ABSTRACTS

PRESENTATION BY TITLE ONLY

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T1

NON-HODGKIN'S MALIGNANT LYMPHOMA WITH MULTIFOCAL EPITHELIOID HISTIOCYTIC REACTION

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According to several clinicopathological studies it was stated that the so-called "Lennert's lymphoma" is not a single well-defined entity but a hetero - geneous group of different disorders including Hodgkin's disease, non-Hodgkin's malignant lymphoma, atypical lymphoepithelioid cell proliferation and angioimmunoblastic lymphadenopathy. In order to investigate the natural history of non-Hodgkin's malignant lymphomas with a high content of epithelioid histiocytes /NHL/ 6 cases have been studied. The histologic, cytologic, ultrastructural and clinical features were analysed. The lymphoid cells in NHL were characterized by round to ovoid and irregular nuclei with pale to clear cytoplasm. Mitoses were frequent. In imprints the small and large lymphoid cells varied, the nuclei tended to be round, nuclear irregularities were present. The lymphoid cells intermingled with scattered epithelioid histiocytes. Ultrastructurally beside nuclear abnormalities in 3 cases nuclear cleavage were also stated. Cases were further classified according to the Kiel system as centroblastic-centrocytic lymphomas. 4 patients had a second biopsies. Seven years after the first biopsy 1 case of NHL transformed itself into Hodgkin's disease. Patients with NHL had Stage III or IV disease commonly with B symptoms. 1 patient died after 19 months from initial diagnosis. Autopsy stated that the epithelioid cell clusters were absent but a seemingly more malignant neoplastic lymphoid process was observed. 5 patients are in partial or complete remission. Of the 6 cases 4 were studied for surface markers. In 2 cases abnormal lymphocytes formed spontaneous E - rosettes.

T2

NODE-BASED T CELL LYMPHOMA: MORPHOLOGICAL DIVERSITY IN THREE IMMUNOLOGICALLY CONFIRMED CASES. D. Banerjee, 4026 Health Sciences Centre, University of Western Ontario, London, Canada N6A 5C1.

Recent studies have indicated that a significant proportion of diffuse non-Hodgkin's lymphomas are derived from peripheral T lymphocytes. Although certain histologic criteria may enable the pathologist to suspect a T cell origin in some diffuse lymphomas, the morphological diversity of T cell lymphomas is such that the diagnosis should not be made by histological criteria alone but must be confirmed by surface-marker analysis. Three cases are presented to emphasize the morphological diversity of node-based T cell lymphomas. Two patients presented with retroperitoneal masses and one with lung involvement. The first case showed a predominance of small lymphocytes, occasional large cells and irregular sclerosis. The majority of the cells had no T or B cell markers but 15% were T lymphocytes. Cytocentrifuge preparations of E-rosettes showed that the rosetting population was morphologically atypical. Characteristic histologic features of node-based T cell lymphomas, such as vascular proliferation and compartmentalisation were absent. The second case showed partial nodal involvement by large non-cleaved cells and occasional multinucleated cells resembling pleomorphic Reed-Sternberg cells. There was some compartmentalisation but no vascular proliferation. Large numbers of benign histocytes were observed. Seventy six percent of the cells formed E-rosettes and the rosetting cells showed a marked variation in cell size and nuclear irregularities. The third case, presenting with lung involvement, showed a mixture of large pleomorphic cells and small-cleaved cells. The large cells showed marked nuclear irregularities and prominent nucleoli. Eighty six percent of the cells formed E-rosettes. There was minimal vascular proliferation or compartmentalisation. All cases showed a small proportion of surface immunoglobulin positive cells with a polyclonal staining pattern.

T3

CLINICO-PATHOLOGICAL STUDY ON 215 CASES OF NON-HODGKIN LYMPHOMAS (NHLs), DEFINIED ACCORDING TO THE KIEL CLASSIFICATION

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A series of 215 adult patients affected with non-Hodgkin lymphomas, consecutively admitted to our Division of Hematology in Pavia from January 1974 through August 1980, was classified according to the Kiel classification. The incidence of each hystologic type (except CLL and HCL), was as follow: lymphocytic type 18%, lymphoplasmocytoid 16%, centrocytic 7%, centroblastic-centrocytic 25%, centroblastic 12%, lymphoblastic 9%, immunoblastic 9% and unclassifiable 4%. The staging procedures were diversified according to hystologic type. The staging laparotomy was performed only in the patients with apparent localized disease after non surgical procedure including the bone marrow biopsy. The majority of our cases (83%), were found in advanced stage of disease (III or IV stages), with or without sistemic simptoms. The bone marrow involvement was present in a high percent of low-malignancy lymphomas (LML), less frequently in the high-malignancy (HML) lymphomas. The primary extranodal were 9% of the entire series of patients; the majority arised from Waldeyer ring (55%), gastrointestinal tract (15%), and both (15%). The other site of origin (15%) were skin, spleen and in a single case the meningis. The hystological variants more frequently associed with the extranodal origin were the lymphoplasmocytoid and the centroblastic. The therapeutical approach was radiotherapy or radiotherapy and adjuvant chemotherapy in true localized disease, monochemotherapy (clorambucil), or CVP for the low-malignancy lymphomas, polichemotherapy including adriamicin and bleomicin for high-malignancy lymphomas. In nine out of 19 patients with lymphoblastic lymphoma, the treatment was the same used in ALL. Complete remission was achieved in 40% of LMLs and in 33% of HMLs. The overall clinically diagnosed neurological involvement was of 4%; all cases belonged to the high malignancy types with or without bone marrow involvement. The median survival for LMLs was longer than 60 mos. with a survival rate of 56% at five years from diagnosis; for HMLs the median survival was of 19 months with a survival rate of 15% at five years. The difference in survival between the two groups is highly significant ($p<0.001$). The majority of long-survivors in the high-malignancy group were primary extranodal. The more appropriate therapeutical approach in lymphoblastic lymphomas is the ALL therapy including CNS prophylaxis.

T4

BONE MARROW INVOLVEMENT IN MALIGNANT NON-HODGKIN'S LYMPHOMAS

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Pretreatment bone marrow biopsies from 71 consecutive patients with non-Hodgkin's lymphoma were reviewed. Diagnoses were assigned according to Kiel classificatio Low-malignancy subtypes were more frequently involved than high-malignancy subtypes (34% versus 11%). A correlation was established between the staging of ly phoma and the frequency of bone marrow involvement, thi last being found in advanced clinical stages only (III and IV).
Morphologic pattern of bone marrow involvement appeared as an important prognostic factor: the median survival of the patients with nodular bone marrow involvement wa longer than that of the patients with diffuse bone marr involvement.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T5

PRIMARY EXTRANODAL MALIGNANT NON-HODGKIN'S LYMPHOMAS: CLINICO-PATHOLOGIC CORRELATIONS IN 41 CASES

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The aim of our research was to analyze the clinico-pathological features and the evolution of a series of 41 consecutive, previously untreated patients with primary extranodal non-Hodgkin's lymphoma.
The most common involved sites were the Waldeyer's ring (17) and the gastrointestinal tract (10).
In 30 patients, disease was limited to a solitary extranodal site (stage I_E); in the other 11 patients there was involvement of regional lymph-nodes (stage II_E).
In 13 patients, radiotherapy was the only treatment used. This group consisted principally of patients with lymphoma of the Waldeyer's ring (8) and of the skin (3). Other 7 patients with lymphoma of the Waldeyer's ring received chemotherapy following primary radiotherapic management. 10 patients (4 gastrointestinal, 2 skin, 2 orbital, 1 epidural, 1 brain) were treated with surgery alone. Chemotherapy or radiotherapy was administered following a curative surgical resection in 11 patients (6 gastrointestinal, 1 breast, 1 thyroid, 1 nasopharynx, 1 tonsil, 1 skin).
The histological pattern (Kiel classification), the Ann Arbor-staging system and the primary involved anatomic site had significant influence on survival.
The excellent response to the initial radical treatment (complete remission in 85% of patients), the rarity of relapses and the long median survival (51.4 months) suggest that, in contrast to their nodal counterparts, primary extranodal lymphomas not infrequently present with "truly' localized disease.

T6

REMARKS REGARDING RADIOTHERAPY (RT) OF NON-HODGKIN-LYMPHOMA (NHL) IN CHILDHOOD. E.A. Bleher, S. Bernasconi, C. Landmann, W. Magdeburg, G. Pipard, H.P. Wagner, SAKK-Section of Radiooncology.
Since 1975 45 children with NHL were treated according to a modified LSA2-L2 protocol (Schweiz.med.Wschr. 109, 767,1979). Of 14 pts. with Murphy-stage I and II disease 12 received local RT of 3000-4000 rads. Of these 12 pts. 1 had progressive disease and 2 relapsed locally or to regional lymphnodes. Only 2 of the 12 pts. died, while 10 are living 2+ - 59+ mos., med. 20 mos.
Of 15 pts. with mediastinal primary 6 received RT with 3000-3900 rads to the mediastinum or as mantle. 2/6 relapsed locally and died. In both RT had to be interrupted for several weeks due to bone-marrow-depression or fever, 4/6 are living for 11+ - 50+ mos., med. 25 mos.
Of the 9 pts. not receiving RT 1 died within 8 days of surgical complications, 2 of drug induced complications and 2 of tumorrelapse. Only 4/9 survive 11+, 12+, 25+ and 48+ mos.
Of 5 pts. with intraabdominal Burkitt-type-NHL 4 received no local RT. In 1 pts. local RT had to be interrupted due to the appearance of CNS-disease. In 4/5 CNS-disease was initially present (1 pts.) or appeared secondary (3 pts.). It was treated with 1530-3600 rads with only short or no remission. All pts. died within 3 - 8 mos. after diagnosis.
The results demonstrate: local RT with LSA_2-L_2-like chemotherapy can control Murphy-stage I and II disease. Although the role of RT is not clearly defined as yet for Murphy-stage III disease with mediastinal primary, toxicity of the combined treatment was not more important than that of CT alone. RT, as used in the past, does not seem to be helpful for intraabdominal Burkitt-type NHL.

T7

PRIMARY CNS-LYMPHOMAS: THERAPY AND PROGNOSIS.

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Eleven patients with primary CNS-lymphomas were treated in our hospital since 1978. One out of three patients with T-derived lymphomas had a neurosurgical tumor removal, all three received X-ray and chemotherapy. Six patients were classified as having a B-cell derived lymphoma; four of these had an operation, three got an X-ray treatment, only two patients received adjuvant chemotherapy. On two patients with unclassified Non-Hodgkin lymphomas an operation was performed, one of them received an adequate postoperative x-raytherapy, none a chemotherapy. Overall prognosis seems to be not too bad: though there were three postoperative deaths (two patients died immediately after operation, one patient three weeks afterwards) - all had B-cell derived lymphomas -, five patients stayed alive for more than one year after operation, three patients are alive now for more than two years. The average survival rate was eleven months; in our patients there was no clear cut correlation of survival time to histological grading - T-lymphomas seem to have a slightly better prognosis. With operation, x-ray therapy and an effective combination adjuvant chemotherapy we conclude even better results might be achieved in future.

T8

NON-HODGKIN LYMPHOMA AND THROMBOCYTOPENIA AND THE DISAPPEARANCE OF LARGE INTRATHORACIC LYMPHOMA MASSES. I. Branehög. Depart. of Oncology University of Göteborg, 413 45 Göteborg, Sweden.

In 49 patients with non-Hodgkin lymphoma presenting with thrombocytopenia (platelet counts < 60 x 10^9/l) the relation of thrombokinetics to quantitative determination of megakaryocytes in bone marrow sections was studied. Concomitant, platelet-associated immunoglobulin was measured. The results were compared to those found in a larg number of patients with other diaseases with altered platelet production (idiopathic thrombocytopenic purpura, myeloproliferative disorders).

In 16 patients with lymphoma the thrombocytopenia was due to increased pooling of platelets in the spleen. In these patients platelet mean life span (MLS) was slightly decreased and the degree of spleenic platelet pooling was proportionate to the size of the spleen.

In 8 patients low platelet levels were due to decrea sed platelet production. There was a significant relation ship between platelet production and megakaryocyte volume showing that platelet production was effective, i.e. the number of platelets produced per megakaryocyte was not impaired by the lymphoma cells. In four patients the thrombocytopenia was due to a combination of these two mechanisms.

In 21 patients the thrombocytopenia was caused by reduced platelet survival (mean MLS 1,2 days as compared to normal 6,9 days). Compensatory to the low platelet counts there was an increased platelet production (mean 3,1 times normal). Significantly elevated levels of platelet-bound IgG were found in this group of patients.

Implications of these findings (indicating antibody mediated platelet destruction) for the disappearance of large intrathoracic lymphoma masses which was seen after extremely low doses of irradiation (diagnostic chest x-ray, irradiation 3-5 Gy) in three cases are discussed.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T9

SERUM LACTIC DEHYDROGENASE IN NON-HODGKIN LYMPHOMAS

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51 patients with Non-Hodgkin Lymphomas (NHL) were evaluated according to their serum Lactic Dehydrogenase (LDH) activity at the time of diagnosis. Mean LDH value in NHL was significantly higher than in normal controls ($p < 0.0005$). Moreover, a statistically significant difference of LDH mean value was found between the Histiocytic and Lymphocytic subgroups ($p < 0.0025$), and the lymphomas with nodular or diffuse histological pattern ($p < 0.0025$), being high LDH levels constantly associated with Hystiocytic and diffuse histology. A highly significant correlation was evident comparing LDH values and presence of systemic symptoms at time of diagnosis ($p < 0.0005$), while the extension of the disease, evaluated by standard criteria for clinical and pathological staging, did not correlate with LDH level ($p < 0.15$). Patients who subsequently achieved a complete remission manifested at diagnosis serum LDH values significantly lower than patients who never entered into remission ($p < 0.001$). A direct correlation of LDH level with survival was then evaluated using the X^2 test for heterogeneity and the Test for Trend in Prognosis; p values for both calculations were statistically significant ($p < 0.005$). LDH level therefore represents a valuable prognostic tool in NHL; the correlation of high LDH values and other histological and clinical parameters is well documented, but further studies on a larger number of cases are needed to evaluate its significance.

T10

HODGKINS DISEASE AMONGST DIFFERENT RACIAL GROUPS - A RETROSPECTIVE STUDY. D.P. Derman, University of the Witwatersrand, Johannesburg, South Africa.

106 black and 209 white patients suffering from Hodgkins disease were seen over a nine year period. The age at diagnosis was significantly younger in black patients wi 28,2% being less than 20 years old compared to 10,7 % amon the whites. Males predominated amongst both the black (71%) and the white (60,5%) groups, and in both there we proportionately greater numbers of females with nodular sclerosing histology than males, whereas mixed cellulari histology was relatively more common amongst male of bot groups. The incidence of the disease was lower amongst blacks. Poor histology predominated in the black group (53,2% mixed cellularity and 19,4% lymphocyte depletion) whereas this histology was seen in the minority of white (34,6% mixed cellularity and 4,9% lymphocyte depletion). Furthermore a greater proportion (82%) of the black patients presented with stage III or IV disease then among the whites (61%). The overall rate of response to thera (91%) overall survival and survival controlled for stage amongst blacks was nevertheless similar to overall rate response to therapy (91%) overall survival and survival controlled for stage amongst whites. Survival of patien with lymphocyte predominant disease (61% at 12 years) wa longer than those seen with nodular sclerosing disease (50% at 12 years) and mixed cellularity (50% at 7,8 year with significant worse survival in patients with lymphocyte depleted disease (50% at 1,2 years). Survivals wer also significantly related to stage varying from 100% at years amongst patients with stage I disease to 50% at ,5 years among patients with stage IVB disease. Black atients with poorer histologies had better survivals th hite patients with similar histology and stage of disea

T11

CLINICAL SIGNIFICANCE OF LYMPHOCYTE NUCLEOLAR TEST (LNT) IN HODGKIN'S DISEASE (HD). Z.Dienstbier, M.Šámal, V.Foltýnová, K.Smetana. Charles University and Czechoslovak Academy of Sciences, Prague, Czechoslovakia.

Recent observations demonstrated an increased percentage of activated circulating lymphocytes in untreated patients with HD. Although the role of such lymphocytes was not clarified, they might reflect a lymphocytic reaction in these patients. For evaluating the clinical significance of these findings, the number of "activated" lymphocytes was investigated by a simple nucleolar test. Fresh dry unfixed smears were stained with buffered toluidine blue and three main nucleolar types in 100 lymphocytes were differentiated in optical microscope. "Active" nucleoli (AN) reflected an active RNA synthesis, ring shaped nucleoli (RN) a reversible decrease and micronucleoli (MN) an inhibition of this process. In 26 untreated patients the mean number of AN (5.8± 0.8 S.E.M.) and MN (24.9±3.7) increased in comparison with controls (2.8±0.1 resp. 11.0±0.4; $p < 0.05$). The number of AN was significantly higher in patients with generalized disease (stage III and IV). In 33 patients after therapy the number of AN was not changed and MN increased (30.4±3.1). In 25 patients in relapse the number of AN and MN continually increased (8.0±1.2 resp. 30.8±3.3). High numbers of RN after therapy are a favourable prognostic sign similarly as in the course of complete remission. Thus, LNT has an unique clinical significance in patients with a complete remission (n=71) when low numbers of RN and increased numbers of AN and MN (5.2±0.4 resp. 23.6±1.4) are often the only laboratory findings providing data on the disease activity.

T12

HEAD AND NECK NON-HODGKIN'S LYMPHOMAS : IMPORTANCE OF A PRECISE EVALUATION OF THE HISTOLOGIC MALIGNANCY FOR THE CHOICE OF THERAPEUTIC REGIMEN

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The diagnosis of NHL of the upper digestive and respiratory tract is usually based on a biopsy which most often consist only of a small piece of histological material. Nevertheless, due to the clo relationship between the cytological type and the long-term prognosis, a very accurate morphological analysis is required before planning treatment.
Three points had been emphasized during a recent study including 60 cases treated at the Curie Institute over the past 6 years :

1 - Classical histologic methods should be effectively completed b more recent ones (including immunological markers), thus leading to an improved characterization of the N.H.L. Whenever it is possible, the biopsy of an adjacent cervical lymph node is strongly recommended.

2 - Most of the patients had an unfavourable histological form. In such cases, it seems that the prognosis might be improved using intensive chemotherapy in addition to local radiotherapy. Relapses were most frequent in cases where such chemotherapy could not be administered (elderly people, tumours for which the degree of malignancy was under estimated due to poor biopsy material).

3 - Many patients experienced an additional gastric localisation, either at the time of the initial work-up, or during the evolution Due to its high incidence, this secondary localisation must be systematically searched for, and could perhaps be prevented by using a therapeutic schedule including maintenance chemotherapy.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T13

PROTEIN SYNTHESIS IN NON-HODGKIN LYMPHOMAS OF LOW AND INTERMEDIATE MALIGNANCY: RELATION TO DIFFERENTIATION AND PROGNOSIS.

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The question of this study was: Does protein synthesis measured in a cell-free system of Non-Hodgkin lymphoma cells correlate to morphologic, immunologic and prognostic features? Following parameters were explored: content of ribosomes, translation activity of endogenous mRNA and poly (U) translation activity. Lymphomas were classified to Kiel nomenclature. In leukemic states blood lymphocytes were analysed for surface Ig, T-cell antigen, receptors for sheep and mouse erythrocytes, complement proteins and Fc. 56 cases of CLL, 11 of immunocytoma, 3 of hairy cell leukemia, 5 of plasmocytoma and 8 of follicular center cell lymphomas were investigated.

Results: All lymphomas have the same content of ribosomes per cell weight. Only in plasmocytomas an increase of ribosome concentration depending on activity of protein synthesis could be observed.
In follicular center cell lymphomas with intermediate malignancy the activity of endogenous protein synthesis was significantly higher than in low grade lymphomas.
In CLL poly (U) translation activity correlates with the prognostic stage of the disease. Mean value of activity in cases with anemia and/or thrombocytopenia (stage 3 and 4 according Rai classification) is six times higher than that of cases with better prognosis ($p<0.01$). This finding is of high specificity. Additionally we measured protein synthesis in five cases which shifted from good to bad prognostic group during the follow-up. In four cases we found a remarkable increase of endogenous and/or of poly (U) translation.
We found no correlation between activity of protein synthesis and the different B-cell surface marker pattern.
Conclusion: Activity of cell-free protein synthesis is a convenient measurable biochemical parameter which correlates with the prognosis of the different entities and in CLL with that of the prognostic subgroups.

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T14

Immune Disorders associated with childhood Hodgkin's Disease

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Immune disorders especially of the autoimmune type are known to be occasionally associated with lymphoproliferative malignancies in adults. In children however this association has been observed only rarely.
We present three children with Hodgkin's disease (HD) in whom the immunopathy either preceded the HD (case II and III) or coincided with the HD (case I).
Case I: A two year old boy presented with Coombs positive hemolytic anemia, bilateral cervical lymphadenopathy and hepatosplenomegaly. Stage III B mixed cellular HD was diagnosed. Remission of the anemia and the HD was achieved with CVPP chemotherapy and mantle irradiation.
Case II: A 13 year old girl developed a chronic nephropathy with microhematuria and proteinuria, Kidney biopsie were consistent with IgA Nephropathy (Berger's disease). Six years later nodular sclerosing HD stage III A occured. With MOPP chemotherapy HD went in remission, the nephropathy however was not influenced.
Case III: A 7 year old boy underwent splenectomy in 1963 for treatment of chronic thrombocytopenia. 1967 autoimmune hemolytic anemia of the warm antibody type developed. 10 years later wide spread HD (stage IV B) occured. With polychemotherapy a complete remission of the HD and the Evans Syndrome was achieved. Radiation was not given to this patient.
Currently case I and II have no evidence of HD 1 and 5 years after the initial diagnosis. The third patient relapsed 7 years after chemotherapy was stopped.

T15

ABVD Therapy for Hodgkin's Disease

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33patients with advanced disease and unfavourable histologic subtypes were treated with ABVD.

20 patients following COPP treatment /primary resistance or relapse/ entered this study.In this group 8 complete, 7 partial remissions were achieved and in 5 cases no effect was seen. 2 patients primarily received ABVD due to special indications and both of them entered remission.

The third group of patients /11 cases/ received previously inadequate chemotherapy in different hospitals. Out of these patients only 4 achieved partial remission and in all the other cases no effect was experienced.

These data clearly indicate that the previous treatment may influence the effectivity of ABVD regimen.

T16

NEW CLINICAL CRITERIA FOR EVIDENCE OF LIVER INVOLVEMENT IN HODGKIN'S DISEASE. P.G. Gobbi, G. Attardo Parrinello, G. Benacorsi, D. Dini, S. Marabelli, S.C.Rizzo. Istituto di Patologia Medica I and Clinica Medica I, University of Pavia, and Clinica Medica I, University of Modena, Italy.

The hepatic involvement in Hodgkin's disease, histologically verified in 133 patients submitted to laparosplenectomy, proved to be related, with statistically high frequency, to each of these clinical findings: result of the liver isotopic scan, liver and/or spleen enlargement, serum albumin ≤ 3.5 g/dl, GOT (or GPT) ≥ 20 mU/ml, serum alkaline phosphatase (SAP) ≥ 209 mU/ml, BSP retention at 45' $\geq 6.4\%$ and erythrocyte sedimentation rate ≥ 50 mm at 1st hr. Furthermore, such clinical findings were jointly evaluated by means of a logistic discriminant analysis, performed on dummy values for both the dependent variable (the liver) and the predictive parameters (the clinical results); generally, 1 was used for positive or altered tests, related to the given limits, and 0 for the negative or normal ones; 0.5 was assigned to dubious outcomes of the liver scan. The simplest function with the best discriminant ability is made by the combined data from liver scan, SAP, spleen enlargement (Splm.), BSP and GOT: +339 L-scan + +260 SAP +146 Splm. +132 BSP +103 GOT. This function correctly identified the involved and uninvolved livers in 18 (function value ≥ 381) out of the 20 histologically positive cases (90% of correct diagnoses) and in 102 (function value < 381) out of the 113 negative ones (90.3% of correct diagnoses).

Since the Ann Arbor clinical criteria for evidence of liver involvement showed, on the same series of patients, correct diagnoses in 68-79% of the cases, it seems that more reliable criteria can be proposed. Liver should be considered involved a) when three or more out of the five parameters indicated above are positive or abnormal (dubious scan included among these) or b) when a markedly abnormal liver scan is associated with alteration of at least one of the other four parameters. Otherwise liver will be uninvolved.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T17

MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN HODGKIN'S DISEASE. **P.G.Gebbi, G. Attardo Parrinello, P. Cavalli, M. Federico, A.U. Di Prisco, V. Silingardi, E. Ascari, C. Mauri. Istituto di Patologia Medica I, University of Pavia, and Clinica Medica I, University of Modena, Italy.**

A multivariate analysis was made on a wide series of patients with Hodgkin's disease in order to provide a joint, comparative, evaluation of the prognostic value of a number of early clinical features that are well-known (or suspected) to be separately related to survival. Between 1971 and 1979, 563 patients were diagnosed; all were staged according to Ann Arbor criteria, including laparosplenectomy in 128 cases. The initial treatment for all stage I A and II A patients and some stage III A patients consisted of high energy radiotherapy. The other patients in stage III A and those with stage B and stage IV disease were admitted to a combined radiotherapy and chemotherapy program or to chemotherapy alone (MOPP).

An exponential distribution of the survival times of the patients was assumed with enough goodness of fit and its parameters were estimated by the method of the maximum likelihood. The clinical characteristics taken into account and their considered values were the following: sex (male or female), age (⩽ or > 40 yr.), site of first apparent involvement (all superficial lymph nodes and mediastinal ones or deep abdominal lymph nodes and any extranodal primitive involvement), stage (I and II or III and IV), histology (LP and NS or MC and LD), general symptoms (A or B) and biological signs ("a" or "b" according to the abnormality of less than or greater than two of the following humoral tests respectively: ESR ⩾ 50 mm at 1st hr., total alpha-2-globulinaemia ⩾ 1 g/dl, fibrinogenaemia ⩾ 450 mg/dl, plasma iron ⩽ 30 ug/dl, plasma copper ⩾ 200 ug/dl and peripheral lymphopenia ⩽ $1.5 \times 10^9/l$).

The estimate of the log likelihood function of the seven parameters, taken one by one and by variable groups, shows that the absolutely best predictors of survival are: stage, age and histology. General symptoms, sex , site of first involvement and biological signs appear less important for prognosis.

T18

INDUCTION OF PROLIFERATION AND DIFFERENTIATION IN VITRO OF HUMAN B LYMPHOMA CELLS

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Monoclonal human B lymphoma cells could be triggered in vitro to D synthesis and increased immunoglobulin synthesis with anti-immunoglobulin antibodies ($F(ab')_2$ fragments). The specificity of the r sponses corresponded to surface immunoglobulin present on tumour cells. Both anti-heavy chains as well as anti-light chains were found to mediate this effect. However, with regard to anti-heavy chains the pattern of responses showed considerable individual var ation even in lymphomas containing both surface IgM and IgD. The sponses were usually dependent on the presence of the tumour promo TPA (12-O-Tetradecanoyl phorbol-13-acetate). These observations should provide new opportunities to relate human B-cell lymphomas normal B-cell differentiation pathways.

T19

BURKITT'S LYMPHOMA (BL) : A CLINICAL STUDY OF 12 CASES FROM NORTH EAST ITALY. E. Grigoletto°, U. Tirelli°, D. Crivellari°, E. Galligioni°, A. Veronesi°, M.G. Trovò°, M.D. Magri°, S. Frustaci°, S. Tumolo°, and A. Carbone +. °Division of Radiotherapy & Medical Oncology, Ospedale Civile of Pordenone. +Department of Pathology, Istituto Scientifico per lo Studio e la Cura dei Tumori, Istituto di Oncologia dell'Università, Genova, Italy.

From January 1975 to December 1980, 12 patients (pts) with histological diagnosis of BL (retrospectively made in 5 pts) according to WHO criteria, were consecutively treated at our institution. Ten pts were males, 2 females, the median age was 31 yrs (range 9-57). All pts were born and lived within a radius of 100 miles from Pordenone, a town of North East Italy, an area of about 500,000 inhabitants. Eight pts lived in rural villages (3 in the same), 4 in 2 different towns, 2 pts were distant relatives. Presenting sites were lymphoid: gastro-intestinal tract was involved in 7 pts (ileocecal region in 4 pts) and lymphnodes in 5 pts. EBV was positive in 1 out of 9 pts examined. Bone marrow (BM) examination was performed in 10 pts, lymphangiogram in 8 pts, CSF examination in 3 pts, peritoneoscopy in 2 pts and LDH in 11 pts. According to Ziegler classification (Cancer, 1972), 2 pts were stage I, 8 pts stage III, 2 pts stage IV. Leukemic status occurred in 4 pts, in 2 pts at presentation. CNS involvement was present in 5 pts, all during the course of the disease. Two pts had both BM and CNS involvement. Treatment was surgery + chemotherapy (CT) in 6 pts, only CT in 6 pts. CNS prophylaxis with 2400 r was performed in 3 pts. CT regimens employed were CVP in 5 pts, CHOP in 3 pts and ABVD in 4 pts. Three CR and 5 PR were obtained, of short duration (median 2 mos). First relapse occurred in CNS in 3 out of 10 pts, 1 pt treated with CNS prophylaxis. Overall median survival (MS) was 8 mos (range 2-25): 7 mos in pts< 30 yrs and 11 mos in pts > 30 yrs; 6.5 mos in pts treated with surgery + CT and 10 mos in pts with stage III and IV. Only 1 pt is alive at 11 mos. BL is a relatively frequent disease in Pordenone area with a high median age and a tendency to cluster. Moreover, presenting sites were lymphoid, EBV was often negative, LDH correlated with tumor burden and treatment employed was usually ineffective.

T20

SERUM β_2-MICROGLOBULIN IN MALIGNANT LYMPHOMA. H Hagberg, A Killander and B Simonsson. Department of Internal Medicine, University Hospital, Uppsala, Sweden.

Serum β_2-microglobulin (S-β_2m) was measured in 133 consec tive patients with malignant lymphoma, all with a normal serum creatinine. In 104 cases, the diagnosis was non-Hodgkin's lymphoma (NHL), and in 29 Hodgkin's disease (HD). In NHL, S-β_2m was raised in 19 % (7/36) of stage I - II disease and in 63 % (43/68) of stage III - IV disease. The corresponding frequencies for HD were 8 % (2/19) stage I - II and 80 % (8/10) in stage III - IV. A high pretreatment level suggested generalized disease Serial determinations of S-β_2m were done during treatment in 24 patients. In patients with increased pretreatment levels S-β_2m correlated well with the clinical course of the lymphoma. In practical clinical use, however, S-β_2m seems to be of limited value fo evaluation of changes in tumor mass.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T21

HODGKIN'S DISEASE: EXPERIENCES OF A BRITISH PROVINCIAL LYMPHOMA GROUP (1970-79)

DR. B. W. HANCOCK, SHEFFIELD, U.K.

The clinical, pathological and treatment statistics of 403 histologically verified cases show differences from other reported large series e.g. a higher proportion of older patients, more mixed cellularity and less nodular sclerosis histology types.

The overall survival for the group at 5 years is 59% and at 10 years is 50% compared with 39 and 25% respectively for 1960-69; for the periods 1970-74 and 1975-1979 the 5 years survivals are 54 and 67% respectively. The following factors are of significant importance in survival assessment: sex ($p = 0.05$), age ($p<0.0001$) site of presentation ($p<0.005$), stage ($p<0.0001$), symptom status ($p<0.002$), histology ($p<0.0001$), ESR ($p<0.05$), treatment received ($p<0.0001$) and response to treatment ($p<0.0001$). 105 patients were selected, on agreed criteria, for laparotomy and splenectomy; the overall 5 year survival of this group is 69%. Septicaemia was seen, in the absence of Hodgkin's disease in 5 splenectomized patients (4 died).

T22

PROGNOSTIC FACTORS AND TREATMENT STRATEGIES IN PRIMARY LOCALIZED GASTRO-INTESTINAL NON-HODGKIN'S LYMPHOMAS.

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While chemotherapy is clearly indicated in the treatment of far advanced extranodal non-Hodgkin's lymphoma (NHL) including gastro-intestinal (GI) involvement, there is some controversy regarding the best treatment for localized disease. We have retrospectively analyzed the course of 54 patients with stage I and II (Ann Arbor) GI-NHL admitted to Roswell Park Memorial Institute in a ten-year period. The primary sites were: stomach 28, small intestine 11, ileocecal 12, large intestine 3. Of 50 evaluable patients 22 were treated by surgery, 16 by surgery followed by radiotherapy (RT) and 12 by RT alone. Disease-free and overall survival was significantly shorter in stage II disease with lymph node involvement beyond the regional nodes compared to stage II with only regional node involvement suggesting a substage of this group. Also, chemotherapy seems to be indicated in all stage II patients with more advanced disease. The modality of treatment was found to be another important prognostic factor. While more than 70% of 28 patients who received RT as part of their primary treatment are free of disease at ten years, about 75% of the patients who had surgical treatment only relapsed within four years. Of all patients who relapsed only three are still alive following secondary treatment. The results of our study suggest that RT should be included in the primary treatment of localized GI-NHL.

T23

NON-HODGKIN'S MALIGNANT LYMPHOMAS CLINICAL STAGES I AND II. Results of radical irradiation with or without chemotherapy + BCG-therapy in 171 patients.

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Fondation BERGONIE, 33076 Bordeaux Cedex (France)

One hundred and seventy one patients with histologically confirmed non-hodgkin's malignant lymphomas at clinical stages I and II were seen before being treated in 15 years ; 157 received a radical irradiation and are available for the analysis. Forty one were treated only by irradiation (R), 29 by R + a short course of chemotherapy (C), 52 by a C-R-C sandwich regimen and 33 by C-R-C + BCG-therapy (I). Disease-free survival improved regularly from lightly treated patients to more heavily treated ones, but this improvement is significant only for high-grade malignancy as defined in Kiel's classification. BCG-therapy eliminated late relapses for all kinds of diseases. Therefore, it seems possible to improve the results for the patients with an association of radiotherapy, chemotherapy and BCG-therapy without submitting them to surgical staging.

T24

SIX DRUG REGIMEN IN THE THERAPY OF NON-HODGKIN'S LYMPHOMA.

I. Horak, Institute of Clinical Oncology, 88102 Bratislava, Czechoslovakia.

Twenty seven adults with advanced malignant lymphoma (the majority in stage IV) were treated with a combination of cyclophosphamide, adriamycin, vincristin, bleomycin, prednisone and methotrexate. The complete remission (CR) rate was 70 %. The overall response rate (complete and partial remission) was 92,6 %. The CR rate in patients with diffuse histiocytic lymphoma (DHL) and diffuse lympho-histiocytic lymphoma (DML) was 87,5%. Only two of the 14 patients with DHL and DML in CR have relapsed and median duration of CR was 31+ months. In patients with diffuse poorly differentiated lymphocytic lymphoma (DPDL) and lymphoblastic lymphoma the CR rate was 45,4 %. Major complications during chemotherapy with six drug regimen were myelosuppression, stomatitis and alopecia. This study indicates that this combination chemotherapy is effective in increasing the CR rate and duration of CR in patients with DHL and DML. Patients with DPDL and lymphoblastic lymphoma did not profit with this regimen.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T25

IS STAGING LAPAROTOMY OF THERAPEUTIC VALUE IN PATIENTS WITH SUPRA-DIAPHRAGMATIC HODGKIN'S DISEASE, CLINICAL STAGE IA-IIA? H.Høst, A. Foss Abrahamsen & O.G. Jørgensen. The Norwegian Radium Hospital Montebello, Oslo 3, Norway.

The impact of staging laparotomy on the prognosis of patients with clinical stage (CS) IA and IIA has been evaluated by comparing the treatment results before and after the introduction of this procedure. Sixty-three patients were treated only on basis of CS in the period Jan. 1, 1968 to May 31, 1970, while 54 out of 60 patients were treated according to pathological stage (PS) in the period June 1, 1970 to the end of December 1972:

The treatment principles were as follows: Patients with stage IA to IIIA disease received radiotherapy alone with the extended field technique, while patients with stage IVA disease had combinations chemotherapy.

Results: 1) The relapses occurred earlier in the patients treated after the introduction of staging laparotomy; that means patients treated according to PS. 2) The survival was not affected by staging laparotomy in patients with Hodgkin's disease CS IA and IIA.

T26

SUBTYPES OF T-CLL.

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13 cases of chronic lymphatic leukemia of T-lymphocyte subtype (T-CLL) were investigated. Methods: light- and electron microscopic morphology; cytochemistry (PAS, acid phosphatase, acid esterase); membrane marker (E- and Emouse-, EA-and EAC-rosettes; T-antigen by fluorescence microscopy, by complement fixation and cytotoxicity tests; SmIg). In special cases in-vitro tests to evaluate cell function were performed (stimulation by several mitogens; NK- and suppressor activit /Dr.E.P.Rieber/). Patients suffering from Sézarys syndrome were not included.
Especially on the grounds of morphological and cytochemical aspects, 5 subtypes of T-CLL could be distinguished: 1. small lymphatic cells, inconspicuous cytoplasm; 2. as (1), but clefted nuclei in at least 2o% of cells; 3. lymphatic cells with abundant cytoplasm and azurophilic granules of peculiar fine structure; 4. as (3), but parallel tubular arrays in at least 1o% of cells; 5. prolymphocytic variant of CLL. Subtypes were analysed according to clinical findings and to the course of the disease. Similarities of different types of CLL cells with physiological subfractions of T-lymphocytes are discussed.

T27

SUPEROXIDE DISMUTASE DEFICIENCY IN HUMAN MALIGNANT LYMPHOMA

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Using polyacrylamid gel electrophoresis and isoelectric focusing mitochondrial and cytoplasmatic superoxide dismutase activity have been determined in lymphocytes from normal subjects and from patients suffering from various malignant lymphoma. In lymphocytes of healthy donors copper/zinc superoxide dismutase as well as manganese superoxide dismutase could be identified whereas the manganesecontaining superoxide dismutase is diminished or lacking in lymphoma lymphocytes.
A protein fraction from human lymphoma spleen has been isolated and characterized by gel chromatographic, isoelectric focusing and atomic absorption spectrosoopy. Using the indirect assay of the nitroblue tetrazolium reduction test the protein fraction was superoxide dismutase active. The specific activity (rate constant) of the lymphoma spleen enzyme was determined by pulse radiolysis and compared with an analogous enzyme isolated from bovine spleen.

T28

THERAPEUTIC OBSERVATIONS ON LONG TERM SURVIVORS IN MALIGNANT LYMPHOMA

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Prolongation of disease-free remission duration obtained by induction therapy in advanced malignant lymphoma patients is essential with regard to their curability. The study was conducted mainly on remission duration and survival for long term survivors among 41 cases of malignant lymphoma : 13 of Hodgkin's disease and 28 of non-Hodgkin's lymphoma, treated with initial therapy in our clinic from 1972 to 1977. Therapeutic regimens were BVCP or B-COP therapy (bleomycin, vincristine, cyclophosphamide and prednisolone) as initial induction therapy and AVIP therapy (adriamycin, vincristine, ifosfamide and prednisolone) for refractory or relapsed cases. Complete remission was obtained 77% in Hodgkin disease and 57% in non-Hodgkin's lymphoma. Prolongati of survival was observed in complate responder group compared with partial responder and non-responder group. The long term disease-free survivors over four years we 3 cases in Hodgkin's disease and 4 cases in non-Hodgkin disease. There is a parallel relationship between survival and initial remission duration, as the long term survivors continue complete remission from initial induction therapy as a result of relatively long maintenance therapy. Histological subtypes of the lon term survivors over 4 years were 2 cases of mixed cellularity and 1 case of nodular sclerosis in Hodgkin' disease, and 3 cases of diffuse histiocytic and 1 case diffuse lymphocytic poorly differentiated type in non-Hodgkin's lymphoma.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T29

IRON, COPPER, AND ZINC LIVER TISSUE LEVELS IN PATIENTS WITH MALIGNANT LYMPHOMAS.

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Levels of iron, copper and zinc in liver tissue and of copper in serum were studied in 53 cases of untreated malignant lymphoma (14 cases of Hodgkin's disease and 17 of lymphocytic and 22 of histiocytic lymphoma). The values were compared with the levels of these metals in the liver tissue of 23 healthy persons. Liver tissue was obtained by means of percutaneous biopsy examination with a Menghini needle. Part of the samples was used for histologic examination, and the remainder for metal level determination. Atomic absorption spectrophotometry was used in determining metal levels in dry liver tissue and in sera. In all malignant lymphoma patients, a significantly higher serum copper level was established ($P<0.05$). A lower iron level in liver tissue was only found in those patients with lymphocytic lymphomas without a lymphomatous process in the liver ($P<0.05$), while lymphomatous hepatic infiltration was associated with a higher iron level and lower copper level ($P<0.05$) Significant changes in liver zinc levels were only proved by higher levels of this metal in patients with histiocytic lymphoma and lymphomatous hepatic infiltration ($P<0.05$). The only redistribution of copper between the serum and liver tissue was found in those patients with lymphocytic lymphomas and lymphomatous hepatic infiltration.

T30

EARLY RESPONSE TO CHEMOTHERAPY AS A PROGNOSTIC FACTOR IN HODGKIN'S DISEASE. M. Kuentz, B. Brun and F. Reyes.C.H.U. Henri Mondor, 94010 Creteil (France)

164 patients with Hodgkin's disease were staged between 1973 and 1979 ; the procedure included a laparotomy for patients staged before 1976 (79 patients). Treatment of localized disease (stages I, II, III_1) consisted of 3 MOPP cycles followed by a subtotal nodal irradiation, including the splenic area in non splectomized patients. Treatment of extended disease (stages III_2 and IV) consisted of 6 MOPP cycles followed by low dosage radiotherapy of initial bulky disease. An evaluation of the response to 3 initial MOPP cycles was performed in all patients by means of extensive clinical staging. 5-year actuarial survival was 88 % in stage I, 80 % in II, 100 % in III_1, 45 % in III_2 and IV. 5-year survival of stage II patients was better in patients who reached complete remission after 3 MOPP than in those who did not, 97 % versus 63 % ($P<0,05$). Similary 5-year survival of stage III_2 and IV was 75 % versus 25 % ($P<0,01$). Therefore the response to initial chemotherapy provides a prognostic index that may serve to delineate a "high risk" group of patients. The latter would deserve agressive therapy while the others would benefit of less agressive combined regimen that should minimize long-term induced complications.

T31

PERICARDIAL EFFUSIONS AS A COMPLICATION OF RADIOTHERAPY FOR HODGKIN'S DISEASE DOSE DISTRIBUTION - IMMUNOPATHOLOGIC FINDINGS.

B. Kurtz, B. Maisch, A.C. Voss, Medizinisches Strahleninstitut Tübingen, 7400 Tübingen, Germany.

From 1969 to 1979 pericardial effusions as a complication of radiotherapy for Hodgkin's disease occurred in 16 patients of the Medizinisches Strahleninstitut Tübingen. The doses at the pericardium ranged from 53 Gy in 4 weeks to 129 Gy during ten years in a case of mediastinal recurrences. Single ventral radiation fields by telecobalt gamma rays proved unfavorable resulting in overdosage of ventral parts of the pericardium. After introduction of mantle field treatment in this institution, only two radiogenic pericardial effusions occurred, which were reversible and of little clinical importance.
In seven of these patients antisarcolemmal and antimyolemmal antibodies could be found. The antimyolemmal antibodies induced a cytolysis of vital adult rat cardiocytes in the presence of complement. In 13 of 14 of a matched group of patients without pericardial effusion after radiotherapy and in 9 patients with pericardial involvement of Hodgkin's disease no autoantibodies were found. These autoantibodies could not only be of diagnostic value but may play a role in the pathogenesis of radiogenic pericardial effusion.

T32

IRRADIATION TREATMENT OF MALIGNANT LYMPHOMAS. SIDE EFFECTS OF MANTLE TECHNIQUE.

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50 patients who have been treated with mantle technique for supradiaphragmatic Hodgkin's disease and non-Hodgkin's lymphomas were studied for side effects at least two years after completion of radiotherapy. We have observed three symptomatic pulmonary reactions, in four patients a positive Lhermittee's sign and twice a reversible pericardial effusion - one of clinical significance. There were no signs of thyroid dysfunction up to now. One patient relapsed 11 months after treatment. Because of these results our actual managing of patients seems satisfactory.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T33

INTERCEREBRAL LYMPHOMA: CLINICAL AND THERAPEUTIC EXPERIENCE WITH 18 CASES

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18 Patients with histologically verified intracerebral lymphoma were followed up. 4 of the patients had intracerebral manifestations of an extracranial malignant lymphoma. 12 patients recieved radiotherapy. In 6 cases this treatment modality could not be applied: in 3 cases because of a poor clinical condition, in 2 cases due to fatal postoperative pulmonary embolism, 1 patient refused radiotherapy. Out of the 18 patients, 12 died after a mean survival of 4.4 months (ranging 2 weeks to 12 months). 6 of the patients who died recieved no irradiation and showed no clinical improvement. The other 6 patients were irradiated with doses aiming at cure in 2 cases accompanied by a partial resection of the tumor. Both showed an improvement of clinical symptoms for 3 respectively 6 months. One of them died after 6 months due to progressive tumor growth the other due to an extensive tumor-like radionecrosis. 6 patients are still alive with a mean follow up of 17.5 months, ranging from 4 to 42 months. All of them had curative irradiation doses, in 2 cases accompanied by a total tumor resection. 5 patients show excellent clinical results, 1 patient remained in a state of slight desorientation.

The combination of surgical resection and radiotherapy seems to yield the best results. The size of the lesion also seems to be of prognostic significance.

T34

MALIGNANT HISTIOCYTIC NEOPLASMS ("LYMPHOMAS"): COMMENT ON HISTOCHEMICAL AND IMMUNOLOGICAL FINDINGS. H. Lang, K. Bürki, J. Müller and M.W. Hess. Inst. of Pathology, 3010 Bern, Switzerland

Malignant neoplasias or proliferative disorders of suspected histiocytic nature have in general been termed "malignant histiocytosis", "histiocytosis X" or "histiocytoma". These labels encompass among others entities such as Letterer-Siwe disease and Hand-Schüller-Christian disease (WHO 1976). In contrast, the existence of a "malignant histiocytic lymphoma" was - until a few years ago at least - not widely accepted. More recently, with the extended use of histochemical and immunological techniques it has been proposed that a number of neoplasms previously termed "reticulosarcoma" might be in fact histiocytic in nature. We have therefore looked out for simple "markers" that would enable the pathologist to recognize such malignant histiocytic lymphomas. Our preliminary results might encourage other investigators to collect similar data to extend our findings.

We report 16 cases of malignant neoplastic disorders which could be called histiocytic. Their common characteristics were as follows: medium to large cell size, considerable cytoplasm:nucleus ratio, variable nuclear shape (indented and/or elongated), slight to moderate cytoplasmic basophilia, a denser reticulin fiber network than found in most malignant lymphocytic lymphomas, lack of viable cells in suspensions prepared for surface immunoglobulin-studies, weakly to strongly positive (diffuse) cytoplasmic reaction for alpha-naphthyl-acetate-esterase (ACE) activity in cryostat sections of fixed tissue as well as of lysosomal enzyme activities such as beta-glucuronidase and N-acetyl-glucosaminidase, absence of detectable intracytoplasmic immunoglobulins tested on cell smears and/or conventional paraffin sections. Presence of intracytoplasmic lysozyme antigen (muramidase) was noted in a small number of cases (2/16) using conventional paraffin sections for direct immunofluorescence.

T35

CELLULAR IMMUNODEFICIENCY IN HODGKIN'S DISEASE: CIRCULATING LOW MOLECULAR-WEIGHT SERUM FACTORS INHIBITING PROTEIN SYNTHESIS.

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The formation of the E-receptor protein, a differentiation marker of peripheral human T-lymphocytes is inhibited on lymphocytes of patients with Hodgkin's disease. This glykoprotein (Owen&Fanger) (Gürtler) shows a high membrane-turnover in the subpopulations of T-suppressor-cells and of cytotoxic T-cells. Inhibition of protein synthesis, of the nucleo-cytoplasmic mRNA-transfer and of mRNA-synthesis (by alpha-amanitin) depletes the cells from the E-receptor protein within 15 and 9o minutes and within 8 and 1o hours.

The lymphocytes of 2o patients with Hodgkin's disease have a low E-rosette forming capacity (32±8% compared to 61-8% of the control group). The lymphocytes of 15 patients are inducible by thymic peptides to form E-rosettes. The sera and serum fractions of 12 patients induce in normal peripheral human lymphocytes an inhibition of E-rosette formation within 6o minutes. Blockage by serum fractions, whose molecular size is above 5.000 dalton, is not induced by PGE_2 which has an essentially lower molecular weight. The inhibition proceeds with a kinetism which is comparable to the inhibition of the protein synthesis and the induction of cAMP-dependent protein kinases. Preparation and caracterization of these inhibiting factors by HPCL is described.

T36

THE IN VIVO EFFECT OF A THYMIC FACTOR (THYMOSTIMULIN) ON IMMUNOLOGI PARAMETERS OF PATIENTS WITH UNTREATED HODGKIN'S DISEASE. M.F. Martelli, A.Velardi, P. Rambotti, C. Cernetti, A.Bertotto, F. Spinozzi, A.M. Bracaglia, B. Falini, and S. Davis; Istituto di Clinica Medica and di Puericultura dell'Universita di Perugia, Ital and Veterans Administration Medical Center, East Orange, New Jerse College of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, New Jersey.

The in vivo effect of a calf thymus extract (thymostimulin, TS) on the E-rosetting capacity, PHA blastogenic response, serum migration inhibitory activity (LIF) and skin reactivity to recall antigens wa evaluated in 19 untreated patients with Hodgkin's disease. In patients the mean percentage of peripheral blood lymphocytes formi E-rosettes increased from 47% to 55.7% ($p \leq 0.001$; normal: 50.9). The mean PHA stimulation index rose with all 3 concentrations teste but did not reach normal values. Serum LIF was positive in only one patient prior to treatment with a total patient mean LIF of 1.03. Nine patients developed a positive LIF following treatment with a mean LIF for all patients of 0.75 ($p \leq 0.005$). Skin tests were positive in 10 patients (52.6%) prior to therapy and 18 patie following therapy (94.7%; $p \leq 0.05$). Thymostimulin, in vivo, appears to return immunologic competency to a population of patient with untreated Hodgkin's disease.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T37

VINCRISTINE-PEPTICHEMIO THERAPY IN MULTIPLE MYELOMA - Merlini, G.P., Riccardi, A., Riccardi, P.G., Balduzzi, F., Epis, R., Ascari, E. - Istituto di Patologia Medica I dell'Università di Pavia - Policlinico S. Matteo - 27100 Pavia (Italy).

Nineteen patients with multiple myeloma were treated with 1-4 courses of Vincristine (0.025 mg/kg e.v. on day 1) associated with Peptichemio (0.8 mg/kg/48 hrs for 3-5 administrations from day 1). Low prednisone and high androgen therapy was associated. Ten patients were untreated and 9 were relapsing during Melphalan or Cyclophosphamide therapy. Twenty-nine courses of therapy were performed: 19 in relapsing and 10 in untreated patients. Therapeutic response was obtained in 23 out of 29 courses applied. Criteria for response were: reduction of M-component concentration more than 50% (complete response) or 25% (partial response), normalization of abnormal parameters (calcemia, BUN) and non progression of the skeletal lesions. The percentage of response was the same in untreated (8 responses: 80%) and in relapsing patients (15 responses: 79%). In the former the complete responses were more frequent (5 complete responses) than in the latter (3). The hematologic toxicity was moderate. Leucopenia less than 2500 WBC/mmc was observed in 9 out of 29 treatment courses: most of these patients were already leucopenic (WBC less than 4.000/mmc) before therapy. Severe thrombocytopenia (platelets less than 50.000/mmmc) occurred in 8 courses, but only in patients with platelets less than 75.000/mmc before treatment. No hemorrhagic accidents occurred. Phlebothrombosis of the injection vein was an almost constant side effect.

Research supported by C.N.R. (Consiglio Nazionale delle Ricerche - Roma - Progetto Finalizzato Controllo della Crescita Neoplastica - Grant no. 80.01947.96).

T38

CRITICAL REEVALUATION OF STAGING LAPAROTOMY (SL) IN HODGKIN'S DISEASE (HD). U. Metzger, H.P. Honegger, K. Urfer, F. Largiadèr. University Hospital, CH-8091 Zurich, Switzerland.

From 1971 to 1980, 110 consecutive untreated patients aged 16 to 64 yrs (66 males, 34,4 ± 13,5 yrs, 44 females, 32,4 ± 12,2 yrs) underwent SL in HD.
SL changed clinical stage (CS) into pathologic stage (PS) as follows:

CS	No.	PS:	I	II	III	IV
I	16		9	2	5	
II	72			40	27	5
III	22			3	13	6

SL modified CS in 7/16 (44%) with CS I, in 32/72 (44%) with CS II and in 9/22 (41%) with CS III. 3 of 22 CS III were found to be PS II.
37 patients (34%) had spleen involvement. Clinically suspected spleen involvement was always confirmed by SL, but in more than 2/3 only the SL revealed the evidence of HD in the spleen. Spleen involvement did not correlate with age, sex, initial sites of disease or B symptoms. There was no hospital mortality and a low operative morbidity (4 atelectasis and pneumonia, 3 infection (2 subphrenic, 1 wound) and 2 small bowel obstruction) following SL.
For CS I and II, SL continues to be a valuable tool in the staging and treatment of HD. Ongoing studies for substages III_1 and III_2, carefully staged by SL, may define another important subset of patients needing SL.
The usefulness of SL seems very questionable in CS III when B symptoms are present, because in fact, all these patients need a combined systemic treatment.
In the future, SL will probably gain importance in the post-treatment period to evaluate residual disease and to select patients who might benefit from further therapy.

T39

"HODGKIN'S DISEASE IN CHILDREN IN KUWAIT" - by M. Samir Motawy, F.R.C.R., Radiotherapy and Oncology Centre, Al-Sabah Hospital, Kuwait.

Sixty cases of Hodgkin's Disease in children 15 years and below were retrospectively analysed with a minimum follow up of two years. Male preponderance was marked in cases below 10 years of age while in older cases there was slight female preponderance. Mixed cellularity type was the commonest. Initial treatment varied according to the stage and was either by radiation, chemotherapy, or both. The actuarial 5 year survival was 58% for all cases. The relapse free survival was 28%. No cases relapsed after 5 years, and all cases of nodular sclerosis type relapsed. No difference in survival or relapse free survival was found between different sexes or between different histological types apart from lymphocytic depletion type. None of Stage I cases died of his disease, but no difference in survival was found in other stages. Older children and cases with mediastinal involvement did better than those below 10 years of age or those with mediastinal involvement. In conclusion, though many cases relapsed, control of the disease was possible. In children, females do not do better than males, and nodular sclerosis type carried a high risk of relapse and mediastinal involvement was a poor prognostic index.

T40

COMBINED MODALITY THERAPY IN NON-HODGKIN'S LYMPHOMA (NHL) WITH FAVORABLE HISTOLOGY. S. Öhl, M. Bamberg and U. Schulz, University of Essen Tumor Center, D-4300 Essen 1, F.R. Germany.

From 1977 to 1980, 46 patients with NHL were studied in a randomized trial to determine the effect of total body irradiation (TBI) in addition to drug regimen in stages III-IV. Induction therapy for group (A) was vincristine, prednisone and cyclophosphamide (CVP) followed by TBI, 150 rads in 10 fractions over 5 weeks. The other group (B) was treated with TBI followed by CVP, to compare the treatment related toxicity and the efficacy to increase response rate. 26 patients were treated with TBI plus CVP and 20 patients received CVP plus TBI. The latter part of each modality was delayed 6 weeks to allow recovery from the myelosuppressive effects of the foregoing one. Complete remission was achieved in 14/26 group A patients and 8/20 treated according the B schedule. There were no acute symptoms during either course or could mortality associated with the treatment be observed. None of the patients have developed acute myeloproliferative syndromes until now, as it has been recognized with increasing frequency by others. Both treatment programs have thus been highly effective in achieving initially excellent responses and prolonged disease-free survival, however, most of these patients ultimately relapsed and required additional therapy. The median time to relapse was for both groups ~ 13 months. The short duration of follow-up allow a reasonable chance of failure to detect a true difference in treatment efficacy although the overall results of this trial represents no significant improvement over our own institutional historical controls.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T41

CHEMOTERAPY OF EXTRAMEDULLARY PLASMACYTOMA (EMP).

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The clinical features and treatment results of 22 consecutive untreated patients (pts) with EMP are presented.
17 pts were stage I, 4 stage II and 1 stage III (Wiltshaw E., Cancer Chemoter. Pharmacol. 1978, 1:167). Of the 17 pts in stage I, 10 had what we call a Locally Advanced Disease (LAD): 3 for multiple primitives and 7 for underlying bone involvement.
10 pts received only Local Treatment (consisting in Surgery or Radiotherapy or both): this will be quoted below as «treatment group 1». 12 other non disseminated pts received Chemotherapy (in 7 associated with «local treatment»); these will be quoted as «treatment group 2». In treatment group 1, 8 pts were in stage I (5 LAD) and 2 in stage II; in treatment group 2, 9 pts were in stage I (5 LAD), 2 pts in stage II and 1 in stage III.
7/10 (70%) pts of treatment group 1 recurred, while only 4/12 (33%) in treatment group 2 recurred. 5/5 LAD pts treated according to group 1 recurred, while only 2/5 LAD in group 2 recurred. It appears appropriate to distinguish in the previously quoted staging system a subgroup of LAD pts within stage I, as requiring a different therapeutic approach.
Of 17 pts treated with chemotherapy for the primitive or for relapse 12 are already evaluable for response. 6/12 (50%) responded to single alkilator agent (median remission duration 10 months, range 4-26); 5/6 responders were previously untreated with chemotherapy.
With multiple chemotherapy (M2 protocol: Lee B.J. et al., Cancer 1974, 33: 533) we observed 8/9 (89%) responses (median remission duration 23 months, range 5-30); 7/8 responders were pretreated with chemotherapy.
These data suggest that multi-drug treatment be better than single agent and that multi-drug chemotherapy be routinely administered after local treatment in all «locally advanced» EMP.

T42

CELL MARKERS (TDT, MONOCLONAL ANTIBODIES, FUNCTIONAL PROPERTIES) IN CASE OF HIGH-MALIGNANT LYMPHOMA WITH MEDIASTINAL TUMOR TERMINATING ACUTE MONOBLASTIC LEUKEMIA.

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The 37-year-old male patient initially presented with a large mediastinal mass and bilateral cervical and axillary lymphadenopathy besides complete sparing of peripheral blood (PB) and bone marrow (BM) of abnormal cells. Histochemical examination of a lymph node section revealed infiltration with medium-sized cells strongly positive for nonspecific esterase pointing towards the diagnosis of acute monocytic leukemia.
Shortly afterwards, the white blood cell count rose to 140 000/µl showing greater than 90% small and medium-sized round cells in the which were negative for common cytochemical stains in contrast to t findings in the lymph node. Terminal deoxynucleotidyl transferase (TdT) activity was slightly elevated in mononuclear cells from the but not in those from the PB. Evidence against the monocytic charac of the blast cells also arose from the lack of adherence to glass s faces, the lack of release of colony stimulating activity (CSA) and from the lack of phagocytosis. A lymphoid nature of the cells was f voured by the lack of viability of bone marrow cells cultured in soft agar.
After a short drug-induced partial remission (vincristine, predniso adriblastine), extensive skin infiltration with large mononuclear cells with lobed nuclei developed. At hematological relapse the unfractionated mononuclear cell population in PB and BM expressed wea TdT activity and massive CSA production. Three major cell populatio could be distinguished on the basis of cytochemical, immunological and functional markers:
20% of the cells were small normal lymphocytes, acid phosphatase po tive and reactive with the monoclonal antibody OKT 8 which characte rized them as T-suppressor cells;
30% of the cells were large monoblasts, strongly positive for nonsp fic esterase, positive with the monoclonal antibody D 5 (specific f monoblasts) and functionally expressed adherence to glass surfaces, phagocytosis and intracytoplasmic lysozyme;
40% of the cells were medium-sized round cells which failed to exhi cytochemical or immunological markers. However, the phorbol diester TPA (12-0-tetradecanoyl-phorbol-13-acetate) induced the transformation of the latter cell type to adherent monocytoid cells suggestin that they were immature precursors of monocytes.
In the terminal phase of the disease, the hematological picture was dominated by medium-sized round cells which lacked adherent and pha cytic properties but showed reaction with the monoclonal antibody D and could be transformed to adherent cells by TPA.
In this case, the appearance of tumor cells of the monocytoid cell neage frozen at various stages of differentiation was observed.

T43

TREATMENT OF REFRACTORY LYMPHOMAS WITH TWO NEW,NON-CROSS RESISTANT, CHEMOTHERAPEUTIC COMBINATIONS.PRELIMINARY RESULTS.

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Two treatment schedules of combination chemotherapy,employing cis-Platinum,Hexamethylmelamine and Epipodophylotoxin (CHE),and cis-Platinum and Vindesine (CV) are tested in patients with advanced stage Lymphomas and refractory to any conventional treatment. Patients with Hodgkin's disease (HD) and non-Hodgkin's Lymphomas (NHL) were randomized separately to either arm of the study,and results were evaluated separately.

So far,four patients with HD and fourteen patients with NHL entered the study.A/patients but one had stage IV disease.One patient with stage III HD had previously relapsed in irradiated area and became refractory to both MOPP and ABVD.All patients had unfavorable histology (4 HD-mixed cellularity,6 NHL-histiocytic diffuse,4 NHL-mixed histiocytic-lymphocytic,4 NHL-lymphocytic,poorly differentiated,diffuse).Three patients with HD received CHE and one CV,while 8 patients with NHL received CHE and 6 received CV.Three of the 4 patients with HD achieved Partial Remission (PR) and survival ranged from 3 to 9+months.Of the 8 patients with NHL on CHE 6 achieved PR and 1 Complete Remission(CR).Of the 6 patients with NHL on CV one achieved CR and 3 PR.Five of the 8 patients on CHE are alive with a survival range from 1 to 9 months,while 3 out of the 6 patients on CV are alive with a survival range from 1 to 4 months.Three patients with HD died of infection while on PR at 3,6 and 8 months,and one patient with NHL died of acute myocardial infarction in PR at one month.Five patients with NHL (2 on CHE and 3 on CV) died of progressive disease at 1 and 9,and 1,2 and 4 months respectively.

It is antcipated that patients in earlier phase of their disease will achieve better and longer remissions.

T44

COMBINATION CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISONE AND THE CONTRIBUTION OF ADRIAMYCIN IN THE TREATMENT OF ADULT NON HODGKIN'S LYMPHOMAS. A report of 131 cases.

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Between January 1973 and January 1979, 131 patients with malignant non Hodgkin's lymphomas (107 lymphocytic lymphomas, 24 histiocytic lymphomas) were treated with cyclophosphamide-vincristine-prednisone (CVP) either alone or combined with adriamycin (CVP-A)

Stage I and II lymphocytic lymphomas were all treated by CVP combined with radiotherapy. The survival curve for this group of patients plateaued at 89% from the 12th to the 60th month which was the end-point of the study.

For stage III and IV nodular lymphocytic lymphoma actuarial survival was 69% at 5 years in the CVP-treated group as compared to 54% at 3 years in the group treated with CVP-A.

For stage III and IV diffuse lymphocytic lymphoma the complete response rate and median survival were respectively 25% and 24 months in patients treated with CVP, as compared to 67% ($p < 0.01$) and 26 months in the group treated with CVP-A.

For histiocytic lymphomas, the complete response rate was 50% in the CVP-treated group as compared to 83% in the group treated with CVP-A. Most remarkable was the fact that while in the CVP treated group median survival was only 17 months, the small group of patients treated with CVP-A exhibited considerably improved survival with a horizontal survival curve at 90% at 36 months (12 patients).

These results show that the CVP protocol remains an excellent treatment for nodular lymphocytic lymphomas. The addition of adriamycin (CVP-A) as well as its inclusion in other drugs combination, has raised hopes for remissions of long duration and even for cures in patients with histiocytic lymphomas. Finally, in diffuse lymphocytic lymphomas, efforts will have to be pursued to improve the prognosis which remains poor despite the increased complete response rate achieved by the addition of adriamycin.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T45

BURKITT'S FREQUENCY AMONG NON HODGKIN'S LYMPHOMAS IN CAUCASIAN CHILDREN

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A series of 124 patients under 16-year old, with a diagnosis of non-Hodgkin's lymphoma (NHL), were studied. The cases were reviewed using the Kiel (by Dr R. Gérard-Marchant) and the Rappaport (by Dr P.A. Bryon) classifications. All the cases were diffuse and poorly differentiated. 60 cases were diagnosed as monomorphic B small non-cleaved NHL having many pathological similarities with Burkitt's lymphoma (BL).

BL could then be the most frequent childhood lymphoma in France. When looking at the clinical features of these cases, it appears that this histological entity corresponds to a well defined disease. Abdominal masses are initially present in 65% of the cases while the jaw is involved in only 4%. The disease is characterized by its overwhelming evolution in the absence of therapy. The immediate risk, especially for extensive disease, is rapid CNS involvement. After 3 or 4 months of remission, relapses may appear by local recurrence, CNS or bone marrow involvements. The evolution is short, 90% of relapses being observed between 4 and 8 months of evolution.

EBV studies performed on 30 cases showed a low frequency of association (see: Lenoir, this Conference). Rearrangements of chromosome 8 bands q23 or q24 considered as a characteristic cytogenetic feature of BL was found in all of the 6 cases studied.

Our study on Caucasian children with NHL indicates that, from histopathological, clinical and cytogenetic criteria, nearly half of the cases are very similar to African BL. Even if the EBV was rarely found to be associated in our cases, the eponym of BL, as pathologically defined, could correspond to a worldwide distributed lymphoma.

T46

IMMUNO-HISTOLOGICAL ANALYSIS OF BONE MARROW INVOLVEMENT IN NON-HODGKIN'S LYMPHOMA.

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Recent advances in the analysis of normal and malignantly involved lymph nodes have demonstrated that in frozen biopsies immunological studies can be performed with only minimal impairment of histological details. These developments have implications for bone marrow (BM) cytology. In particular the immunological analysis of sections from frozen BM biopsies would be mostly useful for analysing the BM involvement in non-Hodgkin's lymphoma (NHL) for the following reasons. Lymphoid nodules are often detected in formalin-fixed paraffin embedded trephine biopsies. This finding alone does not always allow a confident discrimination between benign lymphoid nodules and focal localization of NHL, especially of small lymphocyte type. The analysis of membrane antigens which could give more precise indications, especially as far as the monoclonal kappa or lambda light chain expression of surface immunoglobulin, is nevertheless impaired in these formalin fixed preparations.The immunological membrane marker analysis, performed on BM aspirates, is unfortunately not reliable in this case. Infact nodules may remain attached to the bone trabecules and do not come into cell suspension so that aspirates frequently underestimate the degree of malignant lymphoid involvement.

In this report we describe the preparation of sections from frozen BM trephine biopsies which have been successfully investigated by immunological analysis, of both membrane and cytoplasmic antigens,using conventional and monoclonal antibodies. BM involvement could be detected in several cases of NHL and this technique contributed to the diagnosis in cases where the conventional histology provided equivocal results.

T47

MEDIASTINAL NON-HODGKIN LYMPHOMA IN CHILDREN: PROBLEMS OF DIAGNOSIS AND TREATMENT.

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Of 51 children with Non-Hodgkin-Lymphoma (NHL) diagnosed at the Univ. Children's Hospital Zürich from 1964 to Feb. 1981, 16 (=31 %) had a mediastinal (M) tumor. Only 3 (= 19 %) of them were girls (vs. 31 1/2 % in all the other NHLs). The mean age was 8 years (vs only 6y in the other NHLs).

Due to airway obstruction, 2 children died from operative complications before any treatment. Due to this danger tissue diagnosis was not attempted in 7; in 5 of these, at least cytology was available. In one, histology was obtained later. Because of these difficulties in getting adequate material, we could not do immunologic typing in 6 out of 10 children diagnosed since 1974. All 4 typed (and additional 2 typed in relapse) had from 5 to 98 % E+ tumor cells. Cytologically, 8/13 were of FAB type 1, 3 of type 2 and 2 of type 3 (one a typical M-NHL, but one with widespread disease at diagnosis).

8 (= 1/2) of these patients are still alive (one with disease in the pleura, and 3 with <6 months of follow-up). 4 children are disease free >2 years (3 of them off therapy) 2 of them are girls. All those 7 who relapsed were w/o disease <1 year, only 1 survived longer than 18 months, one is alive at 13 months. The site of relapse was: the bone marrow 4x (3x as first remanifestation), the pleura 3x, and the CNS 2x (once very late: at 27 months, once from a direct extension of the tumor to the thoracic spine.

From these clinical observations, one can conclude that most, but not all M-NHL in childhood are of the T-cell type. Although exact immunologic and tissue diagnosis are very important, they should not be attempted in clearly dyspneic patients before an emergency treatment.

Treatment results (with less than 44 % of the children cured) are still unsatisfactory. As the relapse occurs early, and often in the pleura and in the bone marrow, cytostatic therapy should be intensified even more (but might be shortened), and irradiation fields should be enlarged. CNS-prophylaxis, in most cases, seems to be less important.

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T48

PRIMARY GASTROINTESTINAL LYMPHOMAS-CLINICOPATHOLOGICAL STUDY.

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Fifty-eight cases of primary gastrointestinal lymphomas seen at Henry Ford Hospital, during 1956-1978 were studied. The presenting symptomatology was vague gastrointestinal distress although 3 of the patients had perforated abdominal viscus. There was a 2:1 preponderance of males with an age range of 16-80 years. 20% of the patients had palpable abdominal masses and the radiological examination in most of the patients showed fungating or ulcerated lesions. The primary G.I. lymphomas in our patient group were distributed as follows: stomach -34; small intestine -15; ileocecal junction -4; colon -4; and rectum -1. In 25 cases there was local regional lymph node spread by lymphoma at the time of surgery. Histologically large cell lymphoma (LCL) was more frequent (66%) with 10% having significant plasmacytoid features. Immunohistochemical studies on formalin fixed tissue, where available, showed variety of immunoglobulin chains in the neoplastic cells irrespective of the histologic types. Some clinicopathologic correlation between the length of survival and the stage of disease was observed in patients during the first 10 years.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T49

PRIMARY NON HODGKIN LYMPHOMA (NHL) OF THE SALIVARY GLANDS. A REPORT OF 6 NEW CASES. M. Raphael°, V. Missenard°, C. Chenal°°, M.Le Porrier°, J.C. Bertrand*, M. Auriol**, C. Brocheriou+, Hematology°, Radiotherapy°°, Stomatology*, Pathology**, Departments (CHU Pitie Salpetriere) Pathology Department+ Hopital St. Louis, Paris, France.

Primary non Hodgkin Lymphoma (NHL) of the salivary glands are rare. We describe 6 new cases which were classified according to the criteria for the NHL classification proposed by the expert inter-national panel of pathologists.

Between 1973 and 1980, 5women and 1 man were treated and their cases followed at CHU PITIE SALPETRIERE. The tumor involved the Parotid gland in 3 cases, the Submaxillary gland in 2 cases, and in both glands simultaneously in only 1 case.

When first observed, all patients were at stage 1 (ANN ARBOR classification).

The histology displayed an aggressive appearance. Five cases corresponded to the largecell lymphoma (2 large non-cleaved and cleaved cells, 3 Immunoblastic). One case was of the mixed type. Twocases showed a lymphocytic infiltration associated with the lymphoma, one of them presented a Sjogren's syndrome six months before the NHL.

All patients received radiotherapy at 60 Grays over the primary tumor, and 40 Grays on the regional cervical lymph nodes. Five patients were treated with chemotherapy (3 with MOPP, 2 withCHOP)

Five patients achieved complete remission and no relapse has been observed for 8,7,6,5, and 1 years respectively since treatment.

In conclusion: NHL of the salivary glands, even with a cytologically aggressive appearance, seems to have a better prognosis than the nodal and extra nodal NHL with a similar histological type and clinical stage.

T50

POLYCHEMOTHERAPY AND TOTAL BODY IRRADIATION IN THE TREATMENT OF NON-HODGKIN'S MALIGNANT LYMPHOMAS WITH FAVORABLE HISTOLOGY. Results of a cooperative pilot study.

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Sixty six 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/m2 on day 1 and 15), vincristine (0,7 mg/m2 on day 1, 8 and 15), cyclophosphamide (400 mg/m2 on day 1, 8 and 15) and prednisone (40 mg/m2 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 and to compare these results to chemotherapy alone or TBI alone.

T51

SEARCH OF PROGNOSTIC FACTORS WITH MULTIVARIATE ANALYSIS IN AN UNIFORMELY STAGED AND TREATED GROUP OF PATIENTS WITH NON-HODGKIN LYMPHOMA. Rizzo S.C., Ricevuti G., Gobbi P., Balduini C.L., Marabelli S.

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A search for prognostic factors was performed after studying 67 patients with NHL who were histologically classified according to the Kiel 1974 criteria by the same pathologist. All patients had bipedal lymphography, bone marrow histological evaluation in addition to a large blood study. CVP and CHOP were the two treatment schedules for low and high malignancy according to the original histological diagnosis. A large number of parameters encompassing biological, clinical, histologic, hematological and biochemical features at diagnosis were scrutinized in order to recognize those exhibiting prognostic value as regards length of survival. Parameters with a continuous distribution were assayed comparing survival of patients with the different critical levels of each parameter. The same thing was done for the parameters with more than two possible discrete values (e.g.stage, histotype) testing survival of differently subgrouped patients. The differentiating parameters were admitted by groups, with their critical value that best fitted the survival data, to a factor analysis for multiple way classification. To this purpose an arbitrary threshold limit of 30 months was also assumed for the dichotomic statistical evaluation of survival. The results of our investigation show first of all the scarcity of significant prognostic factors on which to rely, namely ESR, histologic type, stage, in decreasing importance. While the impact played by the last two factors on survival are well known, it is both very interesting and hopefully fruitful that such a trivial and routine laboratory test as ESR, potentially possesses such a meaningful utilization.

T52

THE VALUE OF PERCUTANEOUS LIVER BIOPSY IN CLINICAL STAGING OF NON-HODGKIN'S LYMPHOMAS

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A percutaneous liver biopsy was performed in 200 patients with untreated non-Hodgkin's lymphomas. The purpose of this study was to determine specific and non-specific liver changes and evaluate percutaneous liver biopsy in clinical staging of these patients. There were 72 women and 128 men with an average age of 54.0 years. Lymphocytic lymphoma was diagnosed in 92 patients, histiocytic in 99 and lympho-histiocytic in nine patients (Rappaport). Liver biopsy was performed with Menghini needles. All the biopsy specimens were histologically and cytologically analysed. In the whole group of patients liver involvement with lymphomatous tissue was confirmed in 48 patients (24.0%): histiocytic lymphoma 23 (23.2%), lymphocytic lymphoma 20 (21.7%) and lympho-histiocytic five patients (55.5%). Fortythree out of 48 patients with liver involvement experienced a change in clinical staging after liver biopsy. Chronic persistent hepatitis was found in 30 patients, chronic aggressive hepatitis in eight, liver steatosis in 16 and haemosiderosis in nine patients. Based on these results, it can be concluded that liver involvement with lymphomatous tissue was found in every fourth patient. The authors concluded that the percutaneous liver biopsy is a very useful method in the clinical staging of non-Hodgkin's lymphomas, especially in patients in whom "staging laparotomy" was not perform

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T53

SPREAD OF HODGKIN`S DISEASE. STATISTICAL EVALUATION OF 305 PATIENTS

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In order to test the hypothesis that Hodgkin´s disease does arise in one site and will spread in a predictable pattern, we studied , retrospectively, the clinical data of 305 patients. 132 had a laparotomy performed. The site of primary manifestation was determined for the time of presentation and for the subsequent clinical course. The sequence of manifestation was analyzed for 21 anatomical sites with aid of a computer assisted method.

In a majority of patients the disease seemed to spread in a predictable way along contiguous lymph node chains: spread from right cervical nodes was via the right upper mediastinum to the paraaortal lymph nodes and the spleen whereas left cervical lymphoma lead to direct abdominal involvement bypassing the mediastinum. Abdominal involvement preceded upward spread via the pulmonary hili and the upper mediastinum to the cervical and axillary lymph nodes, i. e. enlarged pulmonary hili and upper mediastinum on the left or on both sides were indicative of abdominal involvement (98 % of the cases with laparotomy (n = 41) and 70 % of the cases without laparotomy (n = 103). The sequence of organ involvement correlated in 86 % of 674 lymphatic regions with the postulated pattern in the patients with laparotomy and relapse in the subsequent clinical course. The degree of neighbourhood of the involved lymphatic areas was according the postulated pattern (- 0,77).In addition the frequency of lymphatic organ involvement was consistent with the hypothesis.

This suggestion of a predictable spread within the lymphaticsystem before hematogeneous dissemination may be important for staging and treatment of patients with Hodgkin´s disease.

T54

IMPAIRED B-LYMPHOCYTE FUNCTION IN PATIENTS WITH HODGKIN'S DISEASE AND NON-HODGKIN-LYMPHOMAS.

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The generation of Immunoglobulin-secreting cells (ISC) upon stimulation with Pokeweed mitogen (PWM) was studied in patients with malignant lymphomas. ISC were enumerated in a reverse hemolytic plaque assay using sheep red blood cells as indicator cells. The experiments revealed that different mechanisms are responsible for the defects of B cell activation and differentiation which are characteristic for these diseases.

In Hodgkin's disease the majority of patients with an active stage of the disease exhibited greatly diminished responses of their peripheral B lymphocytes to PWM. In some of these patients suppressor cells were found to cause the unresponsiveness, in others, however, an intrinsic defect of the circulating B cells - sometimes combined with a defective T helper cell capacity - was observed. Interestingly, some patients with completely abolished responses of the peripheral B lymphocytes exhibited normal reactivity of their splenic B cells.- It could be further demonstrated that the defect of B cell differentiation could be corrected by therapy.

In patients with Non-Hodgkin-Lymphoma an intrinsic B -cell defect was found to be the only cause for the unresponsiveness observed in most of the patients studied. In contrast to the patients with Hodgkin's disease this B lymphocyte defect could not be corrected by therapy. - Isolated T cells from these patients were functinally normal helper cells and none of the hitherto studied patients had demonstrable suppressor cells in their peripheral blood.

T55

INTERPRETATION OF CLINICAL SYMPTOMS IN HODGKIN´S DISEASE.

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The finding of general symptoms in Hodgkin´s disease is considered to represent an unfavourable prognostic sign and expression of the disease activity. Results of clinical and histological classification analysis indicate the possibility of different interpretation of the presence and absence of symptoms in generalized disease.

clinical stage frequency		clinical symptoms frequency		the most frequent histological type frequency	
I+II	40/88(45%)	A	25/40(63%)	LP+NS	18/25(72%)
		B	15/40(37%)	NS+MC	12/15(80%)
III+IV	48/88(55%)	B	31/48(65%)	NS+MC	27/31(87%)
		A	17/48(35%)	MC+LD	13/17(76%)

Asymptomatic generalized disease can be prognostically more serious than that of symptomatic one as it may express the immunological tolerance of the tumor or acquired depression of defensive processes. This conclusion is supported by presented preliminary data on survival of our patients in given classification groups.

clinical stage	histological type	number of patients survived 5 years absolute	relative
IA+IIA	LP+NS	3/ 4	75%
IB+IIB	NS+MC	5/ 7	71%
IIIB+IVB	NS+MC	4/11	36%
IIIA+IVA	MC+LD	1/ 5	20%

The assumption of different significance of symptoms in localized and generalized disease is also supported by the results of laboratory tests.

T56

SECOND MALIGNANCIES IN MALIGNANT LYMPHOMA.

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The development of leukemia following radiation therapy has long been recognized. An augmented incidence of leukemia following combined radiation therapy and multiple-agent chemotherapy became apparent and well recognized in lymphoma patients in recent years. The thyroid gland is another radiosensitive organ which is frequently in the radiation field for treatment of malignant lymphoma. A dose response relationship exists between the radiation dose and the development of thyroid carcinoma up to 1800-2000 rads and then the incidence of thyroid carcinoma declines as the radiation dose becomes higher. However, we have found a very high incidence of thyroid cancer among the patients with Hodgkin's disease (HD). Similar results have been reported by several other institutions. However, only scanty information is available for non-Hodgkin's lymphoma (NHL). The clinical materials of 1400 patients with diagnosis of malignant lymphoma at RPMI between 1910-1960 were reviewed. There were 520 patients with HD and 880 patients with NHL. Male-female ratio was 328/192 for HD and 527/353 for NHL. Mean age of HD was 39 and NHL 53, and average survival was 4.3 years and 3.8 years respectively. Excluding skin cancers, 16 second malignancies were found among HD and 50 in NHL. In addition, 6 patients with NHL developed third malignancies for a total number of tumor of 56, while none of the HD patients had the third malignancy. Sites of these tumors are shown below.

	Brain	Breast	Lung	GI	GU	Leukemia	Thyroid	Others	Skin
HD	0	2	0	2	3	2	3	4	3
NHL	5	4	7	14	14	4	2	6	18

Generally, more second malignancies are found in NHL than HD due to older age of the patients. Six HD and 15 NHL survived more than 30 years. Three thyroid cancer patients in HD group all developed thyroid cancer more than 30 years after diagnosis of HD; 2 were anaplastic and 1 adenosquamous. However, 2 thyroid cancer patients in NHL group were both differentiated carcinoma and incidental finding at autopsy, 6 and 11 months after diagnosis of NHL respectively. Therefore, they cannot be considered as the sequelae of treatment for NHL. We conclude that the thyroid of HD patients is more susceptible to radiation induction of carcinoma than that of NHL patients.

ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

T57

ALTERATIONS IN THE PROTEIN COMPOSITION OF LYMPHOMA CELLS AFTER TRANSFORMATION WITH EPSTEIN-BARR VIRUS (EBV).

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There is little doubt about the causative role of EBV in the genesis of Burkitt's Lymphoma. However, the transformation associated events are totally unknown. EBV-transformed sublines of EBV-negative lymphoma cells offer a model system to study EBV-transformation in vitro because EBV-infection converts EBV-negative lymphoma cells to permanent carriers of the EBV-genome and the EBV-determined nuclear antigen (EBNA) and induces a malignant phenotype. This includes an increased saturation density, reduced serum requirement, reduced membrane microviscosity, reduced anchorage dependence, increased hexose uptake and Concanavalin A agglutinability due to an augmented Concanavalin A receptor density.

So far it was not possible to assign these changes to alterations on the molecular level. We approached this problem by analyzing the proteins from the EBV-negative lines BJAB and Ramos and their sublines transformed by the EBV-variants B95-8 and P3HR-I. 35-S-methionine labeled proteins were separated by high resolution two-dimensional gelelectrophoresis, combining isoelectric focusing and SDS-gelelectrophoresis.

Expectedly we find a complex protein pattern which shows a high degree of homology among the various cell lines. However, we also can detect significant differences. Besides minor alterations we constantly find in 5 out of 6 EBV-positive sublines one additional protein-spot always in the identical position (approx. MW 68k, pI 6.0). On the basis of their molecular weights these proteins are distinct from EBNA.

In conclusion we have shown that EBV-infection of EBV-negative lymphoma cells leads to the appearance of at least one new protein with a size of 68k and a pI of 6.0. The appearance of one possibly identical new protein in 5/6 EBV transformed cell lines, irrespective of the converting EBV-strain and irrespective of the transformed cell suggests that this change is a direct or indirect consequence of the presence of the viral genome and that it is related to the transformed phenotype of the EBV-positive sublines.

T58

LONG TERM SURVIVAL IN RELAPSING HODGKIN'S DISEASE

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Hodgkin's Disease (HD) is a curable entity and even those patient with advanced disease may achieve complete and durable remission. Long term survival in cases of relapsing disease is, nevertheless seldom reported.

14 patients with HD relapsed after a first complete remission induced by radiotherapy (RT), chemotherapy (CT) or combined RT and CT. 5 of the patients were male and 9 were female. Stages I, II, III and IV were represented with the frequency of 1, 10, 2 and 1 respectively. Histopathologic study showed nodular scleros in 9 cases, lymphocyte predominance in 4 and mixed cellularity in one. Initial treatment included RT only in 9 patients, CT only in 3 and combined RT and CT in the remaining 2. The median duration of the first remission was 24 months. At relapse, 11 patients had lymph node (LN) involvement only and 3 had LN and visceral disease. The locations were supradiaphraphragmatic (SD) in 5 cases, infradiaphragmatic (ID) in 5 and both SD and ID in 4. The initial site only was involved in 4 cases, new sites only were involved in 6 and both initial and new sites were involved in 4. All patients achieved a second complete remission with either RT alone (3 cases), CT alone (6 cases) or combined RT and CT (5 cases). 5 of the patients relapsed at least one more time before achieving prolonged remission. The median time span between diagnosis and the end of the ultimate treatment leading to the present remission was 5.5 years. The median disease free survival for all patients since the end of the last induction treatment was 8.25 years (range 9 months-13 years) and the median survival since diagnosis was 13.75 years (range 3.1-29 years).

We conclude that patients with HD who relapse once or several times after a first induction treatment may still achieve prolong complete remission irrespective of the stage at onset or the exte of the disease at relapse. Relapse as such does not exclude long term remission and possibly cure in HD.

T59

PECULIAR SYMPTOMS AND COMPLICATIONS IN T ZONA LYMPHOMAS

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Unusual manifestations in two patients with T zone lymphoma are discussed. Both had generalized lymphadenomegaly beside the enlargement of liver and spleen.

The first patient was a 50 year old woman. In the early period of the disease the histological examination proved that the phenomenons on the skin consisted of infiltrations with atypical lymphocytes. Despite of steroid and cytostatic therapy the patient died by insufficient pulmonary ventilation after six months. The autopsy revealed the infiltration of the lungs with pathological lymphocytes. However, the lethally diminished capacity of the respiration was mainly caused by interstitial pulmonary fibrosis. We suppose the connection between the two findings, i.e. probably the fibrosis was induced by the presence of the malignant cells.

The other patient, a 70 year old female, had a different type of skin alteration: on the cheek and on the earlaps as well as at the fingertips unusual, intensive lividity could be observed. The analysis of the blood protein and the investigations with capillar-microscope revealed the disturbance of microcirculation. We think that was the consequence of the pathological globulin fraction, i.e. kryoglobulim. After successfull combined cytostatic treatment the symptoms almost disappeared.

T60

Sequential non-cross resistant regimens (MOPP and CAVmP) in Hodgkin's disease stage III-B and IV.

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Fourty consecutive patients were treated in a multicentre study with 6 cycles of an alternating scheme of MOPP and CAVmP (C cyclophosphamide 600 mg/m2, A adriamycin 50 mg/m2, Vm : Vm26 60 mg/m2, P prednisone 40 mg/m2) followed by irradiation to a dose of 20 Gy. The aim is to increase CR and cure rates by alternating two effective non-cross resistant regimens and to consolidate the remission by irradiating bulky nodes.

A total of 34 patients completed 6 cycles.

In the first 13 patients the irradiation fields amounted to a total or subtotal nodal irradiation with inclusion of the spleen.

In case of organ involvement the affected organ was also included in the irradiation field.

The irradiation protocol was later changed to an irradiation of the initial involved regions only, because of severe leuco- and thrombocytopenia.

After completion of the chemotherapy 24 (70%) patients achieved a CR, after ending the radiotherapy the percentage of CR was increased to 90%.

Two of the patients in a CR relapsed in an irradiated area, one patient relapsed in an irradiated and a non-irradiated area. The actuarial 18 months survival for the whole group was 85% and the relapse free survival 74%. It is concluded that this alternating schema is at least equally effective as MOPP-. treatment alone.