven cases of Immunoblastic lymphosarcoma (IL) were assessed and treated between 1969 and 1980. IL constituted 11 % of NHL seen during the same period. The male to female ratio was 3:1. The peak age incidence was in the 6th decade. The majority had tumour mass more than 5 cm in its long axis. 77 % of cases presented in stages III and IV. The mediastinum was skipped in 78 % of cases with disease above and below the diaphragm. Initial extranodal involvement was observed in 22 % of cases. Waldyer's ring and the small intestine were the two most common extranodal sites affected. Serum monoclonal gammopathy was detected in 6.5 %. 9.7 % of cases had monoclonal gammopathy in urine, compared to 2.7 % of other types of NHL. The mean concentration of intracytoplasmic immunoglobulins was significantly higher in IL compared to NHL, specially IgA and IgM. 41 % of IL cases showed mono or bi-clonal intracytoplasmic gammopathy compared to 13 % in other NHL. There was no consistant relationship between serum, urinary and or intracytoplasmic monoclonal gammopathy. The overall survival was 26 % after two years. It was significantly better for those patients who attained complete remission at the end of treatment (62 % two years survival) and those with early stage of disease (42 % two years survival). There was a direct relation between the long axis of the tumour and response to treatment. Complete responders had a mean tumour diameter of 4.9 cm, partial responders 9 cm and non-responders 11.3 cm (p less than 0.05).

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 5

A QUANTITATIVE ELECTRON MICROSCOPICAL ANALYSIS OF HISTIOCYTIC AND DENDRITIC RETICULUM CELLS IN FOLLICULAR STRUCTURES OF FOLLICULAR LYMPHOMAS AND REACTIVE HYPERPLASIA. L.H.P.M. Rademakers, J.P.J. Peters, Ph.M. Kluin and J.A.M. van Unnik. Pathologisch Instituut, University of Utrecht, Pasteurstraat 2, NL-3511 HX Utrecht, The Netherlands.

Histiocytic reticulum cells (HRC) and dendritic reticulum cells (DRC) are integral parts of germinal centres. These cell types are also present in follicles of follicular lymphomas. In this study the distribution and ultrastructural appearances of HRC and DRC present in normal germinal centres and in neoplastic follicles were established by means of morphometric methods.

The number of HRC was significantly lower in malignant follicles than in their reactive counterparts. Quantitative analysis of the cytoplasm and phagolysosomes shows that HRC in malignant follicles are smaller and contain larger phagolysosomes of less frequent occurrence, indicating a lower activity in comparison with HRC in reactive follicles. DRC were present in smaller numbers in these structures, as measured by nuclear counts and their relative volume within the follicles. In contrast to reactive follicles DRC in malignant follicles did not have extensive villous extensions on their plasma membrane. The electron dense coating of these extensions representing fixed immune complexes was not present. The ultrastructural features, i.e. infrequent Golgi fields, few cisterns of RER, occurrence of polysomes, indicate that DRC in follicular lymphoma are functionally less active than in reactive lymph nodes.

The ultrastructural differences of reticulum cells from reactive follicles and malignant follicles might be related to the absence of an immune reaction in follicular lymphoma. The frequency and appearance of HRC and DRC may be important as an additional parameter for differentiation of reactive secondary follicules and their malignant analogues.

T 6

LIGHT MICROSCOPIC APPEARANCE AND QUANTIFICATION OF DENDRITIC RETICULUM CELLS IN FOLLICULAR LYMPHOMA AND REACTIVE HYPERPLASIA. J.P.J. Peters, L.H.P.M. Rademakers, J.M.M. Roelofs*, Ph.M. Kluin and J.A.M. van Unnik. Pathologisch Instituut and *Dep. of Medical Physics, University of Utrecht. NL- 3511 HX Utrecht, The Netherlands.

The occurrence of dendritic reticulum cells (DRC) was compared in follicular structures of follicular lymphoma and human lymph nodes with follicular hyperplasia. By comparing microscopic sections with subsequent ultrathin sections, DRC were identified by means of light-microscopy.

Quantitative lightmicroscopic examination of follicular structures showed that the number of DRC was 80% lower in neoplastic follicles. These figures correlate with electron microscopic data, indicating a quantitative recovery of DRC by means of light microscopy.

The number of DRC-cell bodies containing 2 nuclear sections was significant lower in neoplastic follicles. Three-dimensional reconstruction of nuclei showed that these nuclear sections represent separate closely opposed nuclei. The typical opposition of the nuclei allowed stereological calculations of the real frequency of binucleated DRC in the tissue based on the three-dimensional model of nuclear complexes and observed values of binucleated DRC in 1 µm sections. These calculations indicate that 46 to 62% of DRC in reactive germinal centres is binucleated, whereas in neoplastic follicles this figure varies between 16 and 21%.

The lower number of DRC and the lower frequency of binucleated DRC in follicular lymphomas suggest that the differentiation of DRC from stromal cells is less complete in these neoplasms. The lightmicroscopic identification of DRC offers a reliable approach to define the occurrence of DRC as an additional parameter for differentiation of reactive germinal centres from malignant ones.

T 7

RETICULUM CELL SARCOMA OF BONE (RSCB): EQUIVALENT OF NON-HODGKIN LYMPHOMA OF CENTROBLASTIC-CENTROCYTIC ORIGIN?

Ph.M. Kluin, P.J. Slootweg, H.-J. Schuurman, L.H.P.M. Rademakers, and J.A.M. van Unnik. Institute for Pathology, Institute for Oral Pathology and Div. Immunopathology, University Hospital, Utrecht, The Netherlands.

Four cases of primary RSCB, localised within the maxilla (3) or the mandible (1) were investigated by immunohistochemical (3) and electronmicroscopical (2) methods. All cases shared a common clinical presentation of odontogenic infection. A definite histological diagnosis of malignancy was only made after repeated biopsies or revision of original sections. An initial diagnosis of sarcoma other than RSCB was made in 2 cases and led to hemimaxillectomy in one patient. In histology, compartmentalizing fibrosis suggested the sarcomatous origin. Tumour cells, intermingled with fibroblasts, contained nuclear abnormalities as cleavage, folding and lobation. Large cells with multilobated nuclei were prominent in some cases. The B-lymphocytic origin was demonstrated by the presence of B1 antigen and HLA-Dr in 3 and of monotypical sIg in 2/3 cases. The ultrastructural morphology suggested an origin from follicle centre cells by the presence of centroblasts and centrocytes. In one case plasmacytoid differentiation was confirmed by the presence of monotypical cIg. Clinical staging revealed dissemination into cervical lymph nodes in only one patient but extensive local destruction in more cases. Complete remission was achieved after radiotherapy (1), radiotherapy with polychemotherapy (2) or surgical, radio- and polychemotherapy (1). We suggest that primary RSCB is an analogue of NHL, Centroblastic Centrocytic or Large Cleaved, of lymph node. It shares a highly locally destructive growth with infrequent nodal dissemination.

T 8

CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS IN EGYPTIANS BY THE WORKING FORMULATION AND SURFACE MARKERS.

H.N.Tawfik, N. Mokhtar, A.G. Hassanein, M.R.Hamza, E.Jaffe and N.El-Bolkainy. National Cancer Institute, Cairo,Egypt.

A total of 303 cases of malignant lymphomas were present among 3181 malignancies examined at the Pathology Dept of the Cairo National Cancer Institute during 1983, a relative frequency of 9.5% of all malignancies. Of the malignant lymphomas, 36 were extranodal (11.9%) and 267 were nodal (88.1%). Non-Hodgkin's lymphomas formed 69% of the nodal lymphomas. The distribution of the non-Hodgkin's lymphomas is shown in the next table.

	Paediatric	Adult	Total
Low grade:			
Small lymphocytic	1	21	22
Fdlicular small cleaved	—	2	2
Follicular mixed	—	3	3
Intermediate grade:			
Follicular large cells	—	1	1
Diffuse small cleaved	5	19	24
Diffuse mixed	—	27	27
Diffuse large cleaved	1	24	25
Diffuse large non cleaved	2	11	13
High grade:			
Immunoblastic	1	19	20
Lymphoblastic	13	6	19
Nodal Burkitt	12	2	14
Lennert	—	2	2
Unclassified	4	9	13
	39	146	185

Low grade non-Hodgkin's lymphomas formed 14.6%of total Hodgkin's lymphomas. Follicular cases were encountered only in 6 cases (3.2%). Burkitts like lymphoma, previously undescribed in Egyptian literature, was present in 14 cases or (7.6%) of the cases. Surface markers using monoclonal antibodies were done in 36 cases of nodal non-Hodgkin's lymphomas of various histologic subtypes. B cell markers were present in 27 cases (75%), T markers in 4 cases (11.1%) and 5 cases were null.

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T 9

PROGNOSTIC FACTORS IN NON-HODGKIN'S LYMPHOMAS. Bertini M.*, Vitolo U.*, Canta M.*, Paolino F.*, Mazza P.°, Lauria F.°, Jayme A.§, Tura S.°, Paolino W.*. *Divisione di Medicina Ematologia,Ospedale Molinette,Torino,Italy. °Istituto di Ematologia"L. e A. Seragnoli",Policlinico S.Orsola,Bologna,Italy. §Centro di Calcolo Ospedale Molinette,Torino,Italy.

A retrospective study was performed of 510 pts. with NHL observed from diagnosis in two different institutions from 1966 to 1983.Histology has been reviewed according to the Kiel classification and to the Working Formulation (WF) of NHL.Pts. were staged according to AnnArbor criteria.Treatment regimens consisted in chemotherapy alone or in combined modality therapy in most pts, radiotherapy alone was used only in few pts with localized disease.Conventional presenting features were analyzed (through BMDP statistical software 1981)-age,sex,systemic symptoms,primary involvement,stage,bulky disease,extranodal disease, nodular,mixed or diffuse pattern,LDH level,lymphocyte count- and related to response to treatment,survival and disease-free survival.
Pts were subdivided into 3 prognostic groups according to WF:Low-Grade (LGM),Intermediate-Grade (IGM) and High-Grade malignancy (HGM) with significative differences in survival among them (p=0.0000) and testing each one vs each other (p=0.002).A statistical different distribution (p 0.01) of the presenting features were observed among the 3 groups. Factors predicting for CR and survival were analyzed in each of them.
CR was statistically related to (p<0.01):
-LGM: younger age,female sex,no B symptoms,nodularity,no bulky disease, not advanced stage,low lymphocyte count.
-IGM: younger age,localized stage,no bulky disease.
-HGM: no B symptoms,localized stage, no bulky disease.
Survival was statistically predicted by (p<0.01):
-LGM (median 96 mths):CR,no B symptoms,nodularity,not advanced stage, no bulky disease.
-IGM (median 49 mths):CR,no B symptoms,age < 55yrs,localized stage, absence of bulky disease.
-HGM (median 16 mths):CR,female sex,age < 50yrs,no B symptoms,localized stage,absence of bulky disease.
The NCI proposed WF is effective in identifying 3 different prognostic groups of NHL.According to our data a set of prognostic features for response and survival can be found in each of the 3 groups.These prognostic factors should be considered together with histology for a better prediction of a given patient's response to treatment and survival.The significance of these data as a guide for a better management of NHL will be discussed.

T 10

ENZYMATIC AND IMMUNOLOGIC HETEROGENEITY OF CELLS ISOLATED FROM LYMPH NODES WITH NON-HODGKIN'S LYMPHOMA.
Gabriele Losa,Georges Maestroni,Peter Luscieti,Ennio Pedrinis Laboratory of Cellular Pathology,ICP,Locarno, Switzerland.

Cells recovered from lymph nodes of patients with malignant NH lymphomas and with non-neoplastic diseases were examined for their immunological phenotype by surface and cytoplasmic marker analysis and for their biochemical properties by measurement of the plasma membrane associated enzymes.Low activity levels of membrane enzymes were recorded in malignant isolated cells which displayed monoclonal surface Ig antigens positively stained with fluorescent antiimmunoglobulin antisera but no intracytoplasmic Ig synthesis.
NH lymph nodes which contained a mixed population of cells with both Ig and thymic surface markers in association with elements endowed of plasmocytoid features synthesizing monoclonal μ and kappa chains,were characterized by high 5'-nucleotidase level. A third group of NH lymphomas contained a variable proportion od cells with B and T antigens but lacked intracytoplasmic immunoglobulins. Histologically the majority of these lymphomas were of the diffuse mixed type,while the cells were delineated by characteristic activity patterns of plasma membrane associated enzymes.In this group no correlations were noticed between the various enzyme activities with the exception of the 5'-nucleotidase vs. the γ-glutamyltranspeptidase: however, an analogous relationship occurred also in cells of lymph nodes of benign diseases.Furthermore,correlations were observed between the two quoted enzymes and the frequency of both sIg and Leu 2 positive cell populations in malignant lymph nodes, whereas in lymph nodes with benign diseases no correlation emerged.
These findings revealed that the cellular heterogeneity of NH lymphomas,raised by a variable proportion of Ig and thymic antigens positive cells and null cells as well, may be reflected by characteristic enzyme profiles of plasma membrane associated enzymes.At variance, the enzymatic response was found consistently homogeneous in NH lymphomas with a predominant immunologic phenotype. Such membrane properties may in turn relate to metabolic and proliferative peculiarities of malignant cells.

T 11

PURINE PATHWAY ENZYME ACTIVITIES IN MALIGNANT LYMPHOMAS. F. Deméocq, L. Boumsell, D. Godeneche, J.L. Viallard, Y. Richard, J. Chassagne, R. Plagne, J. Lemerle, A. Bernard, Hôpital Saint-Louis, Paris, Institut Gustave Roussy, Villejuif and Centre Jean Perrin, BP 392, 63011 Clermont-Ferrand cedex, France.

We have measured activities of adenosine desaminase (ADA), purine nucleoside phosphorylase (PNP) and ecto-5' nucleotidase (5NT) in cells from patients with various lymphoid malignancies and have compared these activities to the differentiative status of the cells as assessed by monoclonal antibodies and lectins. We have investigated ADA and PNP activities in 120 patients and 5NT in 65 patients. Cells from patients with T lymphoblastic lymphoma (T-LL) and T lymphoblastic leukemia (T-ALL) with surface antigens characteristics of immature T cells had very high levels of ADA and low levels of PNP and 5NT. In contrast, cells from Sezary disease with antigens of mature T cells had low levels of ADA, intermediate levels of PNP and 5NT. Cells from patients with B lymphoid malignancies (B-LL, B-ALL and B-CLL) had low levels of ADA, high levels of PNP and various levels of 5NT.

The enzymes patterns seen in the T cell malignancies were compared with those found in different subsets of normal T cells. It was found that the enzyme patterns of T lymphoblasts resembled those in thymocytes and the Sezary pattern was similar to that of mature T cells. However no clear relationship appeared between subgroups of T lymphoblasts defined by their differentiative status and the purine enzyme activities whereas subsets of thymocytes showed distinct enzyme profiles. These results confirm the high degree of heterogeneity in term of cells surface phenotype and enzymes activities within T cell malignancies (Leukemia Res 1982, 6, 211). The enzymes activities tested might be of value in defining different sub-classes of lymphomas.

T 12

ACTIVITY OF MEMBRANE ASSOCIATED γ-GLUTAMYL TRANSPEPTIDASE (γ-GT) IN ACUTE LEUKEMIA (AL). D.Heumann, J.P. Grob, V. von Fliedner, G. Losa. Ludwig Institute for Cancer Research, Lausanne Branch; Istituto Cantonale di Patologia, Locarno, Switzerland.

Blood and/or marrow samples were obtained from 92 patients suffering from AL and leukemic cells were enriched by Ficoll density flotation. All cases were classified using morphology, cytochemistry and surface markers. The cells were biochemically assayed for terminal transferase (TdT) and plasma membrane associated γ-GT. Serial determinations of γ-GT on normal cells gave the following values (nmole/hr/10^6 cells): 11.5 in granulocytes, 2.5 in monocytes, 9.0 in T-lymphocytes and 14.0 in B-lymphocytes. In myeloid leukemia (AML) we observed an increase of γ-GT activity in immature forms like FAB-M1 classified cases(median value = 18.3). It was normal in more mature FAB-M2 and M3 cases (median = 10.2). Much higher values were recorded in monocytic and myelomonocytic leukemias (medians = 29.7 and 30.2, resp.); extremely high values were only detected among the latter cases (150-250). In lymphoblastic leukemias (n = 41), however, γ-GT was very low (medians = 1.5 and 2.0 for c-ALL and T-ALL, resp.). γ-GT values had a bimodal distribution in the fourteen remainder cases with acute undifferentiated leukemias (AUL) : 9 cases had values between 0 and 2.8 and 5 between 7.0 and 21.0. The correlation with the expression of TdT allowed to split AUL into 2 subtypes : a) a lymphoid subtype (TdT+, γ-GT low); b) a myelo-monocytic subtype (TdT-, γ-GT high); c) an undifferentiated subtype (TdT-, γ-GT low). 13 out of 14 cases fitted in the 3 subtypes. γ-GT may be a sensitive and helpful marker for the myeloid-lymphoid distinction in difficult cases of AL.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 13 Cytogenetic study in B chronic lymphocytic leukaemia (B-CLL).

Bernasconi P., Pagnucco G., Castelli G., Pasquali F., Bernasconi C.

Istituto di Biologia Generale e Genetica Medica, University of Pavia and Divisione di Ematologia, Policlinico S. Matteo, Pavia, Italy.

Chromosome analyses were performed on peripheral blood lymphocytes stimulated with B and T cells activators from seventeen patients with B-CLL. At least 20 metaphases were analyzed from each case with the Q-banding technique. Diagnosis and stage of the disease were determined according to Binet et al (1981).
In four patients cytogenetic analyses were performed at diagnosis. Two of them were classified as stage A, one as B, one as C. None of them had clonal chromosome abnormalities. Thirteen patients were studied while under treatment 15 to 127 months (median = 54) after diagnosis. At the time of the cytogenetic analyses three of the patients were in complete remission, seven were in a stable and non-progressive phase of the disease (five classified as stage A, two as B) and three were rapidly deteriorating (one stage B, two stage C). None of the patients in complete remission had clonal anomalies. Two out of the seven patients in a stable phase had a clonal change: one a trisomy 12, and the other one a deletion of the long arm of a no. 6: del(6)(q23). The three patients with a progressive disease showed acquired anomalies: one had a deletion (6)(q13) and material of unknown origin translocated to the long arms of a no. 11, one a trisomy 12 and a translocation (1;9)(q23;p13), the third one a deletion del(11)(q23).
The incidence of trisomy 12 in our sample is much lower than that of other series from the literature. As to the prognostic value of clonal anomalies the fact that all the patients tested at diagnosis had a normal karyotype while anomalies were found in 2 out of 7 patients in a non progressive phase and in the 3 in a progressive phase of the disease supports the view of Robert et al (1982) that trisomy 12 may have a negative prognostic value and leads us to postulate that this may be the case also for other clonal chromosome anomalies.

Binet J.L. et al., Cancer 48, 198, 1981.

Robert K.H. et al., Scand. J. Haematol., 28, 163, 1982.

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T 14 BURKITT CELL ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) WITH COEXPRESSION OF BOTH B AND T CELL MARKERS AND SUBCLONAL CHROMOSOME ABNORMALITIES IN A MAN WITH AIDS.

M. Berman, J. Minowada, J.M. Loew, M.M. Ramsey, N. Ebie and W.H. Knospe.
Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, USA and Loyola University Stritch School of Medicine, Maywood, IL, USA.

A 45 year-old white male, bisexual, with a two year history of recurrent tonsillitis, tonsillectomy, diarrhea, herpes zoster infection, lymphadenopathy and a reversal of T-helper to T-suppressor cell ratio, was admitted to the hospital in May, 1983 because of fatigue and generalized lymphadenopathy. Although his hemoglobin level was normal, the bone marrow was completely effaced by heavily vacuolated peroxidase, sudan black and PAS negative blasts forms. An axillary lymph node was infiltrated with similar lymphoid cells with a starry sky histology and high mitotic index characteristic of a small non-cleaved cell or undifferentiated lymphoma. Marker studies of marrow blasts had an unusual and possibly unique pattern in that an unequivocal monoclonal K-IgM with HLA-DR and B-cell subset antigen (BA-1) was superimposed with mature suppressor T-cell marker profile (pan-T, mature-T and suppressor/cytoxic-T antigens). The leukemic blasts were totally negative for TdT, HTLV-p19 antigen, common ALL-associated antigen, inducer/helper-T antigen and other immunoglobulin isotypes. Chromosome analysis disclosed the abnormal mosaic male with 70% cells having complement 47,XY,+12,t(8;14)(q24;q32) and 30% cells with the karyotype 47,XY,+12,1q(dup q22-q43),t(8;14)(q24;q32). The diagnosis of B-cell ALL of the Burkitt type was made and the patient was started on Cytoxan, Adriamycin, vincristine and corticosteroids. His further clinical course was complicated by an extensive tumor-lysis syndrome resulting in fatal renal failure. The consistent finding of the specific chromosome rearrangement (8/14 translocation) in all abnormal cells suggests that the cells were derived from a common precursor, but it is unclear as to the efficacy of any correlations between partial T-cell antigen expression in B-cell leukemia with subclonal chromosome abnormalities such as 1q+. Chromosome 1 has been shown to have cell sequences with homology to EB virus in a Burkitt tumor cell line which may be important in the growth transformation of the tumor cells (Proc. Natl. Acad. Sci. USA 80:1987, 1983).

T 15 WALDENSTROM'S MACROGLOBULINEMIA AND CHROMOSOMES

Palka G.[1], Geraci L.[3], Spadano A.[3], Annibale D.[1], Rieve A.[1], Pandoli G.[3], Torlontano G.[2]. Cathedra of Human Anatomy[1], Haematologic Division[3] Hospital of Pescara, Cathedra of Hematology[2] University of Chieti.

Cytogenetic data are reported from 16 patients with Waldenstrom's Macroglobulinemia (WM) aged between 39 and 76, of which 3 have died and 13 are still alive. Chemoterapy regimen comprised courses of Chlorambucil or BCNU and Doxorubicin, one patient also received splenic irradiation. Cytogenetic investigations were perfomed before and after treatment, both on marrow blood by direct culture or after 12 to 24 hours incubation and on peripheral blood stimulated with PHA for 72 hours. Chromosome numbers ranged from 38 to 47, and all patients showed an admixture of diploid metaphases and aneuploid metaphases marked by hyperdiploidy (8 patients),hypodiploidy (8 patients) pseudodiploidy (8 patients). Hyperdiploid and pseudodiploidy metaphases in many instances displayed unrecognizable markers. Diploidy and pseudodiploidy were equally frequent in metaphases from peripheral blood and from marrow blood. Hyperdiploidy and hypodiploidy were more frequently found in peripheral blood metaphases. GTG and RFA banding revealed structural aberrations of chromosomes 1, 3, 4, 9, 14 and numeric aberrations of chromosomes 10, 11, 12, 15, 18, 19, 21. Numeric aberrations, in form of both trisomy and monosomy, prevailingly involved chromosomes 10 and 15 in 8 patients. It may be concluded that karyotype aberrations in W.M. do not differ from generally found in lymphoproliferative disorders. Furthermore, data obtained from either peripheral blood or marrow blood do not appear to differ significantly. In some patients posttreatment cytogenetic study showed persistence of the initial cytogenetic abnormalities, in spite of the monoclonal component from peripheral blood. As also stated in literature, this supports the conception of residual monoclonal B-lymphocyte precursors in lymphoproliferative disorders after treatment induced disease remission.

T 16 PHILADELPHIA (Ph'), 14q+ and 1q+ CHROMOSOMES IN THE COURSE OF BLASTIC CHANGE OF CHRONIC LYMPHOCYTIC LEUKEMIA.

Palka G.[1], Geraci L.[2], Fioritoni G.[2], Apostoli D.[1], Di Sante O.[1] Calabrese G.[1]
Cathedra of Human Anatomy University of Chieti[1], Haematologic Division Hospital of Pescara[2].

Clinical and hematologic data are reported from a 75 year-old female patient with Chronic Lymphocytic Leukemia (CLL) of the splenomegalic variant evolving into a blastic form after a two years' symptom-free and untreated course. Cytogenetic investigations were performed by the direct technique on marrow blood in the course of blastic change. GTG banding was done according to Seabright. All of the 25 metaphases studied were aneuploid with manifold numerical and structural aberrations. Two different clones both with 47 chromosomes could be recognized: 47 XX; 1 q+; 14 q+; 9 p-; +M and 47 XX; 1 q+; +3; -10; +M. These karyotypes were observed in 15 and 10 metaphases, respectively. Some of the aberrations, such as the presence of 1 q+,14 q+, 9 p- and +3 chromosomes are characteristic of lymphoproliferative disorders while the finding of a 22 q- chromosome is very unusual. In this patient it was quite similar to the Ph' chromosome, although the second chromosome involved in the translocation could not be identified because of the compound chromosome aberrations found.This is the second report in literature of an association between a lymphoproliferative disease and the Ph' chromosome. 1 q+ and 14 q+ markers are a common finding in lymphomas and their presence appears to favour leukemic transformation; this patient did actually develop an acute undifferentiated leukemia, and the appearance of the Ph' chromosome may have heralded the occorence of blastic change.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 17

CYTOGENETIC ANALYSIS OF NON-HODGKIN LYMPHOMAS (NHL); CORRELATION WITH HISTOLOGY AND PREVIOUS TREATMENT. J. Takeuchi, H. Ochi, T. Han, H. Ozer, M. Barcos, J. Minowada, E.S. Henderson, A.A. Sandberg. Roswell Park Memorial Institute, Buffalo, N.Y., U.S.A.

We studied the histology (International Working Formulation) and karyotypes of lymph nodes or tumor masses from 35 NHL patients (pt.) 13 untreated and 22 in relapse. On a histological basis, 5 were small lymphocytic (A), 15 follicular (fol.) small cleaved (B), 1 fol. mixed (C), 1 fol. large cell (D), 4 diffuse (dif.) small cleaved (E), 6 dif. mixed (F), 2 dif. large (G) and 1 small noncleaved (J). For chromosome analysis cell suspensions were incubated for 18-36 hrs. at 37°C in RPMI 1640 medium with 16.7% fetal bovine serum; colcemid, .006-.01 µg/ml was added 1-18 hrs. before harvest. G- and/or Q-banding techniques were used for analysis of karyotypes. Twenty-nine cases had clonal chromosome abnormalities; 1 case (histology=E) had a normal karyotype, 4 others (3 pts. of A, 1 pt. of E) could not be analyzed because of low mitotic index and one (B) poor banding. Only 1 out of 29 pts. with abnormalities had a hypodiploid clone and 4 near-tetraploid clones. Common numerical abnormalities were trisomy 7 (8 pts.), trisomy 18 (8 pts.) and trisomy 21 (6 pts.). The most common karyotypic abnormality was 14q+ (17 pts.) including t(14;18)(q32;q21) in 14 pts. Other common structural abnormalities were 6q- (8 pts.) and i(17q) (3 pts.). The 14q+ anomaly was found in 88% of the fol., but only in 27% of the dif. lymphomas. All but 2 cases with t(14;18) were B. Except for 1 case identified as T-cell and 4 other cases as non-T, non-B-cell in origin, all cases which were phenotyped were of B-cell origin. A correlation of the cytogenetics with surface immunoglobulins could not be found; however, it was noted that 4 out of 5 non-B-cell origin had 14q+. Over half of the cases were cytogenetically heterogeneous, i.e., more than 2 abnormal subclones were found in the same tumor. Thus, we divided our cases according to this heterogeneity: Type I: most common subclone constitutes over 50% of cells with abnormal karyotypes, Type II: 25-50%, Type III: <25%. The cytogenetic heterogeneity did not correlate with the histology, though it was more common in untreated than relapsed pts. These results suggest that the treatment (all relapsed pts. had previous therapy) may affect selected clones.

Hetero-	Histology								Patient Status	
geneity	A	B	C	D	E	F	G	J	Untreated	Relapsed
I	1	9	1	1	2	5	1	1	6	15
II	1	1	0	0	0	1	0	0	3	0
III	0	4	0	0	0	0	1	0	3	2

CONCLUSIONS: 1. The most common karyotypic abnormality in NHL was 14q+ (17 out of 30), including t(14;18) in 14 cases. Other common changes were +7,+18,6q- and +21. 2. The t(14;18) was exclusively observed in fol. small cleaved cell type, though it was also seen in other histological types. 3. Cytogenetic heterogeneity was found in more than half of the cases and correlated with pt. status.

T 18

CYTOGENETIC STUDIES IN FIVE HODGKIN DERIVED CELL LINES. C. Fonatsch, Institut für Humangenetik der Med. Hochschule, Lübeck, V. Diehl, M. Schaadt, H. Burrichter, Med. Universitätsklinik, Köln, H.H. Kirchner, Abt. Hämatologie/Onkologie, Medizinische Hochschule, Hannover

Five long-term in vitro cell cultures derived from four patients with histologically proven Hodgkin's disease were examined cytogenetically. Numerical and/or structural chromosome abnormalities were observed in all five lines. Whereas three lines exhibited a diploid (L 591) or hyperdiploid (L 428, L 439) modal chromosome number, L 538 and L 540 (established from the same patient) showed a near triploid karyotype with chromosome aberrations which were alike in these two lines. Although each cell line is characterized by a specific and individual karyotype, several chromosomes and chromosomal regions seem to be nonrandomly involved in the formation of marker chromosomes. When culture conditions were modulated (adaptation to calf serum, treatment with TPA), one of the cultures, L 428, gave rise to two subcultures with immunological, cytochemical and growth properties different from those of the original line. Additionally, new marker chromosomes could be detected in these L 428-derived cell lines. Moreover, L538 and L540 presented an interesting karyotype evolution concerning the chromosome 1 configuration which comprised four different forms.

An attempt was undertaken, firstly, to delineate specific chromosomal breakpoints leading to marker chromosomes in our Hodgkin-derived cell lines, and, secondly, to correlate karyotypic changes with other characteristics of the line.

T 19

RISK OF SUBSEQUENT PRIMARY CANCER IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA. G. Pagnucco, G. Castelli, E. Brusamolino, A. Canevari, C. Bernasconi. Divisione di Ematologia, Ospedale Policlinico San Matteo, Istituto di Ricovero e Cura a Carattere Scientifico, 27100 Pavia, Italy.

We performed a retrospective analysis of 270 consecutive cases of chronic lymphocytic leukemia (CLL) admitted to the Divisione di Ematologia, Policlinico San Matteo of Pavia from January 1974 to December 1982, to assess the risk of developing subsequent primary cancers (SPC). The median follow-up was 40 months (range 1-208 months). Initial treatment consisted of alkylating agents (chlorambucil or cyclophosphamide) in all cases. The observed incidence of SPC in CLL patients was compared with that expected from the incidence rates of Registro Tumori Lombardia - Provincia di Varese, for a population of the same age and sex distribution. The Poisson distribution method was used for statistical analysis. The strenght of association was measured by the exact 95% confidence interval around the ratio of observed (Ob) to expected (Ex) cases, referred as relative risk (RR). The whole group of patients accrued for 1.016 person-years of observation, a mean of 3.76 years per person. Subsequent primary cancers developed in 27 patients (crude rate of 2.6 per 100 person-years); 7 cases were synchronous and 12 cases were methachronous to CLL. Solid tumors other than skin cancer were observed in 22 out of 27 patients. The distribution by tumor site was: lung (7), stomach (4), colon (2), larynx (2), parotid gland (1), breast (1), bladder (1), prostate gland (1), pancreas (1), melanoma (1), Kaposi's sarcoma (1). The relative risk was significantly elevated for: a) all SPC (Ob = 27, Ex = 9.04, RR = 2.9, $p<0.05$); b) SPC excluding skin cancer (Ob = 22, Ex = 8.09, RR = 2.7, $p<0.05$); c) lung cancer alone (Ob = 7, Ex = 2.32, RR = 3, $p<0.05$); d) skin cancer alone (Ob = 5, Ex = 0.94, RR = 5.2, $p<0.05$). However, allowing for a likely 2½ fold underregistration in the control population, the risk of skin cancer became not significant. For all other sites RR exceeded expectation, but did not reach the statistical significance. The results of this study further support the observation that patients with CLL have an increased risk of developing SPC. Defective cellular and humoral immunity and prolonged treatment with chlorambucil or cyclophosphamide may have played an etiological role in the development of second cancers. However, in the present series: a) there is an high incidence of SPC synchronous with CLL; b) the risk for SPC remains fairly constant in each year, throughout the period of follow-up; c) there is a clustering of SPC among patients who early died, before reaching the median survival time. Therefore, these results seem to indicate a lack of correlation in CLL patients between treatment with alkylating agents and incidence of SPC, and that patients who developed subsequent solid tumors had more severe leukemia and immunological impairment.

T 20

IMPROVED STAGING SYSTEM FOR MULTIPLE MYELOMA USING CLINICAL AND MORPHOLOGICAL PARAMETERS. H. Ludwig and E. Fritz (II. Dept. of Medicine, University of Vienna, A - 1090 Vienna, Austria).

The stratification of patients with multiple myeloma into different prognostic subgroups is important both in evaluating individual courses of the disease and as support in selecting appropriate cytostatic treatment. The staging system most often used for this purpose was established by Durie and Salmon (Cancer 36:842, 1975). It depends on various clinical parameters, i.e., bone lesions, hemoglobin, serum M-component, serum calcium, and urine M-component. Our own recent investigation (Blood, in press) demonstrated the prognostic relevance of morphological criteria of cellular differentiation in multiple myeloma. Therefore, a combination of both aspects promised improvement of the prognostic tools.

In this study, a series of relevant clinical and morphological parameters from 85 patients at the time of diagnosis was chosen as input information. By means of Cox's multivariate regression analysis for censored survival data (J. R. Stat. Soc. (B) 34:187, 1972) stepwise selection of significant factors was accomplished and their coefficients were interpreted as relative weights. Optimal prognosis was achieved by the following regression equation:

$$\begin{aligned}\text{Score} = {} & 0.854 \times \text{serum calcium (mg/dl)} \\ & - 0.143 \times \text{hemoglobin (g/dl)} \\ & + 0.344 \times \text{plasmablasts (\% bone marrow cells)} \\ & + 0.097 \times \text{plasma cell infiltration (\% bone marrow cells).}\end{aligned}$$

Stratification into four stages at the cutpoints 7.5, 13.0, and 20.0 yielded distinct survival curves. The discriminative power was highly significant ($p \gg 10^{-14}$, $p \gg 10^{-14}$; Mantel-Cox and Breslow test) as compared to classification according to Durie and Salmon ($p \gg 10^{-9}$, $p \gg 10^{-9}$), MPS ($p \gg 10^{-9}$, $p \gg 10^{-9}$), and the risk criteria of the Myeloma Task Force ($p \gg 0.0005$, $p \gg 0.05$).

By combining clinical parameters and morphological criteria of cellular differentiation, the predictive accuracy of prognostic staging in multiple myeloma could be considerably improved.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 21 CYTOSTATIC TREATMENT OF NUDE MOUSE TUMORS INCUCED BY HETEROTRANSPLANTATION OF HODGKIN- AND NON-HODGKIN-LYMPHOMA CELL LINES

Kirchner, H.H.[1], A. Engert[1], V. Diehl[2]
1) Abt. f. Hämatologie/Onkologie, Medizinische Hochschule Hannover (Leiter Prof. H. Poliwoda)
2) Medizinische Klinik I, Universität zu Köln (Leiter Prof. V. Diehl)

Four human hematopoietic in vitro cell lines (Hodgkin's disease - derived lines L428 and L540, Burkitt's lymphoma line L735 and the lymphoblastic lymphoma line L735 were transplanted into the muscle of nude mice (NMRI nu/nu) as well as into the brain in a second serie of experiments. Tumor bearing mice were treated by intraperitoneal application of Cyclophosphamide, Adriamycin, Etoposid and Vindesine. Effectiveness of treatment was evaluated by measurement of i.m. tumorsize respectively changed survival time of mice with intracerebral tumors. Therapy results in both systems were proven by student's t-test and compared.

Resistance and sensitivity of cell lines tested in the i.c.-system were in good accordance with results in the i.m.-system. Best success of treatment was achieved with the T-lymphoma line L735 with Cyclophosphamide and Etoposid. Cyclophosphamide induced complete remission of i.m.-tumors in several cases whereas in the nude mouse brain the L735 cells relapsed and showed increased drug resistance.

Because of higher tumorrates after i.c. transplantation, especially with primary biopsy material of hematopoietic origin accompanied with short latency periods, the intracerebral nude mouse model should be discussed as a useful tool for testing cell lines as well as fresh specimen on their cytostatic response.

T 22 CHEMOSENSITIVITY OF TUMOR CELLS ISOLATED FROM PATIENTS WITH MALIGNANT LYMPHOMAS AND LEUKEMIAS. (CORRELATION TO CLINICAL DATA)

J.Schwarzmeier, F.Prischl
Ist Medical Clinic, University of Vienna, Austria

Vigorous treatment protocols have substantially increased remission rates in high malignant Non-Hodgkin-Lymphomas. The heterogeneity of the diseases, however, makes it difficult to standardize therapeutic regimens and to give clear recommendations as to the form of maintenance therapy. Pretherapeutic knowledge of chemosensitivity or -resistance of tumor cells should greatly facilitate the selection of appropriate drug combinations.

We have, therefore, evaluated the effect of various antineoplastic agents on the incorporation of nucleic acid precursors into tumor cells obtained from patients with NHL.

To optimize the assay conditions cell suspensions were used and drug effects were first studied on lymphoma cell lines (S-49, Raji, Daudi) using ^{3}H-uridine, ^{3}H-deoxyuridine and ^{3}H-thymidine as radioactive nucleoside precursors. The criteria for specific cytotoxic drug effects were a dose dependent inhibition of precursor incorporation and inhibition rates of at least 20% as compared to control cells not exposed to the drugs. The following substances were tested: doxorubicine, cytosin arabinoside, 4-hydroperoxycyclophosphamide, methotrexate,etoposide, 6-mercaptopurin, vincristine and prednisone. The test was then applied to patients with malignant lymphomas (lymphoblastic, immunoblastic, angioimmunoblastic) as well as to leukemias (AML, ALL, AMOL, hairy cell leukemia). When the in vitro data was compared to the clinical response of the patients, significant correlations could be obtained between the test results and the in vivo effects of the cytostatic agents. 80 -90 percent of the patients, who's blast cells were resistant in vitro did not come into remission. Conversely 60-70 percent of the patients with good in vitro sensitivity responded to therapy with complete or partial remission. When the rate of DNA synthesis of the tumor cells was compared to the inhibitory effect of a number of drugs on precursor incorporation (e.g. adriamycin) no correlation was detected. This indicated that the effect of these drugs was not solely dependent on the proliferative state of the cells.

In conclusion the test system may be a reliable tool to improve chemotherapy in NHL-patients.

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T 23 THERAPEUTIC MANAGMENT OF ANGIOIMMUNOBLASTIC LYMPHOMA ACCORDING TO IN VITRO CHEMOSENSITIVITY TESTING

F.Prischl, R.Pirker, T.Radaskiewicz, J.D.Schwarzmeier
Ist Med.Clinic and Inst.of Path.Anatomy, University of Vienna, Austria

The etiology and pathogenesis of Angioimmunoblastic Lymphadenopathy (AILD) are still poorly understood. Transformations into high malignant lymphomas are well documented. Because of the heterogenous nature of the disease and its potentially malignant character different treatment strategies have been proposed. Knowledge of drug sensitivity of the tumor cells prior to treatment would be helpful in planning an effective chemotherapy and avoiding unnecessary exposure of the patients to cytotoxic agents.

Therefore, we investigated the predictive value of an in vitro test based on the incorporation of nucleosid precursors into tumor cells. This test has already been successfully applied to acute leukemias (Cancer 53,1984). - Material from a lymphnode biopsy of a 58-year-old patient with immunoblastic lymphoma arising from AILD was brought into suspension by gentle mechanical disaggregation. The isolated tumor cells were tested with adriamycine, prednisone, vincristine, etoposide and cyclophosphamide (activated) and the ability of these agents to inhibit the incorporation of ^{3}H-uridine was evaluated. Simultaneously DNA-synthesis was assessed by incorporation of ^{3}H-thymidine. The effect of the drugs was expressed as percentage change of the radioactive precursor incorporation into treated versus untreated samples. Etoposide (60%) as well as adriamycine (55%), 4-hydroperoxycyclophosphamide (49%) and vincristine (40%) showed a specific, dose related effect, whereas with prednisone a minor response was seen.

In correlation to these results, the patient initially did not respond to cortisone monotherapy, but showed rapid recovery when combination chemotherapy was started with vincristine, cyclophosphamid and prednisone. After three cycles with this regime she came into complete remission which now lasts for more than one year.

We believe that pretherapeutic in vitro testing is very helpful in tailuring chemotherapy in AILD, especially in cases where transformations to malignant lymphomas cannot be ruled out.

Supported by grant no.4782 of the Fond zur Förderung der wissenschaftlichen Forschung in Österreich.

T 24 T-CELL LEUKEMIAS WITH MATURE PHENOTYPE.

B Schnitzer, EJ Lovett III, LE Kahn, The University of Michigan, Ann Arbor, Michigan 48109 USA

Five cases of T-cell leukemia were phenotyped immunologically by flow cytometry. Three patients were female and two male. Their ages ranged from 44 to 78 years (mean 67). In three cases, the leukemic cells had multilobulated (knobby) nuclei characteristic of adult T-cell leukemia/lymphoma (ATLL) described most often in Japan, in patients from the Caribbean and only rarely in the United States. One patient presented with hypercalcemia and had antibodies to HTLV. The neoplastic cells of this patient had a helper cell (T4) phenotype. The abnormal lymphocytes of this patient had receptors for Interleukin 2 detected by monoclonal antibody Tac. Electronic sorting revealed that the Tac+ cells were all T4+ cells, while T8 (suppressor) + cells were Tac negative and morphologically normal. Evidence of osteoclastic bone resorption was present. This patient had a spontaneous remission but died of CMV infection without evidence of residual leukemia at autopsy. The multilobulated leukemic cells of a second patient were both T4+ and T8+ and T6 (common thymocyte) negative, while the multilobulated cells of a third patient were T4+. A fourth patient had small lymphocytes with round or slightly irregular nuclei, and the cells were T4+. A fifth patient had T8+ cells, the majority of which bore the NK phenotype. Many of the lymphocytes had cytoplasmic granules. The cells in all cases were TdT negative. None of the patients had a mediastinal mass. These cases illustrate that T-cell lymphocytic leukemias are heterogeneous both morphologically and immunologically.

T 25

ABNORMAL PERIPHERAL BLOOD T CELL DNA CONTENT IN SKIN LIMITED T CELL MALIGNANCY. R.H. Keller, S. Swartz, P. McFadden, T. Milson, J. Herrmann, E. Thomas and C.W. Patrick, The Wood VAMC Marcus Center, Medical College of Wisconsin, 5000 West National Avenue, Milwaukee, Wisconsin, USA 53193.

Mycosis Fungoides (MF) is considered a skin limited T cell malignancy. Although some patients with MF relapse after therapy and others progress to a leukemic phase, the factors associated with recurrent disease remain poorly defined. We, therefore, examined the relationship of the DNA content and the percentages of T cell subsets from skin biopsies (S) and peripheral blood (PB) in this disorder using an EPICS V flow cytometer (FCM), cell sorting and expanded banding karyotyping of sorted cells. Using the relevant T cell subset, typically T4 bearing cells, PB DNA content was assessed and cells removed through cell sorting from chromosomal studies using high resolution banding. Twenty patients with histologically diagnosed MF and four patients with Parapsoriasis en Plaque (P) were studied and compared to normal controls (PB). In all MF patients studied, disease was limited to the skin by laboratory criteria including lymphangiogram and a Sezary cell screen of bone marrow and peripheral blood. In addition, the percentages of ratios of T helper and suppressor cells in the PB of all patients studied were within normal limits. Nonetheless, FCM analysis of the DNA/RNA content of PB lymphocytes demonstrated aneuploidy in 9/20 MF patients and 1/4 P patients with no evidence of aneuploidy in unstimulated or mitogen (PHA) stimulated control PB lymphocytes. In 6 of 20 MF patients, expanded banding karyotypic analysis confirmed the presence of aneuploidy but in 3 MF patients aneuploidy could not be confirmed by karyotypic analysis. Skin mononuclear cells in 4 MF patients and 2 P patients were also examined and each revealed an aneuploid DNA content. All MF patients demonstrating PB aneuploidy by FCM treated with Electron-Beam (EB) therapy continue to demonstrate a PB aneuploid DNA and 3 patients who demonstrated aneuploidy after EB have relapsed 18-24 months after EB therapy. By contrast no patient who demonstrated a normal DNA content by FCM has relapsed after EB therapy. These data suggest that PB involvement can be detected in MF patients by FCM and that PB aneuploidy correlates with prognosis and may select those patients who should be treated with systemic rather than skin limited therapy.

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T 26

PRESENCE OF CELLS WITH HNK-1 PHENOTYPE IN NON-HODGKIN LYMPHOMA: RELATION WITH TRANSFERRIN RECEPTOR EXPRESSION ON MALIGNANT CELLS. H.J. Schuurman[1], Ph.M. Kluin[3], and G.C. de Gast[2]. Div. Immunopathology[1] and Immunohaematology[2], University Hospital, and Inst. for Pathology[3], University of Utrecht, The Netherlands

A potential role of Natural Killer (NK) cells in host defence to tumours, especially lymphoma, has been suggested. NK cells are part of the cell population expressing the HNK-1 antigen. The transferrin receptor (TrR) on the target cell may be involved in the interaction with NK cells. These hypotheses prompted us to evaluate in 78 cases of Non-Hodgkin Lymphoma (NHL) *1* TrR expression on malignant cells, *2* presence and location of HNK-1$^+$ cells, and *3* relation between TrR expression and HNK-1$^+$ cells. NHL were classified according to the Kiel classification, combined with enzyme- and immuno-histo- and cyto-chemistry and electronmicrospopy. TrR and HNK-1 were assessed on frozen tissue sections using monoclonal antibodies in an immunoperoxidase method.

RESULTS. *Normal reactive lymph node:* TrR is present on almost all lymhoid cells in germinal centres of secondary follicles; HNK-1$^+$ cells are present mainly in secondary follicles in scattered location. *NHL of low-grade malignancy* (n=30, a.o. lymphocytic NHL, follicular centrocytic/centroblastic NHL): TrR is not detectable or present in low intensity on part of malignant cells, but in almost all follicular lymphomas the expression is similar to that in normal lymph node follicles. HNK-1$^+$ cells are present in scattered location in diffuse lymphomas; in about half of follicular lymphomas malignant follicles are devoid of HNK-1$^+$ cells, and HNK-1$^+$ cells are present mainly at the border of follicles or in interfollicular areas. *NHL of intermediate malignancy* (n=31, a.o. diffuse centrocytic and/or centroblastic NHL): TrR is not detectable or present in low intensity (most cases). HNK-1$^+$ cells are present in variable numbers in scattered location. *NHL of high-grade malignancy* (n=17, a.o. lymphoblastic lymphoma): there is a strong expression of TrR on almost all malignant cells. HNK-1$^+$ cells are absent in most cases, in some cases a few cells are observed in scattered location.

CONCLUSIONS. *1.* There is no relation between TrR expression on malignant cells and malignancy grade in NHL.

2. Compared with normal reactive lymph node, the number of HNK-1$^+$ cells is about equal in NHL of low-grade malignancy, lowered in NHL of intermediate-grade malignancy, and strongly reduced in NHL of high-grade malignancy. In contrast to the normal situation, HNK-1$^+$ cells can be absent in malignant follicles in follicular NHL.

3. There is no direct relationship between TrR expression on malignant cells and the presence of HNK-1$^+$ cells in NHL.

4. The results do not favour a potential role of HNK-1$^+$ cells (related with cells with NK-cell activity) in host defence to tumour cells in NHL.

T 27

T CELL SUBSETS AND B CELL MARKERS IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL). M.Hautekeete, D.Van Bockstaele, Z.Berneman, R.De Bock, G.Colpin, W.Stevens, M.E.Peetermans. Department of Hematology, University of Antwerp (UIA), Belgium.

In the majority of cases, CLL is characterized by a monoclonal proliferation of B lymphocytes. The minority population of T cells in B CLL has aroused interest because of their possible involvement in the pathogenesis of the disease and some of its complications, as hypogammaglobulinemia. We followed 26 patients with B CLL prospectively over an average period of 18 months, classifying them according to Rai's criteria. Using flow cytometric analysis, we studied OKT3, OKT4, OKT8, Ia and surface membrane immunoglobulins (SmIg) bearing lymphocytes in each stage of the disease, and compared them to the number of mouse rosettes (ME Ros).

The monoclonal B cell population consisted of IgM kappa in 3 patients, IgM lambda in 7, IgD kappa in 2, IgD lambda in 1, IgM,D kappa in 6, IgM,D lambda in 6, IgM,G kappa in 1. We found a significant tendency of serum Ig levels to fall as the disease progresses. We noted a reduction of OKT4 and an increase of OKT8 cells when comparing Rai 0 with Rai 1&2, and with Rai 3&4 stage patients :

0 (n=10) OKT3: 2.9 ± 2.1 OKT4: 1.6 ± 2.1 OKT8: 1.1 ± 0.7
1&2 (n=25) OKT3: 1.8 ± 1.3 OKT4: 1.0 ± 0.7 OKT8: 1.2 ± 1.1
3&4 (n=8) OKT3: 1.9 ± 1.3 OKT4: 1.2 ± 0.8 OKT8: 0.9 ± 0.6

(mean ± S.D. in absolute counts x $10^9/l$). The OKT4/OKT8 ratio decreases as the disease progresses from Rai stage 0 to 4 : Rai 0 (n=10) 1.7 ± 1.0, Rai 1 (n=8) 1.6 ± 0.6, Rai 2 (n=18) 1.5 ± 1.2, Rai 3 (n=5) 1.2 ± 0.3, Rai 4 (n=3) 1.1 ± 0.7. These data suggest that the T cell population could be implicated in the pathogenesis of the disease or some of its complications, but they must be interpreted with extreme caution. In some of our patients, we noticed a large population of lymphocytes (up to 43%) bearing neither SmIg nor OKT markers. Finally, our data comparing the proportion of ME Ros with Ia and SmIg suggest that the latter are more reliable markers for the diagnosis and follow up of B CLL.

T 28

NON-SPECIFIC IMMUNOLOGICAL MECHANISMS AT PATIENTS WITH HODGKIN DISEASE.
S.D.Brkić[+], B.Pendić[+], S.Vučković[+], B.Baničević[++] and Z.Ramić[+++]

+City Clinic Hospital;Internal Clinic "A" [++];Institute for Microbiology and Immunology [+++]Medical Scool,Belgrade

The mechanism of immunological reactivity in 47 untreated patients with Hodgkin Disease (HD) was studied by investigating the reactivity of peripheral lymphocytes to phytohemagglutinin (PHA) and by detection of the sera inhibitory factors on xenogeneic test cells.

Decreased proliferation of peripheral lymphocytes to T dependent mitogenes was found in the culture of lympho cytes supplemented with autologous sera in patients with H.D. These data suggest the existence of inhibitory factors. These factors could modulate the autologous and allogeneic immunocompetent cells.

By measuring the mitogen induced proliferation of rat thymocytes to PHA and Concavalin A (Con A) the presence of inhibitory factors in sera of patients with H.D. was studied. At the same time the mitogen induced proliferation of the same test cells in the presence of sera of healthy controls was studied also.

The sera of all studied patients showed statistically significant inhibitory effect in test cultures in comparison to sera of healthy controls. The degree of inhibition does not change after sera dialysis. It was shown that these inhibitory factors are : thermostable, non-cytotoxic and molecular weight larger than 10.000 daltons.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 29 IMMUNOLOGICAL IMPAIRMENTS IN HODGKIN'S DISEASE. A STUDY OF T-CELL SUBSETS AND THEIR IN VITRO FUNCTION.

L. Bergmann, P.S. Mitrou, M. Demmer-Dieckmann, Div. of Haematology/Oncology, Dep. of Internal Medicine, J.W. Goethe University, Frankfurt, FRG

71 patients with Hodgkin's disease (HD) were tested for lymphocytes and lymphocyte subsets using a series of monoclonal antibodies (OKT3 , OKT4, OKT6, OKT8, Lyt3) and conventional surface markers. Untreated patients with HD demonstrated a reduction of T-cells and especially of the "helper/inducer" subset (OKT4+), whereby the major abnormalities occurred in patients with advanced stages. Patients previously treated by chemo- and/or radiotherapy had a further decrease of OKT4+-cells and a moderate reduction of the "suppressor/cytotoxic" cells (OKT8+). The alterations could be shown to persist even in long-term remitters.

Furthermore, we investigated the PHA induced proliferation of peripheral mononuclear cells and isolated OKT4+ - and OKT8+-cells and the effect of PHA free IL-2 substitution to the PHA response in vitro. The OKT4+- and OKT8+ - cells had been isolated using a panning technique. The results support the hypothesis that those patients with HD, who had a low PHA response, may benefit from Il-2 substitution.

In vitro PWM induced immunoglobulin production (IgA, IgG, IgM) was measured with an ELISA technique. In untreated HD, a depressed in vitro synthesis of all immunoglobulins was observed. In treated HD the IgG production was higher than in the untreated group, whereas the IgM and IgA values were still reduced. The in vitro immunoglobulin synthesis was compared with the serum levels. In treated HD, a significant decrease of serum IgM developed.

T 30 THE ORIGIN OF BURKITT'S LYMPHOMA IN RELATIONSHIP TO B LYMPHOCYTE DIFFERENTIATION PATHWAY.

D. Benjamin, L. Bazar, R.J. Jacobson. Div. of Hematol., Georgetown University, Washington D.C. 20007

As careful analysis of the phenotypic profiles of normal and malignant cells has provided important insights into differentiation and the cellular origin of lymphoma, we have investigated neoplastic cell populations derived from patients with Undifferentiated Lymphoma (UL) of Burkitt's and Non-Burkitt's origin, in an attempt to define the stages of maturation arrest represented in these diseases. The study included 19 cell lines (CL) derived from patients with African Burkitt's (5CL), American Lymphoma (11CL), and from a homosexual patient with Acquired Immunodeficiency Syndrome (AIDS) who developed Burkitt's like lymphoma (3CL). The CL were studied for immunoglobulin (Ig) expression and a series of monoclonal antibodies defining antigens expressed on B lymphocytes, either broadly or at restricted stages of differentiation (B-1, B-2, BA-1, BA-2, HLA-DR, Leu-10, OKT-10, cALL and Surface (S)Ig). While the patterns of reactivities were complex, the CL could be classified into 3 major categories on the basis of phenotypes revealed. These were termed "pre-B", "early-B" and "intermediate B" regarding their patterns of Ig expression and surface antigens. Two CL contained intracellular μ chains (65%) and displayed low levels (13-20%) of surface μ in the absence of detected light chains both in the cytoplasm and on the surface membrane. No Ig secretion was demonstrated. From analogy with normal B-cell pathways these 2 CL were termed "pre-B" cells. HLA-DR, Leu-10 and B-1 were present, but no reactivity with BA-1, BA-2 and B-2 was demonstrated. Thirteen CL were characterized as "early-B" cells. All CL were positive for HLA-DR, Leu-10, B-1 and SIg. IgM secretion (range: 280-2600 ng/ml) was detected in 11/13 CL and cytoplasmic (C)Ig in 12/13 CL. Four CL in which large quantities of IgM secretion were demonstrated (1500-2500 ng/ml) were found to have a variable proportion of cells containing CIgM and CIgG, and were positive for BA-1. Within the "intermediate B" cell category were included the CL derived from the patient with AIDS. The CL were found to secrete huge amounts of IgM (6000 ng/ml), expressed low levels of SIgM but contained high percentage of cells positively stained for CIgM. The cells expressed HLA-DR, Leu-10, OKT-10, BA-2, B-1, B-2 and cALL.

Our results support the possibility that Burkitt's Lymphoma and UL of Burkitt's and Non-Burkitt's origin is one disease which arises from a narrow range of the B lymphocyte differentiation pathway, and each group of tumors might be at a slightly different stage of differentiation. This study also confirms that the phenotypes represented by these diseases and possibly in early B cell development itself, are more complex than previously considered, suggesting that a large number of divergent pathways may exist within multiple compartments of B cell differentiation.

T 31 CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL STAGING, SURVIVAL AND CAUSES OF DEATH.

G. Castelli, G. Pagnucco, E. Brusamolino, A. Canevari, L. Salvaneschi, D. Inverardi, C. Bernasconi. Divisione di Ematologia, Ospedale Policlinico San Matteo, Istituto di Ricovero e Cura a Carattere Scientifico.

A study was done on 241 consecutive untreated patients affected with chronic lymphocytic leukemia (CLL), to retrospectively analyze the survival and causes of death according to the initial clinical stage. The staging followed the Binet's criteria. All patients (170 males, 71 females) were admitted to the Division of Hematology of Pavia from January 1974 to December 1982. Median age at diagnosis was 61 yr (30 cases less than 50 yr). The diagnosis was made on the basis of a peripheral stable lymphocytosis ($>4\cdot10^9$/l) with bone marrow lymphocyte infiltration (>40%). Fifty-nine cases presented a lymphocyte count between 5 and $15\cdot10^9$/l and 62 cases a count higher than $50\cdot10^9$/l. The median follow-up was 36 mos (range 6-118+). Patients in stage A were 123 (51%), in stage B 69 (29%), in stage C 49 (20%). Indolent diseases amounted to 63% of total cases and pure splenomegalic forms to 5% (12 out of 241). Active CLL were characterized by progressive leukemia with or without lymph node swelling and systemic symptoms (15%); in 15 cases the prominent feature was a bulky lymphoadenomegaly (mediastinum 2%, abdominal masses 5%). In 5 cases the bulky disease was accompanied by a lymphocyte count below 20×10^9/l. Besides, 5 cases of prolymphocytoid and 3 of immunoblastic transformation (cytologic shift) were documented. All patient, regardless to their clinical stage and symptoms were treated since the diagnosis. Initial therapy consisted of alkylating agents with or without low-dose steroids in 210 cases (194 chlorambucil at the dose of 5 mg a day; 16 cyclophosphamide, 200 mg a day). Steroids alone were given in 6 patients, spleen irradiation in 18 and polychemotherapy (CVP) in 7 cases with aggressive disease. The median actuarial survival for the entire series was 61 mos; 15% of cases died within the first year, thereafter, the death-rate was constant. Patients with stage A and B showed a median survival of 84 and 50 mos, respectively ($p<0.01$); whereas stages C had a median of 23 mos ($p<0.005$), with a death-rate of 30% within the first year and 14% of long-survivors (>61 mos). As of October 1983, 110 out of 241 patients were dead. Death could be related to CLL in 52 cases (infections 32, hemorrhages 8, anemia 7, cytologic shift 5); in 20 cases was caused by subsequent primary cancers and in 18 by diseases unrelated to CLL (cardiac failure 8, uremic coma 3, hepatic cirrhosis 3, myocardial infarction 2, stroke 2). In 20 patients who died at home, the cause remained unknown. Infection-related deaths mainly occurred in stages B and C (25 out of 32 deaths) after bacterial pneumonitis (12), sepsis (7), urinary tract infections (4), acute hepatitis (1) and generalized herpes zoster (1). Subsequent primary cancers evenly distributed among the 3 stages. Conclusions: a) the prognostic value of the used clinical staging is confirmed; b) the life-expectancy of patients in stage A is shorter than expected for the general population; c) an high fraction of deaths in CLL are due to diseases not obviously related to the leukemia.

T 32 B-NHL: A MULTIPLE PHENOTYPIC STUDY WITH MONOCLONAL ANTIBODIES.

D. Delia, R. Giardini, S. Villa, F. De Braud, A. Costa and F. Rilke - Istituto Nazionale Tumori - Milano, Italy

Lymph-node biopsies from 58 patients with B-NHL (25 centroblastic/centrocytic (Cb/Cc), 2 centroblastic (Cb), 4 centrocytic (Cc), 4 immunoblastic (Im), 22 lymphoplasmacytoid (Lpc) and one cells lymphocytic (CLL) were analyzed in cell suspension with monoclonal antibodies directed against T cells (UCHT2, UCHT4, NA134, Leu 3a, OKT11a), B cells (BA1, Y29-55, FMC7, FMC8) against the HLA-DR monomorphic determinant (DA2), the CALL antigen (Vil A1, J5) and transferrin receptor (OKT9). Xenoantisera against Ig isotypes, K and λ light chains were also employed. The results show that all lymphomas contain T cells with helper (Leu $3a^+$) and suppressor phenotype ($UCHT4^+$) though their ratio in extremely variable. No case was positive for NA134 (a marker for the T6 cortical thymocyte associated antigen). All specimens were positive for HLA-DR and Y29-55 and 95% of them positive for BA1 (1 Lpc and 1 Imb were negative). In two Cb/Cc the number of BA1 cells was 80% lower than the number of neoplastic B cells. 75% and 59% of the cases were positive for FMC7 and FMC8 respectively. These markers did not always stain 100% of the neoplastic B cells. The majority of $FMC7^+$ cases were found among Cb/Cc (77%) and Cc (75%) NHL. 100% of the Imb and Cc NHL and 40 ÷ 60% of the remaining NHL were positive for FMC8. 32% of cases were $CALLA^+$; Vil A1 or J5 reacted with 56% and 18% of Cb/Cc and Lpc NHL respectively. T1 positive ($UCHT2^+$) B cell lymphomas were: 1 of B-CLL type, 3 Cc and 2 Lpc. The expression of the proliferation associated transferrin receptor was the following: the 2 Cb NHL contained 38% and 73% $OKT9^+$ cells and the avarage $OKT9^+$ cells among Imb, Cb/Cc and Cc NHL were 25%, 16%, 10.7% respectively. The single CLL gave 1%. These data partly confirm previous findings, such as the expression of CALLA among B-NHL. In addition they supply new data, such as the expression of the T1 antigen among Cc NHL. Correlation studies between the expression of the transferrin receptor and the labeling index are under way and result will be presented.

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T 33 HLA CLASS I AND II MARKERS IN CHRONIC LYMPHOCYTIC LEUKEMIA.

B. Grosbois*, M. Gueguen**, R. Fauchet**, R. Leblay*, F. Lancelin*, B. Genetet*. - *Service de Médecine Interne Hématologie - CHU. - **Laboratoire d'Histocompatibilité - Centre Régional de Transfusion Sanguine - Rennes - FRANCE.

HLA-A, B, DR and MT, MB markers by microlymphocytoxicity assay using allo-antibodies from multiparous women were studied in a group of 58 unrelated patients with chronic lymphocytic leukemia (C.L.L.) entering a therapeutical prospective protocol. Phenotype frequencies were compared to those of a local control group of healthy subjects. Patients group was divided into two subgroups, according to initial staging : (a) a non tumoral form stage A : no medullar insufficiency less than 3 palpable nodal areas. (b) a tumoral from regrouping stage B : without medullar insufficiency, but presenting at less 3 palpable nodal areas and stage C with medullar insufficiency, undependently of the number of palpable nodal areas.
No significant correlation was found for HLA-A and -B frequencies, neither in all patients, nor in the two subgroups.

HLA-DR PHENOTYPE FREQUENCY IN ALL PATIENTS COMPARED TO CONTROLS AND IN NON-TUMORAL FORM COMPARED TO TUMORAL FORM.

Allèle	*Healthy Controls* N=200	C.L.L. N=58	pc	*Non tumoral* C.L.L. N=30	*Tumoral* C.L.L. N=28	pc
DR1	25.5	6.9	<0.03	10	3.6	N.S.
DRw6	17	32.7	N.S.	46.7*	17.8	<0.08
DR7	24.5	25.9	N.S.	16.7	35.7	N.S.

* Non tumoral DRw6 frequency compared to controls : pc < 0.002.

The first results of MT, MB typing on 22 patients show a MB3 frequency of 36.4 % versus 18,3 % in 71 healthy controls.
As a conclusion, there is a significant decrease in DR1 frequency and an increase in DRw6 frequency in the whole series. DRw6 frequency is preferentially increased in the non tumoral form, while normal in the tumoral form. A non-significant discrepancy appears in DR7 frequency compared in the two subgroups.
Clinical follow up of these patients is purchased : Could HLA typing have any incidence on initial staging, prognosis and then treatment strategy ?

T 34 USE OF THE MONOCLONAL ANTIBODY anti-Y29/55 FOR VERIFICATION OF B - NON-HODGKIN LYMPHOMA

F.Gudat, K.H.Forster,R.Obrist,J.P. Obrecht

Institute for Pathology, Research Department and Oncology Department of the Kantonsspital Basel,University of Basel. Zentrale Forschungseinheit,Hoffmann LaRoche Comp.,Basel

The B-lymphocytic nature of Non-Hodgkin Lymphoma (NHL), particularly of the diffuse and large cell subtypes, can be proven only by immunologic markers. The monoclonal antibody aniti-Y29/55 (mAB y 29/55) may be successfully applied for the diagnosis of B-NHL. By an indirect immuno-alkaline phosphatase method, by an immuno-electronmicroscopic, indirect immuno-peroxidase or rosetting methods, by microcytotoxicity testing and indirect immuno-fluorescence on a panel of normal and neoplastic samples from blood and tissue it could be documented that the mAB Y29/55 exclusively recognizes B-lymphocytes. The cellular differentiation spectrum recognized by this mAB ranges from the small resting B-lymphocyte to stimulated follicle center cells and plasmocytoid cells. Pre-B cells, T-cells and ALL cells are not reactive.

205 blood samples and 27 tissue probes of patients with NHL were analysed. As additional markers were included receptors for sheep- and mouse-erythrocytes, surface Ig and surface antigens detected by mAB's OKT 11, OKT 4, OKT 8, B1 and Leu 10. It could be shown that definition of B or T cell nature is possible by use of this marker combination. In a number of cases the B-cell nature of the neoplastic cell could only be demonstrated by anti-Y29/55 but not by any of the conventional markers. There is also evidence that the mAB recognizes leukemic B-lymphoma cells in subleucemic numbers in blood.

The mAB y29/55 was also applicable to frozen lymphoma tissue sections allowing a discrimination of tumor growth from the distribution of reactive B- and T-lymphocytes.

T 35

PROLIFERATION OF DIFFERENT NEOPLASTIC PHENOTYPES IN CHILDHOOD B-CELL NON HODGKIN'S LYMPHOMA (B-NHL). A.Hirt,C.Baumgartner,P.Imbach,A.Lüthy and H.P.Wagner, Institute for Clinical and Experimental Cancer Research and Department of Pediatrics, University of Bern, Bern, Switzerland.

The majority of B-NHL occuring in children outside endemic areas are histologically identical to Burkitt's lymphoma but do not harbor the EBV genome and do not show the high titers of anti-viral capsid antigen seen in the African form. The abnormal B cells found in these conditions are characterized by i)chromosomal aberrations, most often t(8;14),less frequently t(2;8) or t(8;22) translocations; ii) a high labeling index (LI) after tritiated thymidine pulse-labeling and iii) the presence of surface immunoglobulins (sIg).

Since in experimental animals separate immunoregulatory circuits affecting the proliferation and differentiation of neoplastic B cells were found, it appeared of interest to investigate lymphoid cells from children with B-NHL by combined immunological and cytokinetic methods.

Studies on 16 patients revealed that i) not all cells which were neoplastic by morphological criteria had detectable sIg; ii) three different phenotypes of neoplastic cells were found in 6 patients, two in 2 patients and only one in 8 patients; iii) there was no correlation between the number of phenotypes and the light chain type of neoplastic cells, the sampling site or the LI; iv) significantly more Ia^+ than Ia^- neoplastic cells were proliferating and v) in some patients a small but variable percentage of activated (=Ia^+) T cells were present.

More detailed combined analyses of interrelations between the differentiation and proliferation of neoplastic and normal lymphoid cells are required for a more precise characterization of immunoregulatory circuits in B-NHL.

T 36 EFFECTS OF INDUCTION AND MAINTAINANCE THERAPY WITH TS ON T AND NON-T CELL FREQUENCIES IN HODGKIN'S DISEASE PATIENTS.

A.M. Liberati, Università di Perugia, Italy

We have recently experienced that thymostimulin (TS) has proved effective in restoring defective T cell immunoparameters in pts with Hodgkin's disease (HD) in complete unmaintained remission (CR) (A.M.Liberati et al. AACR 766, 1983). Such effects, however, were limited to the period of TS administration, so a second study was designed to investigate the role of TS maintainance therapy. To this end a group of 10 pts with HD in CR, but persisting decreased levels of circulating ER^+, OKT_{11}^+, OKT_3^+ and OKT_4^+ cells (p=.0001 compared to normal controls) were treated with TS (50 mg I.M.) given either daily or every other day for a period of 34 days (induction therapy). TS administration was then continued twice weekly for a maximum of 5 months. The frequency of ER^+, OKT_{11}^+, OKT_3^+ and OKT_4^+ cells increased during induction therapy (p=.005) regardless of the schedule of TS administration. Restored or normal values of all these T cell subsets were retained throughout the period of TS maintainance therapy. Furthermore pts exhibited along with T cell lymphopenia increased percentages of $OKIa^+$, $LeuM_3^+$, OKM_1^+ and $Leu7^+$ cells (p=.05 compared to controls), but not of $LeuM_2^+$ cells. TS produced a marked but not statistically significant increase in the number of $LeuM_2^+$ cells, while non remarkable effects were observed on the other subsets of non-T cells. TS maintainance therapy, thus, effects a long lasting immunorestoration. Furthermore TS does not affect the frequency of non-T cells but directly influences T and T cell subsets.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 37 EXPRESSION OF A T-CELL ANTIGEN (T101, leu 1) BY B-CELL LYMPHOMAS.

G. Laurent, Centre Recherches CLIN-MIDY/SANOFI Montpellier Cedex, France

. The expression of Tp67 antigen, normally limited to T cells, by neoplastic B cells, is well established. Nevertheless, correlation to other parameters such as histopathological type and immunological markers have received little attention.

. We investigated, on frozen sections, a series of 50 cases of B cell lymphomas using a panel of 21 monoclonal antibodies directed against B cell antigen (heavy and light chains, B cell antigens defined by leu 10 and a pan B antibody from Dako), pan T cell antigens detected by T101, leu 1, leu 4, leu 5, T cell subset antigens recognized by leu 3a, OKT4, OKT6 and miscellaneous antigens detected by an anti-calla (GP 100), leu 7, anti-DRC cells (R4/23), anti-HLA-DR, and OKM1. A three step immunoperoxidase technique was used (monoclonal antibody-rabbit antimouse Ig peroxidase conjugated-swine anti-rabbit peroxidase conjugated).

. T101, leu 1 antigen was detected in 20 of these cases : CLL (10/11), diffuse centrocytic lymphomas (3/8), follicular lymphomas (1/9), follicular and diffuse lymphomas (6/8). This antigen was never observed in high grade malignant lymphomas (10 cases).

. Two results deserve attention : (1) T101 + follicular or follicular and diffuse lymphomas showed most frequently IgM + IgD + surface Ig, inversely T101-lymphomas displayed IgM + IgD-phenotype. (2) Tp67 antigen (T101, leu 1) and calla (GP 100) were found to be mutually exclusive in these lymphomas.

. These results suggest that follicular lymphomas could be derived from two distinct germinal center cell populations : IgM +, IgD -, Calla +, T101 - lymphomas from centroblasts and centrocytes of the germinal center, IgM +, IgD +, Calla -, T101 + lymphomas from a minority of normal B cells identifiable around the edge of germinal center [1].

[1] GOBBI M., CALIGARIS-CAPPIO F., JANOSSY G.
Brit. J. Haemat. 1983, 54, 393.

T 38 ALTERATION IN MEMBRANE GLYCOPROTEINS OF CLL LYMPHOCYTES OF B-TYPE IN WORST PROGNOSTIC STAGE.

Peter A. Maubach, Bertold Emmerich, Adaling Ogilvie, Nikolaus Klecker, Johann Rastetter
Dept. Hematology and Oncology, Technical University Munich, Physiol. Chem. Inst. University Erlangen, GFR.

Progressive chronic lymphocytic leukemia is morphologically characterized by a diffuse and an increasing bone marrow infiltration resulting in anemia and thrombocytopenia. Membrane glycoproteins are supposed to contribute substantially to intercellular behavior. To elucidate the molecular mechanism of the altered growth pattern we studied membrane glycoproteins of CLL lymphocytes from sixteen patients in different prgnostic stages (Binet classification). Samples from Triton X 100 extracted leukemic cells were subjected to SDS PAGE followed by affinity labelling with 125 J Concanavalin A indicating glucose and mannose carbohydrate residues.
By this technique up to twenty one distinct membrane glycoprotein bands from 24.000 to 145.000 daltons can be found in CLL lymphocytes.
Comparing this pattern in lymphocytes from patients in stage A and C a loss of bands and also a decrease of labelling intensity in glycoprotein 78, 92, 105, 116 and 145 K were observed in stage C.
Furthermore it could be demonstrated by follow up studies that a change in glycoprotein pattern preceeds the switch to stage C.
The results indicate that alteration in cell membrane structure may be a factor responsible for clinical deterioration of the disease.
Supported by W. Sander-Stiftung.

T 39 THE NONRELEVANCE OF T4 TO T8 RATIOS TO DISEASE ACTIVITY IN B CELL MALIGNANCIES.

C.W. Patrick, P.W. McFadden, T.B. Buchholz, T.J. Milson, J.A. Libnoch and R.H. Keller, The Wood VAMC Marcus Center, Medical College of Wisconsin, 5000 West National Avenue, Milwaukee, Wisconsin, USA, 53193 and the University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, USA, 53201.

The relationships of T lymphocytes and their subsets were compared to the stage of disease in a spectrum of B cell malignant lymphoproliferations including chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphomas (NHL), Waldenstrum's macroglobulinemia (WM) and multiple myeloma (MM) to establish whether significant correlation existed between disease activity and selected T cell subsets (T4 & T8). One hundred peripheral blood samples of normal, healthy adults (ages 20-66 years, male and female) were compared to 192 patients with various forms of B cell lymphoproliferative disease as follows: CLL (N=85), NHL (N=72), WM (N=5) and MM (N=30). In the patient, all had group peripheral bone marrow (BM) and/or lymph node samples were also included in this study. The PB and BM samples were subjected to Ficoll-Hypaque enrichment and all samples were marked with broad spectrum panels of monoclonal antibodies and analyzed by the EPICS-V flow cytometer. In most instances, patients were followed sequentially over the past 24-month period. Cellular populations displaying unusual histograms or phenotypes were isolated by cell sorting and subjected to additional functional, cytochemical, morphologic (light and electron microscopic) and cytogenetic testing. All data was correlated with clinical staging and analyzed sequentially. Flow cytometric analysis of the monoclonal subsets revealed the following: (a) there is no correlation between T4 (helper/inducer) and T8 (cytotoxic/suppressor) ratios as determined solely by T4 or T8 monoclonal antibodies; (b) percentages of positive events may be misleading if conversion to absolute values (cells/MM^3) is not made particularly in PB samples; and (c) what have been purported to be exclusive T cell subset receptors (T4 or T8) may infrequently be expressed on B cell clonal proliferations. This data suggests that the monoclonal antibodies, T4 and T8, do not measure functional status of help versus suppression in B cell lymphoproliferative disease and additional functional monoclonals are needed clinically.

This work is supported in part by VA Research Service; NIH Grants RR01951, CA30660, HL29390; a VA Clinical Investigatorship, the American Lung Association and the Marcus Foundation.

T 40 MONOCLONAL ANTIBODY STUDIES IN HUMAN B CELL LYMPHOPROLIFERATIVE DISORDERS SUGGEST B1 NEGATIVE, B4 POSITIVE LYMPHOCYTES MAY IDENTIFY, B MEMORY CELLS.

C.W. Patrick, K. A. Harrison, J.A. Libnoch, M.G. Cozine and R.H. Keller. The Wood VA Marcus Center, Medical College of Wisconsin, 5000 West National Avenue Milwaukee, Wisconsin, USA 53193 and the University of Wisconsin-Milwaukee, Wisconsin, USA, 53201.

Lymphocytes from 192 patients with B cell lymphoproliferative disorders were examined with a broad spectrum panel of monoclonal antibodies and conventional surface marker techniques in an attempt to further dissect the compartmentalization of B cell disease. The results were compared with cells from 100 normal adult males and females. Peripheral blood and bone marrow samples were enriched for mononuclear cells using Ficoll-Hypaque density gradients while lymph node material was gently dispersed, washed and directly processed. All samples were pre-incubated with AB negative sera at 37°C to reduce non-specific immunologic binding through the Fc receptors. Cellular populations were marked with B1,B2,B4,Ia, J5, surface G,M,A,D heavy chains and Kappa and Labmda light chain antisera. Eighty patients and 42 normal controls were additionally marked with TQ1, PCA1, plus My7. Analysis was performed using the EPICS V flow cytometer with a minimum of 10,000 cells per marker evaluated. My7 was employed in conjunction with light scatter pattern to define the presence of moncytic and neutrophilic populations. Analysis of B cell markers revealed an interesting phenotype, previously uncharacterized of $B1^-$/B4+ cells, which were selectively removed using cell sorting techniques. The cells were small monomorphic lymphocytes having a well-differentiated appearance. The sorted populations were cultured in various concentrations of Pokeweed mitogen (PWM) for periods of 6,12, 18 and 24 hour periods. (PWM) stimulation revealed the transformation of these 10-15% cells into plasmacytoid or plasma cells within 18 to 24 hours in normals. No evidence of progression through a cleaved cell stage was present at either the light or electron microscopic level. In patients with multiple myeloma and in three of the chronic lymphocytic leukemia group, the numbers of $B1^-$/B4+ lymphocytes transforming directly to plasma cells was increased above normal controls but variable from individual to individual. The $B1^-$/B4+ clones reached their highest incidence in BM Samples. Although preliminary, the evidence suggests that the some or all $B1^-$/B4+ cells may represent the B memory cell compartment. Ongoing studies with the new monoclonal antibody, PCA1, which is purported to be a specific for the plasma cell compartment are being conducted and will be discussed. The B memory cell compartment heretofore has been difficult to characterize may be included in the $B1^-$/B4+ phenotype. Levels of B2 are variable within this phenotype and to date have shown no correlation with level of disease activity or staging.

This work is supported in part by VA Research Service; NIH Grants RR01951, CA30660, HL29390; a VA Clinical Investigatorship, the American Lung Association and the Marcus Foundation.

T 41

^{111}INDIUM-LABELLED LYMPHOCYTE CIRCULATION PATTERNS DURING TREATMENT WITH MONOCLONAL ANTI-IDIOTYPE ANTIBODY IN A PATIENT WITH B-CELL LYMPHOMA. Elaine M. Rankin, Annemarie Hekman and Max Hardeman, The Netherlands Cancer Institute and Academic Medical Centre, Amsterdam, The Netherlands

A 71-year old woman with advanced centrocytic lymphoma was treated with a mouse monoclonal antibody, designated T2, against the immunoglobulin idiotype[§]. During each period of treatment the number of malignant cells in the circulation fell and subsequently rose. To investigate whether this fall in lymphocytes was due to cell kill, or to redistribution of the cells, dynamic studies of labelled lymphocytes were performed. At a time when the patient was not receiving treatment 300 x 10^6 lymphocytes (80% malignant B cells) were labelled with ^{111}Indium oxine (142 µCi) and then re-injected. Serial measurements of blood radio-activity were taken. Blood disappearance curves showed an initial fall until 12 hours followed by a partial return until 24 hours after which there was a slower fall until 118 hours when 25% of the activity was still detectable.

To follow the pattern during treatment, 630 x 10^6 lymphocytes were labelled with 240 µCi ^{111}Indium oxine and re-injected at the same time as an infusion of mouse antibody was begun at a rate of 100 mg/hr over 2½ hrs followed by 40 mg/hr over 40 hours. There was no correlation between the patterns of the lymphocyte count and the labelled lymphocytes.

Time after treatment began	lymphocyte count x 10^9/litre	counts per millilitre blood
1 hr	18.8	5637
2 hr 40 min	17.4	851
3 hr 25 min	14.1	911
4 hr	15.0	6610
5 hr	15.1	7407
6 hr	15.2	1106
12 hr	20.6	1518

Dynamic scanning showed immediate uptake of cells into the lungs at 1 min. Cells then moved out of the lungs into the liver where activity fluctuated within the first 30 min. Serial scans showed slow accumulation of activity in the liver. Some activity was seen in known areas of tumour involvement in the mediastinum, left breast and para-aortic nodes.

This study demonstrates the usefulness of ^{111}Indium oxine labelling of lymphocytes and provides evidence that the reticulo-endothelial system is responsible for cell kill during anti-idiotype therapy.

[§]see abstract number 7

T 42

CLINICAL, HISTOLOGIC AND IMMUNOLOGIC CORRELATES IN DIFFUSE LARGE CELL LYMPHOMA USING MONOCLONAL ANTIBODY REAGENTS FOR PHENOTYPIC ANALYSIS. M. Wheeler, J. Winter, W. Hauck, C. Lamut, R. Marder, A. Epstein, and D. Variakojis. Northwestern University, Chicago, IL 60611, USA.

We have established a registry to collect immunologic, histologic, and clinical data on patients with non-Hodgkin's lymphomas to seek useful predictors of clinical behavior using monoclonal antibody reagents and the Working Formulation for the classification of lymphomas. This is a preliminary report of our experience with the first 32 patients with diffuse large cell lymphoma (DLCL). Since January 1982, our routine processing of lymphoma specimens has included indirect immunoflourescence analysis of single cell suspensions and immunoperoxidase staining of fresh frozen and B-5 fixed, paraffin-embedded tissues utilizing both commercially available monoclonal antibody reagents and those produced in our laboratory including B-cell antibodies LN-1, and LN-2, which react in B-5 fixed paraffin-embedded material. All patients treated for DLCL since January 1982, are included. Records were reviewed to identify age, sex, performance status, the presence of previously established poor prognostic variables (hemoglobin 11 gm/dl, LDH 250 lu/l, mass 10 cm., CNS, bone marrow, or visceral involvement), and response to therapy. All histology was reviewed and the presence of any degree of nodularity was noted. Biopsies were classified as [1] mature B (SIg^+), [2] pre-B ($cy\text{-}mu^+$, SIg^-), [3] primitive B (Ia^+, $LN\text{-}1^+$, or $LN\text{-}2^+$), or [4] T-cell ($OKT3^+$ or $OKT11^+$). Clinical data was available for 31 patients. The mean age was 60; 16 patients were male. Extranodal disease was present in 23, and poor prognostic features in 28. Twenty-three patients were seen at initial diagnosis, and six at the time of first relapse. Three patients with histories of low-grade lymphomas entered the study at the time that evolution to DLCL was first documented. The distribution by histologic subtype was as follows: cleaved, with sclerosis, n=3; cleaved, without sclerosis, n=20; noncleaved without sclerosis, n=8; large cell, unclassifiable, without sclerosis, n=1. Evaluable immunologic data were available for 26 cases. There were 17 mature B, 3 pre-B, 3 primitive B, 2 T, and one primitive unclassifiable lymphomas. Results were analysed using standard chi-square methods and the conventional 5% significance level. An association between SIgM and histologic subtype (p=.047) was the only correlation demonstrated between either a specific cell marker or immunological diagnosis and either any clinical variable or histologic subtype. 11/16 cleaved cell lymphomas without sclerosis were IgM^+. Nonimmunologic correlations included (1) histologic subtype with presence of a large mass (p=.047); (2) performance status with response to therapy (p=.011), and (3) the presence of any nodularity in newly diagnosed cases with bone marrow or CNS involvement (p=.014). Accrual of additional patients is needed to determine the clinical utility of the phenotypic analysis of DLCL biopsy specimens or subclassification according to the Working Formulation.

T 43

BIOCHEMICAL AND IMMUNOLOGICAL DIFFERENTIATION OF MALIGNANT T-CELL LINES INDUCED BY THYMIC HORMONES AND PHORBOL ESTER. A.D. Ho[1], D.D.F. Ma[2], B. Stehle[1], W. Hunstein[1], A.V. Hoffbrand[2], 1. Medizinische Universitäts Poliklinik, D-6900 Heidelberg, F.R.G. 2. Department of Haematology, Royal Free Hospital, London NW3 2QG, U.K.

A number of thymic factors are able to induce surface differentiation markers on normal bone marrow T-cell precursors. Phorbol ester (TPA) promotes differentiation of human leukaemic lymphoblasts as assessed by changes in phenotypic surface markers and terminal deoxynucleotidyl transferase (TdT) activity. Changes in levels of purine degradative enzymes occur during T-cell maturation with a fall in adenosine deaminase (ADA) and a rise in purine nucleoside phosphorylase (PNP) and ecto-5'-nucleotidase (5'NT) activities. We have investigated the effect of thymosin fraction 5 (TMS-F5), thymosin α1 (TMS α1) and TPA on some human leukaemia/lymphoma cell lines [Jm1, MOLT3 (both T-cell lines), KM3 (cALL) and RAJI (B-line)] in expression of the surface markers OKT6 (a marker for immature cortical thymocytes) and OKT3 (a marker for mature T cells) and of TdT, ADA, PNP and 5'NT.

In the T-cell lines JM1 and MOLT3, TMS-F5 and TMS α1 caused one or more maturation changes, e.g. TMS-F5 and TMS α1 caused significant reduction in OKT6 and TMS α1 an increase in OKT3 expression. A highly significant increase of 5'NT - levels of up to 2.6 fold was observed in both T-lines ($p < 0.001$). TMS however did not cause any such changes in KM3 (cALL line) or RAJI (B-cell-line). TPA induced a decrease in TdT and OKT6 expression and an increase in PNP activity in T-cell lines: changes that were compatible with maturation. On the other hand it also caused a fall in the percentage of OKT3 cells and in 5'NT, which were inconsistent with maturation. In addition TPA caused changes in KM3 and RAJI cells.

The present study demonstrates that normal thymic hormone, thymosin fraction 5 is capable of inducing differentiation changes in thymic derived human leukemic cells and thymosin α1 is probably the effective component in this respect.

T 44

IMMUNOLOGICAL INVESTIGATIONS IN A PATIENT WITH IMMUNOCYTOMA OF UNUSUAL PHENOTYPE. M. Gramatzki, G.R. Burmester, B. Manger, H.W. Baenkler, and J.R. Kalden. Institute for Clinical Immunology, University of Erlangen, Erlangen, West Germany.

Cells isolated from a patient with malignant lymphoma were analysed with a battery of monoclonal antibodies (MoAb). The majority of lymph node cells were documented to be of B-cell lineage by reactivity with MoAb BA-1 and B1 and expression of monoclonal surface immunoglobulin (IgD,IgM, lambda light chain). Interestingly, no HLA-DR molecules, which are normally expressed on B-cells,could be detected, despite the use of three different antibodies. This finding could not be explained by plasma cell differentiation, as documented by negativity with MoAb OKT10 and lack of detectable intracytoplasmatic immunoglobulin. The immunological classification as intermediate differentiation stage between B-lymphocyte and plasma ceil was in agreement with the diagnosis of immunocytoma (lymphoplasmacytoid) by the Kiel classification. While no paraproteinemia could be detected, IgG levels were highly elevated (5000 mg/dl). In addition, kappa light chains were excreted into the urine and a somewhat increased number of IgG_κ pos. plasma cells were found in the bone marrow, some of them atypical. Suppressor T-lymphocytes were increased in peripheral blood and lymph node as compared to number of helper T-cells. The unusual phenotype of this lymphoplasmacytoid immunocytoma as well as the related alterations of the immune system will be discussed.

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 45 A SUBPOPULATION OF LYMPH NODE B-CLL CELLS EXPRESSES THE COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN (CALLA).

JJ van den Oord, C De Wolf-Peeters, V Desmet. Dept. Pathology, A.Z. St.Rafael, B-3000 Leuven, Belgium.

In order to determine the distribution of mature and immature lymphoid cells in situ, we studied the tumoral lymph nodes (LN) from 7 B-CLL patients. Frozen tissue sections were treated with antibodies to T-cell subsets (OKT-series), B-cells (BA-series; anti-immunoglobulins; OKIa1), monocytes and granulocytes (OKM1), CALLA (J5) and terminal deoxynucleotidyl transferase (TdT) in a 3-step indirect immunoperoxidase procedure.

The large majority of LN B-CLL cells showed the phenotype $sIg^+BA1^+OKIa1^+$, and was admixed with variable numbers of OKT4 helper/inducer, and $OKT8^+$ suppressor/cytotoxic T-cells. Few $OKM1^+$ mononuclear, and no $OKM1^+$ polymorphonuclear cells were observed. Three out of seven LN contained few $BA2^+$ cells.

In each LN, regularly distributed $J5^+TdT^-BA3^-$ small lymphoid cells were observed, showing no clustering nor specific topographic predilection. J5-immunoreactivity was not due to Fc-binding nor to reactivity with polymorphs.

1. $J5^+$ small lymphoid cells in B-CLL LN may represent slowly replicating pre-B cells which have entered the lymphoid organs, and which proliferate and mature progressively in situ, resulting in a (circulating) $sIg^+OKIa1^+BA1^+$ population. This would explain the early, generalized LN involvement in B-CLL and is in agreement with cell-kinetic and enzymatic studies which favour a small, pre-B cell proliferative compartment in B-CLL LN.
So-called proliferation centers, classically considered to represent sites of growth in B-CLL LN, might instead correspond to areas of antigenic stimulation and subsequent differentiation in a pseudofollicular pattern.

2. J5-immunoreactivity may not be related to the proliferating compartment in B-CLL LN but may be acquired by a subpopulation of B-CLL cells undergoing some transformational event, in analogy with the induction of CALLA during cultivation of peripheral blood mononuclear cells in a diffusion chamber.

Further studies on $CALLA^+$-enriched fractions of LN cell suspensions in B-CLL are needed to characterize the phenotype and function of this $J5^+$ subpopulation more precisely.

T 46 Production of biological mediators by Hodgkin-cell-lines.

H. Burrichter, Universität Köln, Köln, Germany

Hodgkin's disease (HD) shows some atypical features, compared with other malignancies. HD-tumors are characterized by a marked cellular pleomorphism with a low percentage of "Sternberg Reed" (SR) and Hodgkin (H)-cells. Granuloma formation suggests interaction between tumor cells and host. Impairment of immunological response in HD-patients has often been discribed.
We succeeded since 1978 to etablish 5 cell lines from HD material representing H- and SR-cells. In the supernatants of the cell cultures some biological factors could be shown, which interfere with immunological response and regulation of hematopoiesis. The cell lines were found to produce colony stimulating activity (CSA), Interleukin 1 (IL-1) like activity and a factor inhibiting the migration of granulocytes (MIF like activity). Cell supernatant impaired the PWM induced proliferation of normal B-cells. The production of mediators by the HD tumor cell lines suggests that H and SR cells in vivo might influence immunological cooperation and regulation.

T 47 LYMPHOCYTE MIGRATION STUDIES IN PATIENTS WITH HODGKIN'S DISEASE (HD).

John Wagstaff*, Chris Gibson# & Derek Crowther*,
*CRC Department of Medical Oncology, Christie Hospital Wilmslow Road, Manchester M20 9BX, U.K., #Department of Physics, Christie Hospital.

Lymphopenia is a common finding in patients with all stages of HD. (1) This is due to a redistribution of helper T lymphocytes from the blood to the tissues. (2) Because of this, De Sousa (2) suggested that there might be perturbation of the migration and recirculation of lymphocytes in this disease. We have recently developed techniques for studying lymphocyte migration in man (3) and present the results of such studies in seven patients with HD.

Seven patients with untreated HD were studied (IIA = 1, IIIA = 1, IIIB = 5). Two patients were splenectomised. Three of these patients had blood clearance curves which showed a more rapid clearance of cells and to much lower levels than four normal volunteers. No comment could be made on the two splenectomised patients since their clearance pattern was very different. Two clearance curves were normal. In six of the seven patients there was marked preferential accumulation of the labelled cells in the involved nodes by 24 hours. This amount to 4-6% of the injected radio-activity.

It is clear that 'ecotaxopathy' (2) is occurring in HD. If lymphocytes are sequestered in the involved nodes then fewer are available to recirculate through other sites. This may account for the reduced responses to cutaneously administered recall antigens and for the lymphopenia. A hypothesis regarding the aetiology of this phenomenon will be presented.

(1) Case et al (1976), Cancer, 38, 1807
(2) De Sousa (1981), Lymphocyte Circulation, John Wiley & Sons, p.130
(3) Wagstaff et al (1981), Clin.Exp.Immunol., 43, 435.

T 48 NODULAR SCLEROSIS HODGKIN'S DISEASE

V. Romagosa , M. Callis , E. Condom , A. Fernandez , M.Hernandez, Barcelona, Spain

Clinical prognostic factors in Nodular Sclerosis have primarily been related to the presence of a large mediastinal mass, whose treatment with radiotherapy is followed by an increased incidence of relapse as compared to mediastinal involvement by smaller masses. A group of 53 consecutive patients were reviewed , and a 83 % complete remission rate was achieved . Twelve out of fourty-one patients at risk of relapse, did so , (29 % relapse rate). No difference in the freedom from relapse was found in regard to the presence or size of mediastinal involvement .
Overall prognosis showed a different survival in patients with B symptoms and stage IV patients . The former being our single most important factor influencing adversely survival . An attempt to correlate this data with histopathological findings is made.
At least four of the patients, either presented with or developped a peripheral neuropathy associated with active disease .
Since the majority of our patients have been treated with combined therapy , our results suggest a beneficial effect from the addition of COPP chemotherapy to patients with large mediastinal masses.

T 49 DIFFUSE LARGE CELL LYMPHOMA WITH SCLEROSIS LOCALIZED TO THE MEDIASTINUM: A POTENTIALLY CURABLE CLINICO-PATHOLOGIC ENTITY

J.L.Harousseau,J.M.Andrieu, M.F.d'Agay,G.Tricot.Departments of Haematology, 44035 CHR NANTES and Laennec Hosp. PARIS, and department of Pathology, St louis Hosp. PARIS, France.

Thirty four cases of primary mediastinal non Hodgkin's lymphoma were reviewed.Twelve out of them (8 female,4 male) had diffuse large cell lymphoma with irregular nuclei and moderate to severe sclerosis. Their mean age was 38,5 years (range 19 to 60 years). In 10 cases, mediastinal obstruction was clinically evident, including 4 cases with superior vena cava syndrome. Ten patients had no palpable lymphadenopathy, and the other 2 had only supra-clavicular lymph nodes. Pleural and/or pericardial involvement was noted in 10 patients. Bone marrow biopsies and lymphangiograms were always negative. Neuro-meningeal localization was never recorded. Thus, this lymphoma displayed a contiguous endothoracic spread.
Six cases were reviewed retrospectively. Four of them had been treated with chemotherapy and mediastinal radiotherapy : 3 are living in continuous complete remission (CR) (4,70,120 months). One patient was lost for follow-up in CR after chemotherapy and radiotherapy. One patient was treated with chemotherapy only and died in relapse after 22 months. One patient was treated with radiotherapy only and died in relapse after 12 months. Six further patients were treated prospectively with chemotherapy (1 patient with ABVD, 5 patients with Cyclophosphamide1, 5g/m2, Adriamycin 80 mg/m2, Vincristin 1,4 mg/m2, Prednison 80 mg/m2 d1-5, q21 d x 3 courses) and mediastino-susclavicular radiotherapy (40 G). All 6 patients achieved CR and are living and free of disease with a mean follow-up time of 12 months (7 to 19 months). Diffuse large cell lymphoma with sclerosis localized to the mediastinum appears to be a clinico-pathologic entity which can be efficiently treated with chemotherapy and local radiotherapy. The clinical presentation and the prognosis of this lymphoma are totally different from those of mediastinal lymphoblastic lymphoma.

T 50 DETECTION OF LOW NUMBERS OF MALIGNANT CELLS IN T CELL NON-HODGKIN LYMPHOMAS: STAGING AND FOLLOW-UP.

H. Hooijkaas, J.J.M. van Dongen, K. Hählen and G.E. van Zanen. Dept. Cell Biology and Genetics and Dept. of Pediatrics, Subdiv. Pediatric Oncology of the University Hospital/Sophia Children's Hospital, Erasmus University, Rotterdam, The Netherlands.

By double immunofluorescence (IF) staining it is possible to demonstrate, at the single cell level, positivity for the enzyme terminal deoxynucleotidyl transferase (TdT) and for a cell membrane marker. Therefore very small numbers of cells with a particular phenotype can be recognized. The malignant cells in about 50% of the childhood T cell non-Hodgkin lymphomas (T-NHL) and in all T cell acute lymphoblastic leukemia (T-ALL) express both TdT and T cell differentiation markers as recognized by monoclonal antibodies. In normal individuals, cells with the TdT^+/T cell $marker^+$ phenotype can only be found in the thymus. Therefore, the occurrence of cells with this phenotype in extrathymic sites is indicative for malignancy.

Using the double IF assay we are able to detect TdT^+/T cell $marker^+$ cells down to 1 in 10,000. We applied this technique on bone marrow (BM) and peripheral blood (PB) cells of 2 patients with T-NHL at diagnosis and follow-up. The cerebrospinal fluid (CSF) of these patients was screened for TdT positive cells. In both patients, according to clinical and morphological criteria, a diagnosis of T-NHL, stage II (Ann Arbor, 1971) was made. However, combined IF assays revealed that in patient 1 the lymphoma cells ($TdT^+/T1^+/T6^+/T4^+$) were also present in the BM (0.5%) and PB (3%) while in the CSF 2% TdT positive cells were detected. In patient 2 the lymphoma cells ($TdT^+/T1^+/T6^+/T4^+/T8^+$) were also detectable in BM (45%), PB (2%) and CSF (2%). This indicated a more widespread dissemination of the lymphoma cells than was suspected on morphological criteria only.

Patient 1 responded well to chemotherapy and is in complete remission according to morphological criteria as well as combined IF assay analyses 6.5 months after diagnosis. In patient 2, the number of TdT positive cells in the CSF was 2% at diagnosis, 6.5% 4 weeks later and increased to 21%, 12 weeks after diagnosis. However, a relapse in the central nervous system according to morphological criteria, could not be detected until 13 weeks after diagnosis.

Both patients presented with a T-NHL, stage II, although according to the data obtained by TdT as well as combined IF assays, a stage IV would have been a more appropriate classification. Our findings indicate that T-NHL can be more disseminated than would be suspected on the basis of clinical and morphological criteria. This may explain why local treatment of stage I or II lymphomas is often insufficient. The analysis of BM and PB by use of the combined IF assay as well as TdT determinations on cells in the CSF lead to a more accurate staging of TdT positive T-NHL. Both techniques can also be used for the detection of minimal residual disease during follow-up. Consequently they enable individual adjustment of the therapy as well as avoidance of under- or overtreatment of the patient.

T 51 Subtypes of cutaneous T-cell lymphomas.

Günter Burg, Peter Kaudewitz, Kirstin Klepzig, Christian Schmoeckel, Otto Braun-Falco
Department of Dermatology, Ludwig-Maximilians-Universität München

The term cutaneous T-cell lymphoma (CTCL) does not designate a specific disease entity, but comprises a whole bunch of distinct subtypes of cutaneous lymphomas, which have to be differentiated one from another with respect to their clinical, histological and immunological phenotypes.

Out of more than 500 malignant lymphomas of the skin, the characteristic features of small cell (mycosis fungoides, Sézary's syndrome, pagetoid reticulosis, T-CLL) and large cell (T-immunoblastic , T-lymphoblastic) cutaneous lymphomas will be presented.

T 52 LYMPHOMAS IN PATIENTS (PTS) AT HIGH RISK FOR ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS).

T. Ahmed, G. Wormser, R. Stahl, A. Mittelman, M. Friedland, Z. Arlin.
New York Medical College, Valhalla, N.Y.

The incidence of lymphomas has remained relatively constant at 2.2/100,000 over the last several years. Patients who are immunosuppressed appear to be at increased risk for lymphomas. AIDS presently represents the most common cause of death in the New York State Prison System which harbors 10,000 inmates. Since November 1980, 42 patients with AIDS have been diagnosed at Westchester County Medical Center, which serves as a referral center for prisoners. In this population we have noted only 2 cases of Kaposi's sarcoma; in contrast we have seen a total of 8 patients with diffuse non-Hodgkin's lymphoma, 1 with Hodgkin's disease, 1 with angioimmunoblastic lymphadenopathy and 1 with malignant histiocytosis. All of our patients met the criteria of working formulation for high grade lymphoma. No patients with nodular lymphomas were identified. None of these patients met the currently accepted criteria for AIDS. Overall this represents an annual incidence of 23.3 lymphomas/100,000 population per year, a 10-fold increase compared to the normal population. Diffuse lymphomas may represent yet another facet in the spectrum of the syndrome of acquired immunodeficiency. Whether this increase represents the result of immunosuppression that may exist in this population or the result of passage of a transmittable agent requires further study.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 53 LYMPHOBLASTIC LYMPHOMAS/LEUKEMIAS IN THEIR BIMODAL DIFFERENTIATION.

A.C.Feller, B.Doerken, M.R.Parwaresch, K.Lennert, Inst. Pathol., Univ.Kiel, Med. Poliklinik, Univ,Heidelberg, FRG

The growing number of discriminating criteria aviable today, call for a more sofisticated phenotypic definition of malignant lymphomas notably lymphoblastic lymphoma and leukemia.
60 cases of lymphoblastic lymphomas/leukemias were subjected to an immunehistochemical analysis using a set of 23 different monoclonal antibodies. The classic antibodies with specificities for T-(Lyt3, Leu1, Leu2, Leu3, OKT6, TdT) or B-cells(HLA-DR, sIg, B1) and CALLA (VIL-A1) distinguished T-, B-, CALLA, and unclassified lymphoblastic leukemias and lymphomas.In this communication data are presented which document the feasibility of an exhaustive discrimination of lymphoblastic lymphomas/leukemias into their exclusive bimodal differentiation e.g. B or T cell lineage. These results show that the additionally used monoclonal antibodies (T cell lineage: Tu14, Tu33, UCHT1; B cell lineage: To15, HD39, HD37, HD28, HD5, HD26, HD12, Ki-B1, Ki-B2, Ki-B3, KiB4) enable a clear cut classification of these neoplasms and that subtypes designated as cALL or ALL unclassified do not represent homogeneous enteties.
Considering the immunehistochemical results on normal thymi, the data obtained from lymphoblastic lymphoma/leukemia render insight into the line of B and T cell differentiation as well as into the possible phenotypic properties of their common progenitors.

T 54 SERUM COPPER LEVEL AND ERYTHROCYTE SEDIMENTATION RATE IN THE INITIAL EVALUATION OF NON-HODGKIN'S LYMPHOMA

Ron Epelbaum, Nissim Haim, Oren Zinder, and Yoram Cohen. Northern Israel Oncology Center and Department of Biochemistry, Rambam Medical Center, and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 35254, Israel.

Serum copper level (SCL) was studied in 76 untreated patients with non-Hodgkin's lymphoma (NHL) using an atomic absorption technique. Erythrocyte sedimentation rate (ESR) was taken in 58 of these patients as well. A correlation of SCL and first-hour ESR was done with the following variables: sex, stage, symptoms, histology (Rappaport's classification), nodal/extranodal site, bone marrow biopsy, gallium scan, response to therapy, and survival.

There were 44 males and 32 females, with mean SCL (µg/100 ml) of 148.1±34.9 and 172.2±55.1, respectively ($p<0.05$). The two groups had similar ESR. The SCL of the different stages were: I, 137.4±40.7; (N=22); II, 172.3±58.3 (N=17); III, 171.3±34 (N=20); IV, 155.7±40.4 (N=17). Each stage had significantly higher SCL than the 120.4±23 of 37 healthy controls ($p<0.05$-0.001). The high values of SCL in the advanced stages II and III were significantly different from the SCL of stage I ($p<0.05$, 0.01), but no such differences emerged comparing stages II, III, and IV with each other. SCL of patients with "B" symptoms was 181.5±32.9 as compared to 153±47.4 in those without systemic symptoms ($p<0.05$). There was no difference between the ESR of the various stages and between "A" and B" patients. The mean ESR of the whole group was 40/66. On the other hand, no correlation was found between SCL and the histologic subtypes, but diffuse histiocytic (DH) and diffuse mixed (DM) had significantly higher levels of ESR than diffuse lymphocytic poorly differentiated (DLPD) and the favorable group: DH + DM, 60 mm (N=17); DLPD, 34 mm (N=23); favorable, 30 mm (N=18); DH + DM vs DLPD or favorable, $p<0.01$. There was no correlation between SCL or ESR and nodal/extranodal site, bone marrow involvement, and positive gallium scan. Patients with SCL<160 had 83% complete response rate as compared to 69% in patients with higher values, and patients who failed to achieve complete remission had higher SCL than those who did (171±30.3 and 154.6±48.9, respectively). However, these differences were not significant. Survival curve of patients with SCL>160 was similar to that of patients with SCL<160.

In our experience, SCL is not a prognostic parameter in NHL, although in asymptomatic and stage I patients mean SCL is significantly lower. The mean ESR is similar in the various subsets of patients (except for DH and DM histologies), and its value, in the initial evaluation only, is limited.

T 55 EXCISION BIOPSIES FROM THE SPLEEN BY ULTRASOUND GUIDANCE.

B. Glimelius, B. Eriksson, H. Hagberg, P.G. Lindgren, A. Magnusson and C. Sundström. Departments of Oncology, Medicin Pathology and Radiology, University Hospital, Uppsala, Sweden.

It is uncommon to perform biopsies from the spleen because of the fear for haemorrhage, and there are only a few reports concerning aspiration biopsy of the spleen. In the diagnosis of lymphomatous involvement of the spleen non-invasive investigations such as scintigraphy, computarized tomography and ultrasound scan have been found not to be reliable. The method used has been splenectomy. Splenectomy has, however, been questioned as a diagnostic procedure because of the risk of fulminant fatal sepsis in splenectomized patients.

Using a recently described technique (Lindgren Radiol Diagnosis 1982;23:653-56) we have since January 1983 performed excision biopsies from the spleen in 20 patients.

Equipment and technique: An instrument, which consists of a spring-trigger system for firing the two different parts of a Tru-Cut® needle (15.2 cm, cannule 20 mm) was constructed and utilized. The biopsy is done with the guidance of a dynamic ultrasound scanner. Once the needle is within the spleen the instrument is fired by a pressure on the trigger and then automatically the biopsy is performed. One to four biopsies were taken in different directions.

Results: In all the 20 patients one or more biopsies with a length of 20 mm and a diameter of 1.5 mm were obtained. On microscopic examination the tissue was excellently preserved with splenic white and red pulp readily examined in detail. Lymphoma involvement in the spleen biopsies were found in 3 of the 12 patients with Hodgkin's disease and in 3 of 4 patients with non-Hodgkin's lymphoma. Because of suspected malignant lymphoma, biopsies were performed in another 4 patients. One patient was found to suffer from splenic tuberculosis. The biopsy showed typical epithelioid cell granulomas, and there was growth of tuberculosis bakteria from the biopsy. The other 3 patients had normal biopsies. Slight to moderate abdominal pain occured in 6 patients. Three patients had major bleedings and received 2-4 tranfusions. No splenectomy was performed.

Conclusion: Excision biopsy of the spleen by ultrasound guidance with the new technique described is a valuable clinical method which may replace splenectomy in some patients. The side effects with major bleedings seems to occure in between 15-20 per cent of the cases.

T 56 HYPOSECRETING CASES OF ALPHA CHAINS DISEASE : DIAGNOSIS AND FREQUENCY

H. RABHI, M. CHAFFOR, M.C. ABBADI
Laboratory of Immunochemistry,
Pasteur Institute of Algeria,
Laveran Street, Algiers, Algeria

Alpha chain disease (ACD) is mainly characterized by diffuse B-lymphoid cell proliferation localized to small intestine lamina propria and mesenteric lymph nodes. Proliferating cells produce and secrete a population of structurally deleted free alpha chains which constitute the immunological marker of the disease.

At initial stage of evolution, most of the infiltrating cells are mature plasma-cells while immature and more invasive immunoblasts predominate at more advanced period. This morphological evolution might be followed by modification in alpha chain disease protein synthesis and secretion. Indeed, variations in serum alpha chain disease protein concentrations were detected in different patients and also in the same patient according to the evolutionary stage of the disease.

In a recent study, we have shown that alpha chain protein hyposecretion is not a rare event. 10 of 120 sera from patients with clinical features of alpha chain disease contained low amounts of abnormal alpha chains. These molecules were detected only by rocket-immunoselection technique using goat anti-Kappa and Lambda light chains antiserum. At present, hyposecreting cases constitue about 12 % of the total number diagnozed in our laboratory.

These results consistently increased the frequency of the disease and led us to adopt a progressive diagnosis screening including conventional immunoelectrophoresis, immunoselection-immunoelectrophoresis and rocket-immunoselection techniques.

T 57 RADIOLOGICAL FINDINGS VERSUS HISTOLOGIC FEATURES IN GASTROINTESTINAL NON-HODGKIN'S LYMPHOMAS.

Ivo Spagnoli, Gian Maria Danesini, Luca Balzarini, Silvana Bergonzi, Giovanni Viganotti.
Istituto Nazionale per lo Studio e la Cura dei Tumori
Via Venezian,1 - 20133 - Milano,Italy

992 patients' radiographs suffering from previously untreated non-Hodgkin's lymphoma (NHL) were revised.
Gastrointestinal (G.I.) tract involvement was seen in 49/992 cases (5%). A first group (Group I) collected G.I. tract involvements only (24/992 cases): these patients can be classified as example of "primary NHL of G.I. tract" (stage 1).
A second group (Group II) collected 25/992 cases with disseminated lymph nodes involvement and/or visceral localization.
Group I comprised 21 lymphomatous gastric lesions,in the ileocecal area and 1 in the rectum.
Group 2 comprised 23 localizations in the stomach,4 in the small bowel and 3 in the rectum.5patients,in this group,presented multiple G.I. localizations.
Both groups were analyzed by age,sex,five years survival and roentgenological patterns.The Authors,moreover,inquired into possible correlation between histological and x-ray findings.
Our work confirmed that roentgenological distinction from other tumors of G.I. tract is sometimes possible with therapeutic and prognostic implications.

T 58 PRIMARY GASTRIC LYMPHOMA IN THE MIDDLE EAST

Labib Hashimi, Elias Anaissie, Charles Allam, Maryse Khalyl and Philip Salem.
American University of Beirut Medical Center (AUBMC) Beirut, Lebanon.

Twenty five cases of primary gastric lymphoma were diagnosed at the AUBMC during the period 1961-1980 and constituted 25% of all adult primary gastro-intestinal lymphomas diagnosed in the same period and at the same institution. Rigid criteria of selection were employed excluding patients with evidence of lymphoma outside stomach and its regional lymphatic drainage. Age ranged between 33 and 66 years with a median of 53. Male/female ratio was 4/1. The commonest presenting features were epigastric pain and weight loss occurring in 78% of patients. Abdominal mass as well as complications like bleeding, obstruction and perforation were uncommon. The lymphoma was located in the distal third of the stomach in half of the patients where site of tumor was delineated. All patients had non-Hodgkin's lymphoma except one who had Hodgkin's. Diffuse large cell lymphoma was the most common histopathologic subtype (76%). Lymphoma involved the whole thickness of stomach including serosa in 10 patients. The overwhelming majority of patients had pathologically documented regional nodal metastasis at the time of diagnosis. In conclusion, there were two main differences between our data and those emanating from the West: (1) the proportion of gastric to primary gastro-intestinal lymphomas was three times higher in the West, and (2) diffuse large cell lymphoma was more common in the Middle east.

T 59 RESULTS OF A MULTICENTRIC PROSPECTIVE STUDY OF PRIMARY DIGESTIVE NON HODGKIN LYMPHOMAS.

Y. Parlier (secretary) A. Najman (Chairman)
Service des Maladies du Sang, Hôpital St. Antoine 75012 PARIS.

Seventy patients have been included in this cooperative study between october 1977 and october 1982.
Seventeen patients with limited disease (I_D and II_D) were randomized between 3-weeks chemotherapy and whole abdominal radiotherapy or chemotherapy for three years. Fifty three patients with disseminated disease (III_D and IV) were treated with chemotherapy alone during 3 years.

Low grade lymphomas (14) received a cyclophosphamide-vincristine-prednisone association. Intermediate (46) and high grade (10) lymphomas received cyclophosphamide-vincristine-prednisone with adriamycin.

The overall complete remission obtained was 60% (42 patients) with 13 patients relapsing within 6 to 38 months.

Low grade and intermediate grade lymphomas survival were respectively 72% and 52% at five years. High grade lymphomas survival was 0% at 42 months. Limited and disseminated lymphomas survival were respectively 64% and 44% at five years. No significant relation to survival was observed concerning stage or histologic type (NWF) or according to the treatment of limited stage of disease

Statistically significant prognosis were (1) the primary digestive site of disease : stomach (28) 67% survival at five years, mesenteric nodes (8) 50%, multiple site (15) 44%, small and large intestive (19) 27% ($p<0,005$) (2) the initial response after treatment : complete and partial responders or treatment failure, respectively 59% survival at five years and 26% at 18 months ($p<0,005$)

No survival difference was proved for the twenty eight gastric lymphomas according to gastrectomy or not.

T 60 GASTRIC NON-HODGKIN'S LYMPHOMA (GNHL):CLINICAL PRESENTATION AND TREATMENT RESULTS.

C.R. Meier, K. Albrecht, C.G. Schmidt
Innere (Tumorforschung) und Chirurgische Klinik, Universitätsklinikum der GHS Essen, D - 4300 Essen, FRG

Forty-five (29 male, 16 female) patients (pts) with GNHL were seen between 1969 and 1983. Mean age at diagnosis was 51 ($\pm$ 14, range 19 - 74). Symptoms, mostly epigastric pain, preceded the diagnosis by up to 1 month in 16, by 2-6 months in 10, and by over 6 months in the remainder. Gastroscopy established the diagnosis in only 10/34 (29%), although abnormalities were noted in 16 more pts. In 35 pts, the diagnosis was made at laparotomy. 23 pts. had "unfavorable" (e.g. histiocytic), 21 "favorable" (e.g. nodular), and 1 unclassifiable histologic subtype. Staging revealed 14(31%), 14(31%), 2(4%), 2(%), 4(9%), and 7(16%) pts in stage IA, IIA, IIB, III, IVA, and IVB, respectively. 14 pts succumbed to progressive disease; 31/45(69%) are currently alive. Median survival was at least 61 months. 4 pts are alive with disease. Survival was strongly dependent on stage: 12/14(86%) of IA and 11/14(79%) IIA pts are in complete remission (CR) vs. only 2/13 (15%) stage IV pts. Histology apparently had no influence. Of 38 pts undergoing gastrectomy as initial therapy, 25(55%) currently are in CR. 11 pts had only gastrectomy (8 stage IA, 3 stage IIA); 1 died, but 10 are in CR for 5-155 months. 14 pts had gastrectomy followed by chemotherapy (CRX), and 9 others had it with CRX and radiotherapy (RRX) in succession. Only 1 stage IVB pt,of infavorable subtype, is in CR off treatment 66 months after aggressive therapy; other surviving pts had initial stages I-IIA. Out of 6 pts with advanced disease who initially received CRX, only 1 with inoperable stage IIA reached a long-term unmaintained CR. The CRX used most often was Cyclophosphamide, Vincristine, Methotrexate, Prednisone in combination. - These data underline the importance of surgical resection in GNHL. The role of combined modality therapy in GNHL still requires clarification.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 61 GASTRIC NON-HODGKIN'S LYMPHOMA (NHL): A RELATIVE RARE ENTITY IN NORTH-EASTERN ITALY.

Carter G., Segati R., Pappagallo G.L., Gobbato L., De Besi P., Salvagno L., Fornasiero A., Endrizzi L., and Fiorentino M.V.

Department of Oncology, Medical Oncology Division - PADUA (ITALY)

From January 1970 to December 1983, 23 out of 550 patients (pts) with NHL had their primary in the stomach. Sex: 14 males and 9 females. Age ranged from 18 to 74 years (median 55). Karnofsky PS ranged from 40 to 90 (median 80). Body weight fall greater than 10% (over 3 months) was observed in 11 pts, abdominal pain in 8, vomiting in 5, bleeding in 5, palpable abdominal mass in 1. Initial clinical diagnosis was radiologic in 14 pts, endoscopic in 6, and peritoneoscopic (with biopsy) in 3. Stage (according to Ann Arbor) was IE in 3 pts, IIE2 in 14, IIIE in 1, and IV in 2; 3 pts are currently under study. Therapy: surgery (total gastrectomy in 8 pts, partial in 9) was adopted alone in 3 pts, plus chemotherapy (CT) in 6, plus CT and radiotherapy (RT) in 8; CT (CHOP regimen in 10 pts, and monotherapy in 7), was adopted alone in 1 pt, and plus RT in 2. Survival differed according to time of study: from 1970 to 1973 (A group) all 7 observed pts have died (survival ranging from 5 to 79 months, median 5), while from 1974 to 1983 (B group) 15/16 pts are alive (1 died at 67 months), with survival ranging from 1+ to 118+ months (median 37+). The A and B groups differed in PS (A group: 40-80, median 60; B group: 70-90, median 90), and in treatment modalities (most of monochemotherapy-treated pts within A group); later diagnosis and staging could also have contributed to the shorter survival of A group pts. A single pt presented a lung epidermoid carcinoma after gastrectomy (surgery represented the sole treatment from lymphoma). The 23 "gastric primary" pts did not differ in sex, age, and PS from the total NHL group (550 pts); the 4.18% frequency figure may represent a negative selection bias.

T 62 GASTRIC NON-HODGKIN'S LYMPHOMA AS COMPARED TO OTHER NON-HODGKIN'S LYMPHOMA IN NORTHERN ISRAEL IN THE YEARS 1968-1982.

Y. Cohen, N. Haim, M. Ben Shachar, Y. Ben Arie, E. Robinson, Northern Israel Oncology Center and the Department of Pathology, Rambam Medical Center, Faculty of Medicine,Technion,Haifa,Israel.

During the period 1968-1982, 423 previously untreated patients(pts) with non-Hodgkin's lymphoma (NHL) were referred to the Northern Israel Oncology Center for further evaluation and treatment. 37 pts had gastric NHL (GNHL) at presentation and 386 had other NHL (ONHL). The male/female ratio was 1.5:1 for GNHL and 1.2:1 for ONHL (NS). The mean age was 53.2±16.4 y and 50.2±23.3 for GNHL and ONHL respectively (NS). Stage distribution for GNHL was: Stage Ie-16 pts(43.2%), Stage II-e 15 pts (40.5%), Stages IIIe & IVe - 6 pts(16.2%). For ONHL these figures were: Stage I & Ie - 114(29.5%), Stage II & IIe - 93(24.1%) and Stages III, IIIe & IVe - 179(46.4%). (x^2, $p<0.01$). Only 25 pts with GNHL were classified according to Rappaport. 12 pts had pre-Rappaport classification, 3 pts (12%) had diffuse lymphotic well differentiated(DLWD), 1 pt (4%) had nodular lymphocytic poorly differentiated (NLPD), 9 pts (36%) had diffuse lymphocytic poorly differentiated (DLPD), 9 pts (36%) had diffuse histiocytic (DH) and 3 (12%) had diffuse mixed (DM). For 306 ONHL pts who were classified according to Rappaport, the figures were for DLWD - 37 pts (12.1%), NLPD - 43 pts (14.1%), DLPD - 67 pts (21.9%), DH 80 pts (26.1%) and 16 had DM (5.2%). 23 GNHL pts underwent a radical operation, 5 debulking procedures, 2 explorative laparatomy and 6 had a biopsy only. Follow-radical surgery, 20 were treated by radiation therapy aimed at the upper abdomen. Radiation therapy was administered using high energy radiation equipment (60-Cobalt or 8 MeV linear accelerator). The mean radiation dose of 20 pts treated following radical surgery was 3168±355 rads. 15 pts were treated by combined chemotherapy (CT). 6 received CT as the only treatment and 9 received CT following surgery with or without radiation therapy. The mean follow-up of GNHL pts was 49.4 m and for ONHL it was 37.7 m. The actuarial 3 and 5 y survival for GNHL pts was 61% and for ONHL it was 61.6% and 53.7% respectively (NS). The actuarial 5 y survival of the complete responders was 77.9% and 74.3% for GNHL and ONHL respectively. The 2 y survival of ONHL non complete responders was 29.8%. None of the GNHL non complete responders survived at 2 y following diagnosis. Pts who underwent radiation therapy following radical surgery (with or without chemotherapy) had 74.5% 5 y survival. The above data indicates a similar survival of GNHL and ONHL pts, regardless of differences in Stage and subtype distribution. Gastric surgery (either subtotal or total) followed by radiation therapy, allows considerable cure rate in gastric non-Hodgkin's lymphoma. Adding adjuvant chemotherapy to pts with unfavorable histologies should be investigated.

T 63 PRIMARY GASTRIC LYMPHOMA: CLINICAL ASPECTS IN 14 PATIENTS.

Sabbioni R.,Perini A.,Todeschini G. and Cetto G.L. Ist.Pat.Med. Cattedre di Ematologia e di Oncologia Medica, Università di Verona.

Fourteen adult patients (9 males,5 females) affected by primary gastric lymphoma without peripheral or mediastinal adenopathy, as well as hepatic or splenic involvement,and without a leukemic phase,surveyed from July 1973 to December 1983, are considered.The median age was 55 years (range 31-76). The lesion was mostly on the lesser curvature of the stomach localized. The mosts common presenting symptoms were abdominal pain, weight loss, nausea or vomiting, anorexia, gastrointestinal bleeding, fever or peptic disease symptomatology. The most useful investigations to establish the diagnosis were barium meal (abnormal in all the patients who had G.I.radiographsland gastroscony examination. The diagnosis was established by endoscopic biopsy in 8 out of 9 pts in whom this examination was performed or at laparotomy (6 cases). Thirteen pts underwent laparotomy; eleven pts underwent gastric resection or total gastrectomy; the remaining two pts had a diagnostic laparotomy only. 2 cases were classified centroblastic-centrocytic, 2 immunoblastic, 2 lymphoplasmocitoid, 2 centroblastic, 1 T-zone lymphoma, 1 histiocytic, and 4 cases could not be classified histologically. Not homogeneous treatment was performed: 7 pts received chemotherapy post surgical resection; 3 underwent only gastrectomy; 1 had chemio and radiation therapy after operation; 3 had no surgical resection (2 chemotherapy and 1 chemio and radiotherapy only). None the less, no significant difference in survival was observed: five out of six pts with stage I disease are still alive without symptoms (only one pt died 18 months after diagnosis of unknown causes). It should be stressed that three out of eight pts all belonging stage II disease died: two of them did not undergo gastric surgery.
Diffusion of disease appears the most important prognostic factor. Therefore, both diagnostic and therapeutic relevance of gastrectomy are stressed.

T 64 PRIMARY GASTROINTESTINAL NON-HODGKIN'S LYMPHOMAS: RESULTS OF CHEMOTHERAPY.

G. Bellesi, A. Bosi, S. Di Lollo*, L. Andreucci**, P. Rossi Ferrini. Cattedra e Div. di Ematologia, *Ist. di Anatomia Patologica, **Servizio di Fisica Sanitaria U.S.L. Università Firenze.

A series of 47 cases of primary gastrointestinal lymphomas (GIL) were selected for this study from 390 consecutive previously untreated patients with non-Hodgkin's lymphomas (NHL). Diagnostic specimens were obtained by endoscopic or intraoperative biopsy. The sites were: stomach (31 cases), small bowel (5), ileum-cecum (4), large bowel (4), multiple (4). Thirty-two patients were male and 15 female (M/F ratio = 2,13). Mean age was 51 (range 12-78). The histology, according to the Rappaport classification, was: DWDL 4 cases (9%); NPDL 3 (6%); DPDL 23 (49%); DH 16 (2%); unclassificable 1 (2%). Stage was in accordance with the Ann Arbor staging system modified by Musshoff for GIL: 13 patients were classified as IE (28%); 6 (13%) as IIE1; 14 (30%) as IIE2; 3 (6%) as IIIE and 11 (23%) as IV. Curative chemotherapy was employed in 40 patients: DPDL were treated with Fi2/74 protocol (Adriamycin 40 mg/m2 i.v. day 1; Vincristine 2 mg i.v. day 2 and 9; Bleomycin 10 mg/m2 day 2, 3, 9 and 10; Cyclophosphamide 300 mg/m2 i.v. day 4, 5, 11 and 12; Prednisone 40 mg/m2 p.o. from day 3 to 12. DH were treated with Fi3/74 protocol where VM26 (50 mg/m2) replace the Vincristine. Patients with favourable histology (NPDL and DWDL) were treated with CVP regimen. Complete remission (CR) was obtained in all patients with localized disease, in 33% of patients in stage IIIE and in 20% of patients in stage IV. The site of involvement did not influence CR. Patients with DH gained more easy CR than patients with DPDL (90,9% vs 70%). Survival data were analyzed with actuarial analysis to determine factors influencing the outcome of therapy. Age appeared to influence survival: 53% of patients more than 60 year-old were alive at 5 years compared to 83% for patients aged between 30 and 60. Histology influenced survival: patients with histiocytic type had a better chance of achieving a prolonged survival than patients with lymphocytic patterns (100% vs 72%). The site of involvement did not affect the survival rates. The extent of disease had a very significant influence on survival: at 5 years the survival rate for patients with generalized disease (stage IV) was 36% compared to 100% for the group with localized disease (stages IE, IIE1, IIE2).

T 65

ORBITAL LYMPHOMA:LONG-TERM RESULTS OF THERAPY OF 21 PATIENTS. A.R.Bianco,R.V.Iaffaioli,G.Bonavolontà*,A.Pezzullo,and A.Contegiacomo.Division of Medical Oncology,and Division of Clinical Ophtalmology*,University of Naples Medical School II, Naples,Italy

Twentyone patients with non Hodgkin's lymphoma involving the orbital structures were studied between 1975 and 1983.Twelve patients presented with disease confined to the orbit;in the remaining the orbital involvement was part of a systemic disease.The patients,12 males and 9 females,had a median age of 58 years(range 12-80).Histopathology was the following:diffuse well differentiated lymphocytic lymphoma in 4 patients,diffuse poorly differentiated lymphocytic in 10,diffuse histiocytic in one,diffuse mixed histiocytic-lymphocytic in 2, undifferentiated non-Burkitt in one,unclassified in 2,pseudolymphoma in one.Pathological staging was done according to Ann Arbor recommendations.Six of the twelve patients with primary orbital lymphoma were treated with local excision alone and they all relapsed,2 locally and 4 with systemic disease,from 6 to 51 months following surgery(median 18 months).The six remaining patients received adjunctive therapy after initial surgery,consisting of either local radioterapy(4 patients) or chemotherapy(2 patients).One patients relapsed in the radiotherapy group;the remaining five patients have been in complete remission from 8 to 69 months from beginning of therapy.

Fourteen patients with stage IV disease,9 at presentation and 5 following relapse after treatment for localized disease,were treated with combination chemotherapy,which included regimens such as CVP, CHOP,BACOP,and MOPP.Eleven of the fourteen patients so treated have been in remission,6 partial and 5 complete,for 6 to 42+ months from beginning og chemotherapy.

In conclusion,in stage I_EA orbital non Hodgkin's lymphoma,adjunctive treatment,either radio- or chemotherapy,after local surgery seems warranted.In patients with stage IV disease the presence of orbital involvement does not seem to influence the response of the disease to chemotherapy.

T 66

PRIMARY NON-HODGKIN'S LYMPHOMAS OF THE CNS. U. Bogdahn, S. Bogdahn, H.G. Mertens, D. Dommasch, R. Wodarz, P.H. Wünsch, P. Kühl.

We report on 10 patients with primary Non-Hodgkin's lymphomas of the brain and 1 patient with a primary epidural manifestation (mean age 48.9 years, mean survival 10.2 months). Pathological CSF was found in all 9 patients examined (pos. cytology in 7/9 cases). Either solitary tumors, diffuse periventricular infiltration or diffuse cerebral infiltration (encephalitis like syndrome) were seen in computer-assisted tomography, whereas angiographical findings were unspecific. Among other histologies a lymphoblastic (convoluted T-cell) and a T-immunoblastic lymphoma were found. Patients who had received radiotherapy (± surgery) had a mean survival of 17.1 months, compared to a mean survival of 1.48 months in patients who had not received X-ray therapy. Results for chemotherapy were not evaluable because of low patient numbers. In addition, an overview of 83 well-documented cases of the literature tries to characterize main histological and topographical distribution,histology, patient's age and therapy-related survival, as well as epidemiology and radiology of this disease group. Compared to a 5-year-life expectancy of 2.3% in secondary lymphomatous CNS-involvement patients with primary CNS-Non-Hodgkin's lymphomas have a 5-year-life expectancy of 30%. Finally, new diagnostic and therapeutic approaches will be discussed.

T 67

HIGH FREQUENCY OF CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT IN PRIMARY LYMPHOMAS OF THE TESTIS ?

GANEM G., CHAHINE G., CARDE P., HAYAT M.,KAMIONER

The primary lymphomas of the testis are rare (1,8 °/$_{oo}$). Sixteen lymphoma patients with initial involvement of the testis were treated between 1973 and 1983. Patients characteristics are as follows : mean age is 46 years (6 - 75). Diffuse histologic pattern was recorded in all patients. Cytologic type was noted as immunoblastic (8 patients), lymphoblastic (2 patients) and "largecells" in 6 patients. Clinical stage was IEA in 4 patients IIEA in 6 patients and stage IV in 6 patients according to the Ann Arbor Classification.

Central nervous system involvement with clinical symptoms (headache, impairment of cranial nerve with or without meningeal symptoms), occured in seven patients. the diagnosis was made on cerebro-spinal fluid examination whether CT scan was abnormal in 6 patients. CNS involvement was present at onset in 4 patients while it occured between 9 and 14 months from diagnosis in the 3 other patients. Let us notice that none of the 3 patients who underwent a prophylactic treatment on central nervous system had later CNS involvement. Other characteristics were : bilateral testicle involvement (3 cases), subcutaneous infiltration (3 cases) and Waldeyer ring involvement (2 cases).

Treatment varied according to stage. All but one stage IV and two patients (one stage IEA and one IIEA) had an initial chemotherapy. Initial radiotherapy was given in 7 patients with adjuvant chemotherapy in 4 cases. One patient (75 years old) could not be treated and died one month. Another patient, first seen elsewhere had no treatment until the relapse 6 months after surgery. Median survival of the 16 patients is 15 months.

CNS involvement in patients with lymphoma of the testis appears more frequent than previously noted. This finding may have clinical implications for the initial work-up treatment.

T 68

PRIMARY EXTRANODAL LYMPHOMAS IN EGYPT. N. El-Bolkainy, N.Dahba, G.O'Conor, N. Gad-El-Mawla and M.Morad. National Cancer Institute, Cairo,Egypt.

A study was made of 138 Egyptian patients with malignant lymphoma whose initial clinical presentation was at an extranodal site.Included in this series are lymphomas in sites other than lymph nodes, spleen, thymus or Waldeyer's ring. The case material was compiled during 1982 and 1983 from a consecutive pathology series (total of 9722 cancers) examined at NCI, Cairo and a private pathology laboratory. Extranodal lymphomas constituted 16.5% of all cases of lymphomas (838 cases). Males predominated with a sex ratio of 1.7:1. Pediatric cases (age 16 years and younger) contributed 21.7% (30 cases). Gastrointestinal lymphomas were the most common (50 patients ie. 36%). The distribution was 19 in small intestine, 18 in stomach and 13 in colon. The head and neck was involved in 19 patients, bone 16 cases, soft tissue 16 cases, skin 12 cases, spinal 8 cases and other sites in 17 patients. Histologically, only 5 cases were Hodgkin's disease (3.6%). Non-Hodgkin's lymphomas were classified according to the NCI sponsored " Working Formulation ". Contrary to the previous belief, Burkitt's type lymphoma is not uncommon in Egyptian children. Moreover, the pattern of histopathologic types varies markedly among different sites. Thus, Burkitt's lymphoma was frequently observed in the small intestine (10/19) and to a lesser extent in the colon (4/13), but in the stomach none was observed and the majority of cases (9/18) were diffuse large cell type.

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 69 NON-HODGKIN'S LYMPHOMA (NHL) OF THE NASAL CAVITY, PARANASAL SINUSES AND NASOPHARYNX. ANALYSIS OF 26 CASES.

Edna L. García de Díaz, Sergio Loera F., Leticia Rodríguez M., Benjamín López Ariza, Agueda López Pérez and José C. Díaz Maqueo
Servicio de Hematología. Hospital de Oncología. CMN. IMSS. MEXICO.

322 patients (pts) with NHL were included in different prospective treatment protocols from January 1 1980 till April 30 1983. In this group we found 46 cases (14.2%) with lymphomas of the nasal cavity, paranasal sinuses and nasopharynx. 20 pts were not evaluable. Initial symptoms in the evaluable group were: nasal obstruction in 9 pts, local pain in 7, foreign body sensation in 6, nasal discharge in 3, swelling of the nasal or maxillary area in 3 and epistaxis in 1. 23% of the pts were heavy smokers, 19% had suffered of chronic infectious or allergic upper respiratory tract diseases and 19% presented a combination of smoking and chronic inflamatory process. 81% of the pts had stage I or II and 19% had stage III or IV. Predominant histological subtype was Diffuse large cell lymphoma (13 pts), with 7 cases of Diffuse small cleaved cell, 4 Diffuse mixed, 1 polymorohic reticulosis and one unclassified. All but one, who had mixed follicular and diffuse histology, belonged to diffuse group. 16 pts (61.5%) are still alive with a mean total survival (TS) of 23.3 months (ms); 8 pts are death with a mean TS of 5.7 ms and 2 pts are lost without active disease at 19 and 28 ms respectively. 9 pts (34.6%) had initial bone involvement with a mean TS of 15.3 ms (s=9.4) and 6 pts continue with Complete remission (CR) and the other 3 died with active disease. The mean TS for the rest of the group is 19.3 ms (s=19.1). The mean TS for pts with large cell lymphoma is 15.2 ms (s=11.2), 6 ms (s=4.6) for pts with mixed lymphoma and 19.3 ms (s=10.2) for pts with small cleaved cell lymphoma. TS in relation to stage shows 18.9 ms (s=17.1) for localized forms and 13.8 ms (s=12.8) for disseminated forms with p=0.5, not statistically significative. These pts were treated with different prospective protocols consisting mainly of radiotherapy for localized forms, with or without adjuvant chemotherapy and combined chemotherapy, with or without adjuvant radiotherapy, for disseminated forms. At present we are including these pts in 3 different prospective specific protocols started in May 1 1983. The follow-up study of the present group of pts has not been concluded yet.

T 70

EXTRANODAL (EN) MALIGNANT LYMPHOMA (ML) OF THE HEAD AND NECK -A REPORT OF 49 CONSECUTIVE PATIENTS.

B.W. Hancock, M. McGurk, J. Goepel, Royal Hallamshire and Weston Park Hospitals, Sheffield, UK.

Of 1002 consecutive cases of ML referred to the Sheffield Lymphoma Group from 1970-1982 inclusive, 58 patients were recorded as presenting with EN lymphoma of the head and neck. Evaluation of clinical records and histology excluded 9 cases. Tonsillar and thyroid lymphomas formed 47 and 24% respectively of the series. All cases were of non-Hodgkin's type. The mean age was 57 years (range 28-82); tonsillar lymphoma showed a male (16:7) and thyroid lymphoma a female (3:9) predominance. There were 24 stage I_E, 22 stage II_E and 3 stage III_E (modified Ann Arbor). Histology (British National Lymphoma Investigation classification) was Grade I (low grade) in 13 and Grade II (high grade) in 36 patients. Radical radiotherapy was the primary treatment in 42 patients; 2 of the others had surgery alone and 5 had combination chemotherapy. Complete response (CR) was seen in 40 patients and 20 of these have not recurred. Of the 29 who did not have a sustained CR only 5 are alive, 2 with residual lymphoma. Recurrence, usually within months of primary treatment, was invariably outside the irradiated field distributed equally between lymphatic and extranodal sites; the abdomen was the site of recurrence in 12 patients. Follow up is from 1.6 - 13 years (mean 6.5). Cumulative survival for all patients is 46.5% at 6 years. Analysis by histology grade and clinical stage showed 67.6% for Grade I, 29.9% for Grade II; 65.7% for stage I and 40.9% for stage II. Tonsillar lymphomas fared worst. EN head and neck lymphomas are potentially curable by local radiotherapy; however the unfavourable effects of high grade histology and regional disease are re-emphasised by this study.

T 71 THE PATTERN OF MALIGNANT LYMPHOMA IN THE EASTERN PROVINCE OF SAUDI ARABIA.

E.M. Ibrahim, M.B. Satti, A. Abdel Satir, H.Y. Al-Idrissi.

Malignant lymphoma (ML) constitutes one of the commonly encountered malignant diseases in this region. In a period of one year, sixty new patients were diagnosed. Seventy percent of those patients have lived most of their lifes in the southern parts of Saudi Arabia, a known endemic area of malaria. Malaria antibodies were tested in twenty-five of those patients. High titres were reported in five patients, three of whom had lymphoblastic Burkitt's lymphoma. This observation could point out a causal relation between Burkitt's lymphoma and malaria in the South. However, accurate establishment of this relation and the role of malarial endemicity in the distribution of other types of ML is yet to be confirmed in a large-scale epidemiological survey. Other environmental factors need to be explored.

Of all cases, there were eleven HD, of the remaining ML, eight were abdominal, seven mediastinal, one primary in bone, one primary in thyroid and the rest presented with peripheral lymphadenopathy. Poorly differentiated lymphocytic and mixed lymphocytic-histiocytic constituted the majority of cases. Low response rate was reported and this was related to several factors: long median duration between symptoms to diagnosis (9+ months), seventy percent of patients had stage III-B and IV-B at presentation. High incidence of accomanying infection at diagnosis, and high folow-up drop-out rates. These factors are challenging for oncologists in developing countries. Not only aggressive therapy, but also continued public medical education is needed.

T 72 PREFERENCIAL OCCURRENCE OF LEUKEMIAS AND MALIGNANT LYMPHOMAS IN FAMILIES OF PATIENTS WITH HODGKIN'S DISEASE

Hj. Müller, A. Gencik, W. Weber
Laboratory of Human Genetics, Dept. of Research of the University Clinics, Kantonsspital, CH-4031 Basel and Dept. of Genetics, University Children's Hospital, CH-4005 Basel Switzerland.

Pedigree data were systematically collected by a geneticist from 1) 28 patients (age between 12 and 60 years, average years 32,14), suffering from Morbus Hodgkin 2) 91 patients with breast cancer and 3) 165 patients (no children) with different malignancies. In the average 50 members (range 20 to 121) per family were included in the study. Persons with leukemias and malignant lymphomas are found in 46,42% of families with an index-patient suffering from Hodgkin's disease. On the other hand these malignancies occurred only in 8.6% of the families in which the index-patient had breast cancer and only in 10,9% of 165 families in which he had a different solid tumor. This survey shows that in the families of patients with Hodgkin's disease malignancies do not occur in the same frequencies which are expected on the basis of the tumor spectrum and their incidence in the general population. It will be demonstrated how genealogical analysis enables familial predispositions to be identified.

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T 73

CHILDHOOD ABDOMINAL LYMPHOMAS IN THE MIDDLE EAST

L Hashimi, E Anaissie, C Allam, M Khalyl, P Salem.
American University of Beirut Medical Center (AUBMC)
Beirut, Lebanon.

Thirty three children with abdominal lymphomas presenting in gastro-intestinal tract or mesentery were diagnosed at AUBMC during the period 1961-1980. Other abdominal lymphomas were excluded. Median age was 5 years. Male/female ratio was 1.5/1. The commonest clinical finding at presentation was an abdominal mass (66%). 42% of patients presented with intestinal obstruction, perforation or bleeding. Abdominal pain was present at diagnosis in 39% of patients. Lymphoma was apparently confined to intestine and/or mesentery in 47% of patients. The remaining patients had advanced abdominal disease (stage III and IV). Apparent primary was in intestine in 18 patients and in mesenteric lymph nodes in 14. Of the 12 patients who had a primary in the small intestine, the location of the tumor was in the ileum or ileo-cecal region in 10. 7% of patients had lymphoma limited to mesenteric lymph nodes. All patients had non-Hodgkin's lymphoma and in 90% the lymphoma was high grade malignancy. 60% of patients had undifferentiated lymphoma (Burkitt's or non-Burkitt's). Lymphoblastic lymphoma occurred in one patient. Only one patient had lymphoma cell leukemia at presentation. CNS involvement at diagnosis was not documented. None of the patients had stomach lymphoma or Hodgkin's disease.

T 74

NON-HODGKIN-LYMPHOMA (NHL) AND ACUTE LYMPHOCYTIC LEUKEMIA (ALL) OF CHILDHOOD PRESENTING WITH PLEURAL EFFUSION.

H.J.Plüss and W.H.Hitzig. Univ.-Children's Hospital, CH-8032 Zürich.

The incidence of thymic enlargement has not been very high in our NHL and ALL (35% of NHL, 5% of ALL). But of 11 children with ALL and 10 with NHL with a thymoma, 6 (=28.5%, 3 ALL and 3 NHL) presented with pleural effusion. 4 were boys, and 2 (both with ALL) were girls; all except one ALL were diagnosed between 1979 and 1982. Age at diagnosis was between 2 and 9 1/2 years. 2_9(both with ALL) had a WBC of $25\text{-}30.10^9/l$, all others around $10.10^9/l$. Platelet count was normal in all. Hepatomegaly was noted in 3 (2 ALL, 1 NHL), and splenomegaly in 1 ALL. Diagnosis was made rapidly except in one boy with pleural pain for 2 weeks, who was treated as pleuresy because no cytology had been made from the first aspirate. In 4 (including all 3 NHL), T-markers were found on the blasts (including those from pleural fluid), in 2 ALL, marker studies were not possible.

The treatment results in these 6 children were very disappointing: all except one had a relapse within 3 to 15 months (4x local, 1x in the CNS). Secondary bone marrow invasion occured in one of the NHL, CNS-disease was only observed in the one girl who had not gotten any CNS-prophylaxis. All 3 NHL, and 1 ALL had been treated with an $LSA_2\text{-}L_2$-type protocol, and the NHL had gotten mediastinal irradiation[2](afound 3500r).

Only one boy (of age 9 1/2 at diagnosis, and with a long delay of diagnosis (of almost one months from first symptoms) is still in continuous complete remission since 56 months now (and off treatment). One girl (with ALL) is alive at 47 months, but with a 2d bone marrow relapse.

Thymic NHL, and ALL with thymic involvement, apparently still represent a poor risk group, if pleural effusion is found. The prognosis appears specially bad, if other risk factors (like organ infiltrates or a high WBC) ar present.

T 75

SECONDARY IMMUNODEFICIENCY OF CHILDHOOD MALIGNANT LYMPHOMAS

I.Vuković, M.Janković, J.Simonović, G.Konjević, University Children's Hospital, Belgrade, Yugoslavia

Secondary immunodeficiency in malignant diseases often appears due to damage of immune mechanisms by malignant process or as a consequence of radiation treatment and chemotherapy.

In this report we present the estimation of humoral and cell-mediated immune response in 35 children (18 with Hodgkin's and 17 with Non-Hodgkin's lymphomas) by testing serum immunoglobulins A, M and G, T and B lymphocytes and isotopic PHA-LT.

In HL patients, IgA and IgM serum levels were significantly decreased (p 0,01) in comparison with the values prior to therapy. Decreased IgG values were also found but with another significance (p 0,05). Cell-mediated immunity was also impaired since T and B lymphocytes of peripheral blood were decreased. Although in some patients low values of lymphocytes were found, the decrease was not significant (p 0,05). In most patients in vitro PHA reactivity of lymphocytes was diminished since PHA-LT values were decreased (p 0,01).

In patients with Non-Hodgkin's lymphomas, there was no serum IgG decrease. Serum IgA drop was near the significance limit (p 0,05) and serum IgM levels were significantly decreased (p 0,01). T lymphocyte values were normal and B lymphocyte values were lower (p 0,05). PHA-LT values were approximately at the prior to therapy levels.

These investigations are important to establish the level of severity of radiation treatment and chemotherapy in inducing secondary immunodeficiency.

T 76

STAGE IV NON-HODGKIN'S LYMPHOMA IN CHILDREN
CLINICAL STUDY OF TWENTY-FIVE CASES

Timur Sumer, M.D, Mohammad El-Mouzan, M.D
Baker Al-Awamy, M.D.

King Faisal University School of Medicine and Medical Scineces, Dammam, Saudi Arabia.

Twenty-five children with previously untreated stage IV non-Hodgkin's lymphoma were studied for a period of 4 to 32 months (median 18 months). All patients had bulky disease and the diagnosis were confirmed by biopsy. Histologically, all were classified as diffuse type; there were three histiocytic, 7 lymphoblastic convoluted, 5 lymphoblastic non-convoluted, 4 undifferentiated Burkitt's and 6 undifferentiated non-Burkitt's lymphoma. Twenty-two patients had bone marrow involvement; 14 with greater than 25% lymphoblasts, and 8 with less than 25% lymphoblasts.

Treatment consisted of Vincristine, Cyclophosphamide, I-Asparaginase, intrathecal Methotrexate and intermediate dose Methotrexate during induction and consolidation. Maintenance therapy consisted of daily 6-Mercaptopurine, weekly Methotrexate and four weekly pulses of Vincristine, Cyclophosphamide and Prednisone for 24 months.

At the time of evaluation, eight patients had relapsed and died, 4,6,6,7,8,9,12 and 12 months after the diagnosis. Seventeen patients were alive with no evidence of disease.

Toxicity was minimal and could be managed by drug dosage adjustments and supportive therapy.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 77 POLYCHEMOTHERAPY AND TOTAL BODY IRRADIATION IN THE TREATMENT OF NON-HODGKIN'S MALIGNANT LYMPHOMAS WITH FAVORABLE HISTOLOGY

Results of a cooperative pilot study

P. Richaud, Groupe Cooperateur Pierre et Marie Curie, Fondation Bergonie, 33076 Bordeaux Cedex (France)

More than 80 patients with malignant non-Hodgkin's lymphomas with favorable histology were treated by an association of radio + chemotherapy. The patients were classified stage III or IV after a radioclinical work-up without surgical investigation. Induction polychemotherapy (C.V.P.A.) consisted of one course of an association with adriamycine (35 mg/m^2 on day 1 and 15), vincristine (0,7 mg/m^2 on day 1, 8 and 15), cyclophosphamide (400 mg/m^2 on day 1, 8 and 15) and prednisone (40mg/m^2 from day 1 to day 14). Afterwards the patients received a monochemotherapy for six weeks in order to allow bone marrow recovery before (TBI). Irradiation consisted of two series of 0.75 Gy in 5 fractions on 5 consecutive days with 2 weeks interval of rest. Lastly after an interval of 4 weeks, the patient again received a course of chemotherapy indentical to the first one (C.V.P.A.).

This protocol was well tolerated, easy to carry out, reproducible and dit not burden the patients. Its immediate efficacy and good tolerance have incited us to carry out further long term studies on a larger number of patients to compare these results to chemotherapy alone or TBI alone and to randomize them for a B.C.G.therapy.

T 78 COMBINED THERAPY IN EARLY STAGES NON-HODGKIN'S LYMPHOMAS (NHL).

Comella P., Scoppa G., Abate G., D'Aprile V., Bruni G., Pergola M., Coucourde F., Zarrilli D.
Tumor Institute, Naples - Italy

From April 1978 to November 1982, 60 previously untreated patients with NHL other than of the gastrointestinal tract in early stage after a minor surgical staging (laparoscopy) were treated with combined therapy. Twenty-five patients in stage I received a locally-extended Cobalt therapy up to a mean dose of 44 Gy and, after a 4-week rest period, were submitted to 6 cycles of combination chemotherapy. Thirty-five patients in stage II initially received 3 courses of combination chemotherapy, than after a 3-week rest period were submitted to Cobalt therapy (the same as for stage I) and finally after 3 other weeks they received 3 further courses of chemotherapy. Combination chemotherapy was chosen on the basis of histologic classification (according to Rappaport): 22 pts with favorable histology received CVP and 38 pts with unfavorable histology received CHOP. Response to therapy, probability of survival and relapse of pts may be summarized as follows:

CHARACTERISTICS	%CR	% SURV	% SURV of CRs	% RELAPSE
All patients	85	57	68	12
stage I	100	85	85	4
stage II	74	41	56	19
favorable histol.	91	74	82	0
unfavorable histol.	82	50	62	20

We conclude that a combined therapy in early stages NHL obtained a high CR rate. However, there were some pts in stage II that did not reach a CR regardless of histology. We hope that a better knowledge of the biologic characteristics (i.e., labelled index, estimation of in vitro sensitivity to chemotherapy) might improve the outcome of pts with NHL. To date, we think that a combined therapy remains the best treatment for early stages NHL, unless a careful surgical staging selects pts to be treated with irradiation alone.

T 79 The Role of Radiation Therapy (XRT) in Patients With Localised Non-Hodgkin's Lymphoma (NHL)

S.B. Sutcliffe, M.K. Gospodarowicz, T.C. Brown, Teresa Chua, R.S. Bush

The majority of patients with NHL have advanced disease, and the majority of those treated with XRT for localised disease subsequently relapse. Combination chemotherapy (CT) may be curative for patients with advanced intermediate (IG) and high-grade (HG) lymphomas, thus selection of patients for XRT for apparently localised disease assumes importance if optimal treatment is to be provided.

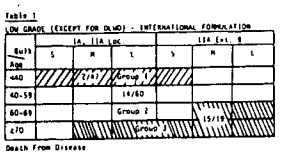
Prognostic factors determining cause-specific survival were derived from 716 patients (≥17 years) with clinical stage (CS) I and II NHL referred between 1967-1978. Significant independent prognostic factors ranked by Cox Regression were disease bulk, age, stage and histology.

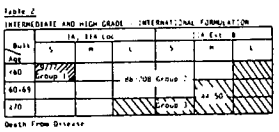
The effect of XRT was determined by analysis of 496 patients receiving XRT as first therapy. As relative rates of death from disease differed markedly for low-grade (LG) versus IG/HG histologies, cause-specific mortality was analysed using multiple prognostic factors for LG and IG/HG histologies separately.

Within LG histology, 3 prognostic groups were identified by age, stage and bulk of disease (Table 1) - Group I and II had a 98% and 75% long term survival respectively with survival curve plateau indicating 'cured' populations. Group III demonstrated a constant rate of death from disease analogous to patients with advanced LG NHL. The actuarial 10-year relapse rate for Group I and II patients was 46%.

Similar multifactorial analysis of death from disease for CS I and II IG/HG NHL revealed 3 prognostic groups identified by age, stage and bulk of disease (Table 2). Cause-specific mortality for Group I, II and III were 15%, 45% and 90%, with relapse rates of 30%, 55% and 90% respectively. There was no significant effect of histology on survival or relapse within Group I and II IG/HG NHL.

This analysis suggests the following points: 1. patients with CS I and II LG lymphoma can be cured by XRT; 2. patients with LG and IG/HG NHL with a high expectation of cure by XRT may be identified by clinical attributes -- within IG/HG NHL such identification is not dependent upon histological subtype; 3. patients with localised lymphoma who may benefit from initial CT +/- XRT may be identified by clinical features determined at presentation.





T 80 NON-HODGKIN'S LYMPHOMAS IN LEUKEMIC PHASE: CLINICAL ASPECTS AND THERAPEUTIC RESULTS IN 54 CASES.

Pasini F., Ambrosetti A., Todeschini G., Martinelli L., Cetto G.L. Ist.Pat.Spec.Med. Cattedre di Ematologia e di Oncologia Medica, Università di Verona, Italy.

Between '73 and December '83, 54 patients (21 females and 33 males) with leukemic lymphomas were referred to our Institution. All patients with hystologically documented non-Hodgkin's lymphoma had a full clinical, histological and haematological evaluation, acute and cronic lymphocitic leukemia beeing excluded. Patients were divided into two groups: high grade malignancy (19 patients) and low grade malignancy lymphomas (35 patients).

a) The 19 patients (14 males, 5 females, median age 37 yrs) with high grade malignancy lymphomas were all treated with intensified chemotherapy regimens including Adriamycin, Vincristine, Cytoxan, Prednisone plus L-Asparagina se in some cases. The actuarial median survival is 14 months. 9/19 patients were leukemic at onset before the induction chemotherapy was started (actuarial median survival:8 months). Only 4 out of these 9 patients (44,4%)achieved a Complete Remission (C.R.).In the remaining 10/19 pts (mean survival 17.5 mo.) leukemic phase appeared 3 to 32 months after the diagnosis of lymphoma; the mean survival of these patients after leukemic conversion was 6,5 mo. 4/10 achieved a C.R. Therefore the mean survival of the patients in leukemic phase did not significantly differ in the two groups (8 mo.versus 6,5 mo.).5 out of 8 patients who achieved a C.R. relapsed.C.R. rate and median survival in high grade malignancy lymphomas are significantly lower than in A.L.L. according to data available in literature as well as in our A.L.L. series.

b) In all but 6 of the 35 patients with a low grade malignancy leukemic lymphomas (19 males, 16 females, median age 59 yrs) leukemic phase was documented at diagnosis. They were mainly treated with single agent chemotherapy. The actuarial median survival is 33 mo. and is lower than CLL survival.Moreover, the presence of thrombocytopenia and anemia at diagnosis appears to be of some relevance in worsening survival.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 81 COMPARATIVE EVALUATION OF ABVD vs. ABV AS INDUCTION TREATMENT FOR MALIGNANT LYMPHOMAS.

Beretta G.,Tedeschi L.,Fraschini P.,Arnoldi E.,Labianca R.and Luporini G. - Medical Oncology Dept.,San Carlo Borromeo Hosp. Milano 20153 Italy.

During 2 years we have admitted to a prospective randomized study 50 consecutive patients(pt) aged < 71 years,previously untreated histologically proved Hodgkin's disease(HD) or non Hodgkin's lymphoma,pathologically staged((PS)according to the current criteria. The aim of the study was to comparatively evaluate ABVD regimen versus ABV(same as ABVD,without dacarbazine). The dose-schedules were as follows :

adriamycin	A	25 mg/mq i.v.	days 1 and 15	(1 course= 2 ABV±D administrations = 1 month treatment)
bleomycin	B	10 mg/mq i.m.		
vinblastine	V	6 mg/mq i.v.		
±dacarbazine	D	375 mg/mq i.v.		

The induction treatment plan consisted in 2 ABV±D courses followed by 2 C-MOPP(cyclophpsphamide,vincristine,procarbazine,prednisone) in HD PS III B-IV and in NHL PS III-IV, or 2 ABV±D followed by radiotherapy in HD PS II A(bulky)-II B-III A and in NHL PS I-II.

Therapeutic results. 30 pt with HD are at present evaluable after 2 and 4 months'treatment. 14 pt were PS III B or IV. The results* are :

	after induction (2 courses)								after 4 mo.	
	all pt		st.III-IIIA		st.IIIB-IV		nod. scler.		all stages	
	CR	PR	CR	PR	CR	PR	CR	PR	CR	CR+PR
ABVD	25%	75%	33%	66%	16%	83%	16%	83%	50%	100%
ABV	27%	66%	33%	66%	25%	75%	20%	80%	72%	100%

Treatments have essentially the same activity in our series. ABVD and ABV regimens are also very similar also in terms of projected relapse free survival and overall survival(actuarial evaluation).

In NHL(non Hodgkin's lymphomas) the ABV±D/C-MOPP program failed to produce an acceptable response rate: we have achieved only 1 CR + 6 PR out of 17 evaluable pt(41% response rate). Therefore this regimen has recently been abandoned.

Toxicity* was in the usual range known for ABVD, the only difference being the qualitative and quantitative reduction of vomiting in the ABV regimen ($p < 0.01$),when measured after 2 courses.

According to present experience, ABV appears to be an effective part of our treatment program for Hodgkin's disease. The exclusion of dacarbazine(D) from ABVD combination does not reduce therapeutic effectiveness, but it is able to minimize the gastrointestinal toxicity, making this regimen subjectively more acceptable to the treated patients.

* W.HO. criteria, Cancer 47:207-214,1981.

T 82 High-dose chemotherapy and non-frozen autologous Bone Marrow Transplantation in advanced resistant Hodgkin's disease and in "high grade malignances" non Hodgkin's lymphomas.

ANGELO M. CARELLA, GINO SANTINI, MARINA MARTINENGO, ANGELA CONGIU, EDOARDO ROSSI, DOMENICO OCCHINI, DOMENICO GIORDANO, SANDRO NATI, RENATO VIMERCATI, RAFFAELLA CERRI, SALVINA BARRA PROSCOVIA SALUSCIEV, GIUSEPPE LERCARI, ALBERTO M. MARMONT. Hematological Division, S. Martino's Hospital, Genova (Italy).

From September 1979 to May 1983, 26 patients with haematological malignances and solid tumors were treated with high dose chemotherapy (HDC) and autologous bone marrow transplantation without criopreservation (ABMT).
10/26 had malignant lymphomas: 7 Hodgkin's disease (HD) in advanced stage resistent (4) or relapsed (3) CcVPP or MOPP-ABVD + TCT ± CEP protocols and 3 non Hodgkin's lymphomas (NHL) (2 lymphoblastic and 1 centroblastic diffuse) of which 2 cases was in CR after CHOP protocol.
4 patients were prepared with HDC - BCNU (mean dosage 1000 mg/m^2); another case with BCNU (400 mg/m^2) + Cyclophosphamide (CFM) (2 g/m^2) and the last 5 cases with BCNU (600 mg/m^2),CFM (5 g/m^2) and Vinblastine (15 mg/m^2).

Results

NHL: 3/3 cases are now in CR 2 to 19 mo. after ABMT.

HD: One patient died in aplasia without reconstitution. 5/6 patients entered a CR following HDC and 5 are now alive, but only 4 in CR 2-27 mo. post ABMT.
Recovery to a WBC count above 1000/mm^3 occurred on day 15 (median) and recovery of platelet count above 20.000/mm3 occurred on day 19 (median).
The total number of nucleated bone marrow cells harvested ranged from $0.8 \cdot 10^8$/kg to $2.4 \cdot 10^8$/kg (mean 1.6 ± 0.7)
The number of nucleated cells reinfused ranged between 0.68 - $2 \cdot 10^8$/kg (mean 0.99±0.47 :mean cell recovery of 71±29%).

In conclusion, this study has shown that the use of BM stored at 4°C leads to adeguate hemopoietic recovery and HDC may be offered as an alternative treatment to lymphomatous patients refractory or relapsed on conventional chemotherapy.

T 83 High-grade Non-Hodgkin`s Lymphomas: results of multimodal treatment in 147 cases.

Calavrezos A., Heilmann H.-P., Kuse R. and Hausmann K., Allg. Krankenhaus St. Georg, Hamburg, Germany

From 1976 - 1982, 147 patients with high-grade Non-Hodgkin`s lymphomas were treated at St.George`s hospital, Hamburg.In the majority of immunoblastic, centroblastic and unclassified lymphomas,treatment was started with chemotherapy (COP, BACOP, CHOP,IME; HOAP-BLEO). When full remission was achieved, a consolidating systemic radiotherapy of the upper and/or lower half of the body was followed. Lymphoblastic lymphomas were treated according to the ULMER protocoll. The KAPLAN-MEIER-7-year-survival-estimate was 58 % for immunoblastic lymphomas,46 % for centroblastic lymphomas and 62 % for unclassified lymphomas. Lymphoblastic lymphomas had a 7-year-survival of only 11 %.. Severe comorbidity was seen in 35 %, in patients elder than 60 years even in 61 %. 47 % of all patients with immunoblastic, centroblastic and unclassified lymphomas had extranodal manifestations. 21 recurrent cases had a bad prognosis: only 6 patients achieved a remission once more (4 of them initially in stage I). 15 died in progressive disease. The highest rate of uninterrupted full remission was achieved by combined modality: in 112 cases of immunoblastic, centroblastic and unclassified lymphomas, uninterrupted full remission was achieved by radiotherapy alone in 6 of 18 cases (33 %), by chemotherapy alone in 12 of 33 cases (36 %), and by combined modality in 42 of 58 patients (72 %). KAPLAN-MEIER-estimates for different lymphomas and various stages are given and problems and aspects of therapy are discussed.

T 84 CHEMOTHERAPY OF RELAPSING OR REFRACTORY HIGH GRADE MALIGNANT NHL WITH CCNU, ETOPOSIDE, VINDESINE, HIGH DOSE METHOTREXATE AND DEXAMETHASONE: TOXICITY AND PRELIMINARY RESULTS.

M. Freund, L. Plaumann, R. v.Roemeling, J. Casper, R. Metzner, S. Le Blanc, B. Schilling, E. Schmoll, H. Poliwoda, H.J. Schmoll. Div. of Haematology and Oncology, Medical School, Konstanty Gutschowstr. 8, 3000 Hannover 61, FRG.

Treatment results of refractory or relapsing high grade malignant NHL usually are disappointing. Therefore we studied an alternative regimen composed of 5 drugs which are in general not used in first line therapy: CCNU 80 mg/m2 orally d 1, Etoposide 80 mg/m2 i.v. d 1-3, 22-24, Vindesine 3 mg/m2 i.v. d 1 + 22, Methotrexate 1,5 g/m2 i.v. d 1 + 22 followed by folinic acid rescue after 24 h 4 x 15 mg/m2 for 3 days and Dexamethasone 4,5 mg orally d 1-14, 3,0 mg d 15-28, 1,5 mg d 29-42. Repeatment of course at day 43.
Eight patients are treated up to now, all of them are evaluable, Histology of NHL according to Kiel classification was: centroblastic 2, immunoblastic 2, high grade malignant without classification 2. One patient had acute lymphatic leukaemia. Pretreatment characteristics: Last preceeding pretreatment consisted of CHOP, CHOP + Etoposide, COP + Bleomycin alternating with Adriamycin + Etoposide + Prednisone. The case with ALL was pretreated with the "Riehm"-protocol. Some of the patients had had irradiation and other chemotherapy (COP, COPP, ABVD e.a.) before. Five patients were in relapse after 1 or 2 complete remissions with an interval of 1-5 months. One patient had progressive disease under chemotherapy after 2 complete remissions, two more were progressive under chemotherapy without preceeding complete remission. Preliminary treatment results are: 1/8 CR, 3/8 PR, 1/8 MR, 3/8 progressive disease. Following toxicity was observed in 9 treatment-courses: leukopenia 3000-3999/µl: 3/9, 2000-2999: 2/9, 1000-1999: 1/9, < 1000: 2/9. Thrombopenia: 75000-99000/µl: 1/9, 50000-74000: 1/9, < 25000: 1/9. In 5/9 courses elevations of GPT, in one case up to 134 U/l, in 4/9 courses elevations of AP were observed. Vomiting usually occurred at day 1. Two patients had diarrhea, 1 exanthema. Alopecia was moderate. Fever occurred in one case. There were no drug-related deaths.
We conclude that the suggested treatment regimen has a tolerable toxicity. Treatment results are encouraging.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 85 COMBINED CHEMOTHERAPY(CT)WITH ALTERNATING NON-CROSS RESISTANT REGIMENS(C-MOPP/ABVD)AND RADIOTHERAPY(RT)IN POOR RISK PATIENTS(PTS)WITH HODGKIN'S DISEASE(HD).E.Grigoletto,U.Tirelli,A. De Paoli,V.Zagonel,M.G.Trovò,A.Veronesi,E.Galligioni,M.D.Magri,S.Frustaci,D.Crivellari,F.Figoli and S.Tumolo.Division of Radiotherapy & Medical Oncology,General Hospital,Pordenone,Italy.

Combined CT with alternating non-cross resistant regimens and low dose involved-field RT has been evaluated in HD at MSKCC(MOPP/ABDV/RT in 57 untreated pts with stage IIB-III-IV:4-year RFS for CRs,84%;CTR 66:907,1982),at Yale University(MOPP/ABVD/RT in chemically untreated pts > 40 yrs and/or with stage IV:3-year RFS,87%;CTR 66:871,1982)and at EORTC(MOPP/CAVmP/RT in 50 untreated pts with stage IIIB-IV:3-year RFS,73%;Cancer 52:1558,1983).The aim of this study is to further evaluate such promising approach in poor risk HD employing larger volumes and higher doses RT.From May 1979 to December 1982,43 consecutive untreated pts(28 males,15 females,median age 37 yrs,range 17-72)with unfavourable stage IIA(bulky mediastinum in 3 pts,mixed cellularity or lymphocytic depletion in 2),stage IIB(7 pts),stage III(19 pts)or stage IV(10 pts)entered a prospective study.C-MOPP/ABVD were given to all pts for 6(IIA),9(IIB-IIIA)or 12 cycles(IIIB-IV)and in case of CR or PR ≥ 75%,3000-4000 rad extended-field RT was delivered in almost all pts with stage II and III.In stage IV pts,RT was given at lower doses prevalentely to areas of initial bulky disease.Two pts withdrew from therapy after the first ABVD(1 pt alive at 26 mos,1 dead at 33 mos). The table reports the results obtained in 41 evaluable pts:

	No(%)of pts with —				No of pts	Overall relapse-free survival
No pts	CR after CT	PR after CT	CR after CT-RT	PR after CT-RT	not irradiated	at 4 yrs (%)
41	37(90)	4(10)	39(100)	0	2	90 — 78

Median follow-up is 29 mos(12-52).CT alone yields a CR rate of 90%.RT increased this rate to 100%.Relapses occurred in irradiated areas in only 1 of 6 pts(liver).Three pts died with HD(2 with stage IV,1 with stage IIIB),2 of them had not been irradiated.One of these pts died of bone marrow toxicity after ABVD.In 8 pts,CT was stopped prior to the planned 9 or 12 cycles due to nausea and vomiting from ABVD.RT caused no severe toxicity.One pt developed a second malignancy,a foot malignant melanoma,during RT.We conclude that this combined treatment is feasible although toxicity from ABVD is of concern.In addition,high CR and survival rates are obtainable, even in a general hospital. However,a longer follow-up is necessary to assess long-term toxicity and survival and to correctly compare our results to those published in the literature.

T 86 LIVER COMPLICATIONS IN LYMPHOMAS TREATED WITH A COMBINATION OF CHEMOTHERAPY AND RADIOTHERAPY. J.P. Le Bourgeois, E. Haddad and M. Kuentz. Département de cancérologie, Hôpital Henri Mandor, F 94000 Creteil France.

From 1978 to December 1983, 28 lymphoma patients (24 with Non Hodgkin Lymphoma including 22 with gastro-intestinal tract involvement and 4 with Hodgkin's disease) have been treated with combined chemotherapy-radiotherapy to the whole or the upper 1/2 of the abdomen. There were 19 males and 9 females. Mean age was 40 (range 21-69). The 4 patients with Hodgkin's disease were all stage IV with liver involvement. In the pre-treatment assessment, 17 patients had normal liver biopsies, 2 had positive liver biopsies, 3 had normal liver biochemistry and 6 had abnormal liver biochemistry. All pts, except 1 were irradiated after complete remission was achieved with chemotherapy. In 23 pts, adriamycin was includedin the chemotherapy protocols (mean total dose 180 mg). In all pts the whole liver was irradiated to a total dose of 20 Gy/10 fractions/17 days but the left lobe received between 20 Gy and 40 Gy in 20 fractions in 35 days. The mean interval between chemotherapy and radiotherapy was 4 weeks (range 2-28 weeks). Twenty-three pts survive, 22 NED. The mean follow up time is 25 mths (range 3-50). Two pts died rapidly from their disease. Ten pts survive without liver abnormality. Nine pts have had only biochemical abnormalities. The most constant being an elevation of alkaline phosphatase 5 weeks (range 0-12 wks) after completion of radiotherapy, generally returning to normal after approximately 12 mths but sometimes persisting for as long as 2 yrs. In 1 case it has persisted for 42 mths (liver biopsy showed an iatrogenic lesion). Seven pts have presented with both clinical and biochemical signs of liver insufficiency. The illness was mild or transient in 4 of these pts of whom 1 died of renal complications and 2 have persisting biochemical abnormalities (33 mths after treatment); 1 of these 2 pts had a liver biopsy (right lobe) which showed co-existence of early (centro-lobular necrosis) and late (periportal fibrosis) signs of radiation hepatitis. The other 3 pts presented with acute life threatening problems with clinical signs of icterus, hepatomegaly and ascites with raised alkaline phosphatase SGOT, SGPT. Biopsy in each case revealed typical veno-occlusive disease with centrolobular venous obstruction and haemorrhagic necrosis. All 3 cases recovered with symptomatic treatment only after a period of 4-6 wks. In summary, we underline the importance of recognizing and diagnosing this complication and not confusing it with disease relapse.

T 87 A NATIONAL CANCER CARE PROGRAM FOR NON-HODGKIN'S LYMPHOMA IN SWEDEN - PART III. CHOP VERSUS MEV FOR THE TREATMENT OF NON-HODGKIN'S LYMPHOMA WITH UNFAVOURABLE HISTOPATHOLOGY.
H. Hagberg and C. Lindemalm. Dept. of Medicine, University Hospital, Uppsala and Dept. of Oncology, Karolinska University Hospital, Stockholm, for the Swedish Lymphoma Study Group

Within a cancer care program for non-Hodgkin's lymphoma in Sweden a prospective randomized trial has been performed comparing the treatment results of a CHOP regimen with a MEV regimen in patients with generalized non-Hodgkin's lymphoma of unfavourable histopathology. Between Jan. 1979 and Dec. 1982, 153 adult non-selected patients were included in the study. Nineteen patients initially received local radiotherapy and were included in the study at the time of systemic relapse. The remaining patients had no prior treatment before entering the study. The CHOP regimen consisted of Cyclophosphamide 750 mg/m^2 day 1; Adriamycin 50 mg/m^2 day 1, Vincristine 2 mg day 1 and Prednisone 75 mg days 1-5. The MEV regimen consisted of Cyclophosphamide 800 mg/m^2 day 1; Methotrexate 20 mg/m^2 day 3 and Vincristine 2 mg day 4. Length of cycle 21 days. Responding patients received a total amount of 9 cycles.

Results: The complete remission rate for 67 evaluable patients receiving CHOP was higher (61%) than for 74 patients receiving MEV (24%) ($p<0.001$). The relapse rate was 18/41 (44%) in the CHOP group and 11/18 (61%) in the MEV group (not significant). The number of patients living in a first complete remission was thus 23/67 (34%) in the CHOP group but only 7/74 (9%) in the MEV group. The difference is highly significant, $p<0.001$. However, there is still no significant difference in the overall survival between the two treatment groups. This is probably due to the more efficient treatment at relapse among the patients who started with MEV than in those who started with CHOP. We conclude that the CHOP regimen is superior the MEV regimen in NHL patients with unfavourable histopathology.

Participating clinics: see part I.

T 88 CHOP-THERAPY IN HIGH GRADE MALIGNANT NON-HODGKIN LYMPHOMAS (NHL). R.Heinz,E.Neumann, P.Aiginger,J.Pont,J.Schüller, G.Walcher,H.Hanak,Th.Radaszkiewicz,E.Sinn,M.Wirth,Ch.Dittrich, J.Kühböck,N.Honetz,G.Alth,A.Stacher (Vienna Lymphoma Study Group).

51 patients with high grade malignant NHL, 15 patients with lymphoblastic lymphoma (T-LB and patients with bone marrow involvement in excess of 40% blasts were excluded), 16 patients with immunoblastic lymphoma, 18 patients with centroblastic lymphoma and 9 patients with centrocytic large cell lymphomas were treated with a modified CHOP-schedule independent of the stage of their disease. Because of the advanced age of our patients (median age 60 years, range 22-85 years) dosis reduction was done in patients with more than 60 years. Response rate and survival time differ significantly according to the histologic entities, which stresses the relevance of the Kiel classification. Prognostic factors like blood sedimentation rate, LDH, B-symptoms, bulky tumor masses and extranodal involvement influenced prognosis significantly. Ann Arbor stages were of limited value as far as prognosis is concerned. It could be shown that the outcome of patients in I A - II A was excellent, but patients with II B and an accumulation of poor prognostic factors do considerably worse than patients with stage III. A riskfactorscore which should be used as a stratification tool in future studies will be described. It seems noteworthy that advanced age did not effect prognosis adversively in our trial, which can be contributed to our dosis reduction schedule.

T 89 PROGRESS IN THE THERAPY OF POOR RISK NON-HODGKIN LYMPHOMAS. 1o YEARS SURVEY OF THE 3rd MEDICAL DEPARTMENT OF THE HANUSCH-HOSPITAL, VIENNA.

R.Heinz ,A.Stacher and G.Baumgartner.

Between 1973 - 1983 173 patients (1oo ♂: 73 ♀) with NHL of unfavourable histology were admitted to our hospital. Pathologic-histologic diagnosis was established in all cases according to the Kiel classification. 51 patients suffered from centroblastic lymphoma (37primary CB, 14 secondary CB), 4o patients from immunoblastic lymphoma (3o primary IB, 1o secondary IB), 45 lymphoblastic lymphoma (27 LB unclassified, 9 T-LB, 7 Burkitt like LB,2 secondary LB). In 14 cases the diagnosis NHL high grade malignancy was not subclassified because of technical reasons. In the evaluation 23 patients with large cell centrocytic lymphoma were included because of the poor prognosis and the need of aggressive therapy in this entity. Symptoms at presentation, frequency of extranodal involvement and factors influencing therapeutic outcome and prognosis will be described. The evaluation of survival time proved that aggressive initial chemotherapy in early stage of disease, done in recent years, was the main factor improving the outcome of the patients. It is obviously that long term survivors in patients treated before 1979 when irradiation and/or COP was given, were extremly rare. After administering an age-adjusted CHOP schedule disease free long term survival was achieved in most of the patients with localized diseases. But there still exist lots of problems in patients with accumulation of adverse prognostic factors (advanced stages, elevation of LDH at the begin, gastrointestinal or bone marrow involvement, bulky tumor masses). Therapeutic approaches done at our hospital in this high risk patients population will be discussed.

T 90 CURRENT THERAPEUTICAL RESULTS IN B-LYMPHOBLASTIC LYMPHOMAS AND UNCLASSIFIED Kil-POSITIVE LYMPHOMAS.

Kayser,W., Euler,H.H., Gassmann,W., Schmitz,N., Gülzow,K., Sprotte,V., Löffler,H., II. Med.Clinic University of Kiel (FRG).

Successful therapeutical trials in advanced B-lymphoblastic lymphomas have long been missing. In addition the appropriate therapy of Kil antigen-positive lymphomas is still unknown. These formerly unclassifiable high grade malignancies are characterized by positive staining with the monoclonal antibody Kil which is derived from Hodgkin cell lines (SCHWAB, STEIN et al.1982). Actual therapeutical experiences are necessary to solve these clinical problems.

Four patients with B-lymphoblastic lymphomas stage IVB (Burkitt type in three patients, non-Burkitt type in one patient) were treated with two different chemotherapy protocols (CHOP or the B-lymphoblastic lymphoma protocol of the German NHL study for children and adolescents, BFM 81, respectively). Three patients rapidly entered remission after the first course of chemotherapy, whereas one patient treated with CHOP died in week 8 after diagnosis having had only transient improvement. One patient was lost from follow-up after disease-free survival of 4 months. Two patients recently treated by the childrens lymphoma protocol are in current disease-free survival of 3.5 and 4 months, respectively. These results although preliminary underline that advanced B-lymphoblastic lymphomas are not longer rather untreatable diseases if adequate aggressive therapy is chosen.

Three patients suffering from Kil antigen-positive high grade malignant lymphomas stage IIIB and IVB, respectively (all female, age ranging from 17 to 70 years) were treated with conventional Hodgkin protocols (COPP or alternate therapy with COPP and ABVD, respectively, and radiotherapy). All patients are currently in complete remission 15+ to 20+ months after diagnosis. To the best of our knowledge these observations show for the first time that these immunologically characterized high grade malignant lymphomas can successfully be treated by conventional Hodgkin therapy thus possibly reflecting a clinical relationship to Hodgkin's disease.

T 91 CHEMOTHERAPY (CT) OF NON-HODGKIN'S LYMPHOMA(NHL).

G.V.Kruglova, R.A.Abdyldaev, D.Y.R.Pendharkar, Oncology Research Centre,Moscow 115478, USSR.

With the intent of studying effectiveness of CT case reports of 578 patients (pts) with NHL were reviewed. Histologic typing was performed using WHO criteria. Most cases were in advanced stages (st) III-IV (89.5%). Treatment regimens employed included: high and standard doses of cyclofosfamide, asparaginase, COP, CHOP, VAMP, CAMP (C-cytoxan, A-ametopterin, M -6-MP, O or V -vincristine, P-prednisone, H-hydroxyldaunomycin). Response rate for combination CT was superior to single agent CT, being 73-93% and 37-51% resp. in all histological types. The complete response (CR) rate was 20-42% for combination CT, while for single agent CT it was just 7.6%. There was no difference noticed in overall response rate for untreated and treated pts. However, CR rate was higher in pts receiving no prior therapy as compared to treated pts (37-41% and 12-27% resp.). In localized st I-II disease CT was found to be very effective with 93-100% pts responding (73-85% CR rate). In advanced st IV disease response rate was 70-80%, while CR rate was 12-44%. In high grade pathology single agent CT was effective in 51% of pts (CR rate - 8-11%) and combination CT in 77-93% (CR rate - 25-45%). In low grade pathology the CR rate was 0% for single agent CT and 10-20% for combination CT (overall response rate 52-77% and 63-88% resp.).

The results confirm definate superiority of combination CT over single agent CT, but no difference was noticed between different regimens. In stage I-II disease combination chemotherapy can be employed succesfully.

T 92 TREATMENT OF DIFFUSE "HISTIOCYTIC" NON-HODGKIN'S LYMPHOMA WITH CHOP COMBINATION CHEMOTHERAPY, FOLLOWED BY MONTHLY CYCLOPHOSPHAMIDE AND VINCRISTINE AS MAINTENANCE, FOR TWO YEARS FROM THE INITIATION OF THERAPY.

Pangalis G.A., Roussou P.A., Anagnostopoulos N., Mitsoulis-Mentzikoff Ch., Kokkinou S., Kittas Ch.†

Hematology Unit, 1st Dept. of Internal Medicine, Laikon General Hospital of Athens and Dept. of Anatomic Pathology† Section of Medicine, University of Athens School of Health, Athens, Greece.

Thirty patients with the histologic diagnosis of diffuse "histiocytic" non-Hodgkin's lymphoma were uniformely staged and prospectively treated in the Outpatient Leukemia and Lymphoma Clinic of our Hospital from 1979-1982 with nine cycles of CHOP combination chemotherapy (cyclophosphamide 700mg/m^2 day 1, Adriamycin 40Omg/m^2 day 1, Vincristine 1.4mg/m^2 day 1 and Prednisone 60mg/m^2 days 1-5) given every 21 days. Maintenance therapy with cyclophosphamide (700mg/m^2) and vincristine (1.4mg/m^2) was scheduled to be administered every month to all patients, for 24 mos from the initiation of CHOP combination chemotherapy, with the hope to prevent early relapse of the disease. In 11 patients with primary extranodal location of their disease (seven in the stomach and four in the small intestine) surgical excision of the tumor mass was performed. In eight patients with a large primary tumor mass (d > 10cm) local Co^{60} radiation therapy was given after the completion of CHOP and before the initiation of maintenance chemotherapy. In all 17 patients (100%) with limited disease (clinical stage I and II) complete remission was achieved, while in the group of patients with advanced disease (clinical stage III and IV) complete remission was obtained in 69% (9/13). The median survival of the complete responders was similar in both groups reaching 48 mos in 75% of them, while the median overall survival regardless of complete remission was 48 mos for the 80% of patients with limited disease and for the 55% of patients with advanced disease. No statistically significant differences were observed between the various survival curves of patients with limited and advanced disease ($p < 0.5$). The preliminary results of this prospective therapeutic trial of diffuse "histiocytic" non-Hodgkin's lymphoma are comperable with those reported in the literature by other investigators. However, the justification of the maintenance chemotherapy, as administered in this group of patients, remains to be seen.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 93 A PHASE II CLINICAL TRIAL OF ORAL VP-16-213 IN NON-HODGKIN LYMPHOMA

H. Nakada, J. Inagaki, N. Horikoshi, K. Inoue, Y. Okada, K. Ikeda, N. Usui, K. Adachi, A. Tada, T. Mukaiyama, Y. Kuraishi, M. Ogawa

Dept. of Clinical Oncology, Cancer Institute Hospital, and Cancer Chemotherapy Center, Tokyo

A total of 20 patients with advanced non-Hodgkin lymphoma (NHL) refactatory to various combination regimens containing adriamycin, cyclophosphamide, vinka alkaloids and/or bleomycin were treated with oral administration of VP-16-213 at a dose schedule of 200 mg/d for 5 days repeating in 4-week intervals.

There were 2 CRs (10%) and 8 PRs (40%) with a median duration of remission of 14 weeks ranging from 3 to 122 weeks.

Leukopenia less than 4,000/cmm occurred in 80% of patients and a median nadir was 2,100/cmm reaching it 14 days later and 8 days needed for recovery, on the other hand, thrombocytopenia less than 100 $\times 10^3$/cmm occurrred in 20% of patients.

Non-hematologic toxicities were alopecia (78%), anorexia (32%), nausea (25%) and vomiting (20%), and these were well tolerated.

The result indicated that VP-16-213 is effective for NHL and lacks cross-resistance to vinka alkaloids, anthracyclines and alkylating agents.

T 94 A PILOT STUDY WITH VP 16 AND PREDNIMUSTINE IN ELDERLY PATIENTS (PTS)WITH NON-HODGKIN'S LYMPHOMA(NHL):PRELIMINARY RESULTS.

U.Tirelli,V.Zagonel,S.Frustaci,F.Figoli,A.De Paoli,F.Brema,A. Carbone,E.Grigoletto.Div. of Radiother.& Medical Oncology,General Hospital,Pordenone;Centro di Riferimento Oncologico,Aviano,Pordenone,Italy.

The aggressive combination chemotherapy(CT)regimens commonly employed in NHL are unlikely to be tolerated by most elderly pts.A retrospective analysis of 15 pts with NHL $\geq$ 65 yrs treated at our institution with CVP showed a significant toxicity with 2 possibly treatment related deaths.A prospective phase II trial of VM 26 in 20 pts $\geq$ 70 yrs with previously untreated advanced NHL seen at our institution showed an overall 50% objective response rate with 5 CRs,2 of them substained after 2 yrs,without any significant toxicity.The only disadvantage was the weekly iv infusion of VM 26.The other epipodophillotoxin VP 16,however,is available even per os and has approximately the same activity and toxicity of VM 26 in NHL.Prednimustine,prednisolone ester of chorambucil,in a cumulative review of several european trials,yielded 77% overall response rate in 128 pts with NHL without any significant toxicity.With this background,VP 16 and Prednimustine,both given per os,were thought to be a safe and active CT regimen for elderly pts with NHL.Between April 1983 and November 1983,18 pts $\geq$ 69 yrs(69-86, median 76)were consecutively treated with VP 16 100 mg/m^2 per os for 5 days and Prednimustine 100 mg/m^{2}per os for the same 5 days every 3 weeks for at least 2 cycles prior to the evaluation of the response. No consolidation radiotherapy was administered to responding pts.9 pts were previously treated and 9 previously untreated.The latter pts constitute a prospective group of consecutive pts $\geq$ 70 yrs treated with VP 16 and Prednimustine as first line treatment in NHL.The table reports the results obtained so far:

No pts	Working Formulat.	Responses obtained in pts — prev.untreat.	prev.treated	Total
11	High-Intermediate	5/6(3CR,2PR)	4/5(2CR,2PR)	9/11(82%)
7	Low	1/3(1CR)	1/4(1CR)	2/7.(28%)
Tot.18		6/9(66%)	5/9(55%)	11/18(61%)

The duration of CRs are 7+,7+,7,4,3+ and 3+ mos.Median follow-up is 3 mos(range 1-8).6 pts are still in treatment.Toxicity consisted in nausea and vomiting in 4 pts(G2 in 3 pts and G1 in 1),alopecia in 14 pts (G3 in 6 pts,G2 in 7,G1 in 1),leukopenia in 11 pts(G3 in 2 pts, G2 in 7,G1 in 2),anemia in 2 pts(G2 in 1 pt each),thrombocitopenia in 2 pts(G3 and G1 in 1 pt each).

T 95

Cis-DICHLORODIAMMINEPLATINUM (CISPLATINUM) AND ETOPOSIDE (VP16): AN EFFECTIVE COMBINATION IN POOR PROGNOSIS MALIGNANT LYMPHOMA,

I.R. Judson and Eve Wiltshaw, Dept. Biochemical Pharmacology, Inst. Cancer Res., Sutton, Surrey and Royal Marsden Hospital, London.

In a preliminary study, 25 patients with non-Hodgkin's lymphoma (NHL) unresponsive to standard combination chemotherapy were treated with cisplatinum 50mg/m^2 i.v. x1, plus VP16 100mg/m^2 i.v. daily x 3 q. 3wks. An average of 3 courses were given. All patients were heavily pre-treated: 65% had received prior radiotherapy plus chemotherapy, 29% 3 or more different drug regimens. 17 patients were evaluable for response. There were 5 complete remissions (CR) 29%, and 4 partial remissions (PR) 24%, giving an overall response rate of 53%. The response duration for CR was 12-48 wks. Median survival for patients in CR was 20wks compared with only 5wks for non-responders. Toxicity included nausea and vomiting, alopecia, minor renal impairment and myelosuppression. This was occasionally severe; wbc <1,000/mm^3 3 patients (18%), platelets <50,000 5 patients (29%). There was one treatment-related death in a patient with bone marrow infiltration. The response rate for this drug combination which is superior to that reported for either single agent (PR only: cisplatinum 26%, VP16 30%) led to its inclusion in a sequential non cross-resistant drug regimen for poor prognosis NHL. Early results are encouraging.

T 96 CONTINUOUS 5-DAY INFUSION OF VINDESINE IN PATIENTS WITH REFRACTORY MALIGNANT LYMPHOMAS.

J.A. Gastaut, B. Mascret, D. Maraninchi, N. Tubiana, Y. Carcassonne Institut J. Paoli-I. Calmettes 232, Bd de Ste. Marguerite 13 009 MARSEILLE

Vindesine (VDS) in I.V push has been shown as an effective agent in the treatment of leukemias and malignant lymphomas. Its very short serum half-life suggested to give it as a continuous 5 day infusion. We treated patients with malignant lymphomas with doses ranging from 0.7mg/m^2/d to 2mg/m^2/d. The infusions were done in a central catheter to avoid toxicity with a peristaltic pump. They were repeated according to response and haematologic tolerance. Twenty eight patients entered in this study : 3 with hodgkin s disease (HD) and 25 with non hodgkin lymphomas (NHL). All had disseminated progressive mesurable disease which failed to respond to previous chemotherapy (always including other vinca alkaloid agents). They were 17 males and 11 females with a median age of 58 years (range : 21 to 77) and a median karnofsky score of 40% (range : 20% to 80%). The median number of previous different drugswas 5 (3 to 13). Sixteen received previous radiotherapy (57%). Response to treatment was evaluated in 24 of the 28 patients. There was no complete remission, 9 patients had partial response, 7 had minor response and 8 patients failed to respond. In 3 patients who failed to respond to VDS bolus a response was obtained with VDS continuous infusion. The delay before response was generaly short but the length of the response was also short in most cases. Haematologic toxicity was moderated. Clinical toxicity occured in 13 patients : neurologic (5 cases), gastrointestinal (5 cases) and alopecia (8 cases). Continuous 5 day infusion of VDS is an efficient regimen without serious toxicity. We now use it in combination with other drugs for conditioning regimen in autologous bone marrow transplantation for malignant lymphomas.

T 97 RANDOMIZED COMPARISON OF ONCOVIN AND VINDESINE COMBINATION CHEMOTHERAPY IN NON-HODGKIN LYMPHOMA

D.Fritze,M.Heim,W. Mebes ,C.E.Schwarz,A.C.Ho,V.Grimm, P.Drings,W.Queißer,U.Abel. We wished to compare Oncovin(COP/CHOP) and Vindesine(CVP/CHVP) chemotherapy with regard to efficacy and side effects. 56 patients (35 men,21 women,median age 59 years) were randomized to receive either COP/CHOP (n=28) or CVP/CHVP (n=28). They were stratified according to histologic type(Kiel classification). Treatment: Oncovin (1.4 mg/m^2 IV) or Vindesine (3 mg/m^2 IV), Cyclophosphamide (650 mg/m^2 IV), Adriamycin (40 mg/m^2 IV for high grade malignant NHL), and Prednison(40 mg/m^2) orally day 1-5. Cycles were repeated after 3 weeks for at least six times.Eligibility included histologically confirmed stage III/IV NHL, measurable disease,tumor progression during the last 8 weeks,resistance to Chlorambucil/Prednison in CLL. Results: The 2 groups of Oncovin(COP/CHOP)and Vindesine (CVP/CHVP)chemotherapy were well balanced according to sex,age,"low grade"(n=40) and"high grade"(n=16)malignant NHL,predominant site of metastasis,stage, B-symptoms(n=15),and prior therapy. 3 pat died during the first 3 weeks of trial. Overall, COP/CHOP and CVP/CHVP proved to be equally effective.Of the 47 evaluable patients,57% showed complete(n=10)and partial(n=17)remissions according to SAKK criteria;15%(n=7)were treatment failures. Median duration of remission is in excess of 11/2 years. Survival of responders differs from that of pat with tumor progression(P=0.0006,LogRank).Toxicity did not differ between the Oncovin and Vindesine regimens.However, pat with moderate-severe polyneuropathy while on Oncovin could continue safely with Vindesine combination chemoth.

T 98 COMPARISON BETWEEN 4'EPIDOXORUBICIN (IMI-28) AND ADRIAMYCIN IN POOR PROGNOSIS NON-HODGKIN LYMPHOMAS (NHL-PP) : A RANDOMIZED STUDY

M. De Lena, G. Colucci, P. Calabrese, F. Marzullo, M. Brandi, A. Pellecchia, A. Cramarossa. OSPEDALE ONCOLOGICO, BARI - ITALY.

To compare the therapeutic activity and the cardiotoxicity of ADM and IMI-28 in NHL-PP, from February 1982 to December 1983, 21 patients were randomized to receive therapy A (CTX 750 mg/mq i.v. d 1, ADM 50 mg/mq i.v. d 1, VCR 1,4 mg/mq i.v. d 1-8, BLM 10 mg/mq i.v. d 1-8 and Methilprednisolone 80 mg/mq i.m. d 1→5) or B in which IMI-28 took the place of ADM at the same dosage and with the same modality of administration until September 1983 when the dosage was increased to 60 mg/mq; both regimens A and B were recycled every 21 days. The patients were considered as having a poor prognosis as they presented with an unfavourable histology (intermediate-high grade as W.F.) and/or bulky disease and systemic signs. At present 18 patients are examinable and their characteristics are reported below.

Regimen	Sex	Age	Histology (W.F.)			Stage		Systemic
	M/F	(mean)	L.	I.	H.	I-II	III-IV	signs
A	2/7	42	1	6	2	2	7	4
B	5/4	46	1	4	4	3	6	2

In stage I-II, the patients were treated with 3 cycles of chemotherapy →RT on involved fields → 3 cycles of chemotherapy; chemotherapy only was administered in stage III-IV until clinical progression or a pathologically documented complete response was obtained. Blood pressure, EKG and EKG-Holter were controlled at each cycle of chemotherapy and bidimensional echocardiography was performed every two cycles. The therapeutic results obtained are summarized below.

Regimen	No.	Response		Characteristics of CR					Duration
	Pts.	CR	PR	Stage		Histology			CR (mo.)
				I-II	III-IV	L.	I.	H.	
A	9	7(78%)	2	2	5	1	4	2	6+ 6+ 12+ 13+ 17+ 18+ 24+
B	9	6(67%)	3	2	4	1	3	2	2+ 4+ 10 12 23+ 24+

The toxicity was similar in the two regimens and, in particular, leukopenia (W.B.C.≤2000/mmc) was observed in 25% of the cases,piastrinopenia (P.P.≤100000/mmc) in 6%, alopecia in 75%, paresthesias in 22% and cystitis in 6%. At present no cardiologic evaluation is possible because of the small number of patients who received a dose of IMI-28 and of ADM superior to 300 mg/mq.

T 99 PHASE II STUDIES WITH ALPHA-2 INTERFERON (IFN) IN HAIRY CELL LEUKEMIA (HCL).

R.J. Spiegel, E.M. Bonnem, Schering-Plough, Kenilworth, N.J./U.S.A. 07033.

A single prior study has suggested that Hairy Cell Luekemia may be peculiarly sensitive to interferon therapy (Quesada et al, NEJM, 310: 15, 1984). To confirm this observation we recently initiated a large scale Phase II trial of recombinant alpha-2 interferon (Schering) in patients with HCL who have previously been splenectomized and are now in an accelerated stage of their disease with transfusion dependence, thrombocytopenia, or leukopenia. Patients receive either a fixed dosage of 10 x 10^6 IU/M2 SC tiw or a low initial dose of 2 x 10^6 IU/M2 SC tiw with subsequent escalation if they fail to respond. To date 9 patients have been entered, most within the last two months. Preliminary results in 4 patients now evaluable for response are promising. Patient N. 1 normalized his platelet count after 6 weeks, from 17,000 to 250,000/mm3. Patient N. 2 was transfusion dependent, but had a normal WBC and platelet count; this patient had a significant reticulocytosis and normal hematocrit by eight weeks. Patient N. 3 began pancytopenic and transfusion dependent. After four weeks, his WBC normalized and granulocytes increased; platelet count and hematocrit also normalized. This patient also had a Mycoplasma pneumonia at entry that cleared during treatment. Patient N. 4 was transfusion dependent and by week 4 of therapy achieved a normal HCT and a WBC which rose from 800 to 3300 with a normal differential. Final assessment will include bone marrow evaluation and evaluation of N-K cell activity. Toxicity has been mild. One patient (N. 4) required treatment interruption due to a septic episode which resolved promptly. Constitutional symptoms have been prevalent as the major adverse side effect of IFN therapy. Patient accrual continues and updated results will be presented.

T 100 HIGH AND LOW DOSE ALPHA-2 INTERFERON TREATMENT FOR HIGH AND LOW GRADE NON-HODGKIN'S LYMPHOMA (NHL).

Richard D. Leavitt, Richard S. Kaplan, *Eric Bonnem, *Meredith Grimm and *Seth Rudnick. University of Maryland Cancer Center, Balto., MD 21201 and *Schering Corp., Kenilworth, N.J. 07033

Twenty-one patients with NHL have been treated with interferon at the University of Maryland Cancer Center since June, 1982. Twelve patients with low grade histologies (5 patients with hairy cell leukemia, chronic lymphocytic leukemia, well differentiated lymphocytic lymphoma or Waldenstrom's; 5 with International Working Formulation (IWF)-B; 2 with IWF-C received interferon 10 million U/m^2, SQ, TIW for at least 6 months or for an additional 2 months following maximum response. All patients had advanced NHL: 11 patients were stage IV. Patients were heavily pretreated with up to 8 previous chemotherapy regimens (median 2), and 6 with previous radio-therapy. Three patients achieved partial remission (PR). One patient (IWF-B, stage III, and treatment refractory), now on interferon for 9 months, achieved PR at 2 months and continues to improve. One patient (IWF-C, stage IV) received interferon for 6 months, is in PR 4+ months, and is off treatment. One patient with hairy cell leukemia is in PR with improvement in anemia and neutropenia after 2 months of interferon. Toxicity was tolerable in all patients. Flu-like symptoms and fatigue occurred in all patients but was not dose limiting. Myelosuppression, especially occurring with marrow NHL, and occasional moderate SGOT elevations improved with dose reduction. Mild confusion in 2 patients resolved promptly.

Nine patients with high grade histologies (3 with IWF-E, 3 with IWF-F, 1 with IWF-G, 1 with IWF-H, 1 with IWF-I) received interferon 50 MU/M^2, IV for 5 days every 2-3 weeks. All patients had advanced NHL: 7 patients were stage IV; only 3 patients had previously achieved CR. Sites of involvement were: marrow - 6 patients; pleura - 2; lung or bone - 1 each; lymph nodes - all. Six patients had progressive disease after 2-4 cycles of interferon. Three patients had interferon stopped for toxicity - 2 with dyspnea and confusion; 1 died from GI bleed and aspiration. Despite flu-like syndrome, myelotoxicity, and elevated SGOT, 5 patients safely tolerated full or escalated doses.

Low grade NHL, even relapsing after intensive previous treatment, is responsive to interferon. In the overall experience of the several centers using this dose and schedule of α-2 interferon, 9 of 20 patients with lymphomas IWF-B and IWF-C achieved PR. Lower dose interferon is well tolerated even during prolonged administration in these patients. High grade NHL is not highly responsive to interferon, even when given at extremely high doses. Toxicities are substantial. However, because other available treatment for high grade NHL at relapse is inadequate, further study is necessary to determine if certain histologic subtypes are responsive to interferon.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 101

DISPLACEMENT OF T-LYMPHOCYTE SUBSETS OF PERIPHERAL BLOOD, SPLEEN AND LYMPH NODES IN UNTREATED CHILDREN WITH HODGKIN'S DISEASE. Paolo Paolucci,Vico Vecchi,Giovanni Malpezzi,Laura Serra,Franco Munizza,Donatella Granchi and Patrizia Preti,M.D. III Department of Pediatrics,University of Bologna,40138 BOLOGNA-Italy.

We analize the distribution of lymphocyte sub-population of peripheral blood,spleen and involved tissues in Hodgkin's disease (HD) patients at diagnosis using monoclonal antibodies (MoAbs:Ok T11;OK T3; OK T4;OK T8 Ortho Pharmaceutical Corporation).Moreover we examined in vitro responses of peripheral blood spleen and lymph nodes lymphoid cells to phytohemagglutinin (PHA).Studies were performed on 14 freshly diagnosed untreated patients with histologically proven HD seen between 1978 and 1983.The median age was 9 years (range 5-15);11 patients were males and 3 females.1 patient had pathological stage (PS)I;6 PS II; 5 PS III_S, 2 PS III disease. All but one had Class A.Peripheral blood (PB) was studied in 14 patients,spleen (S) in 14 and lymph nodes (LN) in 3. Ten normal blood donors,similar in age and sex distribution to the patients with HD provided controls for the patient group.Tonsil suspension obtained for diagnostic purpose, from 3 patients with tonsillitis,were used as control for LN.In addition 5 histologically normal spleens removed from accident victims were evaluated.Results: no differences were observed between the total peripheral blood lymphocytes count of HD and control children.T-cell subsets resulted slightly decreased in patients than in controls both percentually as absolute numbers,but statistically significant reduction of circulating T-lymphocytes showing the "helper/inducer" ("H/I": $OKT3^+$, $OKT4^+$) phenotype was observed.This finding was more evident in advanced stages.Decreased values of T-cells with the "Cytotossic suppressor" ("C/S": $OKT3^+$,$OKT8^+$) phenotype were only found in children with advanced disease.High percentages of $^{\circ}OKT3^+$ and $OKT4^+$ lymphocytes were found in the spleens of HD untreated patients;the involved spleen showed "H/I" cells much higher than uninvolved ones.Also iinvolved lymph nodes contained higher percentags "H/I" T-cellsthan tonsil. We did not observe an increased %s of monocytic cells as previously reported by others.The results reported suggest that children with HD as well as adults show altered distribution of T-lymphocytes expressing the "H/I" phenotype between blood and lymphoid organs involved by the disease.In vitro responses to PHA were variable,therefore our data do not support the hypothesis that PHA response of PB,S and LN lymphoid cells may be reflect displacement of T-cell subsets in HD patients.

T 102

Immunobiology of Hodgkin's Disease
Richard J. Ford, Jerry Tsao, Shashi Mehta:
University of Texas; M.D. Anderson Hospital;
Houston, Texas 77030, U.S.A.

Hodgkin's disease (HD) is a pleomorphic human lymphoreticular neoplasm. The malignant cell lineage of this lymphoma is controversial, but it appears to have at least some characteristics of a macrophage. Our studies indicate that when the malignant cells are grown in vitro (Reed-Sternberg (RSC) and mononuclear variant Hodgkin's cells (HC) culture supernatants contain Interleukin 1 (IL-1) activity, the biological actions of which may account for the histopathologic appearance of the nodular sclerosis (NSHD) lesion. In addition to the nature and functional characteristics of the malignant cell, a second important question relates to the nature of the T cell immunodeficiency in HD patients which may account for significant morbidity and ultimately mortality. This defect is usually manifest by cutaneous anergy to recall antigens hyporesponsiveness to T cell mitogens and depressed mixed lymphocyte culture (MLC) reactivity. The Interleukin growth factor system now provides a framework for understanding T cell activation and proliferation, which can be dissected in various disease states with putative immunoregulatory disturbances. We have studied 14 patients with untreated NSHD using the Interleukin framework as the basis for evaluating T cell responses in these patients. In these studies, the IL-1 responses from peripheral blood mononuclear cell (PBMC) adherent cells was equivalent to that of age/sex-matched controls. The response of lectin-activated patients T cells to exogenously provided IL-2 (TCGF) was also normal. However, the generation of IL-2 activity was significantly impaired when patients PBMC were stimulated with T cell mitogens. Further studies on the nature and possible mechanism of the IL-2 defect in HD patients will be discussed.

T 103

FERRITIN IN HODGKIN´S DISEASE.
Dienstbier, Z., Heřmanská, Z., Kopřivová, H., Novák, F., Blehová, Z. Institute of Biophysics and Nuclear Medicine, Faculty of General Medicine, Charles University, Prague, Czechoslovakia.

In view of the reported association of Hodgkin´s disease and ferritin the determination of serum ferritin and the immunofluorescent detection of ferritin-bearing circulating lymphocytes in these patients was done. Antibodies against human placental ferritin prepared in our laboratory were used.

The elevated serum ferritin levels, positive by counter electrophoresis (≥ 300 ng/ml), were found in 65% of 40 patients at presentation. Any relation to clinical stage, histological classification or systemic symptoms was not observed by this semiquantitative method. This elevation was not noted in 70 controls and in most of 60 patients in complete remission, exoluding 4 patients later relapsed, and another 7 elevations remain unexplained. During progression or relapse of the disease ferritin levels are found elevated in 63% of 37 patients.

The number of ferritin-positive lymphocytes in 11 untreated patients exceeded highly that detected in healthy subjects, i.e. 25-60% vs. 0.4%. After successful treatment their proportion decreased to 0-22% and increased again in patients in relapse (24-52%). In these cells iron could be detected by cytochemical staining only after the treatment with antibody. Negative correlation with mature quiet and E-rosetting peripheral lymphocytes was found. On the other hand, no association with cytochemically detected T-helper subpopulation could be demonstrated. The elevated serum ferritin levels were not dependent on the peripheral monocyte counts or their activation neither connected with the number of ferritin-bearing lymphocytes.

Our results support the presumed role of ferritin in the immunological disturbances in patients with Hodgkin´s disease.

T 104

CAN HIGH DOSE GALLIUM IMAGING AND HIGH RESOLUTION CT SCANNING REPLACE STAGING LAPAROTOMY IN STAGE IA AND IIA HODGKIN'S DISEASE?
Joshua D.E., McLaughlin A. and Kronenberg H.

The aim of this study was to determine whether recent refinements in gallium and CT scanners would allow accurate pathological staging without laparotomy in patients with Stage IA and IIA Hodgkin's disease. Previous staging laparotomy studies have shown that approximately 30% of patients with Stage I and IIa disease have abdominal disease but these studies were performed prior to the days of accurate CT and triple-pulse gallium scan analysis. In the Royal Prince Alfred Hospital we have been sequentially performing computerised abdominal tomography and high dose gallium scanning on all our patients with Stage Ia and IIa disease. CT scans were performed with an Ohio Nuclear Delta 2010 CT body scanner and patients were scanned after oral and IV contrast agent using 10 mm scans at 15 mm intervals. Whole body gallium studies were performed using 10 mCi gallium citrate and scans were performed at 48 and 72 hours after injection. These were performed on a large field camera using triple pulse high analysis and area scanning. All patients were submitted to staging laparotomy if the results of the CT scan showed no abdominal disease and if in addition there was positive supra-diaphragmatic gallium uptake and negative infra-diaphragmatic gallium uptake, i.e. an intrinsic patient control. Eleven patients with these findings have been studied, 7 had nodular sclerosing disease, 2 had mixed cellularity and 2 lymphocyte predominant disease. All had normal laparotomy findings and in particular splenic disease was not identified in any of this group. The patients subsequently had mantle radiotherapy without adjuvant chemotherapy.

We therefore feel that patients with clinical Stage I and IIa disease whose abdominal CT scans and gallium studies which showed no infra-diaphragmatic disease may be a sub-group which will be free of disease on staging laparotomy and the operation in this group of patients may be a totally unnecessary procedure. Furthermore there is considerable evidence to suggest that even if these patients do ultimately relapse, their survival with salvage chemotherapy will be no different from those who are accurately staged.

In our experience both these scanning procedures in combination are excellent procedures for determining whether pathological disease will be found on routine staging laparotomy.

T 105 CORRELATION OF LYMPHANGIOGRAPHY AND GALLIUM SCAN IN HODGKIN'S AND NON-HODGKIN'S LYMPHOMAS.

F.Buffa, M.G. Aragno, A.Gallamini, P.F.Giriodi, R.Motta, G.Nova, P.Torre, M.Valente, G.F.Camuzzini. Ospedale S.Croce, 12100-Cuneo.

Out of 79 new patients with malignant lymphomas investigated between 1979 and 1983, lymphangiograms and gallium scans were both performed in 31 cases with Hodgkin's disease (22) and non-Hodgkin's lymphomas (9) before treatment. A dose of 5 mCi of Gallium-67 citrate was injected and scanning was on average performed after 48-72 hours. In the first 10 cases a rectilinear scanner and in the last 21 a gamma-camera were used. The procedures were independently reviewed by physicians of the Nuclear Medicine and by radiologists, who were not aware of the previous interpretations and of the clinical and histological data. For each case six sites were considered (right and left paraaortic, iliac and inguinal regions) and the results were reported as conclusive (positive or negative) and equivocal. In the 31 patients the conclusive results were 83,9%, the equivocal 16,1% and the concordance rate between the two procedures was 51,6%. Considering the sites (186) the percentages were not significantly different: conclusive results 80,1%, equivocal 19,9%, concordance rate 61,1%. As to the anatomical regions the higher concordance rate was observed for the paraaortic areas (61,3%) and the lower for the iliac (45,8%) and inguinal regions (46,8%). Slightly higher concordance rates were observed in the group of non-Hodgkin's lymphomas. Lymphography appears to yeld more positive results in comparison with gallium scan (21 cases and 81 sites versus 18 cases and 40 sites) and less negative results (7 cases and 83 sites versus 11 cases and 128 sites) being the equivocal data almost superimposable (3 cases and 22 sites versus 2 cases and 18 sites). Gallium scanning, which is characterized by high degree of sensitivity, specificity and accuracy in the overall staging, although less significant for some subdiaphragmatic areas, may elicit sites undetectable by lymphography such as liver, spleen, the hilar and celiac nodes. The two procedures must be considered complementary to each other.

T 106 USEFULNESS OF GALLIUM-67 SCANNING IN THE PRIMARY STAGING OF PATIENTS WITH MALIGNANT LYMPHOMA

M. E. Heim, E. Wetzel, H. Rademacher

Gallium-67 citrate has a high affinity for some human, as well as animal neoplasms and several reports on gallium scanning in malignant lymphoma had shown variable scan accuracy with 50 - 80 % true positive results. In a retrospective study we analysed the clinical usefulness of 67-gallium scanning for the primary staging of malignant lymphomas. 74 patients (36 females, 38 males) with histologically confirmed malignant lymphoma were analyzed prior to treatment. 34 patients had Hodgkin's disease (25 nodular sclerosis, 9 mixed cellularity), 40 Non-Hodgkin's lymphoma (26 low grade, 14 high grade malignancy). Each patient received 3 m Ci gallium-67-citrate i.v. and whole body scans were taken at 48 and 72 hours. The results of standard diagnostic procedures were compared with the gallium scan in a case and site analysis. In Non-Hodgkin's lymphoma cases were correctly classified in 48 % with 30 % false negative scans, the percentage of correctly classified sites was 89 % with a sensitivity of 39 %. There was no significant difference between low and high grade malignancies. In Hodgkin's disease 53 % of all cases were correctly classified as positive or negative, 23,5 % were false negative or positive. Site classification was correct in 90 %, sensitivity was 50 %. Sensitivity was much better in nodular-sclerosis (60 %) when compared with mixed cellularity (24 %). The detection rate was best for mediastinal (62 %) and hilar (82 %) lymphnodes, while many abdominal lymphnodes were missed (sensitivity 26 %). There was no case of upstaging as a result of gallium scanning. In conclusion gallium scanning has only limited value in the routine primary staging of patients with malignant lymphoma.

T 107 PATTERNS OF LATE RELAPSE IN HODGKIN'S DISEASE.

M. Ben-Shahar, Y. Ben-Arie and Y. Cohen, Northern Israel Oncology Center, Rambam Medical Center, Haifa, Israel.

During the years 1980-1982, 203 previously untreated patients (pts) with Hodgkin's disease (HD) were referred and treated in the Northern Israel Oncology Center. One hundred and forty-nine (73.4%) of them achieved complete remission (CR). However, 64 pts (42.9%) have subsequently relapsed. In 13 pts (9 of them histology proved) it was a late relapse (LR) (after 3 years free of disease). The patterns of the late first relapse were studied. The mean time of LR pts to 1st relapse was 54 months (median 45m, range 36-112m). There were 5 males and 8 females. The mean age was 27.6 yrs (range 10-61 yrs).

The distribution of LR pts at initial presentation, according to histologic classification and stage, were similar to that of all pts. 61% of LR pts were clinically staged. Initial stages of LR pts were: Stage I - 3 pts, II - 6 pts, III - 2 pts and IV - 2 pts. Only 4 pts (30.7%) had B symptoms at initial presentation.

Most pts (69.2%) had been treated by radiotherapy alone (mantle field or total lymphoid irradiation at 4000 rad tumor dose). The others had received combined chemotherapy and radiotherapy. At relapse, 61.5% of LR pts had B symptoms. Nine LR pts had nodal recurrence and 3 had a mixed pattern (nodal and extranodal). Only 4 pts relapsed in previously involved site. Five of 12 nodal recurrences were in contiguous extension and 4 were exclusively in new sites. The spleen was involved at LR in 4 of 9 pts. Seven of 9 pts who had had only supradiaphragmatic disease at initial presentation relapsed below the diaphragm.

Gallium scan was performed in 8 pts with LR and was positive in all of them. Erythrocyte sedimentation rate (ESR) was generally high at LR (mean 74 mm in 1st hour). All LR pts were treated following relapse; 77% by chemotherapy alone and the rest by a combined modality treatment. Nine pts (69%) achieved CR.

As yet seven pts (53.9%) are alive, 4 of them (30.8%) are with no evidence of disease. Six pts died; 4 died of HD and 2 succumbed to a second malignancy (1 - leukemia and 1 - non-Hodgkin's lymphoma), while being free of HD.

The mean survival time of LR pts from diagnosis was 94m as compared to 52m of those with an early relapse ($p<0.001$). The 5 and 10 years survival of the LR pts was 83.4% and 63.4% respectively. The presented data indicate: in most LR pts the relapse is in previously non-involved and non-contiguous site. Initial understaging might be the cause for subdiaphragmatic recurrences. LR pts might be rescued by further treatment and their survival is significantly better than that of early relapse pts.

T 108 ACUTE LEUKEMIA (AL) AS SECOND PRIMARY AFTER HODGKIN'S DISEASE (HD).

Cartei G., Cendron R., Pappagallo G.L., Ferrazzi E., Aversa S., Daniele O., Stefani G.P., and Fiorentino M.V.
Oncology Department, Medical Oncology Division, PADUA (ITALY)

From Jan.1958 to Dec.1983, 18 out of 1107 (1.62%) HD patients (pts) developed AL (10 males, 8 females; age 22 to 60 years, $\bar{x}$ and median (m) 40 years. 1/18 had synchronous HD + AL. Prevalence of AL by HD subtype was 3% in L.P., 2% in N.S., 1.6% in M.C. No case of AL has occurred among the 5.9% of cases with L.D. Interval between initial HD and AL diagnosis in 17 pts was 24 to 297 months (mo.) ($\bar{x}$ 74, m69). HD therapy included RT in 2 pts, poly-CT (pCT) in 1, RT + pCT in 8, RT + pCT + Nitrosoureas in 6. According FAB classification AL types were M5 in 5 pts, M4 in 5, M3 in 1, M1/M2 in 4, pre-M1 in 1, and LAL in 2. Clinically 4 pts presented with infection (i), 8 with i and coagulopathy (c), 4 with "fever", 2 with paraneoplastic ADH syndrome, 6 with persistent anemia or leukopenia. A preleukemic syndrome was diagnosed (in 11/18 pts; 1 to 6 mo.) previous to AL (anemia in 5 pts, leuko-trhombocytopenia in 2, monocytosis in 1, lymphocytosis in 1, c in 1, aplasia in 1). Cariotype study (11/18 pts) in overt AL gave in 8/11 abnormalities of the C group chromosomes.

	m	range		m	range
Hb (g/100 ml)	8.9	4.0-15.0	MCV (μ^3)	100	78-120
WBC ($x10^3$)	15	3.7-88.3	Plat. ($x\ 10^3$)	120	15-580
% Blasts	80	15.0-99.9	LDH (U/lt)	460	130-1020
Fibr. (mg/100 ml)	520	220-980	Alk.Phosph.(U/lt)	138	59-731
FDP (μg/ml)	10	5-110	Albumin(g/100 ml)	3.6	2.7-4.5

2 pts died before induction therapy (IT) (c, i). 2 pts refused IT. IT in 12 cases included ADM, ARA-C, and TG; among the 12 pts, 5 had also VM26 and 4 others VP16; 1 pt received high-dose ARA-C; 1 LAL pt received ADM, VCR, and Prednisone; 1 pt with synchronous AL had L2 regimen and other drugs. Survival (14/18 treated pts) ranged from 15 to 383 days ($\bar{x}$ 109, m72); overall survival (18 pts) ranged from 1 to 383 days ($\bar{x}$ 88, m57.5).

Stage, age (over 40 years), hystotype, pCT + RT, correlated with AL occurrence; median interval from HD to Al (synchronous case excluded) was 94 mo. (22-39) below 40 years of initial age (9 pts), and 50 mo. (40-60) over 40 years (8 pts).

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 109

Late Complications after treatment of Hodgkin's disease.
Rossi E., Marmont A., Damasio E., Repetto M., Occhini D. Department of Hematology S.Martino's Hospital Genova; Siracusa A., Vitale V. Department of Radiotherapy Galliera's Hospital Genova; Bentivoglio G., Chiodi S., Spinelli S., Barbero P., Medica F. Ist. Clin. Ost. Gin. Unyversity of Genova.

Since 1974 we have treated 512 HD and observed three major types of late complications: 1) ANLL induced
2) Failures in genital functions
3) Persistent chronic hepathitis

1) We observed 9 ANLL and one dyseritropoietic anaemia (preleukemic syndrome). 5 out of the 9 ANLL had been preceded by preleukemic states lasting from one to 20 monthes. 7 patients were treated for leukemia either with combined protocols or monochemotherapy (ARA-C high or low doses). We observed in ARA-C treated patients two PR of respectively 30 and 45 days. One patient was submithed to BMT from an allogenic donor resulting in CR.

2) 26 women age 13-42 were monitored for FSH, LH, E2 levels after treatment with: CT+RT without λ (I group)
CT+RT with λ (II group)
No patient in the I group developed permanent amenorrhea (age 14-32; treatment: MOPP and/or ABVD and/or RT mantle)
60% of the patients in the II group developed permanent amenorrhea throught the whole follow-up of 6-125 monthes. Two patients in the II group returned to regular menses after 34 and 48 monthes respectively. We observed a statistical correlation between hormonal levels and ovaric functions, particularly with estradiol levels ($p = 0{,}001$)

3) Six patients developed persistent chronic hepatithis HBsAg positive. No patient had syntoms in relation to an acute phase of viral hepathitis . Clinically we observed hepathomegaly and increased levels of GOT, GPT, γGT and ACP.
Liver biopsies showed an hepathocytic degeneration and a lymphoid infiltration into Kupfer's spaces.
Relation with immunodeficiency are considered.

T 110

PRESERVATION OF OVARIAN FUNCTION AFTER INVERTED Y RADIOTHERAPY IN HODGKIN DISEASE. A NEW SURGICAL METHOD OF TRANSPOSITION.

A.Gaetini°,A.Levis+,A.Urgesi*,M.Nano°,M.De Simone°
P.Gabriele*,R.Ragona*,S.Anglesio§,M.A.Crocca Vasinor.
Ospedale Molinette Torino,Italy.
°Patologia Chirurgica II°dell'Università.
+Divisione Medicina E-sez. di Ematologia.
*Divisione di Radioterapia dell'Università.
§Servizio di Fisica Sanitaria.

Oophoropexy is a widely accepted treatment method in young females to be treated with inverted Y radiotherapy for Hodgkin disease.Generally the ovaries are medialized in a retrouterine position.A variable percentage of patients treated with this thecnique develops amenorrhea as a consequence of irradiation.A new surgical thecnique,high abdominal oophoropexy,has been proposed by our group with the aim of reducing radiation dose to the gonads. High abdominal oophoropexy is a moment of diagnostic laparosplenectomy;the gonads are mobilized from the pelvis and fixed between the colon and the abdominal wall laterally to the kidneys.The peritoneum of the mesoovarium is dissected;the utero-ovaric ligament and artery,the lateral tubaric artery,and the vessels reaching the ovaric hilum from the tube are ligated and dissected.The vessels of the infundibulum are conserved and maintain the vascularization of the ovaries which can be moved in the upper abdomen dissecting the infundibular peritoneum. Computer dosimetry shows that the average dose delivered to the gonads fixed in the upper abdomen is less than one half of the dose calculated behind the posterior wall of the uterus, the most common site of gonadal transposition, when 18 Mev X rays are used. With ^{60}Co beams the ratio is even higher.
Twelve patients have been treated up to now and all have regular menses and normal blood levels of sex hormones. Two of them delivered normal babies.
Details of surgery and computer dosimetry are discussed by the Autors.

T 111

HODGKIN'S DISEASE (HD) AND PREGNANCY

W.F. Jungi, O. Schildknecht, A. Wick, F. Kästner and Th. Hardmeier for the Eastern Cooperative Oncology Group (OSAKO), Medizinische Klinik C, Kantonsspital, CH-9007 St.Gallen.

Within the last few years we have seen in Eastern Switzerland 6 female patients with Hodgkin's disease presenting first in pregnancy. In 5 cases (4 x first, 1 x sixth pregnancy) the further course of the gravidity and the birth were uncomplicated (cesarean section in 2). 2 patients didn't need tumor therapy at all, 3 received supradiaphragmal irradiation. All 5 children developed normally. 1 patient had later a 2nd child. The 6th patient, advised to get pregnant in order to improve her HD IV B with heavy pulmonary infiltration!, had a catastrophic course with birth of an underdeveloped acidotic child (with full recovery) and death of the mother 40 hours later.
4 patients delivered after radiotherapy only, whereas 7 patients became pregnant 1-13 years after combined chemo-radiotherapy for HD. None of the 4 children born after long-term chemotherapy with various regimens showed any evidence of malformation. There were 2 intended, 1 spontaneous abortion. A synoptic collection of all the patient's data and review of the literature will be presented.
Conclusions: 1. First detection of active HD in pregnancy is a rare, but critical concurrence of two independent conditions with no risk for the offspring. Interruption is only indicated in case of infradiaphragmal or disseminated disease necessitating immediate treatment. Otherwise limited staging and supradiaphragmal irradiation is appropriate, with complementary measures postpartally.
2. After 2 years recurrence- and treatment-free follow-up there is no reason to dissuade from pregnancy. In case of active disease pregnancy precludes treatment and endangers the mother's and child's life.

T 112

GONADAL FUNCTION IN MALES AFTER COMBINATION CHEMOTHERAPY FOR HODGKIN'S DISEASE IN CHILDHOOD. Vico Vecchi*,Laura Serra*,Maria Pia Villa^,Andrea Pession*,Emanuele Cacciari^,Guido Paolucci*,M.D. - *III and II^Departments of Pediatrics,University of Bologna-40138 BOLOGNA-Italy.

The effects of chemotherapy on gonadal function have been investigated in 6 males treated for Hodgkin's disease during childhood. All patients were prepubertal at the time of treatment and their ages were 5,5,6,7,9,11 years respectively.Using the Ann Arbor criteria the pathologic stage was:stage I,three patients;stage II,three patients. Five of them received MOPP (nitrogen mustard,vincristine,procarbazine, prednisone),six courses or more,plus involved field radiation therapy (IF-RT),the remaining patient received monochemotherapy with vinblastine (0,2mg/Kg every two weeks for 18 months)plus IF-RT.No patients had had abdominal irradiation.All patients were off-therapy from 5 to 9 years at the time of the study.The pubertal status of each was defined by the staging technique of Tanner.Testicular size was assessed by comparison with the standards of the Prader orchidometer.Semen analysis was performed at periods of 4-9 years after treatment had ended.Serum follicle stimulating hormone (FSH) and luteinizing releasing hormone (LHRH) concentrations were assessed by specific radioimmunoassays as well as testosterone levels.Endocrinological assessment did not performe concurrently to semen analysis.Results:puberty has proceeded normally in all patients.The testicular volume was normal.Basal FSH and LH concentrations and the peak gonadotropin responses to LHRH were normal in all patients.The basal testosterone levels and testosterone responses to human chorionic gonadotropin (hCG) stimulation test ranged in normal values in 3 pubertal boys,whereas two patients,both prepubertal at the time of endocrinological assessment,had abnormal testosterone responses. Four out of five boys who received MOPP chemotherapy had absolute azoospermia on semen analysis, one patient showed sperm count of 2 million/ml.Patient who received Vinblastine had a sperm count of 22 million/ml;sperm were motile and showed normal morphology. Conclusions:the available data from large groups of adolescent and adult males revealed that the probability of recovery of spermatogenetic function and fertility after MOPP chemotherapy is low.The incidence of gonadal damage in prepubertal children treated for Hodgkin's disease has not been extensively studied.However our data suggest that irreversible azoospermia may be a frequent long term complication of MOPP chemotherapy in children.Nevertheless the observation that the patient who has been treated with vinblastine did not show germinal epithelium damage is very interesting.

T 113 HODGKIN'S DISEASE IN TROPICS - A PERSPECTIVE.

N. Lalitha, K. Gharpure, M. Krishna Bhargava, Division of Medical Oncology, KMIO, Bangalore-29 (South India).

This is a retrospective study of 225 cases of Hodgkin's Disease seen during a period of 10 yrs from 1974 to 1984, mainly to understand the natural history of the disease as prevalent in Tropics.
Hodgkin's Disease seems to be more aggressive in tropics as compared to any series in the west as majority of the patients have unfavourable histology (50% M.C. 10% L.D.) constitutional symptoms (80%) with unstable immune system 60% of patients are under 30 yrs. Peak age incidence being 6-10 yrs. It is more common in males M:F ratio 4:1.
Mean duration of illness at presentation is 2 yrs. In 20% of patients duration is less than 6 months and it behaves more like a systemic disorder. The tempo of the process seems to be more rapid and it may be dependent on racial factors and or nutritional factors.
Certain highlights in clinical manifestations are 55 patients had significant hepatomegaly with raised alkaline phosphatase 10 with icterus and 15 with ascites at presentation. Onehundredten patients had huge splenomegaly. During the course of the disease 10 had bone involvement 2 had skin infiltration and 7 had parenchymal lung involvement. This study brings to light two important manifestations in the natural history of the disease.
At presentation 70 patients had significant pallor and 25 patients had not only lymphopenia but also polymorphonuclear lucocytosis. In one case of childhood H.D. with severe anaemia and huge splenomegaly bone marrow aspiration showed marked myeloid hyperplasia simulating C.G.L.. This was before starting any treatment.
Fifteen patients all in stage IV B had C.N.S. manifestations in the form of focal seizures, cranial nerve palsies long tract involvement with abnormal CSF findings in 10 patients. All these patients did not have high cervical node disease. One case of childhood H.D. had progressive staxia with bilateral 6.th nerve palsy for one year preceding the development of lower cervical lymphadenopathy which showed H.D. (M.C.) with cerebello pontine atrophy in C.T. Scan.
Mopp chemotherapy with local or extended radiation to residual and initial areas of bulky lesions seem to favour longer survival in stage IV disease. Persistence of fever in spite of treatment seems to be a grave prognostic factor.

T 114 CLINICOPATHOLOGICAL STUDY OF ADULT HOGKIN'S DISEASE IN SAUDI ARABIA.

T.I. Mughal*, W.A. Robinson, M.A. Padmos, and S.A. Al-Hazzaa. King Faisal Specialist Hospital, Riyadh, Saudi Arabia (*Present address: Department of Medicine, University of Colorado Medical School, Denver, Colorado, U.S.A.).

We reviewed 81 consecutive adult patients with Hodgkin's Disease (H.D.) treated at King Faisal Specialist Hospital from August, 1975 through to August 1982, to assess the clinicopathological features of adult H.D. in Saudi Arabia. This was the first extensive study of its kind and our data suggests that H.D. in Saudi Arabia represents an intermediate picture between that seen in the developed and the developing world. Of the 81 patients, there were 57 (70.4%) males and 24 (29.6%) females with a male:female ratio of 2.38:1. Median age for males was 29.9 years and for females 23 years, with two distinct peaks at 18 and 48 years; bimodality being more striking in females. The most common histologic sub-type was mixed cellularity (59.3%) followed by nodular sclerosis (23.5%), lymphocyte predominant (4.9%) and depleted (3.7%). Eightysix percent of patients had advanced (Stage III and IV) disease at presentation - 36 (63%) males and 19 (79%) females. Extranodular involvement was evident in 40% of this group with bone marrow (B.M.) involvement being most common (47%) followed by hepatic (25%) and pulmonary (22%). Splenic involvement was found in 6 (7.4%) patients, at laparotomy. No striking genetic, familial, or ethnic group factors emerged. Furthermore, no specific environmental or occupational risk factors were evident, neither was time space clustering phenomena observed.

T 115 HAS THE SPLENIC INVOLVEMENT IN HODGKIN'S DISEASE (H.D) ANY INFLUENCE ON THE PROGNOSIS AND THE THERAPEUTIC PROCEDURE?

P.Ponticelli, L.Arganini, G.P.Biti, L.Cionini, S.Di Lollo, V. Mungai - University-Hospital Department of Radiotherapy, University Pathology Department, Florence.

Several authors think that the hematologic spread of H.D. passes through the spleen: in this way it would be logical a radio-chemotherapy association. On the other hand other authors (less in number) think that H.D. in spleen would have the same prognosis as HD in nodes with no influence on the therapy.
In our Institution 380 patients treated between 1970 and 1983 were submitted to staging laparosplenectomy; 214 out of those were males and 166 females. In 365 patients the onset of the disease was supradiaphragmatic, while only in 15 it was infradiaphragmatic. As just stated the incidence of splenic involvement in patients with supradiaphragmatic onset is higher in late stages - IA 3/42 (7%), B 1/2; II/A 49/196 (25%), B 7/25 (28%); IIIA 33/64 (51.5%), B (22/30 (73%); IV 4/6 - on the other hand surprisingly the incidence of splenic involvement when the disease was infradiaphragmatic in origin is only 2/15 (13.3%) - I and II A 0/11, IIB 2/3, IIIA 0/1.
The main clinical and pathologic features (sex, stage, hystology, number of sites and areas involved, splenic or nodes involvement) were related to the therapy and to the results obtained. The results show that the figures of relapse incidence (minimum follow-up 2 y) in path. st. I-II, IIIS, IIISN and IIIN are respectively 23%, 41.9%, 45,4% and 57% in patients treated only by radiotherapy, while they are 30%, 15%, 27% and 40% respectively in the group treated by radio and chemotherapy. In particular the incidence of dissemination (hematological spread) is, in the same groups, respectively 9.4%, 16%, 24%, 21% in RT group, and 20%, 7.6%, 18% and 40% in RT+CHT group.
Eventually the AA have correlated the macroscopical findings of involved spleens with the results.
No significant differences were found from the point of view of the hematological spread between the patients without or with (either miliaric or nodular) splenic involvement, in spite of the therapeutic procedures adopted (radiotherapy or radiotherapy plus chemotherapy).

T 116 FAILURES IN THE TREATMENT OF HODGKIN'S DISEASE. A SURVEY OF 56 CASES OUT OF 1014 TREATED PATIENTS.

F. Teillet-Thiebaud, B. Asselain, J. Bernard, F. Teillet. Groupe d'Etudes sur la maladie de Hodgkin. Hôpital Louis Mourier -92701 Colombes Cedex- Hôpital Saint-Louis -75010 Paris-

Between 1965 and 1979, 1014 patients stages I to IV Hodgkin's disease have been treated according to various therapeutic trials all of them using chemotherapy (ch) prior to irradiation (Rx). The initial treatment, (ch)+(Rx), failed with 56 patients (F) : 5,5%. Failure was defined after completion of initial treatment that is 1) No response (N.R.) 10/1014 : 0,9%. 2)Incomplete Remission (ICR) 35/1004 : 3,5%. 3) Early relapse within 3 months after an apparent complete remission (ER) 11/969 : 1%. Survival rate of (NR) patients is 0% at 27 mths and identical for (ICR) and (ER) patients : 0% at 60 mths. There is no consistant difference according to the type of initial treatment. At the time of diagnosis it is impossible to identifie (F) patients : no predictable data can be drawn-up from age, sex, delay of diagnosis, pathological type and spread of the disease even though the (F) patients ratio increases with the extent of the disease :

Stages	Number Patients	(F)	%
IA - II2A	408	10	2
IB - IInA	399	27	6
IIIA, B	123	10	8
IV	84	9	10

The patient's response to prior (ch) seems to be the best indication of failure of complete initial treatment : 100% of (F) patients are in ICR after 3 (or even 6) cycles of MOPP and/or ABVD. Such an early selection may be of interest specially in diffuses stages III and stages IV Hodgkin's disease. In such cases it may be preferable to have recourse as soon as possible to more intensive treatment including autologous bone marrow transplantation.

T 117

TREATMENT RESULTS WITH COMBINATION CHEMOTHERAPY: ADRIAMYCIN, BLEOMYCIN, VINBLASTINE AND IMIDAZOLE CARBOXAMIDE (ABVD), IN ADVANCED HODGKIN'S DISEASE (HD). Victor J. Torras G., Edna L. García de Díaz, Agueda López Pérez, José G. Díaz Maqueo, Sergio Loera F. and Enrique Arechavala P. Servicio de Hematología. Hospital de Oncología, CMN, IMSS, MEXICO.

From January 1980 to December 1981, 32 patients (pts) with advanced HD were treated with ABVD alone or in combination with radiotherapy (XRTh). There were 22 males (68.7%) and 10 females (31.3%), with a median age of 40 years (range 18-65). ECOG performance status was: 0-3, 28 pts and 4, 4 pts. 13 pts (40%) belonged to low socio-cultural level and 19 pts (60%) to medium level. Histologic subtypes were as follows: Nodular sclerosis (NS) 10 pts (31%), Mixed cellularity(MC) 16 pts (50%), Lymphocyte depletion (LD) 4 pts (12%), with a high content of epithelioid histiocytes (so-called Lennert's Lymphoma) 1 pt (3%), unclassified (UC) 1 pt (3%). 9 patients (28%) were stage III-B, only 1 pt (3%) stage IV-A and 21 pts (66%) stage IV-B. One pt was not staged. Laparotomy was performed in 8 pts (25%). 20 pts had liver involvement (62.5%), 6 pts bone marrow (19%), 2 pts (6%) lung and 3 pts (9%) showed other organs involvement (CNS, bone, paranasal sinuses and orbit). 7 pts were not evaluable (5 were lost and 2 were early deaths). There were 22 (88%) complete responses (CR) and 3 (12%) partial responses (PR). The response rate related to histology was: NS 5 pts (83%) had CR and 1 pt (17%) PR; MC 12 pts (86%) had CR and 2 pts (14%) PR; LD 3 pts (100%) had CR as well UC and high content of epithelioid histiocytes pts. The response rate related to stage was as follows: stage III-B 5 pts (83.3%) had CR and 1 pt (16.7%) PR; stage IV 17 pts (94.4%) had CR and 1 pt (5.6%) PR. the unstaged pt had PR. 11 pts (34%) received adjuvant XRTh. The CR group pts have a median duration of disease free interval >25 months (ms) and a median survival rate >32 ms. 2 pts died at 35 and 37 ms respectively with active disease.