ABSTRACTS

POSTER PRESENTATIONS

Poster Session I

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P 1 DNA ANEUPLOIDY IN HODGKIN'S DISEASE: A MULTI-PARAMETER FLOW-CYTOMETRIC ANALYSIS WITH CYTOLOGIC CORRELATION. John Anastasi, Kenneth D. Bauer, and Daina Variakojis, Dept. of Pathology, Northwestern University Medical School, Chicago, Illinois, USA

In 15 cases of Hodgkin's disease, we studied the DNA content of isolated nuclei from deparaffinized tissue by using multi-parameter flow cytometry. We employed an antinucleolar antibody preparation (Greenfield, RS et al. Proc. AACR 24:792, 1983) as well as a secondary antibody that had been conjugated with fluorescein isothiocyanate. By simultaneously quantitating nucleolar fluorescence and DNA content, we detected rare but distinct aneuploid populations among the nuclei with brightly stained nucleoli. DNA aneuploidy was found in each case when we used this multi-parameter analysis, but was detected in only one case when DNA content was analyzed alone. With the multi-parameter analysis we found two to four aneuploid populations in each case. These populations exhibited incremental duplications of DNA content which suggested endopolyploidy, i.e., replication of DNA without accompanying nuclear division. The aneuploid stem line was hypodiploid or hypotetraploid in six cases, hyperdiploid in seven cases, and near-triploid in two cases. These various abnormalities in ploidy showed some correlation with histologic subtypes, but only when subtype variants were considered. Cell sorting showed that some nuclei with more than four or nearly eight times normal DNA content resembled nuclei of typical Reed-Sternberg cells. Many nuclei with an intermediate aneuploid DNA content resembled nuclei of mononuclear Reed-Sternberg cells. The near-diploid and near-triploid nuclei corresponded to nuclei of cells which were not readily recognizable as neoplastic in histologic sections. We conclude that analysis of DNA content can provide further insights into our understanding of the neoplastic cells in Hodgkin's disease and may offer an objective basis for studying heterogeneity in this disorder.

P 2 DOES DNA CONTENT HAVE PROGNOSTIC SIGNIFICANCE IN HIGH GRADE NON-HODGKIN'S LYMPHOMA?
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Flow cytometric analysis provides a method for the rapid estimation of DNA content in tumour cell populations. To date, published data in non-Hodgkin's lymphoma suggests that aneuploidy and high proliferative activity, measured by S phase percentage or proliferative index (PI) (percentage of cells in the S phase and G2M phase of the cell cycle) correlates with high grade histology and therefore poor prognosis.

Using this technique on paraffin-embedded tissue we have studied 180 patients with high grade non-Hodgkin's lymphoma (in Kiel and Rappaport) all of whom have received uniform treatment, to establish the clinico-pathological correlations and prognostic significance of ploidy and proliferative index in this group of aggressive lymphomas. Prior to analysis all histological specimens were reviewed by one pathologist to ensure adequate tumour representation.

47% of the patients studied had aneuploid tumours, and the PI for the group varied from 1.5% to 45% with a mean of 15.9%. The PI correlated with histological grade in the Kiel classification: the lymphoblastic and immunoblastic lymphomas having a significantly higher PI than the other histological subtypes ($p = 0.005$). No such correlation was found between PI and histological categories by Rappaport. PI was also significantly associated with response to therapy: 60% of patients with a low PI (<20%) achieved complete remission compared to only 33% of patients with a high PI (>20%). There was no significant association between ploidy status and histology by Kiel or Rappaport nor was there a significant correlation with remission status. In addition, DNA content was not significantly related to clinical stage nor sites of disease. In a Cox multivariate analysis for prognostic factors neither ploidy nor PI significantly predicted for the overall survival, relapse-free survival nor survival after attainment of complete remission.

We conclude that within unfavourable histology non-Hodgkin's lymphoma, DNA content as measured by a flow cytometric analysis is not a strong predictor of clinical outcome.

P 3 SURVIVAL FOLLOWING COMBINATION CHEMOTHERAPY IN ADVANCED HIGH-GRADE NON-HODGKIN'S LYMPHOMAS (NHL). RELATION TO PROLIFERATIVE ACTIVITY OF THE CELLS. L. Brandt, H. Olsson, Dpt of Oncology, University Hospital, S-221 85 Lund, Sweden

It is largely unknown why some patients with advanced aggressive NHL achieve long-term survival following chemotherapy whereas others with a clinically and histologically similar disease and treated in the same way die from progressive disease within a relatively short period. In the present study of advanced high-grade NHL age, histology, stage and initial treatment were compared in short-term and long-term survivors. The proliferative activity of the lymphoma cells, thymidine labelling index (LI), was recorded at diagnosis.

Eighteen patients with high-grade lymphomas (Kiel classification) stage II-IV were initially treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOP + methotrexate, MEV (methotrexate, cyclophosphamide, vincristine) or COMLA (cyclophosphamide, vincristine, methotrexate, leucovorin, cytosine arabinoside) and have been followed for a minimum of 3.7 years or until death. Twelve patients have died within 3 years after diagnosis (range 0.1-2.7, median 1.5 ys) and 6 patients have survived for more than 3 years (range >3.7->8.6, median >5.1 ys). Age was comparable in the two groups, median 62 and 61.5 respectively. Four of the 12 short-time survivors and none of the long-term survivors had lymphoblastic lymphoma. Other morphologic classes were comparable in the groups. Stage III-IV was diagnosed in 11/12 and 6/6 respectively. The distribution of treatment regimens was similar in the two groups. LIs were considerably higher in the short-term survivors, median LI= 8.1 (range 2.4-21.4), than in the long-term survivors, median LI=1.1 (range 0.2-4.2) ($P<0.01$). Excluding the lymphoblastic lymphomas the difference is still large, median 9.6 versus 1.1 ($P<0.01$).

It is concluded that combination chemotherapy may induce long-term survival in advanced high-grade NHL if the proliferative activity of the tumour cells is low. A high proliferative activity is associated with poor response or early relapse resistant to further therapy. It is proposed that in rapidly proliferating lymphoma tissue a large number of mutants may arise and that some of them are spontaneously drug resistant already at diagnosis. This assumption is supported by a previous finding of larger numbers of clonal chromosome aberrations in NHL with high LIs than in lymphomas with low LIs (Brandt et al. Scand J Haematol 1986:37:106-110).

P 4 IMMUNOGLOBULIN (Ig) AND T CELL RECEPTOR (TCR) GENE REARRANGEMENT IN HODGKIN'S DISEASE. A. Raghavachar[1], T. Binder[2], C.R. Bartram[3], Departments of Transfusion Medicine[1], Internal Medicine III[2] and Pediatrics II[3], University of Ulm, D-7900 Ulm, FRG

In the past, morphologic, electron microscopic and immunophenotypic analyses have been extensively used as an adjunct to the histopathological diagnosis and classification of Hodgkin's disease. To further characterize the lineage and clonality of Hodgkin's disease we have investigated the rearrangement of Ig and TCR genes in lymph node DNAs obtained from 35 Hodgkin's disease patients. Diagnosis and classification of each lymphoid neoplasm was established by conventional histopathologic criteria and comprised all subtypes of Hodgkin's disease. Southern blots were hybridized to Ig heavy chain, Ig light chain as well as TCR-β and TCR-γ specific probes. As a result from these studies, we detected clonal rearrangements of Ig genes in six, and TCR genes in five specimens, irrespective of the histopathological subtypes. The intensity of rearranged bands in every case suggested the presence of minor clonal populations of B or T cells. These findings will be discussed in the context of recent reports with conflicting data on Ig and TCR gene rearrangements in Hodgkin's disease.

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P 5 IDENTIFICATION OF A NOVEL TRANSFORMING GENE IN PATIENTS WITH PRENEOPLASTIC B-CELL BY PROLIFERATIVE DISORDERS. T. Ernst, G. Cooper, Department of Medicine and Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA USA

Preneoplastic B-cell lymphoproliferative disorders provide the opportunity to identify, characterize and subsequently follow a specific cell type which in 30-50% of cases will evolve to a frank neoplasm. We have identified 3 patients with characteristic B-cell disorders which clinically and histopathologically appear benign. Cell surface antigen expression suggested a polyclonal disorder by virtue of approximately equal expression of both kappa and lambda immunoglobulin light chains. Immunoglobulin heavy chain rearrangement however showed a clonal expansion of B cells which was unassociated with the Epstein-Barr viral genome.

Using the NIH 3T3 focus formation assay, high molecular weight DNA derived from the abnormal B-cells and normal T-cells from each patient were scored for transforming activity. Multiple human Alu repeat positive foci were obtained from B cell transfectants from each patient whereas the T cell DNA was negative for focus forming ability. Second round transformants were used to clone, by human Alu repeat homology, genomic DNA of 12-15 kbp in length which is shared in multiple transformants derived from all three patients.

The relevance of this gene is the evolution of preneoplastic B-cell disorders and the multistep progression of lymphomagenesis is currently being investigated.

P 6 PRODUCTION OF B CELL GROWTH FACTOR (BCGF) LIKE ACTIVITY BY A NEOPLASTIC B NON-HODGKIN's LYMPHOMA CELL LINE. R. Haas, S. Kiesel, N. Jamal, M. Tweedale, H. Messner, W. Hunstein, B. Dörken, Dep. of Int. Med. Heidelberg, FRG; OCI, Toronto, Canada.

The proliferation of normal human B cells depends on the activation by an appropriate antigen or mitogen followed by the action of B cell growth factor (BCGF). Human BCGF is heterogenous with a low (14-16 KD) and high (50 KD) molecular weight fraction. It could be demonstrated, that neoplastic B cells from patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia can proliferate in vitro in the presence of greatly purified BCGF. We investigated an NHL cell line (OCI.LY1) derived from a patient with a high grade malignant lymphoma for the autocrine production of growth factor activities. The cell line was derived from a bone marrow aspirate and propagated in liquid suspension culture containing 10% human plasma (free of EBV transformation). For the growth factor production 2 x 10^7 cells/ml were set up in IDMEM supplemented with 1% BSA and incubated at 37°C for 48 hrs in 5% CO_2. The supernatants were tested for the growth factor activity on the autologous NHL cell line, normal tonsillar B cells of high density, a T cell line (CEM-C7) and a myeloid cell line (HL-60). We measured the ^{3}H-thymidine incorporation after a total culture period of 72 hrs. A representative example of the results on the NHL cells can be seen in the following Table.

TARGET	OCI.LY1	RAJI
	cpm*	cpm*
CONTROL (IDMEM+10% FCS, $1x10^4$ cells/well)	7886	22536
SUPERNATANT		
6.25 %	15962	63636
12.50 %	13822	57370
25.00 %	14366	69730
BCGF (Cellular Products, Buffalo, N.Y.)		
6.25%	15746	59284
12.50%	12816	61433
25.00%	15384	63241

*Standard deviation was always less than 10%.

Our data suggest that the OCI.LY1 cell line is capable of producing a growth factor like activity. Its biological activity closely resembles the human BCGF. In addition, this activity has the biological property to replace BCGF as a second signal for the in vitro proliferation of normal human tonsillar B cells. Its B cell restriction is demonstrated by the lack of any stimulatory effect on a T or myeloid cell line.

P 7 THE FUNCTIONAL EFFECT OF RECOMBINANT INTERLEUKIN-2 (IL-2) ON THE IN VITRO GROWTH AND PROLIFERATION OF NON HODGIN'S LYMPHOMA CELLS. R. Haas, S. Kiesel, S. Hohaus, A. Lüdemann, W. Hunstein, B. Dörken, Department of Internal Medicine, Heidelberg, West Germany.

In 1976 Morgan et al. described a biological activity derived from supernatants of long-term cultured T-cells which was capable of maintaining the proliferation of human T cells. This growth factor could be identified as a glycoprotein consisting of 133 amino acids. According to its biological property it was called T cell growth factor (TCGF) or later interleukin-2. Like other hemopoietic growth factors it exerts its biological functions by binding on specific receptors expressed on the different target cells. It plays a major role in the activation and proliferation of T cells which are stimulated and - according to their functional repertoire - display their helper-, suppressor-, or cytotoxic effect. Recently, it could be demonstrated, that IL-2 has a stimulatory effect on normal B cells. Furthermore it is able to increase the secretion of immunoglobulins by plasma cells and the expression of specific interleukin-2 receptors on T and B cells. It could be shown that specific IL-2 receptors are present on the cell surface of B non-Hodgkin's lymphoma cells. The objective of our study was to investigate the biological effect of recombinant IL-2 on different B non-Hodgkin's lymphoma cell lines. These cell lines (free of EBV transformation and dependant on human plasma express the IL-2 receptor in different densities. In a semisolid clonogenic culture assay (methylcellulose 0.9%, human plasma 30%, and 2 ME $2x10^{-5}$M) the incubation with IL-2 in different concentrations (1 U/ml up to 100 U/ml) caused a decrease of 35-40% in average in the number of colonies dependant on the cell lines tested. Similarly the mean ^{3}H-thymidine uptake in the presence of IL-2 in identical concentrations was only 65-75% compared to the controls in a 72 hr culture period. The data demonstrate that IL-2 has a suppressive effect on the proliferation and the clonogenic growth of B non-Hodgkin's lymphoma cells. We conclude that IL-2 exerts its effect by inducing a differentiation process in the lymphoma cells like it has been demonstrated for normal B cells and thereby decreasing the proliferative and clonogenic capacity of the leukemic cells. For the future it has to be evaluated if these in vitro results could be exploited for new therapeutical strategies in the treatment of patients with non-Hodgkin's lymphomas.

P 8 SOLUBLE INTERLEUKIN-2 RECEPTORS LEVELS IN THE SERUM OF PATIENTS WITH HODGKIN'S DISEASE: A NEW BILOGICAL MARKER OF DISEASE ACTIVITY. F.Vinante, S.Romagnani, R.Zambello, F.Benedetti, P.Parronchi, E.Maggi, A.Ambrosetti, M.Chilosi, G.Semenzato, and G.Pizzolo, Cattedra di Ematologia and Istituto di Anatomia Patologica of Verona University; Istituto di Medicina Clinica of Padova University; Cattedra di Patologia Medica IV of Firenze University, Italy.

Increased levels of a soluble form of the interleukin-2 receptors (sIL2R), either released by neoplastic cells or by activated T cells, have been recently demonstrated in a number of pathological conditions. Since the IL2R is strongly expressed by Hodgkin and Reed-Sternberg cells and is also present in reactive T cells in tissues involved by Hodgkin's disease (HD), we investigated the serum levels of sIL2R in this disease. The sIL2R levels have been measured in over 100 cases using a "sandwich" ELISA test and evaluated in relationship with various clinico-pathological parameters. Sera were collected at diagnosis and, in a number of cases, also at different periods after therapy. Increased levels (>500 U/ml) were detected at diagnosis in 75% of cases. The mean sIL2R values were higher in more advanced stages (stages III+IV = 1392±877) as compared to the initial ones (stages I+II = 912±809) ($p<0.02$). The highest statistical difference was found between the values observed in stages A as compared to B (stage A = 843±669; stage B = 1756±1049; $p<0.001$). With few exceptions, cases with values at diagnosis within the normal range (<500 U/ml) had a limited disease (stages I or II) with no constitutional symptoms (stage A). The treatment-induced clinical response was followed by a rapid normalization of sIL2R levels, as opposite to the finding of increased values in patients with relapse or progressive disease. Beside representing a new biological tool for monitoring the disease status and the effect of therapy, the detection of increased levels of sIL2R in HD seems of relevance to understand the pathogenetic mechanisms of the immunological abnormalities observed in this disease. In fact, the excess of sIL2R might remove "in vivo" the available IL2 and block the IL2/IL2R modulation necessary for a large number of biological responses. As a consequence, some IL2 dependent phenomena would be affected, including most of those which are impaired in HD, such as T-cell proliferation, cutaneous delayed type hypersensitivity, and regulation of NK activity. Some biological evidences supporting this interpretation will be presented.

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P 9 SERUM INTERLEUKIN-2 (IL-2) LEVELS IN HODGKIN'S DISEASE (HD)

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An increasing amount of experimental evidences in animals and men would suggest that many of the clinical, biological and cytologic features of HD may be mediated by interleukins, mainly IL-1.

IL-2, that is synthesized by IL-1 activated T lymphocytes, is a strong stimulating factor for all T subpopulations and probably for B cells, too.

We studied the IL-2 serum levels in 33 patients with HD, 18 males and 15 females, 18 to 70 years old, observed between 1979 and 1984. All were staged according to Ann Arbor raccomandations: histotypes were nodular sclerosis in 15 cases, mixed cellularity in 14, lymphocyte depletion in 2 and unclassifiable in 2. One patient was in stage I, 7 were in stage II, 18 in stage III and 7 in stage IV. Nineteen out of 33 were B stages.

Serum IL-2 was measured at diagnosis by means of a solid phase enzyme immunoassay based on the dual antibody immunometric sandwich (Genzyme Corporation, Boston MA).

Patient mean value was 468,3 mU/ml (SD 326.9). No clear differences were seen in IL-2 mean levels in relation to sex, histotype, stage and symptoms (A or B).

No correlations were seen between IL-2 levels and erythrosedimentation rate, serum albumin, alpha-2-globulins, gamma-globulins, fibrinogen, copper and peripheral lymphocyte count, all parameters indirectly IL-1 activated.

IL-2, as measured in the peripheral blood by the enzyme immunoassay used, does not seem to correlate with the main clinical manifestations of HD; moreover, as clinical marker of disease activity, it shows no advantages in comparison with those more commonly used.

The lack of apparent correlation between IL-2 and other IL-1 mediated biological factors might be explained by a cellular or a regulatory T cell defect.

P 10 rGM-CSF RESCUE OF GRANULOPOIESIS AFTER ABLATIVE CHEMOTHERAPY AND TOTAL BODY IRRADIATION (TBI): CASE REPORT OF A T-LYMPHOBLASTIC LAMPHOMA PATIENT.

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Recently recombinant granulocyte-macrophage colony stimulating factor (rGM-CSF) has become available for in vivo trials. We report on a 20 year old woman with stage IV A lymphoblastic T-cell lamphoma with mediastinal bulk. Initial treatment consisted in an ALL--regime containing DNR, VCR, MTX, ASP, ARA-C, VP-16 (SAKK 33/86) from 2.86 to 6.86, followed by mediastinal irradiation (1000 cGy). On August 7, an autologous bone marrow transplantation was performed with a conditioning regime of CYT and TBI. After a transient increase, the white blood count (WBC) dropped and by end of September the bone marrow was severely hypoplastic, the patient's WBC and thrombocytes remaining low with persistenly less than 50/mm3 granulocytes. She remained dependent on platelet and erythrocyte transfusions. In this situation, with a minimal chance of spontaneous recovery, she was treated with 250 μg rGM-CSF daily by 24h infusions during 10 days, beginning October 21st. An early increase in total WBC to 1000/mm3 (mainly lymphocytes) was followed by a steady recovery of her granulocyte counts after 4 weeks, culminating in a total WBC of 2000/mm3 on day 46, with 44 % segmented and band forms. A slow concommitant raise of monocytes to 250/mm3 and reticulocytes to 4-6% and stable values for platelets and erythrocytes were observed. Lymphocytes demonstrated an early doubling in absolute numbers to 500/mm3 and then stable values. Granulocytes declined to intermediary values after 9 weeks (1000/mm3 WBC, 600/mm3 granulocytes). Simultaneous granulocyte function tests indicated marked improvements of oxygen metabolism measured as O_2^- production and chemotaxis measured in a Boyden chamber system. During this time period the patient was free of infectious episodes and remained fully ambulatory. This case illustrates possible longterm effects of a 10 days continuous rGM-CSF infusion on granulocyte numbers and functions. Further trials in more patients are needed to corroborate these findings.

P 11 EFFECTS OF ALPHA-INTERFERON THERAPY IN PATIENTS WITH HAIRY CELL LEUKAEMIA: A MULTIPARAMETER LONGITUDINAL EVALUATION.

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In this study we report the results of a longitudinal evaluation of several clinical, histological and biological parameters in 9 patients with hairy cell leukaemia (HCL) treated with recombinant alpha-2 interferon (a-IFNr, Shering Corp.), given subcutaneously three times a week (2 x 10^6 IU/s.m.) for 12 months. Beside the strict surveillance of clinical and haematological parameters, the study included the histological and immunohistological analysis of bone marrow biopsies, the evaluation of NK in vitro activity of PBMC, and the measurement of the serum levels of interleukin-2 receptors (sIL2R). Most of these investigations were performed before and after 1,3,6, and 12 months of IFN therapy, and at regular intervals after stopping therapy in some cases. A substantial clinical and haematological improvement was obtained in all cases but one, as judged by the normalization of blood counts and spleen size. The clinical improvement was followed by a progressive reduction of neoplastic bone marrow infiltration which was minimal, but still detectable in all cases by immunohistology, at the end of IFN treatment. Also, the serum levels of sIL2R, which were very high before treatment (mean$\pm$SD = 25,858$\pm$11,846 U/ml), progressively decreased but never returned within the range of normals (normal controls = 232$\pm$118 U/ml). The NK in vitro activity, which was extremely low before treatment, started to rise after three months, and reached normal values after 6-8 months in most cases. Three months after stopping IFN treatment, sIL2R levels were already increased, and showed an inverse correlation with the NK activity which started to decrease. The variations of these latter biological parameters preceded in all cases the clinical and haematological evidences of relapse. Taken together, our data suggest that a complete clearance of neoplastic cells from the bone marrow is unlikely to occur in HCL after IFN treatment. Furthermore, a biological evaluation seems very accurate in monitoring the response to IFN therapy and to detect the early signs of clinical relapse.

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P 12 INTERFERON PRODUCTION IN LYMPHOPROLIFERATIVE DISEASES.

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Alpha-interferon (A-IFN) has been used in the treatment of lymphomas, myelomas, hairy cell leukemias and other malignancies. Very little, however, is known about the metabolism of this naturally produced immunomodulator in human malignancies. We have assayed IFN production by fresh peripheral blood cells from patients with non-Hodgkin lymphoma (NHL), Hodgkin's disease (HD), hairy cell leukemia (HCL), T-cell lymphoma (TCL), chronic lymphocytic leukemia (CLL) as well as by cells from normal (N) controls. Triplicates of 36 x 10^4 freshly drawn unseparated leucocytes were incubated in medium alone or supplemented with inactivated Newcastle disease virus (NDV), 700 μg/ml of corynebacterium parvum (CP) for 24 h or with PHA (4 μg/ml) for 72 h to stimulate respectively A-IFN (NDV and CP) or G-IFN (PHA) production. Supernatants were assayed for their capacity to protect the appropriate cell cultures against the cytopathic activity of vesicular stomatitis virus. Results are expressed in laboratory units (LU).

Average (median) LU of IFN produced after stimulation by :

Type	N	0	A-IFN (NDV)	A-IFN (CP)	G-IFN (PHA)
N	6	4 (5)	134 (57)	161 (96)	99 (82)
HCL	2	4 (4)	8 (8)	H (4)	66 (66)
HD	10	5 (5)	58 (43)	37 (21)	39 (17)
CLL	9	5 (5)	8 (8)	7 (6)	176 (96)
NHL	9	5 (5)	34 (24)	33 (40)	177 (68)
TCL	4	5 (5)	33 (5)	29 (8)	10 (6)

We thus show that in HCL and in CLL, A-IFN production in vitro is apparently abrogated and that in NHL (whether T or B) and in HD to a lesser extent, peripheral leucocytes display a reduced capacity of A-IFN production. It is noteworthy that in CLL, a disease often complicated by cytopenia, G-IFN production appears to be greater than normal.

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IFN THERAPY IN PERIPHERAL T-CELL LYMPHOMAS (PTCL). C. Gisselbrecht*, B. Coiffier**, M. Simon***, E. Lepage*, Y. Devaux**, M. Boiron*. St-Louis Paris*, E. Herriot Lyon**, C.H.U. Lille ***

PTCL, excluding lymphoblastic lymphoma and mycosis fungoïde (MF),are a morphologically heterogeneous group of non-Hodgkin's lymphomas. They are characterized by a poor prognosis, very often refractory to conventionnal chemotherapy. New chemotherapy regimens have been reported to have CR rates of 70%-75%, however sustained CR remains to be seen. IFN therapy has been reported to be active in lymphoproliferative malignancies such as MF, hairy cell leukemia, follicular non-Hodgkin's lymphomas. However no clinical trials has been published on PTCL. We reported 11 cases of PTCL treated with IFN recombinant. Mean age was 45 y. (range 30-69) male 7 pts female 4 pts. IFN recombinant (Intron A) was administered subcutaneously at the dose of 5Mx3/week in 8 pts, 10 M/day in 4 pts. Response was evaluated after at least one month of treatment. 7 pts were in relapse after initial intensive chemotherapy including Adriamycine and Cyclophosphamide, of whom 3 were refractory to salvage chemotherapy, 3 pts were in partial response after chemotherapy and 1 pt had received only corticosteroids therapy. Initial stage distribution was : IV, 8 pts, III, 2pts, II, 1 pt with bulky lymphadenopathies. Clinical symptoms were found in 9 pts. Response to IFN therapy was as followed: 1 CR persisting more than 14 months, 1 major response lasting more than 10 months ; 2 partial responses lasting 6 and 2 months, 2 stable diseases and 5 failures. Except for flu-like syndrom and grade 1 hematotoxicity, no adverse toxicity was seen. 3 pts died from progressive disease. IFN has activity in PTCL and will be evaluated on a larger number of patients.

P 14

DEOXYCOFORMYCIN FOR THE TREATMENT OF REFRACTORY T AND B CELL LYMPHOMA --- CORRELATION TO BIOCHEMICAL PARAMETERS. A.D.Ho, W.Knauf, K.Ganeshaguru, P. Stryckmans, W.Hunstein, A.V.Hoffbrand, Med. Univ. Poliklinik, 6900 Heidelberg, F.R.Germany, Institut Jules Bordet, Brüssels,Belgium, Royal Free Hospital and School of Medicine, London, U.K.

Deoxycoformycin (DCF) is a potent adenosine deaminase inhibitor and has been shown to be effective in lymphoid neoplasia. In a prospective phase II trial (EORTC protocol 06852), the efficacy of this drug in some rare T and B cell neoplasia is investigated. Deoxycoformycin was administered at 4mg/m² IV weekly for 3 weeks and then every other week X 3 to patients who were resistent to conventional treatment.16 patients are now evaluable for response: 3 of 6 patients with Sézary Syndrom,2 of 2 patients with T-chronic lymphocytic leukemia (CLL),1 of 2 patients with T-prolymphocytic leukemia (PLL),and 3 of 3 patients with hairy cell leukemia (refractory to treatment with interferon alpha) showed a major partial response. One patient each with B-CLL,B-PLL and Mycosis fungoides did not respond.Simultaneously we have studied the in vitro and in vivo effects of the drug on DNA strand breaks,adenosine deaminase (ADA) activity, dATP levels and NAD levels in the leukemic cells. In vitro, incubation of the leukemic cells with DCF ($10M^{-5}$) and deoxy-adenosine (10^{-6}M) invariably caused a prompt suppression (already at 4h) of ADA activities. Subsequently dATP levels were elevated and NAD levels were depleted in most samples after 24h. No correlations could be found between these in vitro parameters and clinical response. DNA strand breaks of >50% were found in 9 of 14 cases after in vitro incubation and these data seemed to correlate with clinical response to DCF. Studies of the ADA, dATP and NAD levels in the leukemic cells taken from the patients at 24h, 48h and 5 days after the first administration of DCF also showed that intracellular ADA was suppressed, dATP accumulated and NAD levels decreased in most cases. Again, the extent of dATP accumulation and of NAD depletion did not correlate with clinical response. DNA strand breaks in the leukemic cells in vivo seemed to be the parameter that correlate with clinical response. Thus NAD depletion and DNA strand breaks seemed to be involved in response to DCF therapy. Except for determination of DNA strand breaks, there is as yet no in vitro test predictive of clinical response.

P 15

ADULT T CELL LYMPHOMAS: A CLINICO-PATHOLOGICAL STUDY. H.M. Earl[1], L. Morittu[1], R.L. Souhami[1], W.J. Smith, A.D. Ramsay[2], P.G. Isaacson[2], 1) Dep. of Radiotherapy and Oncology, and 2) Dep. of Histopathology, Univ. College Hosp., Gower Street London WC1, England

A study of 25 adult patients with T cell lymphomas was carried out. The tumours were classified according to the scheme proposed by A G Stansfeld (Lymph Node Biopsy Interpretation. Churchill Livingstone p300-329. 1985). Enzyme histochemistry was found to be of limited value in the identification of T cell lymphomas. Immunocytochemistry using a panel of monoclonal antibodies against T cell antigens, showed a degree of correlation between the immunological profile and morphology, with cases in the pleomorphic large cell (PLC), and monomorphic large cell (MLC) groups showing limited expression of T cell antigens. Rearrangement of the beta-chain of the T cell receptor gene was detected in 12 of the 14 cases studied, and all showed germ-line immunoglobulin genes.

The clinical features revealed a heterogeneous group of patients with an age range of 16-79 years (median 50 yrs), and a male predominance (16M:9F). At presentation 18/25 (72%) had lymphadenopathy, whilst 11/25 (44%) presented at extra-nodal sites: skin(5), lung(2), serous effusions(2), bone(1), soft tissue(1), testis(1), bladder(1) and tongue(1), with 7/25 (28%) having exclusively extra-nodal disease. Previous history of note included mycosis fungoides(3), chronic eczema with dermatopathic lymphadenopathy(1), coeliac disease(1), rheumatoid arthritis(1), and 1/2 West Indian patients had positive HTLV-I serology. 2/5 patients presenting with skin infiltration had severe necrotic lesions.

23 patients were treated with intensive chemotherapy (the majority with M-BACOD), one patient with prednisolone and chlorambucil and one patient with radiotherapy alone. 24/25 (96%) responded to initial treatment, with 15/25 CR(60%). 14/25 patients (56%) have now relapsed and 11/25 (44%) have died (Survival: 6-34m, Median 12m). On relapse all patients developed generalised lymphadenopathy, including those presenting with extra-nodal disease, and 3/25 (12%) developed CNS involvement, 2/3 having had bone marrow disease at presentation. Survival rate at one year was 52%.

Adult patients with T cell lymphomas form a heterogeneous group, with a variable clinical course, morphology and immunocytochemical reactivity. Further follow-up should help to define this group more clearly.

P 16

PERIPHERAL T-CELL LYMPHOMA. R. Liang, D. Todd, T.K. Chan, K.L. Wong, F. Ho, S.L. Loke. University Departments of Medicine and Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong.

31 Chinese patients with peripheral T cell lymphoma (PTCL) were reviewed. Using the modified Japanese lymphoma group classification, there were 9 (29%) of the pleomorphic type, 16 (52%) immunoblastic lymphadenopathy (IBL) - like, 2 (7%) T-zone lymphoma and 1 (3%) Lennert's lympho-epithelioid type. 3 (9%) were not classifiable. According to the Working Formulation, there were 13 (42%) diffuse mixed, 5 (16%) diffuse large cell, 10 (32%) diffuse immunoblastic and 3 (10%) unclassifiable lymphomas. All were positive for T11 (E rosette receptor antigen). 54% (15/28) were positive predominently for T4 (helper T cell) and 46% (13/28) for T8 (suppressor T cell). T4/T8 staining was not done in 3. The median age of the patients was 57 years (range 21-90 years). There were 17 males and 14 females. They usually presented with advanced disease and while 13 (41%) patients had bone marrow involvedment, central nervous system disease was not seen. The IBL-like type was associated with a positive Coombs test and polyclonal hypergammaglobulinaemia. 5 of the 9 pleomorphic type were checked for antibody to HTLV-I virus and all were negative. PTCL was associated with poor prognosis which was not influenced by the histologic subtypes and the T4/T8 phenotypes. Of the 29 patients who received chemotherapy, 14 (48%) had complete remission, 5 (17%) partial remission (duration 4, 5, 7, 9, 20+ months) and 10 (35%) had no response. 4 of the complete responders (28%) relapsed (at 4, 6, 9, 13 months). The disease-free survival of the complete responders and the overall survival of all patients at 2 years were 30% and 41% resepctively. The complete response rate of 13 consecutive patients who received the BACOP/L17M regime (BACOP x 3 as induction followed by the L17M consolidation/maintenance regime as for acute lymphoblastic leukaemia) was significantly better than the 16 historic controls who received other less intensive regimes (CHOP, CVP, Vincristine, Chlorambucil), 84% versus 19% ($p < 0.01$). The relapse rate was also significantly lower, 9% versus 100% ($p < 0.001$). There appeared to be an improvement in the disease free survival of the complete responders (80% versus 0% at 18 months) as well as the overall survival of all patients (60% versus 36% at 18 months) but the differences did not reach statistical significance.

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P 17 CIRCULATING IMMUNE COMPLEXES (CIC) IN ANGIOIMMUNOBLASTIC LYMPHADENOPATHY (AILD). H.H.Euler, C.Schilling, B.Glass, A.C.Feller, K.Lennert, H.Löffler, 2nd Dept.Internal Medicine and Institute of Pathology, University of Kiel, Kiel, FRG.

We investigated the subtype of CIC in the sera from 33 untreated patients with AILD as defined by morphology and immunohistochemistry. All of those cases investigated for DNA-rearrangement of the T-cell antigen receptor showed clonal T-cell proliferation (ß-chain rearrangement).
As compared with normal controls (n=207) and with other T-cell lymphomas (T-zone lymphomas, pleomorphic lymphoma and Lennert's lymphomas; n=22), 3% polyethylene glycol precipitable CIC in AILD were significantly ($p<0.005$) elevated (183 ± 134 mg/dl), they expressed an IgM-rich and C4-poor subtype with a significantly elevated IgM/C4-quotient within the 3% PEG precipitable material, they were not C1q-binding, and the complement mediated immune complex solubilization capacity (CMIIP) was not reduced.
Among the investigated CIC-parameters, a distinctly elevated IgM/C4-quotient was found to have the highest specificity for AILD (35.2 ± 78.7), as compared with other T-cell lymphomas (4.6 ± 7.5) or normal controls (1.7 ± 1.2) ($p<0.005$).
Few exceptions with normal CIC levels were found in AILD with predominance of CD8+ lymphocytes.
AILD patients with stages II-III disease revealed lower levels of CIC than patients with stages IV.
A similar subtype of CIC was found in some reactive lymphadenopathies with distinct polyclonal B-cell proliferation, e.g. HIV-, EBV- or CMV-infection, but rarely in non-Hodgkin's B-cell lymphomas or Hodgkin's disease.
Thus, the determination of the subtype of CIC is suggested to provide an additional diagnostic tool in patients with AILD.

P 18 LYMPHOPLASMACYTOID AND SMALL CELL CENTROCYTIC LYMPHOMA: The experience at St. Bartholomew's Hospital 1972-1986. M.A. Richards, P.A. Hall, W.M. Gregory, A.G. Stansfeld, J.A.H. Amess, T.A. Lister. ICRF Departmentof Medical Oncology, St. Bartholomew's Hospital, London EC1A 7BE.

The Kiel classification of non-Hodgkin's lymphoma (NHL) identifies two major subgroups - 'Low Grade' and 'High Grade'. The low grade lymphomas are divided into follicular and diffuse subtypes. Lymphoplasmacytoid (LPC) and small cell centrocytic (SCC) are the 2 major subtypes of diffuse low grade NHL. The presentation features and outcome for 62 patients (pts) with LPC and 50 pts with SCC lymphoma managed at St. Bartholomew's over a 16 year period were reviewed and compared with the outcome for pts with follicular and high grade lymphomas.

Nineteen of the 112 pts had localized (stages $I\text{-}II_E$) disease - 18 of the 19 having extranodal disease. The gastrointestinal tract was the primary site of involvement in 12 cases. The survival for pts with localized disease was excellent. 18 are currently alive with median follow up of 8 years.

Ninety-three pts had advanced disease. Lymph node enlargement was present in the vast majority of pts with either LPC or SCC lymphoma. Both groups had a high incidence of splenomegaly, hepatomegaly, bone marrow and peripheral blood involvement. Massive splenomegaly was, however, more commonly found in pts with SCC lymphoma. Nearly 50% of pts with advanced LPC lymphoma had a monoclonal paraprotein band.

Pts with advanced disease were treated with either chlorambucil or CVP, both achieving similar results. The outcome was similar for both histological groups. Survival for these pts was poor (median 40 months) with less than 20% surviving 5 years. Long term survival was worse than that for pts with either follicular or high grade NHL. Multivariate regression analysis identified advanced age ($p = 0.001$), elevated aspartate transaminase ($p < 0.001$) and failure to respond to treatment as adverse prognostic factors.

P 19 CLINICO-PATHOLOGIC AND IMMUNOLOGIC ASPECTS OF PRIMARY CUTANEOUS LARGE CELL LYMPHOMAS OF FOLLICLE CENTER ORIGIN. C.J.L.M. Meijer[2a], R. Willemze[1ab], E. Scheffer[2b], W.A. v.Vloten[1c], J.Toonstra[1c], S.C.J.v.d.Putte[1c], Dept. of Dermatology[1] and Pathology[2], Free University, De Boelelaan 1117, 1081 HV Amsterdam[a], Univ. Hosp. Leiden[b], State Univ. Utrecht[c], The Netherlands.

The clinical, histological and immunological characteristics of 16 diffuse large cell lymphomas of follicle center origin (FCO) with only skin lesions at presentation are described. These patients presented with nodular and tumorous skin lesions, which in 10 of 16 cases were confined to a circumscribed area on the trunk. Histologically, these lymphomas showed nonepidermotropic diffuse dermal infiltrates, mainly consisting of large follicular center cells, with a variable admixture of small cleaved cells, immunoblasts, T-lymphocytes and macrophages. The relative numbers of large cleaved (centrocytes) and large noncleaved cells (centroblasts), respectively, varied considerably in these lymphomas. Immunophenotypically, almost all lymphomas expressed monotypic surface immunoglobulins and HLA-DR antigens, whereas all lymphomas were reactive with B-cell-associated monoclonal antisera B1 and Leu14. The percentage of T9+cells ranged from 40-80%; no correlation with clinical behaviour was found. Thirteen of the 16 patients are currently alive and in complete remission, with a median survival of 40 months. In 8 of the patients the development of large tumorous lesions had been preceded for one to twenty years by slowly progressive papular and plaque like lesions clinically suggestive of Jessner's disease. It is concluded that the large-cell lymphomas of FC origin of the skin represent a clinicopathologically and immunophenotypically homogenous group of neoplasms, which appear to have a favorable prognosis.

P 20 PHENOTYPIC ANALYSIS OF DIFFUSE LARGE CELL LYMPHOMA IN PARAFFIN SECTIONS: THE RELATIONSHIP TO PROGNOSIS AND NATURAL HISTORY S Hart P Toghill G Vaughan-Hudson KA MacLennan , Dep. Histopathology, Queen's Med. Ctr., Nottingham, England

Recently produced monoclonal antibodies are now available which recognise B and T lymphocytes in paraffin sections (MB_1, MB_2, and MT_1 Euro Diagnostics Ltd). These reagents reliably discriminate between B and T cell non Hodgkin's lymphomas and the results of paraffin sections immunophenotyping correlate well with those obtained on frozen sections. Using the indirect and ABC immunoperoxidase techniques we have stained 106 cases of diffuse large cell lymphoma (81 nodal, 25 extranodal) with MB_1, MB_2, and MT_1, for immunoglobulin light and heavy chains and with a monoclonal antibody reactive with HLA-DR in paraffin sections (HL40).

The 25 stage 1E extranodal lymphomas (5 upper aerodigestive tract, 5 CNS, 5 gastrointestinal tract, 5 testicular, 3 thyroid and 2 bone) all stained with MB_1, MB_2 or both. 19 expressed monoclonal cytoplasmic immunoglobulin and 21 expressed HLA-DR. Staining of tumour cells was not observed with MT_1. With the exception of 5 primary CNS lymphomas there was an excellent response to local radiotherapy with a long disease free survival.

61 of the nodal diffuse large cell lymphomas stained for MB_1, MB_2 or both and 47 contained monoclonal cytoplasmic immunoglobulin. Six showed positive staining with MT_1 indicating a T cell lineage which was confirmed by frozen section immunohistology. A lineage specific marker could NOT be detected in 14 cases.

There were no significant differences in the survival and response to therapy of B cell, T cell and "null" cell nodal diffuse large cell lymphomas. The only factor conferring a significant survival advantage ($P<0.01$) was the presence of strong surface staining for HLA-DR.

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P 21 INTRATUMOR HETEROGENEITY IN NON-HODGKIN'S LYMPHOMA.

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Most Non-Hodgkin's Lymphomas (NHL) can be properly classiffied according to their lineage and stage of maturation. However, in some cases discrepancy between histological classification and clinical course exists. This may be due to genotypic and/or phenotypic intratumor heterogeneity, either present at presentation of the disease or developing later on. In the present study, morphologic heterogeneity was studied in uniformely fixed, processed and plastic embedded biopsies. Multiple positive biopsies of 115 patients from the University Hospital, diagnosed between 1974 and August 1985 were reviewed (323 biopsies; 22 post mortem specimen). Differences in growth pattern and well known cytologic variation as paratrabecular centrocytic/lymphocytic bone marrow infiltrates in Centroblastic/Centrocytic lymphoma (CB/CC) were not considered as discordance.
Out of 41 patients with >1 initially positive biopsies, 13 showed discordant morphology in these biopsies (33%). Discordances existed between biopsies of soft tissues (lymph node n=11; spleen n=2; tonsil n=1; stomach n=1; lung n=1) and bone marrow (n=13). In most cases, bone marrow biopsies suggested a lymphoma of lower malignancy grade (n=6) or less maturation (n=6), but sometimes a reverse discordance was found (n=2 and n=1 respectively). Most discrepancies were found in patients with Immunocytoma (n=5), nodular CB/CC (n=3), Centroblastic (n=3) and Centrocytic (n=2) lymphoma, as diagnosed in soft tissues. In 2 cases, a concomitant lymphoblastic lymphoma and in 1 case, a plasmablastic lymphoma was found in the bone marrow.
In 23 out of 89 cases with available positive follow up biopsies (27%), discordant morphology was found. Most cases were found in Chronic Lymphocytic Leukemia (CLL; n=7), Immunocytoma (n=5), nodular CB/CC (n=6) or Centrocytic lymphoma (n=5). In 6 cases tumor progression was found at post mortem eximination.
Our data confirm the older data of literature on initial heterogeneity, based on staging laparotomy. They stress that NHL cannot be regarded as tumors simply blocked in one stage of maturation, and that morphology can change during follow up in a considerable number of patients.

P 22 STATUS OF NON-HODGKIN'S LYMPHOMA IN EGYPT.

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Malignant lymphomas(ML)constitute the third most common cancer amongst adults,and the first common cancer in the pediatric cancer patients in Egypt.From January 19[illegible] till December 1985,1032 cases of ML were collected at the NCI,Cairo;675 cases were of the Non-Hodgkin's type representing 65.4%.There was a male preponderance of a 3:1 ratio.Average age was 45 years.Histo-pathology according to the working formulation showed that 15.1% were of the low grade type,51.2% of the intermediate, and 32.7% of the high grade type,with 97% of the diffuse type.Burkitt-like lymphoma,previously undescribed in Egyptian material,was present in 10.8% of cases.Skin lesions were encountered in 8.7% of cases.Primary nodal presentation was in 88.1% of cases,and primary extranodal in 11.9%.The latterwas mostly;56.2%,in the gastrointestinal tract.Primary lymphoma of the small intestine IPSIT was encountered in 25 cases.In all the NHL cases the tumour burden was always high,with an average of 8 cm in a group of lymph nodes.The cases with B symptoms were 53%.Clinically the workup staging revealed 1[illegible]% stage I,11% stage II,27% stage III,and 48% stage IV. Immunologic typing in 107 cases showed that 70 were of the B type,[illegible]% of the T type,and 13 of the Null type. Response of this aggressive lymphoma to chemotherapy was studied in 100 cases who recived CHOI therapy.It consisted of:vincristine 1.4 mg/m.square,adriamycin 50 mg/m.square,and cyclophosphamide 750mg/m.square;i.v. day one,together with prednisone 100 mg daily for 5 days.Courses to be given every 21 days,for 8 courses. In cases with favourable histology,complete remission (CR) was obtained in 9/17 cases:53%,and partial remission (PR) in 5/17 cases:29.4%.In cases with unfavourable histology CR was obtained in 33/79 cases:41.7%,and PR in 23/79 cases:29%.Thus in 96 fully evaluable patients an overall response of 82.4%,and 70% was respectively obtained.The median survival for CR patients is 36 + months,for PR patients 26 + months,and 5 months for non-responders.Toxicieties were none or mild in 33%, moderate in 36%,severe in 18%,life-threatening in 10% and fatal in 3%.

P 23 CLINICAL AND PATHOLOGICAL FEATURES OF MALIGNANT LYMPHOMAS IN CHINA.

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Malignant lymphoma is a common cancer in China. On a nationwide retrograde survey, the age-adjusted mortality rate was 1.16 (male 1.35, female 0.96) per 100,000, composed 1.73% (male 1.68%, female 1.77%) and ranked 11 among all malignancies. On a review of 2500 cases consecutively seen during 1958-1983 in Cancer Institute & Hospital, Chinese Academy of Medical Sciences, Beijing, the following clinical and pathological features are revealed: 1. The proportion of Hodgkin's disease is much lower than that in Western countries, but similar to Japan and India; 2. Among non-Hodgkin's lymphoma (NHL), the percentage of T-cell lymphoma was higher. In a review of the slides of 553 lymphoma cases from 5 geographic areas, demonstrated possible regional variation in the prevalance of cases with T-cell morphology. The highest rate was 33% and the lowest was 20%; 3. More than 95% of our NHL cases were diffuse type, while nodular type less than 5%; at the same time, only 5% of all NHL patients were low grade, and more than 30% belonged to high grade; 4. In 100 patients of NHL primarily developed in Waldeyer's ring, there were 34 cases with gastrointestinal involvement, particularly the stomach and small intestine; 5. In analysis of lymphoblastic lymphoma/leukemia patients showed their prognosis was very poor, but that of immunoblastic lymphoma was good, while that of mycosis fungoides and Burkitt was reasonable. In order to improve the clinical results of multimodality treatment in malignant lymphoma, the factors influecing the long-term survival are also analysed and will be discussed further.

P 24 PROGNOSTIC FACTORS IN NON-HODGKINS LYMPHOMA STAGE I TREATED WITH RADIOTHERAPY.

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The Ann Arbor staging system has been extensively used in non-Hodgkin's lymphoma (NHL). The important prognostic function of the staging system in NHL seems to be the recognition of stage I. Radiotherapy in stage I has been reported to result in long-term disease-free survival (DFS) in a high proportion of the patients. To further improve the results for NHL stage I it is of importance to recognize subgroups of patients with high relapse rates after radiotherapy. The outcome for 156 consecutive patients treated between 1969-1983 were analyzed according to different pretreatment variables. The treatment consisted of local radiotherapy in 147 patients, 11 of these patients recieved adjuvant chemotherapy (COP) as part of a randomized study. Nine patients were only operated upon.

Results: Among the 147 patients receiving radiotherapy complete remission was obtained in 93%. The estimated overall 5 and 10-year survival for the 156 patients was 79% and 72 %, respectively. The DFS for all patients was at 5 and 10 years 60 and 58%, respectively. The 71 patients with nodal involvement (Waldeyer's ring not included) had a slightly higher relapse rate (52%, 10 year) than the 85 patients with extranodal (62%, 10 year). Among the nodal lymphomas, unfavourable clinical course was observed in patients presenting with a node > 5 cm in diameter. Involvement of the Waldeyer's ring and other sites in the gastro-intestinal tract were favourable (79% DFS, 10 year survival) than other extranodal sites (48% DFS survival). No difference in DFS survival was found between the 3 different histopathologically defined prognostic groups i.e low-grade, intermediate-grade and high-grade malignant NHL.

Conclusion: Disease-free survival after local treatment of NHL stage I varies according to size of the tumor and site of presentation. As high-grade NHL are curable with combination chemotherapy, additional treatment can today only be recomended for this group. According to this study, patients with nodal involvement and extranodal sites outside the gastro-intestinal tract may be recommended such treatment.

P 25 NON-HODGKIN'S LYMPHOMAS (NHL) WITH SURFACE IgD ARE ASSOCIATED WITH A BETTER PROGNOSIS, INDEPENDENT OF MALIGNANCY GRADE.

P. Kluin, K.v.Groningen, M.v.d. Sandt, P. Spaander, J.te Velde, H. Haak, T. Stijnen, R. Otter, The Working Party NHL of the Comprehensive Cancer Centre West. THE NETHERLANDS

In the region covered by the CCCW, a population based registry of all NHL (ALL, CLL, primary cutaneous T-cell lymphoma and myeloma excluded) yielded 381 new cases from June 1981 until December 31, 1984. All NHL were reclassified according to the Kiel classification by a panel of 3 pathologists. In more than 70 % frozen material was available for (immuno)phenotyping. Apart from histological and clinical parameters, the prognostic significance of the immunophenotype was determined. Within B-NHL which comprised 88% of all phenotyped lymphomas, the presence of surface IgD (sIgD) appeared to be a major parameter for prolonged survival. No relationship between expression of light chain isotype and other heavy chains with survival was found.
Survival probability curves showed a significant higher survival for sIgM+,sIgD+ NHL (n=32; 75% survival point not yet attained) against sIgM+,sIgD- NHL (n=81; 50% survival 25 months; p=0.001). This difference appeared not related to malignancy grade according to the International Working Formulation : in low grade lymphomas no deaths occurred in the sIgM+,sIgD+ group (n=11) against 6 within 50 months in the sIgM+,sIgD- group (n=19; n.s.). In intermediate grade NHL, prognosis was much better (p=0.02) in sIgM+,sIgD+ cases (n=20) with a 75% survival point not yet attained, and a 50% survival of only 18 months for sIgM+,sIgD- NHL (n=48). No high grade NHL with expression of sIgD were found against 10 tumors with sIgM.
Confoundig with other important prognostic parameters as clinical stage (15 and 16% stage I) and age (mean age 61 and 63 yr) was excluded. Light chain isotype distribution was identical with other B-NHL. An association between CD5 and sIgD expression was found (p=0.001). However, no relationship between CD5 and survival existed. This may be caused by the exclusion of overt CLL from this study.
It is concluded that the expression of sIgD is an important independent prognostic parameter for survival in B-NHL.

P 26 ADVANCED STAGE LOW GRADE NON-HODGKIN'S LYMPHOMA (NHL): PROGNOSTIC FACTORS FOR SURVIVAL.

U. Vitolo, M. Bertini, A. Levis, L. Orsucci, M. Canta, G. Cametti, A. Decrescenzo, A. Jayme and L. Resegotti. Div. Ematologia, Ospedale S.Giovanni Battista, Torino, Italy.

55 patients (pts) with advanced stage low-grade NHL treated over a 11-year period from 1973 to 1984 were retrospectively evaluated. Histologic diagnosis was reviewed according to the Working Formulation (WF). 49% had small lymphocitic (SL), 22% follicular small cleaved (FSC) and 29% follicular mixed small cleaved and large cell (FM). 11% were advanced stage II ($\geq$3 nodal sites or bulk disease), 22% stage III and 67% stage IV. 62% had bone marrow involvement, 24% had bulk disease and 13% B symptoms. All patients were initially treated regardless of their clinical presentation. Therapy was not randomly assigned and consisted of single agent chemotherapy (chlorambucil or cyclophosphamide) in 36% or combination chemotherapy (CVP or CVP-ABP) in 64%.
CR rate was 40%. In a multivariate regression analysis the achievement of CR was adversely affected ($p<0.02$) by:B symptoms, low absolute neutrophil count (ANC), bulk disease, single agent chemotherapy and SL histology. Stage, age, bone marrow involvement, anemia ant trombocytopenia did not affect CR rate. Median survival (MS) for all 55 pts was 93 mo. In an univariate analysis survival was significantly better for pts with no symptoms (A:MS 93 mo vs B:MS 17 mo $p<0.01$), with no stage IV (II+III:MS not reached, IV:MS 54 mo $p<0.01$) and pts in CR(CR:MS not reached, NR:MS 58 mo $p<0.02$). Histology, bulk, type of therapy,age did not affect survival rate. However a multivariate regression analysis for survival showed that only B symptoms ($p=0.01$) and low ANC ($p=0.05$) were significant independent factors in predicting a worse outcome. Such an analysis failed to demonstrate the survival advantage of an initial CR. All the analysis were performed within each histologic sub groups (SL and FSC+FM) and the above results were confirmed. Pts were retrospectively subdivided in 2 groups: GP1 34 pts who,because their clinical presentation, would be elegible for observation only and GP2 21 pts who need treatment up front. MS was:GP1 93 mo vs GP2 49 mo ($p<0.01$). Within each group there was no difference in survival between CRs and NRs. These data support the current conservative approach of watch and wait policy and palliative therapy in low grade NHL. However most of these pts die of their disease and mainly those with poor prognostic factors, are in urgent need of new treatments.

P 27 PERSISTENT GENERALIZED LYMPHADENOPATHY (PGL) VS MALIGNANT LYMPHOMA (ML): SIMILARITIES AND DIFFERENCES IN CLINICAL AND LABORATORY FINDINGS AT PRESENTATION.

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The purpose of this study is to document the clinical and laboratory findings at presentation of 38 intravenous drug abusers with pathologically documented PGL and 50 patients with biopsy proven ML (30 HD, 20 NHL) not related to AIDS, all aged 40 years or less and consecutively seen and evaluated with a similar clinico-pathological approach since May 1984 in a single Institution in Italy. Their main clinical and laboratory findings at presentation have been compared and statistically analised (x= $p<0.05$; xx= $p<0.001$). Results:

	PGL (N=38)	%	ML (N= 50)	p
I.V. drug abuse history	100		0	xx
HIV antibodies	100		0	xx
Postero-cervical nodes	55		2	xx
Latero-cervical nodes	89		46	xx
Axillary nodes	97		24	xx
Mediastinal nodes (x-ray)	0		62	xx
Abdominal nodes (LAG & CT scan)	100		31	xx
Splenomegaly (Clinical & CT scan)	77		50	n.s.
Fever	26		26	n.s.
Night sweats	32		14	x
Weight loss	18		10	n.s.
Infections in the previous year	87		6	xx
EBV antibodies (past exposure)	94		74	x
↑ESR	38		74	xx
↑Cupper	56		61	n.s.
↑LDH	3		20	x
↑β2 microglobulin	82		41	xx
T4/ T8 < 1	74		32	xx
Policlonal ipergammaglobulinaemia	82		22	xx
Anaemia	0		30	xx
Thrombocytopenia (<150.000)	0		0	-

Although pathology is the decisive diagnostic tool, our results document that selected clinical and laboratory findings may contribute to a better differentiation of PGL from ML not related to AIDS. Therefore, at this time of AIDS epidemic, young ($\leq$40 year old) patients presenting with generalised lymphadenopathy, apparently not related to known groups at risk for AIDS, should be evaluated also according to a protocol which include the detection of symptoms and signs and laboratory data significantly increased among the PGL patients group.

P 28 PRIMARY BRAIN LYMPHOMAS IN AIDS.

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The occurrence of primary brain lymphoma without evidence of systemic lymphoma is a characteristic of AIDS associated malignancy. These lymphomas have been documented in high risk groups which have included both homosexuals as well as intravenous drug abusers. Since August, 1983 we have seen 9 patients with primary brain lymphoma and they constitute the subject of this report. All 9 patients were male intravenous drug abusers with a median age of 31 years old. Seven of the 9 were incarcerated in the New York State prison system. Eight of the 9 patients were diagnosed by brain biopsy and in one patient the diagnosis was an incidental finding at autopsy. Presentation included altered mental status, obtundation and hemiparesis. Computerized tomography of the head disclosed single or multiple hypodense lesions. In all instances biopsy showed high grade lymphoma. Survival in all patients was short with none surviving beyond three months despite therapy. Treatment included whole brain radiation therapy, procarbazine,and nitrosourea which did not result in significant tumor regression. Three patients did not receive lymphoma directed therapy because of complicating medical conditions. These included interstitial pneumonia, concurrent cerebral toxoplasmosis and sepsis. In this context, it is important to find reversible conditions that may also occur in this setting. The diagnosis of cerebral toxoplasmosis which may also present as central nervous system mass lesion is a reversible infectious complication which can be readily diagnosed and treated with appropriate antibiotic therapy. Serologic studies as well as biopsy is essential to the complete evaluation of patients with central nervous system mass lesions. We conclude that 1) central nervous system lymphoma in the setting of AIDS is highly refractory and the diagnosis establishes a poor prognosis; 2) complicating medical conditions may preclude aggressive treatment of this tumor; 3) radiation therapy, nitrosourea and procarbazine are ineffective; 4) accurate diagnosis of possible reversible causes of reversible intracerebral mass lesions should be aggressively pursued; 5) alternate therapies for primary brain lymphomas may include high dose systemic chemotherapy.

P 29

PRIMARY CENTRAL NERVOUS SYSTEM NON-HODGKIN'S LYMPHOMA (PCNSL): A CLINICAL, RADIOLOGICAL AND PATHOLOGICAL STUDY OF 51 PATIENTS IN THE CT-ERA (1974-1986). B. O'Neill, P. Banks, J. O'Fallon, J. Earle, J. Colgan. Comprehensive Cancer Center, Mayo Clinic/Foundation, Rochester, MN 55905. USA

In the 12 years of CT scanning at Mayo, 51 patients had indeterminate parenchymal brain lesions pathologically confirmed as PCNSL. Patients with occult lymphoma or with predisposing conditions were excluded.

Diagnosis was established by biopsy (17), craniotomy (31), CSF cytology (1), or autopsy (2). The PCNSL cohort was 32 men and 19 women, ages 9 to 84 (mean 56.6 years). Duration of symptoms was short (mean 8.7 weeks; range 0 - 104 weeks). Patients presented with neurologic symptoms of diffuse (20) or of focal (18) origin, or of both (13). Most tumors displayed large-cell morphology (25, plus 7 immunoblastic). Other histologies included mixed-cell type (6), poorly differentiated lymphocytic type (8) and small lymphocytic type (3). CT scanning displayed a distinctive, almost pathognomic appearance.

Distinct PCNSL subgroups appeared: 1.) a large group (74.5%) with symptoms of less than 10 weeks duration; 2.) a majority with large cell histology (62.7%); 3.) a large group whose diagnosis was made at or beyond 40 years of age (84.3%); and 4.) a small group with PCNSL and intraocular lymphoma (21.6%). Three patients developed late systemic recurrence (intestine, testis, kidney). We will present the clinical, radiographic and pathologic features of these patients and will correlate treatment outcome with them.

P 30

PRIMARY CHEMOTHERAPY FOR LOCALIZED NON-HODGKIN'S LYMPHOMA OF UNFAVORABLE TYPE ARISING FROM EXTRANODAL SITES. K. Sampi, Saitama Cancer Center, 818 Komuro Ina, Saitama-ken 362, Japan

Thirty-nine evaluable patients with localized stage of non-Hodgkin's lymphoma of unfavorble type arising from extranodal sites were treated with primary chemotherapy consisting of CVP (2 patients) or C-MOPP (2 patients) or anthracycline-based combination chemotherapy (35 patients). Patients with stage I of tumor $\geq$5 cm in diameter and with stage II were eligible for this study. There were 22 men and 17 women, ranging in age from 26 to 85 years with a median age of 63 years. Twelve patients were aged over 70 and 5 over 80. The primary chemotherapy consisted of 650 mg/m^2 of cyclophosphamide on day 1, 45 mg/m^2 of adriamycin on day 1, 2.0 mg/m^2 of vindesine on day 1 and 40 mg/m^2 of prednisolone on day 1 to 5. 60 mg/m^2 of epiribicin was used in patients over 80 years in stead of ADM. This combination chemotherapy was repeated every 4 weeks and given 11 cycles. Tumor was originated from Waldeyer's ring (35 patients), Stomach (2 patients) and uterus (1 patient) and parotid gland (1 patient). There were 2 cases of stage I disease and 37 cases of stage II disease. Histology was classified by the use of Lymphoma Study Group in Japan which is almost similar to the Working Formulation. Histologic subtypes were follicular large (1), diffuse large (34), diffuse mixed (3), and duffuse medium (1) lymphoma. Seven patients had a bulky tumor of more than 8 cm in diameter. The surface marker of tumors was examined in 11 cases, of which 4 were T-cell Lymphoma. A complete response induced by chemotherapy was obtained in 32 (89%) of the 36 patients with a measurable tumor. Only one of three patients who did not attain the complete response was expired. The average course of anthracycline-based combination chemotherapy was 10 (range 2 - 10). Twenty-one patients received radiotherapy of the involved field. Of the 36 responders, only 4 recurred. The complete response was well sustained with an actuarial relapse-free survival of 83 % at 5 years. To date 5 patients expired; three of these died after a recurrence, one under complete remission and the remaining one without attaining the CR. The survival curve of all patients became flat at 38 months and was well sustained with an actuarial survival of 85%. This report regimen is highly effective treatment strategy for patients with clinically apparent localized NHL of extranodal sites.

P 31

PRIMARY EXTRA NODAL LYMPHOMA IN THE MIDDLE EAST. P Salem, E Anaissie, S Geha, C Allam, J Jabbour, L Hashimi, N Habboubi, N Ibrahim, M Khalyl. American University of Beirut Medical Center (AUBMC), Beirut, Lebanon.

417 evaluable patients with non-Hodgkin's lymphoma were diagnosed between January 1974, and December 1983, at the AUBMC. Of these, 183 (44%) had extra nodal lymphoma, and are the subject of this abstract. The lymphoma was diffuse in histopathological pattern in 95%. The commonest subtype of lymphoma was diffuse large cell (60%). Burkitt's lymphoma of documented extra nodal origin occurred in 18 patients. The most common primary was the gastrointestinal tract (GI), accounting for 46.5% of patients. This was followed by Waldeyer's Ring (19%), and bone (6%). Among gastrointestinal lymphomas, the lymphoma was primary in small intestine in 75%, and stomach in 25%. Primary small intestinal lymphoma was of the Immunoproliferative Small Intestinal Disease (IPSID) type in 50% of the cases, while in the remaining 50% the lymphoma was of the non-IPSID category. IPSID was characterized by chronic diarrhea, weight loss, presence of a diffuse uninterrupted, dense, mucosal cellular infiltrate involving the entire length of the small intestine, and was frequently associated with Alpha Heavy Chain Protein. Non-IPSID presented with abdominal mass, or symptoms related to small intestinal obstruction, bleeding or perforation. The disease was segmental in the small intestine, with the intervening segments being free of lymphomatous disease. Both, the dense mucosal cellular infiltrate, and Alpha Heavy Chain Protein which occur in IPSID were lacking in this category of lymphoma. Gastric lymphoma occurred in 21 patients with a median age of 50 years. Diffuse large cell lymphoma occurred in 76% of patients. 34 patients had Waldeyer's Ring lymphoma, and 66% of them had the lymphoma in the tonsillar region, while 20% in the nasopharynx. In 7 patients involvement of the GI tract was documented either at presentation or during the course of the disease. In conclusion lymphomas in the Middle East are characterized by: 1) The high incidence of extra nodal lymphomas among non-Hodgkin's lymphomas. 2) The high incidence of gastrointestinal lymphomas among extra nodal lymphomas. 3) The presence of IPSID - a disease which is peculiar to the region, and 4) The rarity of follicular lymphomas.

P 32

THERAPY-INDUCED OVARIAN FAILURE (OF) IN WOMEN TREATED FOR HODGKIN'S DISEASE (HD). A STUDY OF 85 CASES. E. Morra, M. Lazzarino, D. Inverardi, S. Merante, E. Orlandi, A. Canevari, C. Bernasconi. Divisione di Ematologia, istituto Scientifico Policlinico S.Matteo, Pavia, Italy.

We studied 85 consecutive premenopausal women successfully treated for HD, to assess the effect of different first-line treatments on gonadal function. All patients (pts) had completed therapy a mean of 45 months earlier (minimun follow-up 12 mos). Ovarian functional status was assessed on the basis of menstrual pattern (regular menses, RM, irregular menses, IM, amenorrhea, AM), fertility histories, and on measurements of estradiol (E_2), and serum gonadotropins, both basally and after administration of LH-RH. Of 82 evaluable women who had regular menses prior to therapy, 32 (39%) showed posttreatment persistent AM, 8 (9.8%) presented IM and 42 (51.2%) RM. Hormone levels corresponded to menstrual status. The 42 pts with RM showed a mean FSH of 7.3 mUI/ml, mean LH of 7.7 mUI/ml, and mean E_2 of 102.1 pg/ml. Patients with AM had significanlty higher ($p<0.001$) gonadotropin levels (mean FSH of 63.9 mUI/ml, mean LH of 47.8 mUI/ml) and lower ($p<0.01$) E_2 levels (mean 19.2 pg/ml). As would be expected with OF, in amenorrheic women there was an exaggerated response to LH-RH. The group of pts with IM had intermediate levels of gonadotropins (mean FSH 31.3 mUI/ml, mean LH 26.1 mUI/ml) and erratic E_2 levels (mean 99.4 pg/ml), typical of the perimenopausal ovary.

Ovarian damage appeared to be directly related to cumulative gonadal exposure to therapy: intensity of chemotherapy (CT) including alkylating agents and procarbazine, additional pelvic radiotherapy (RT). None of the 12 pts treated with only RT excluding pelvis developed OF. Irreversible AM occurred in 21/58 pts (36.2%) after CT$\pm$RT excluding perlvis, in 10/11 (91%) after CT+RT including pelvis, and in one pt treated with total nodal irradiation (TNI). Regarding the effect of the different types of CT on menstrual pattern, 21/54 (38.8%) of pts treated with MOPP-based CT$\pm$STNI and none of the 4 pts given ABVD$\pm$STNI developed amenorrhea. Regarding the correlation between age at the time of treatment and ovarian functional status, women below the age of 30 tolerated more intensive antineoplastic regimens before onset of AM. No spontaneous abortions nor fetal malformations were reported in 13 pregnancies occurring in 10/23 still menstruating women not practicing birth control. This study also shows the prophylactic and therapeutic efficacy of treatment with estroprogestinic combinations. Regarding the protective effect of combined estrogen and progesterone given throughout CT, of 11 pts (median age 24 yrs, range 15-45) thus "covered" during MOPP-based CT, only one developed OF. This compares favourably with the 46.5% incidence (20/43) of OF observed in similarly treated pts (median age 26 yrs, range 13-45), not receiving hormone protection. In addition, hormonal replacement administered to 11 young women with therapy-induced OF proved to resolve the physical and emotional problems due to early menopause.

P 33

HODGKIN's DISEASE (HD) IMMUNOSCINTIGRAPHIC IMAGING WITH AN ANTI-STERNBERG-REED CELLS MONOCLONAL ANTIBODY (MAb). PRELIMINARY RESULTS IN 4 PATIENTS. P. Carde[1], L. Manil[1], M. Pfreundschuh[2], F. Boudet[1], B. Caillou[1], M. Hayat[1], C. Parmentier, V. Diehl[2].
1. Institut Gustave-Roussy, Villejuif, France.
2. Medizinische Universitätklinik I, Köln, FRG.

The H-SR-1 MAb (raised against the L428 HD-derived cell line ; DIEHL et al, Cancer Surveys 4 : 399, 1985), displaying the same immunoreactivity pattern as Ki-1, was used for immunoscintigraphic detection of HD in 4 untreated patients. After protein A purification from crude ascites, the MAb was labeled with ^{131}I by the iodogen method. Each patient received 0.5 mg H-5R-1 labelled with 48 to 67 MBq ^{131}I. Scintigraphic acquisitions (CGR gammacamera) were performed daily (for up to 6 days) and the best results could be obtained after 2-4 days. Briefly, we detected several cervival (2 patients) and mediastinal (2 patients) HD lymph nodes when larger then 2 cm in diameter; we also observed in one patient a strong hyper uptake in an HD involved but not enlarged spleen. In order to test the specificity of ^{131}I-H-SR-1 localization, one of these patients was also injected with 0.5 mg of a control anti-alpha-fetoprotein MAb labeled with ^{123}I (111 MBq). A moderate but significant specificity index of 1.3 could be achieved and was correlated with differences in imaging patterns.
On the whole, these preliminary results demonstrate that IS is feasible in HD. The real clinical interest and the specificity of this method deserve to be confirmed in a larger series of patients in which IS and biopsic data should be correlated.

P 34

DIAGNOSIS OF LYMPHOMAS IN BODY FLUIDS BY FLOW CYTOMETRY. B. Schnitzer, Department of Pathology, University of Michigan, Ann Arbor, MI, USA.

Diagnoses and classifications of non-Hodgkin's lymphomas are usually established on the basis of morphologic features in biopsies of lymphoid tissue. Lymphomas may also be diagnosed and classified by correlating cytologic features of neoplastic cells in cytocentrifuge preparations with phenotypic analysis by flow cytometry. Fifteen cases of lymphoma both new and recurrent were diagnosed and classified and immunophenotyped by flow cytometry in cerebrospinal (CSF), pleural (PF) and abdominal fluids (AF). A diagnosis of lymphoblastic lymphoma with varying phenotypes was initially established in the CSF of 2 patients and in the pleural fluid of 2 others. A diagnosis of recurrent small cleaved B-cell lymphoma, 2 IgM, lambda, 1 IgM, kappa, was made in the PF of 3 patients and a small cell B-cell lymphoma (IgM, IgD, kappa) and 2 small cell T-cell lymphomas, both in leukemic phase (T8+ and T4+, T8+, T6-, TdT-) were demonstrated in 3 other patients. One patient who had an erroneous diagnosis of large cell noncleaved lymphoma in a gastric biopsy was correctly diagnosed as having small noncleaved (non-Burkitt's) lymphoma (T10+, B4+, B1+, Ia+, IgM+, lambda+, CALLA+) in an AF. An 11-year-old female with a paraspinal mass was diagnosed as having an early B-cell lymphoma and spared an operative procedure through analysis of cells in the spinal fluid (CALLA+, B4+, TdT+). A lymphoma with a hyperdiploid DNA content and an identical phenotype was established in the PF of a 73-year-old female with a history of carcinoma of breast and a pleural effusion. Another patient was diagnosed as having a post-thymic T8+ lymphoma in the CSF. This lymphoma was found to be otherwise confined to both adrenal glands, producing adrenal insufficiency. The diagnosis of large cell immunoblastic lymphoma with suppressor cell phenotype was confirmed by immunoperoxidase staining of frozen sections of biopsies from both adrenal glands. Finally, a patient with recurrent chylous pleural effusion, usually seen in patients with malignancies, was shown to have a benign polyclonal lymphoid population. We conclude that flow cytometric immunophenotyping of cells from body fluids together with morphologic examination of cytocentrifuge preparations can assist in establishing diagnoses, classifying new and recurrent non-Hodgkin's lymphomas and differentiating them from benign lymphoid proliferations.

Poster Session II

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P 1 COMPARISON OF NON INVASIVE INVESTIGATIONS AND INITIAL LAPAROTOMY IN STAGING OF HODGKIN'S DISEASE IN ADULTS.

J.R. Delpero*, J.A. Gastaut*, J. Jaubert**, D. Fière***, Y. Carcassonne*, P.C. Brizard** and J.J. Viala*** for the LMS-H-80 Study Group. * Institut J. Paoli-I. Calmettes, Marseille, **Hôpital Nord, Saint-Etienne, *** Hôpital Edouard Herriot, Lyon, France.

186 exploratory laparotomies with splenectomy were performed during initial staging of 296 patients with stage I, II A-B and III A Hodgkin's disease. This report compares the results of lymphangiography, ultrasonography and CTscan to the histological findings of laparotomy. Normal lymphangiograph images correlated with normal histological findings in 79 % of cases (15/26) ; for pathologic images, no lymph node involvement was showed in 42 % of cases (10/24) ; for suspicious lymphangiographs, normal lymph nodes were found in 65 % of cases (22/34) and involvement in 35 % of cases (12/34). Lymph nodes assessed as normal during ultrasonography and CT scan were histologically disease free in 71 % (46/65) and 83 % of cases (62/75) respectively. Pathological lymph node involvement detected by CTscan corresponded to Hodgkin's disease in one out of 2 cases (11/22). Spleen assessed as normal during ultrasonography and CTscan was histologically disease free in 65,5 % (76/116) and 65 % of cases respectively ; splenomegaly was Hodgkin's-related in 47 % (8/17) and 33 % (2/6) of cases respectively. The predictive value of ultrasonography and CTscan was not better than clinical examination : histological evidence was normal in 66 % of patients with unpalpable spleen while histological evidence of Hodgkin's disease was found in 55 % of patients with palpable spleen. Normal ultrasonographic images of the liver were confirmed by histological findings in 88 % of cases (102/116) where as ultrasonographic images of enlarged liver were confirmed histologically in only 19 % (3/19) of cases. For CTscan investigations of the liver normal findings were confirmed histologically in 93 % (63/68) of cases but none of the 9 abnormal images were confirmed histologically. In this series staging was revised in the light of histological evidence in 35 % of cases (65/186) : 75 % to a more advanced stage and 10 % to a lower stage. Depending on the therapeutic approach being used, laparotomy is still a valuable investigative procedure.

P 2 RESULTS AND THERAPEUTIC CONSEQUENCES OF STAGING LAPAROTOMY IN HODGKIN`S DISEASE: A CONCEPTUAL STUDY.

H.H.Gerhartz (1), M.Löffler (2), M.Pfreundschuh (2), E.Hiller (1), K.Smith (2), U.Rühl (3), W.Wilmanns (1), V.Diehl (2) for the German Hodgkin Study Group (2), Med. Klinik III, Klinikum Großhadern, Munich University (1), Med. Klinik I, Köln University (2), Deptm. of Radiotherapy, Städt. Krankenhaus Berlin-Moabit (3).

We compared the results of clinical (CS) and pathological staging (PS) in 253 patients with Hodgkin`s disease who underwent laparotomy with splenectomy (Lap) while being evaluated for inclusion in a multicenter trial. The value of non-invasive diagnostic variables as well as the impact of Lap and new selection criteria on therapeutic strategies have been analysed. In 80 of 248 patients in CS I-III a higher stage was detected by Lap (32%): 27/56 CS I-, 46/146 CS II-, and 7/46 CS III-patients. When patients in CS I-II with or without surgically detected infradiaphragmal disease were compared no significant differences were found with respect to the presence of constitutional symptoms, erythrocyte sedimentation rate (ESR), alkaline phosphatase, and eosinophils. Patients with infradiaphragmal disease, however, had a higher incidence of mixed cellularity histology, somewhat higher lymphocyte counts, and less frequently a large mediastinal tumor but these differences were not marked enough to allow a reliable prediction of abdominal involvement. In 66 cases results of Lap influenced the therapeutic approach of the current chemotherapy study (26%). 56 of these were CS I-II patients without clinical risk factors who received combined modality treatment (CMT) instead of radiotherapy (RT) alone. Thus, the absence of clinical risk factors did not predict a negative Lap. Only 1 of 5 patients in CS III without clinical risk factor received more extensive chemotherapy (CT) after being identified as PS IV. If the current therapeutical approach would be changed and in addition to clinical parameters like a large mediastinal mass, extranodal disease and spleen involvement, a high ESR or involvement of 3 or more lymphatic areas were considered as risk factors qualifying for combined CT plus RT Lap would have become unnecessary in 121 of the cases (53%). Only 5 of these would have had a stage IV and 14 patients would have a stage III B undetected by non-invasive diagnostic methods. In conclusion, only patients in CS I-II without clinical risk factors who are eligable to RT alone should still undergo Lap, because an occult infradiaphragmal disease can be exspected in 36%. In patients with clinical risk factors qualifying for CMT this procedure is unnecessary due to little influence on the therapeutic approach.

P 3 SPLENECTOMY IN HODGKIN'S DISEASE: A POSSIBLE RELATIONSHIP WITH SECOND ACUTE LEUKEMIA.

* G. Cartei, * R. Cendron, **G.L. Pappagallo, ** S.M.L. Aversa, ** M.V. Fiorentino

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** Division of Oncology, Ospedale Civile, 35100 Padova, Italia

Twenty-one of 1169 consecutive Hodgkin's Disease patients treated at Padua from January 1958 to March 1984 subsequentely developed 21 acute leukemias. The multivariate analysis (Cox's model) confirmed others previous findings regarding the role of advanced stage, and age at diagnosis more than 40 years. Moreover analysis indicated that splenectomy as staging procedure was the most important factor in the regression model predicting for a second acute leukemia. The 504 splenectomized patients did not differ by pretreatment characteristics (sex, age, histological subgroup, pathological stage) and therapy modalities from the 665 unoperated ones.

Step No.	Variable Entered	Log Likelihood	Improvement Chi-square	Improvement P-value	Global Chi-square	Global P-value
0		-126.709				
1	Splenectomy	-118.747	15.924	0.000	15.994	0.000
2	Age	-113.879	9.736	0.002	26.434	0.000
3	Stage	-109.358	9.043	0.003	34.080	0.000

Pattern symbol in Fig. 1	Conversion Factor	age more than 40 years	advanced stage	splenectomy
A	0.096	no	no	no
B	0.445	no	yes	no
C	1.792	yes	yes	no
D	14.672	yes	yes	yes

P 4 PROGNOSTIC GROUPS IN CLINICALLY STAGED LOCALIZED HODGKIN'S DISEASE.

S.B. Sutcliffe, M.K. Gospodarowicz, Princess Margaret Hospital, 500 Sherbourne Street, Toronto, Ontario Canada.

A retrospective review of 502 adult patients with clinical stage I & II Hodgkin's treated at the Princess Margaret Hospital between 1968 and 1982 identified clinical stage, patient's age, systemic symptoms and histology as statistically significant prognostic factors.

Three distinct prognostic groups were identified based on stage, patient's age and histology (table 1). The 367 patients treated with radiotherapy alone (XRT) cause specific survivals (CSS) at 10 years were: 96% in group I, 89% in group II, and 42% in group III. Corresponding relapse free-rates (RFR) at 10 years were: 78% in group I, 65% in group II and 26% in group III.

Group 2 patients treated with involved field XRT achieved 50% RFR at 10 years while the RFR was 67% for patients treated with upper mantle radiation and 75% for patients treat ed with extended field irradiation. In group 3 patients extended field radiotherapy did not reduce the risk of relapse. RFR's at 10 years for group 3 patients were: 30% for mantle XRT, 25% for involved field XRT and 20% for extended field XRT.

One hundred and thiry five patients were treated with combined modality approach. The group 2 patients treated with CT + XRT achieved 77% RFR at 10 years versus 65% RFR in those treated with XRT. There was however no significant difference in CSS for group 2 patients treated with CR + XRT (85%) and XRT (89%). Group 3 patients treat ed with CR + XRT had significantly better RFR (65% for CT + XRT versus 26% for XRT) at 10 years. The use of combined modality approach in group 3 resulted in improved survival (CSS at 10 years 74% for CT + XRT versus 42% for XRT alone).

The prognostic groups identified facilitate selection of patients for the initial treatment with the combined modality approach.

Table 1

<table>
<tr><th rowspan="2">Histology</th><th rowspan="2">Age</th><th colspan="3">CLINICAL STAGE</th></tr>
<tr><th>IA High Neck</th><th>IA Other IIA</th><th>IB + IIB</th></tr>
<tr><td rowspan="2">LP + NS</td><td>≤ 50</td><td rowspan="3">GROUP I</td><td rowspan="2">GROUP II</td><td></td></tr>
<tr><td>> 50</td><td rowspan="3">GROUP III</td></tr>
<tr><td rowspan="2">MC + LD</td><td>≤ 50</td><td></td></tr>
<tr><td>> 50</td><td></td></tr>
</table>

P 5 PROGNOSTIC FACTORS FOR THE SURVIVAL OF PATIENTS WITH STAGES IIIB & IV HODGKIN'S DISEASE (HD). AN ANALYSIS OF 303 PATIENTS IN LONDON AND MANCHESTER.

J. Wagstaff*, W. Gregory+, R. Swindell*, D. Crowther*, A. Lister+.
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303 patients with stages IIIB & IV HD treated with MVPP chemotherapy and radiotherapy to sites of previous bulk(≥5cm) have analysed for prognostic factors affecting survival using Cox regression analyses. CR rates were similar (London = 62%; Manchester 68%) as was survival (London = 66%; Manchester = 73% at 5 yrs).

Analysis of the Manchester data identified age (≤45 yrs vs >45), lymphocyte count (≤0,75 vs >0,75 x 10^9/l) and gender as independent significant ($P \leq 0,05$) factors. The good prognosis patients (age ≤ 45 and lymphocyte count >0,75) had 5 & 10 yr survivals of 93 & 77% respectively. The poor prognosis patients could further be divided by sex, the 5 and 10 yr survival being 43 & 30% for males and 67 & 67% for females.

Analysis of the London data identified the same good prognosis group (5 & 10 yr survivals = 81 & 75%).But the poor prognosis patients (age≥45 or lymphocyte count ≤0,75) were further divided by Alk. Phos. (≤100 vs>100 IU/l) rather than gender (5 & 10 year survivals: Alk. Phos. ≤100 = 59 & 47%; >100 = 27 & 16%). The differences between these two analyses probably reflect differences in the patient populations treated in the two centres.

When either model was applied to the other data set discrimination of prognostic groups was found to be excellent. Using these models it is possible to prospectively identify a poor prognostic group of patients based on pre-treatment characteristics. Thus making it possible for alternative or more intensive therapies to be focused on this group of patients.

P 6 FIVE -YEAR RESULTS OF THE POF 81/12 REGIMEN FOR 147 HODGKIN'S DISEASE (HD), CLINICAL STAGES (CS) IA-IIB. J.M. Andrieu (Paris, Laennec), B. Desablens (Amiens), P. Casassus (Bobigny), L. Semsebé (Brest), J.L. Harousseau (Nantes CHU), A. Lemevel (Nantes CAC), N. Ifrah (Angers), J.M. Tourani (Paris, Laennec), C. Dauriac (Rennes).

From 10.81 to 12.85, 147 patients (pts) with HD CSIA-IIB (with or without) contiguous involvement) were treated according to the POF 81/12 trial. Their characteristics were: Sex M 75, F72 ; Age (years) min 13, max 64, median 29 ; Histology LP 6, NS 104, MC 29, LD 2, Uncl. 6 ; CS IA 29, IIA 71, IB IIB 47. All pts received 3 monthly cycles of ABVD (mg/m2, days 1 and 15 : Adr 25, Bleo 10, VBL 6, DTIC 375 plus methylprednisolone 200) except non mediastinal CS IA who received 1 ABVD cycle only. Pts in complete remission (CR) and partial remission received extended focal radiotherapy (RT) (30 to 40 Gy according to age) and prophylactic short lumbo-aortic and splenic RT (20 to 30 Gy). 7 failures (2 IIA, 5 IIB) occurred by progressive disease after ABVD (6) or residual disease after RT (1). They received additionnal salvage chemotherapy. 3 pts relapsed (2 IIA, 1 IB) after 7 to 20 months of CR. 3 pts died after 13 to 23 months of survival (failure: 2 IIB, sudden death in CR after thoracocenthis for post RT pleural effusion: 1 IIA).
As of january 1rst 1987, median follow-up is 36 months (min 12, max 62). 5-year actuarial survival (SV Z) and relapse (R Z) rates are given in the Table.

CS	PTS	SV Z	PTS IN CR	R Z
IA-IIB	147	97.6	140	2.7
IA	29	100	29	0
IIA	71	98.5	69	3.2
IB, IIB	47	94.6	42	4.2

Up to now to our knowledge, this combined modality regimen for HD CS IA-IIB compares favorably to all reported trials.

P 7 COMBINED MODALITY FOR STAGE IIIB-IV HODGKIN'S DISEASE (HD).

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75475 Paris cedex 10 - France.

Although the prognosis of patient (pts) with advanced HD has improved with the use of intensive combination chemotherapy (CT), nearly half of these pts still die. In an attempt to improve upon results, our protocol consisted of 4 cycles of CT, MOPP versus MOPP alternating with ABVD, clinical restaging and nodal extended fields radiotherapy (RT,40 Gy) for major responses ; partial responders (PR) received additional CT before RT. From 01-81 to 02-86, seventy four previously untreated pts with advanced HD were entered onto this protocol, of whom 67 are evaluable. There were 47 males, 20 females, mean age was 35 y (13-69), 20 pts were over age 40. Pathology included NS-30, MC-30, LP-1, LD-1, unclassified-5. 66 pts were clinically staged, and one after laparotomy. Stage distribution was 1III B 18 (27%), III2 B 14 (21%) and IV A-B 35 (52%). Extranodal disease was present in 3 stages IIIE and bone marrow-10, liver-10, lung-5, bone-4 and several -6. Pts were randomly assigned to receive 4 cycles of MOPP or 4 cycles of MOPP alternating with ABVD Adriamycin 30 mg/m² IV days 1,8 ; bleomycin 2 mg/m² SC days 2-5 ; vinblastine 6 mg/m² IV days 1,8 ; DTIC 200 mg/m² IV days 1,8). 47 pts received 4 cycles (MOPP 20 pts, MOPP/ABVD 27 pts), 18 pts received more than 4 cycles (12 PR and 6 failures) ; 2 pts received less than 4 cycles because of toxicity. After CT, 16 pts in PR (5 CS IIIB, 11 CSIVB) underwent surgical restaging with splenectomy, normal in 9 pts, abnormal in 7 pts. RT consisted of mantle plus inverted Y fields in 39 pts, plus spleen in 25/39 non splenectomized pts, mantle plus para-aortic and spleen in 20 pts, mantle alone in 3 pts. No RT was delivered in 4 failures and one early death. 54 pts received a total dose of 40 Gy, 8 pts received a reduced dose (15-25 Gy) over supra and/or infra-diaphragmatic fields. After 4 cycles of CT, the complete remission rate (CR), PR and failure was respectively for stages IIIB, 25 %, 72 %, 3% and for stages IV 20%, 68.5%, 11.5%. Results were similar after MOPP and MOPP/ABVD. After CT+RT, CR, PR, failure rate was respectively 87.5%, 9.5%, 3% for stages IIIB and 63%, 17%, 20% for stages IV. Six pts relapsed (1 IIIB, 5IV) after 3 to 33 months of CR ; 2 pts reached a second permanent CR. Fifteen pts died initial failure : 9 ; relapsing pts : 2; iatrogenic deaths : 2 under treatment and one in first CR ; one acute leukemia). The actuarial survival at 54 months is 86% and 70.7% for stages IIIB and IV respectively. Updated results will be presented.

P 8 ROLE OF RADIOTHERAPY IN "HIGH-RISK" STAGE II AND III HODGKIN'S DISEASE (HD) TREATED WITH COMBINED MODALITY TREATMENT.

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From 1977 through 1984, 64 patients (pts) with "high-risk" stage II and III HD (B symptoms, or bulk mediastinal mass, or "E" lung disease) were staged without laparotomy and treated with 6 courses of MOPP chemotherapy (CT) followed by radiotherapy (RT): subTNI (mantle + upper abdominal port) in stage II and TNI in stage III. Complete remission rate to CT was 78.1% (50 pts). 14 pts (21.9%) showed partial remission or resistance to 6 courses of MOPP. 9/14 pts with persistent disease after CT were converted to CR with the subsequent RT. 9-year disease-free survival (DFS) rates were: CRs after CT 84.3%, CRs after RT 62.5% respectively (p=0.04).
Tolerance to RT was analyzed in the 50 pts in CR after MOPP. All 19 pts in stage II completed RT plan: only 3 needed a dose reduction (< 30 Gy) in the upper abdominal port.
The whole intended TNI plan was not completed in 11/31 stage III pts. Of these in 5 pts RT was discontinued because of persistent cytopenia: 3 received subTNI and 2 only mantle port. In the other 6 pts a reduced RT dose (< 30 Gy) was required mainly in the pelvic port. However RT was always delivered to the sites of previous bulk disease.
There were no differences in 9-year DFS between the pts who properly completed the entire RT plan and the pts who did not (81.2% vs 85.7%). 5 pts developed ANLL: 4/5 received TNI and 1 subTNI.
Our data suggest that after 6 courses of MOPP, TNI is difficult to complete due to myelosuppression and the long-term toxicity of this therapeutic program is very relevant. Moreover pts in CR after 6 courses of MOPP who received a limited RT had the same prognosis of the pts who received the entire RT plan.

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P 9 TWO CYCLES OF MOPP (2MOPP) AND RADIATION THERAPY (RT) FOR STAGES III_1A AND III_1B HODGKIN'S DISEASE (HD).

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Seventy-six patients (pts) with stage III_1A and 26 with stage III_1B HD were treated with 2MOPP and RT. For 64 pts, RT consisted of sequential treatment to the mantle, upper 2/3 of the abdomen, and the pelvis. The remaining 38 received only mantle and upper abdomen RT, and 7 of these also received low dose lung RT as prophylaxis of pulmonary relapse. One hundred of these pts were staged by laparotomy (LAP). Mantle RT was first administered for control of local disease in those unable to undergo surgery prior to therapy, followed by LAP. All received 2MOPP after LAP, except for 2 who had clinical stage III disease with splenic involvement. Five and 10-year survivals (Surv) were 91% and 84% for III_1A pts and were both 91% for III_1B pts ($p>.1$). Five and 10-year freedom from progression (FFP) figures were both 86% for III_1A pts and were 85% and 78% for III_1B. Five-year Surv and FFP of pts who did not receive pelvic RT were 92% and 82%. Results are shown as follows:

	Total No. Pts.	5-Year Surv	5-Year FFP
All III_1	102	91	86
Pelvic RT	64	92	82
No Pelvic RT	38	90	82
III_1A	76	91	86
Pelvic RT	47	89	85
No Pelvic RT	29	93	83
III_1B	26	91	85
Pelvic RT	17	86	88
No Pelvic RT	9	94	78

Features which did not predict for disease progression, besides B symptoms, included age over 40, mediastinal involvement, number of involved nodes, histopathologic subtype, order of LAP/RT, and presence or absence of nodal disease in the celiac-portal complex. Fifteen pts (14.7%) had progressive disease; of these, 6 were salvaged with chemo or radiotherapy, 8 died of HD, and 1 is alive with disease. All of these relapses or deaths occurred within 7 years. Three other pts (2.9%) died with treatment-related complications without HD relapse. This analysis demonstrates that pts with III_1A and III_1B treated with 2MOPP and RT have results similar to those for pts treated with programs using more chemotherapy, and that pelvic RT is not necessary for such pts receiving combined modality therapy.

P 10 CHEMOTHERAPY ALONE VS. COMBINED MODALITY TREATMENT FOR STAGE IIIA HODGKIN'S DISEASE: AN EIGHT-YEAR FOLLOW-UP OF A SOUTHWEST ONCOLOGY GROUP (SWOG) STUDY #7518.

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SWOG conducted between October 1975 and April 1980 a clinical trial including 137 cases of HD Stage III (A&B) in which patients were randomized to receive chemotherapy alone (CT) as 10 courses of MOPP plus low dose bleomycin (LDB) vs. combined modality therapy (CR+RT): three courses of the same chemotherapy followed by total nodal irradiation (TNI). The contributing physicians were SWOG members affiliated with academic, military, and private practice (Cancer Control Institutions). The staging included obligatory laparotomy and pathology review (Lymphoma Pathology Panel and Central Repository). This is a report of data from the 92 eligible Stage IIIA cases. With the median follow-up time of surviving patients over 94 months, the results are as follows:

	CT	CT+RT	P
Complete Remission (CR) Rate	87%	95%	0.28
8 Yr. Relapse Free (RF) Rate	65%	75%	0.58
8 Yr. Survival Rate	78%	83%	0.56

No statistically significant differences by histopathological subsets, size and distribution of disease (mediastinum, abdominal Stage III A-1 vs A-2, pelvis, extent of splenic involvement) were detected. On the (CT) limb 56% of the patients completed 9-10 cycles of MOPP+LDB; on the (CT+RT) limb 24% of the patients had low doses in the inverted Y with relapses in the abdomen occurring in two of these cases. The acute toxicities of the two regimens were graded as comparable though qualitatively slightly different. On (CT+RT) there were two cases of AML and one late marrow failure vs one AML and one late marrow failure on (CT). The majority of relapses on (CT) occurred in original sites of disease. These data suggests that for the initial therapy of Stage IIIA Hodgkin's disease, (CT) or (CT+RT) may be equally effective; however, the number of deaths and relapses in this study is small.

P 11 ALTERNATING COMBINATION CHEMOTHERAPY ABVD/MOPP vs ABVD/OPP IN ADVANCED STAGE HODGKIN'S DISEASE (HD)

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Eighty-two patients affected by previously untreated advanced stage HD were randomly allocated to receive one of the following chemotherapeutic regimens: i. four courses of ABVD alternating monthly with 4 courses of MOPP; ii. four courses of ABVD alternating monthly with 4 courses of OPP (vincristine 1.4 mg/m^2, i.v., on days 1, 8, 15; procarbazine 100 mg/m^2, p.o. daily on days 1-21; prednisone 40 mg/m^2 p.o. daily on days 1-21). All patients achieving complete remission (CR) subsequently received a consolidation radiotherapy delivered on previously affected areas (total dose 20 Gy) and on spleen region (total dose 40 Gy). Removal of meclorethamine, a well documented leukemogenic drug, together with intensified scheduling of vincristine, procarbazine and prednisone, were performed in order to reduce long-term complications and improve therapeutical response. Forty patients (clinical stage I B: 2 pts; II B: 10 pts; III B: 16 pts; IV A/B 12 pts) entered ABVD/MOPP arm, whereas 42 patients (stage I B: 2 pts; II B: 14 pts; III B: 11 pts; IV A/B: 15 pts) were treated with ABVD/OPP. Clinical characteristics of patients are similar in both groups. The mean follow-up was 21.5 and 22.5 months respectively. In the ABVD/MOPP group response rate was 92% (CR 77.5% and partial remission (PR) 15%) and 85.7 (CR 78.5% and PR 7%) in the other one ($P > 0.05$). All partial responder patients achieved CR after radiotherapy. Number of systemic symptoms and of involved sites, significantly affected the response rate, in the whole population of patients regardeless of treatment. Hematological toxicity was similar in both groups whereas neurotoxicity was more relevant in ABVD/OPP group (21%) as compared to the other one (13%). A trend toward a higher actuarial relapse free survival (RFS) rate was observed in the ABVD/OPP group compared to the other arm (97% vs 67% at 33 months, respectively; $p = 0.05$); while the actuarial overall survival rate was similar in the two groups (98% vs 96% respectively). In conclusion, the seven multi-drugs alternating regimen ABVD/OPP allowed the achievement of a response rate similar to that obtained employing alternating ABVD/MOPP. However, a longer follow-up is required in order to confirm the observed higher relapse free survival rate in the ABVD/OPP arm.

P 12 PABIOE (prednisolone, adriamycin, bleomycin, vincristine, and etoposide) alternating with ChlVPP for Hodgkins disease - a new regimen.

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There are theoretical reasons why alternating two non-cross resistant CT regimes should improve overall survival in advanced Hodgkin's disease (HD) and at least one randomised trial supports this suggestion. The widely used MOPP/ABVD regimen has the disadvantage of severe subjective toxicity causing some patients (pts) to stop treatment early. We have modified this regimen with the aim of reducing this toxicity. Dacarbazine has been replaced by etoposide, mustine by chlorambucil and the two vinca alkaloids have been switched to equalise myelotoxicity. (**ChlVPP:** Vinblastine 6 mg/m^2 i.v. days 1 and 8, Procarbazine 100 mg/m^2, Chlorambucil 6 mg/m^2 and Prednisolone 30 mg/m^2 all p.o. days 1 to 14. **PABIOE:** Adriamycin 40 mg/m^2 i.v. day 29, Bleomycin 10 mg/m^2 and Vincristine 1.4 mg/m^2 both i.v. days 29 and 36, Etoposide 200 mg/m^2 p.o. days 30,31,32, Prednisolone 30 mg/m^2 p.o. days 29 to 43). The regime repeats on day 50 i.e. a 7 week cycle. Pts received a minimum of 3 full cycles with a minimum of 2 cycles after CR. Most patients received treatment on an out-patient basis.

115 pts with HD not previously exposed to CT have been treated with this regime. 9 pts had relapsed after previous XRT. Median time on study is 93 weeks. Median age of the pts is 34. Clinical stages (CSt) of the pts are: CSt I = 5 (all bulky disease), CSt II = 33, CSt III = 42, CSt IV = 29, Not fully staged (at least CSt II) = 6. 68/115 pts had 'B' symptoms. Histological types after central pathology review are lymphocyte predominant = 14, nodular sclerosis = 50, mixed cellularity = 24, lymphocyte depleted= 12, histology not yet reviewed= 15.

89 pts have completed CT and are evaluable for response and toxicity. 66 (74%) achieved CR as a result of CT with 16 (18%) achieving PR. Following XRT to sites of residual disease 73/89 (82%) were in CR. For pts with CSt III or IV disease CR rate was 45/57 (79%) before XRT. 8 pts have relapsed within 2 years of completing treatment (81% relapse-free). 15 pts have died, 6 of recurrent or progressive HD.

18/89 pts developed neuropathy but in only 6 was this severe enough to stop further vinca alkaloids. 37/89 developed infections during treatment though in most cases this was mild. 15 pts had infections requiring in-patient treatment 5 with septicaemia. Nausea and vomiting were generally mild and no patient refused treatment because of subjective toxicity. There were 6 treatment-related deaths.

The regime ChlVPP/PABIOE is active in advanced HD with a high response rate. Toxicity is acceptable with less subjective toxicity than MOPP/ABVD. This regime deserves comparision with standard, non-alternating treatment in a prospective, randomised trial.

P 13 PRELIMINARY RESULTS OF A CYCLIC-ALTERNATING CHEMOTHERAPY (CVPP/DBVCy) IN ADVANCED HODGKIN'S DISEASE

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Two chemotherapy regimes for treatment of patients with advanced Hodgkin's disease (stage III_2A - IV) were compared in a randomized prospective study:
Group 1: CVPP (cyclophosphamide, vinblastine, procarbazine and prednisone) versus
Group 2: CVPP/DBVCy (CVPP, rubomycine, bleomycin, vincristine and Cytostasan^R).

Eigthy previously untreated patients were entered into the study between Jan. 1982 and Dec. 1984. Both groups are comparable (age, sex, stage, histology).

Treatment results:	CVPP (n=40)	CVPP/DBVCy (n=40)
CR	23 (57,5%)	24 (60%)
PR	7 (17,5%)	11 (27,5%)
NR	10 (25%)	5 (12,5%)
in first CR	16/23 (69%)	13/22 (59%)
median observation	30,5 mo	29,5 mo
RFS 1 year	20/22 (91%)	22/24 (92%)
RFS 2 years	13/18 (72%)	12/21 (62%)
survival 1 year	36/40 (90%)	36/40 (90%)
survival 2 years	21/28 (75%)	21/25 (84%)

The differences between both groups are not statistically significant, neither in respect of response nor of survival and relapse free survival.

Conclusions:
There is no difference in the response to treatment in the two groups the trial. The response rates are comparable to those of other studies. There are also no statistically significant differences in respect of the number of relapses and the relapse free survival after one and two years.
At present we cannot confirm a superiority of cyclic-alternating CVPP/DBVCy-chemotherapy in advanced Hodgkin's disease.

P 14 SALVAGE THERAPY WITH CEP IN RELAPSING RESISTANT HODGKIN'S DISEASE.

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Various salvage regimens have been proposed for resistant Hodgkin's disease (HD); preliminar results are promising but heterogeneous, and optimal treatment has not yet been defined. We have assessed the efficacy of CEP schedule (Lomustine, Etoposide, Prednimustine) as salvage chemotherapy (CT) in patients with resistant HD (not responders to primary CT or relapsing within 12 months).

Between January 82 and December 86, 16 patients, 10 males and 6 females, aged 15 to 66 years (median 38) were treated with CEP; 14 were in advanced stage (9 IVB, 1 IVA, 4 IIIB), 2 in IIA bulky; 6 patients were not responders to primary therapy, 10 in early relapse; 12 patients are statistically evaluable (8 relapsing, 4 not responders). All patients were treated with MOPP-ABVD concomitantly (M/A) or sequentially (M-A). Data concerning response to CEP according to previous CT are summarized in the following table:

prev.CT	nr.pts	+RT	CR	PR	NR	Relapses	DFS(mos)	Deaths
M/A	7	2	3	3	1	1(6mos)	3 ,9+	2
M-A	5	1	2	2	1	1(10mos)	28+	3

The number of CEP cycles administered ranges from 3 to 16 (median 6); they were well tolerated and toxicity was mild.

Results: 5/12 pts. (42%) achived CR, 5/12 PR; 2 pts. did not respond (NR). The overall response to CEP was 83% (10/12).

Response varied according to condition of disease:

	CR	PR	NR	Rel.(mos)	DFS	Deaths
not responders to CT =4	1	2	1	-	3	3
relapsed after CT =8	4	3	1	2 (10,6)	9+,28+	2

7 patients are alive, 3 in CR (3+,9+,28+), 4 with active disease (5+, 7+,12+,60+).

Conclusion: CEP appears to be effective as salvage regimen in patients with HD resistant to MOPP and ABVD. Response seems better in pts early relapsing after primary CT. Toxicity is acceptable.

Further studies on more numerous series of patients are needed to confirm the present data.

P 15 SALVAGE THERAPY (ST) AFTER FAILURE OF MOPP/MOPP-ABVD IN ADVANCED HODGKIN'S DISEASE.

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From 1970 to 1985, 38 patients (pts) with advanced Hodgkin's disease, in whom initial chemotherapy with MOPP (27 pts), MOPP-ABVD (8) and ABVD (3) failed, were treated for salvage. Twenty-one pts had relapsed after initial complete remission (CR), whereas 17 had resistant disease while receiving the first chemotherapy treatment. In 31 pts the ST was chemotherapy: MOPP-11, ABVD-8, MOPP-ABVD-6 and CEP± ABVD-6. Twenty of those were treated with non-cross resistant regimens. Twelve pts (39%) achieved CR, with a median duration of response 9 months (m) (3-147m), however, 8 pts relapsed and 2 developed leukemia. In 7 pts radiotherapy was the only ST. Five pts achieved CR, but a durable remission (>1 year) was obtained in only 2 pts. Actuarial 3 year survival after ST was 40% for all pts, 62% for complete responders(CRs) and 18% for non-responders (CRs vs non-CRs, $p<0.05$), with a 30 m median follow-up of all pts. The actuarial probability of freedom from relapse in CRs, at 3 and 5 years after ST, was 46% and 28%, respectively.

Two pre-treatment characteristics were found predictive of response to ST and survival. 1) Systemic symptoms at the initiation of ST. In asymptomatic pts 62% (13/21) achieved CR and the 3 years survival from ST was 67%, compared to 23% (4/17) CR rate and 8% survival in symptomatic pts ($p<0.02$ and $p<0.001$, respectively).

2) Duration of initial remission. In 13 pts whose first remission had lasted more than one year, 9 (69%) achieved CR compared to 1 of 8 pts with short initial remission (<1 year)($p<0.02$). Yet, the 3 year actuarial survival after ST in both groups was similar, 58% and 46%, respectively (p=NS). In 17 pts with initial resistant disease, CR was 41%. However, the duration of response was brief and 3 year actuarial survival after ST was 14% ($p<0.05$)

Our data confirm that salvage chemo- or radiotherapy after failure of first-line combination chemotherapy induce long term remission in only a small fraction of pts. The necessity for new treatment programs for this group of pts is evident.

P 16 DEXAMETHASONE, HIGH DOSE ARA-C AND CISPLATIN (DHAP) AS SALVAGE TREATMENT FOR RELAPSING HODGKIN'S DISEASE.

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Based on the observation of synergism between Cisplatin and Ara-C observed in colonic and lymphoma cell lines, this combination was given to 24 patients (pts) with progressive relapsing Hodgkin's disease. All pts received a combination of dexamethasone 40 mg IV for 4 days, Cisplatin 100 mg/M2 in a 24 hr continuous IV infusion, followed by Ara-C 2 g/M2 in a 3 hr infusion which was repeated 12 hrs later (DHAP). Hydration with normal saline and mannitol (50 g/liter) was given for 30 hrs. Treatment courses were repeated every 3-4 weeks. There were 14 males; median age was 27 (range 15-52 yrs). Thirteen pts had "B" symptoms, and 19 pts had extranodal involvement which included lung and pleura frequently. Three pts had bone marrow involvement. Seven pts had refractory disease and never had achieved complete remission (CR). All pts had received prior MOPP (or CVPP) and Adriamycin-containing regimens, and 5 pts had prior autologous bone marrow transplant (ABMT). There were 2 early deaths among those 5 who had prior ABMT and poor marrow reserve. Of the remaining 22 pts, 15 were assigned to receive 2-3 courses of DHAP followed by ABMT consolidation. Among these, 6 (40%) pts achieved CR and another 5 (33%) obtained partial remission (PR). All but 4 of these 15 pts are alive. The deaths included 3 non-responders and one pt who relapsed at 5 months post ABMT. The 7 other pts who were not candidates for ABMT (older than 50 yrs, bone marrow involvement and/or prior ABMT) continued to receive DHAP for 6-8 courses. There were 2 CR's and 3 PR's. Overall, DHAP had induced a 73% response rate in this heavily pretreated group of pts. CR was related to tumor burden. Pts with high tumor burden, defined as having more than one area of extensive nodal involvement or more than 2 extranodal sites, achieved only 28% CR rate, while pts with low tumor burden obtained 40% CR rate. Myelosuppression has been acceptable and reversible elevation of serum creatinine was seen in 4 pts. These data show that DHAP is an effective treatment in Hodgkin's disease, especially when combined with ABMT.

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P 17 HIGH DOSE ETOPOSIDE, CYCLOPHOSPHAMIDE ± CARMUSTINE IN CONJUNCTION WITH INFUSION OF AUTOLOGOUS BONE MARROW: A PROMISING TREATMENT FOR REFRACTORY OR RELAPSED HODGKIN'S DISEASE. T.Ahmed, S.A.Gingrich, D.Ciavarella, E.J.Feldman, J.Ascensao, M.Coleman, A.Mittelman, Z.Arlin. New York Medical College, Valhalla, N.Y. and Cornell Medical Center, New York.

Despite the success of combination chemotherapy regimens in Hodgkin's disease, 15% of patients do not achieve complete remission (CR) and 30% relapse. Cures with salvage chemotherapy are infrequent in this subset of patients. High dose chemotherapy followed by autologous bone marrow infusion (ABMT) has been used successfully to treat such patients.

Twenty-one patients with Hodgkin's disease that had been treated with radiotherapy and multiple chemotherapy regimens (median 3 regimens, range 1->6) underwent myeloblative chemotherapy with etoposide (VP-16), cyclophosphamide (CTX) and carmustine (BCNU) followed by an ABMT. The median age was 27 (range 16-40). At the time of ABMT, 15 had visceral disease, and 7 had nodal disease. Nineteen were refractory to the last regimen used. Five had never achieved a complete remission despite aggressive multiagent therapy. All patients received CTX 120mg/kg (4.8 gm/m²), VP-16 1500-2000mg/m² and BCNU 450-600mg/m² infused over a 48 hour period. BCNU was not used in the first two patients entered in this program. This was followed by ABMT. The median nucleated cell number harvested was 2.7 X 10^8/kg (range 0.9-4.7). Seven patients had complete remission of disease lasting 1-11+ mos, 3 pts had >50% decrease in tumor lasting 3-20+ mos. Of the five patients who were refractory to initial chemotherapy, three achieved complete remission and one a partial remission. Three patients had early deaths and 3 pts are too early to evaluate. Toxicity included 2+-3+ mucositis in 17 pts, hepatotoxicity in 13 pts (fatal in one), sepsis in 10 pts, hemorrhagic cystitis in 3 pts and respiratory failure resulting in death in 3 pts. We conclude that high dose myeloablative chemotherapy followed by ABMT induces a high remission rate in refractory HD and in some pts may result in long term survival.

P 18 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR RELAPSED HODGKIN'S DISEASE S. Jagannath, J.O. Armitage, K.A. Dicke, F.B. Hagemeister, S.L. Tucker, L.J. Horwitz, W.S. Velasquez, W.P. Vaughan, A. Kessinger, F. Cabanillas, G. Spitzer. University of Texas M.D. Anderson Hospital, Houston, TX; and University of Nebraska Medical Center, Omaha, NE.

Sixty-two patients with relapsed Hodgkin's Disease were treated with cyclophosphamide, carmustine, etoposide (CBV) and ABMT. There were 36 males; the median age was 28 years (15-56 years). The number of prior chemotherapy combinations was ≤ 2 in 35 patients and > 2 in 27 patients. The performance status was excellent (Zubrod 0) in 39 patients and symptomatic (Zubrod 1-3) in 22 patients. MOPP regimen was the most common initial therapy and 24 patients failed to achieve a complete remission to the initial therapy. There were 45 patients failing last salvage chemotherapy attempt, while 17 were responding to last therapy including two who achieved CR and were intensified with CBV. 47 patients had bulky (> 5cm) and/or extensive nodal disease or two or more extranodal disease sites (high tumor burden) at time of ABMT. Chemotherapy dosage schedule was given as described previously (Ann Intern Med 104:163-168, 1986). There were only 4 early deaths, all with mediastinal relapse at the time of ABMT, all having received the highest dose of etoposide at 900mg/m^2 and 3 of them with prior mediastinal radiation. Following CBV therapy, 30 patients were in CR including 2 patients intensified in CR; 18 achieved partial response (PR); and 10 had progressive disease (PD). Only 7 of the 30 patients in CR have relapsed for a median follow-up of 24 months (6-60 months). Multivariate analysis reveals that patients with low tumor burden, ≤ 2 prior chemotherapies, and good performance status (Zubrod 0) had a high probability of CR and subsequent relapse-free survival. CRs induced by CBV therapy are durable, and this therapy should be the preferred choice for Hodgkin's Disease patients once they have relapsed after MOPP/ABVD-like regimen.

P 19 MELPHALAN AND AUTOTRANSPLANTATION FOR HODGKIN'S DISEASE. Russell, J.A., Berry, J., Houwen, B., Jones, A.R., Poon, M-C., Blahey, W.B., Geggie, P.H.S., Ruether, B.A., Division of Hematology/Oncology, Calgary, Alberta, Canada.

Nine patients (pts) with Hodgkin's disease (HD) which had relapsed at least once were treated with a "priming" dose of Cyclophosphamide, 300 mg/m^2, followed a week later by Melphalan, 140 - 220 mg/m^2 I/V. They then received autologous, noncryopreserved bone marrow (1.56 - 4.23 x 10^8 nucleated cells/kg) 8 - 18 hours later. Recovery to AGC > 0.5 x 10^9/L took 14 - 52 days (median 20), platelet recovery to 20 x 10^9/L took 16 - 89 days (median 31). Eight pts were given broad spectrum antibiotics, two had documented bacterial infections. Six pts experienced nephrotoxicity demonstrated by proteinurea and/or increase in creatinine, two of these had transient high output renal failure. Other complications included mucositis (WHO Grade 3 - 4) (four pts), hemorrhagic pericarditis (one pt) and reversible venoocclusive disease (one pt).

Responses were as follows:

Status of Disease	# pts.	CR or CCR* (duration in months)	PR (duration in months)
Resistant relapse	4	2 (5,70+)	2 (4,8)
Responding relapse	4	3 (2+,21+,27+)	1 (3)
CR	1	1 (6+)*	
TOTAL	9	6	3

One pt died of HD at eight months. Of three pts who had previously received five or more chemotherapy combinations, none are in CR compared with five of six pts who had two to four previous regimens.

Melphalan is clearly capable of producing durable remissions in moderately pretreated pts with HD in whom prolonged control of disease is very unlikely with conventional therapy. We believe this drug merits further study in this situation to determine whether it is as useful as other conditioning regimens used before autotransplantation for HD.

P 20 AUGMENTED CYCLOPHOSPHAMIDE, BCNU, AND ETOPOSIDE (CBV) AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN PROGRESSIVE HODGKIN'S DISEASE (HD). S.E.O'Reilly, J. Connors, N. Voss, R. Fairey, G. Herzig, P. Klimo, G. Phillips. Bone Marrow Transplant Program of British Columbia, A. Maxwell Evans Clinic Cancer Control Agency of British Columbia and Washington University, St. Louis MO.

Patients with progressive HD despite previous optimal chemotherapy (CT) and radiotherapy (RT) are usually considered incurable with conventional therapy. Intensive CT and ABMT can produce durable CR in these patients.

Between 2/85 and 9/86 20 pts with recurrent HD were entered on this study. Median age was 26, range 18-39, 11 males. One had no previous response to treatment, 13 were in 1st relapse, 5 in 2nd, and 1 in 4th, all had received multidrug chemotherapy including doxorubicin that produced prior remission in 17. 11 had previous extended field RT. CT free intervals were 19 pts <2 yrs (13<1 yr, 8<6 m).

Protocol treatment included cytoreductive MVPP (mustard, vinblastine, procarbazine and prednisone) x 2 cycles for pts who had sustained >3 m response to prior chemotherapy, followed by involved field RT to any lymph node sites originally >5 cm prior to high dose C(1.8g/M²/day x 4, day -7,-6,-5,-4), B(0.6g/M² x 1, day-3) and V(0.4g/M² q 12 h x 6 day -7,day -6, day -5) followed by cryopreserved autologous marrow (18 pts). 2 pts with marrow involvement received allogenic marrow (1 pt) or peripheral stem cell transplant (1 pt) on day 0. 2 pts achieved a PR, 1 progressed and died at 6 m, 1 is alive without progression at 3 m, 16 pts achieved a CR, 2 have relapsed at 10, and 10 m and remain alive at 11 and 12 m. All others remain in CR at 4,4,5,6,6,7,9,9,9, 11,16, 17, 20, 23 m.

6 pts had documented bacterial sepsis, 1 of whom died, 1 had candida cellulitis, 1 mycoplasma pneumonia, 3 herpes simplex stomatitis. Altogether 2 pts died <day +30, 1 from sepsis and 1 from cerebral edema, these were the two most heavily pretreated pts.

High dose CBV CT, and ABMT, has acceptable toxicity. The sustained CRs are encouraging.

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P 21 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN THE TREATMENT OF 25 ADVANCED RESISTANT HODGKIN'S DISEASE PATIENTS.

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Twenty-five patients with disseminated Hodgkin's disease (HD) resistant to the most widely used combination chemotherapy, were treated with high-dose chemotherapy (HDC) and ABMT. The HDC consisted in two patients of BCNU (700mg/mq),in one of Cyclophosphamide (Cy) 60mg/Kg X2 days and Total Body Irradiation (10Gy) and in twenty-two patients of CVB protocol (Cy 5-6g/mq, VP-16 400-600mg/mq and BCNU 600-800mg/mq)(Carella et al. Eur.J.Cancer Clin.Oncol. 21,607,1985). Twenty-two patients had the BM suspension refrigerated at 4°C for 40 hrs. (range 38-48 hrs) until reinfusion; the last three cases had their BM cryopreserved. Seventeen out 25 patients (68%) achieved a response and twelve (48%) a complete remission. Now, five patients remain alive in unmaintained CR at 2,19,32,46,55 months after ABMT; in the other cases, reasons for failure included relapse of HD (ten patients), or death due to aplasia (one patient) or disseminated sepsis (one patients).
These results show that HDC and ABMT may be highly effective in inducing CR in resistant HD patients; however, the high rate of relapse suggests that this approach could be indicated not only for patient resistant to multiple drug combinations, but also and perhaps even more, as second line treatment of high-risk HD patients after a CR obtained with MOPP+ABVD protocol.

P 22 FOLLOW UP OF PATIENTS WITH RECURRENT HODGKIN'S DISEASE TREATED WITH CONVENTIONAL CHEMOTHERAPY AND AUTOLOGOUS MARROW SUPPORT.

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Heavily pretreated patients (pts) with recurrent Hodgkin's disease (HD) often fail further salvage therapy because of poor hematological tolerance which compromises delivery of potentially curative therapy. This treatment program attempted to circumvent this problem. Between 5/82 - 12/84 12 pts with recurrent, marrow-negative, HD underwent autologous marrow storage immediately prior to salvage chemotherapy. 7 pts were in 1st, 2 in 2nd, 2 in 3rd, and 1 in 4th relapse. 10 had received previous CT+RT, 1 CT alone and 1 RT alone. After marrow storage all 12 received conventional dose CT (10 MOPP/ABV Hybrid, 1 ABVD, 1 MOPP/Adria) for up to 8 cycles. On the day of treatment if granulocytes were <900/dl or platelets <70,000/dl full dose CT was given and marrow reinfused the next day. CT was resumed when granulocytes <1200 and platelets >100,000. 8 pts required ABMT and 13 ABMT's were performed. Hematological recovery was good.

There was 1 toxic death (herpes pneumonia) and 2 minor herpetic infections, 3 pts had one episode of febrile neutropenia, 1 pt had cholecystitis, 2 pts required brief platelet support and 1 had reversible bleomycin lung toxicity.

A high dose intensity was achieved, median treatment delay over 8 m was 2 wks. For nitrogen mustard, the median dose delivered was 97% (86-100%), Adriamycin was also 97% (81-100%). All 12 pts achieved a CR. 1 died of toxicity in CR. 6 are in continuous CR at 25,29,32,33,38 and 51 m since end of therapy, 5 relapsed at 2,4,11 11 and 18 m off therapy. 2 have died, 1 is alive with disease and 2 more are back in remission following radiotherapy.

Autologous marrow reinfusion permitted delivery of dose intense chemotherapy on a tight schedule to patients who had failed MOPP chemotherapy ± RT. Only 2 of these pts had received prior doxorubicin based therapy, one of whom remains in CR at 51 m.

P 23 LATE RELAPSES (L.R.) IN HODGKIN'S DISEASE (H.D.).

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Most of relapses (R.) in patients treated for Hodgkin's disease occur within two years from the primary treatment, whereas the R. are rare events after five years. Early relapses (E.R.) clearly are due to therapeutic failure, whereas it is difficult to state the biologic significance of late relapses (L.R.) in the natural history of the disease.
In order to analyse the R., and particularly L.R., the records of 576 consecutive patients with H.D. seen at our Institution between 1955 and 1978, with a minimum follow-up of 7 years, were reviewed. The male: female ratio was 1.2:1 and the distribution by age subgroups was as follows: 0-15 y. = 44 pts.; 16-35 y. = 299 pts.; 36-55 y. = 187 pts.; more than 55 y. = 44 pts. The histologic subtype was N.S. in 40% of cases, M.C. in 40%, L.P. in 14% and L.D. in 6% of cases. At the completion of staging procedures, 67 patients were classified as Stage IA, 5 as IB, 242 as IIA, 52 as IIB, 104 as IIIA, 80 as IIIB, 16 as IVA and 12 as IVB. The treatment modality was: radiotherapy alone in 436 pts., radiotherapy plus chemotherapy in 112, and chemotherapy alone in 28.
325 out of these patients had a relapse of the disease after their primary treatment. Of these R., 48% occurred in the first year after treatment, 79% within 3 years, 90% within 5 years, while only 5.5% after 7 years. Type of R. (True Recurrence = T.R.; Marginal Recurrence = M.R.; Nodal Extension = N.E.; Systemic Dissemination = S.D.) was analysed in these patients in relation to the interval from the primary treatment: the R. occurring within the first year were in equal proportion T.R., N.E. and S.D.; the R. occurring between second and fifth year after treatment were predominantly N.E.; while the R. occurring later were predominantly T.R. No relationship was observed between the time of relapse and the clinical characteristics at diagnosis (sex, age, histology, clinical stage, mediastinum, number of sites involved). We have only observed that the patients relapsing later than 7 years seem to have more favorable clinical characteristics at diagnosis (but not significantly).
This fact and the observation that later relapses are often T.R. suggest the hypotesis that they represent a new disease rather than a relapse of the previous disease.

P 24 FATAL COMPLICATIONS FOLLOWING TREATMENT IN HODGKIN'S DISEASE.

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A total of 337 patients with Hodgkin's disease were evaluated for the occurrence of intercurrent fatalities after radiotherapy (RT), chemotherapy (CHT), combined modality therapy (CMT) or salvage chemotherapy (SCT). Causes of death were compared with the expected risk, calculated from mortality statistics of the Netherlands' population. Sixty-seven patients died from progressive Hodgkin's disease; in 37 deceased patients death was caused from intercurrent fatalities. A total of 165 patients was treated with RT; 10 fatalities were observed in 81 patients achieving a sustained complete remission (CR). Eighty patients needed SCT; 6 of them died from intercurrent fatalities. A total of 76 patients received CHT as initial treatment; 4 deaths occurred during induction therapy and 6 lethal complications were observed in those in CR. A total of 96 patients received CMT; 5 of them died from complications during induction therapy, 4 of them after they entered CR, and 2 of them while on treatment for relapsing Hodgkin's disease.
In total 7 leukemia's were observed, 6 leading to death. Nineteen patients suffered from second solid tumors, including 4 non-Hodgkin's lymphomas, and 12 of them died. The hazard of developing leukemia appeared 35 times higher than expected in an age- and sex matched Netherlands' population, the hazard of second solid tumor appeared 2.5 times increased. ($P < 0.001$). Nine patients experienced myocardial infarction or acute death, 8 of them died. The expected number of cardiovascular deaths in an age- and sex matched population was 7. Therefore, we did not find evidence of an increased risk for cardiovascular diseases in patients treated for Hodgkin's disease. The 10-year actuarial risk of developing intercurrent fatalities was 4.9% in patients < 40 years and 34.7% in those > 40 years. ($P < 0.001$). Treatment modality, stage and histologic subtype were not prognostic factors for intercurrent death. Notably the risk of dying from fatal non-lymphoma related events was not diminished in patients treated with RT only compared to those being exposed to CHT.

P 25 TESTICULAR FUNCTION IN BOYS TREATED FOR HODGKIN'S DISEASE. PROSPECTIVE EVALUATION IN 68 BOYS OF THE DAL-HD-78 AND DAL-HD-82 THERAPY STUDY.

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Testicular dysfunction is a major complication in adults treated with MOPP-chemotherapy for Hodgkin's disease. While Leydig cell function is generally reported to be normal, the incidence of infertility is as high as 80 % (Sherins et al. 1973). It was the aim of this study to evaluate testicular function in boys treated with OPPA and COPP-chemotherapy (vincristine, prednisone, procarbazine, adriamycine, cyclophosphamide).

In 68 boys, aged 12.94 ± 2.09 years (mean ± SD) at diagnosis, a standardized intravenous LHRH-test was performed at a mean chronological age of 17.82 ± 2.18 years. Basal and stimulated FSH-values were more than 2 SD above normal in 39.7 and 52.9 % of the cases indicating severe impairment of spermatogenesis. FSH values were 14.31 ± 9.75 U/l (basal) and 25.55 ± 17.08 U/l (stimulated) with normal values of 7.17 ± 3.46 U/l and 9.42 ± 4.79 U/l.

Basal LH values were in the upper range of normal with 8.78 ± 3.69 U/l, while stimulated LH was 49.38 ± 23.69 U/l and thus well above the value observed in the control group (17.28 ± 3.99 U/l). This idicates that in addition to the impairment of spermatogenesis Leydig cell function is altered, though testosterone values are within normal limits (20.24 ± 9.02 nmol/l).

It appears that within our therapeutic regimen procarbazine is the major contributing factor for the overall incidence of testicular dysfunction. The frequency of elevated basal FSH-levels rises from 27.8 to 37.5 to 64.3 % with cumulative procarbazine doses of < 4000, 4000 - 8000 and 8000 to 12000 mg/m^2.

We conclude that impaired sperm production and compensated Leydig cell failure are major late sequelae in boys treated for Hodgkin's disease. We suggest that parents and patients are informed about these side-effect prior to therapy and that LHRH-tests and/or spermiograms are performed during the long term follow-up of these patients.

P 26 SEXUAL FUNCTION AMONG ADULT PATIENTS (PTS) WITH MALIGNANT LYMPHOMA (ML) UNDERGOING COMBINATION CHEMOTHERAPY (CT).

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The purpose of this retrospective study is to evaluate the sexual function among adult pts with ML at the diagnosis, during CT and follow-up. Pts aged 18-45 years without evidence of disease 2 years from the completion of CT (C-MOPP/ABVD, MOPP, ABVD, CHOP for a median number of 10 cycles, range 4-24) were considered evaluable. After verbal consent a questionnaire was given to 46 pts 31 of them actually filled it in (18 males, 13 females; median age 39 yrs, range 22-53; 18 Hodgkin's, 13 non-Hodgkin's lymphomas). For the purpose of this report, only weekly sexual intercourses and quality of sexual life as reported by 29 pts with stable heterosexual relationship have been evaluated. The median number of reported weekly sexual intercourses before the onset of the disease was 3, at the time of diagnosis was 2, during CT was 1, after 1 year from the end of CT was 1.5 and later was 2. The quality of sexual life was considered satisfactory before the onset by 90% of the pts, at diagnosis by 55%, during CT by 45%, after 1 year from CT by 60%, and later by 70% of the pts. At the time of diagnosis the decrease of sexual function was attributed to the worsening of the general conditions (40%),less desire (40%) and change of life style (25%); whereas during CT to the worsening of the general conditions (55%), less desire (55%), dispaurenia (50%), change of life style (25%) and loss of erection (20%). Sexual ormones tested, in particular FSH, seem not to correlate with the sexual function observed. In conclusion, sexual function of adult pts with ML is impaired at the time of diagnosis and during CT; however, during follow-up, it significantly improved almost at the same level reported before the onset of the disease. Therefore the long term sexual function of adult pts with ML as evaluated in this study does not seem to be significantly impaired by CT.

P 27 ACUTE NON LYMPHOID LEUKEMIA AND SOLID TUMORS FOLLOWING THERAPY OF HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA: A 10-YEAR UPDATE.

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During the period 1971-1984, 429 consecutive patients with Hodgkin's disease were treated at the Division of Hematology, Pavia. The entire cohort amounted to 2168 person-years (p-ys); treatment groups consisted of radiotherapy (RT) alone (170 p-ys), chemotherapy (CT) with MOPP (425 p-ys) or MOPP alternated to ABVD (240 p-ys); RT and adjuvant MOPP (769 p-ys); RT and salvage CT (MOPP: 320 p-ys; ABVD: 204 p-ys). In patients with multiple relapses, nitrosourea and podophyllotoxin derivatives were also employed (120 p-ys). This cohort is analyzed to assess the incidence of acute non lymphoid leukemia (ANLL) or solid tumors (ST) after treatment. Within a median follow-up of 8 years, 28 new malignancies (6%) were documented (14 ANLL and 14 ST). The 10-year actuarial estimate and relative risk (RR = observed/expected ratio) of ANLL and ST by therapy group were as it follows:

		Leukemia				Solid tumors			
Therapy	no. of patients	no. of cases	actuarial risk %	RR	p	no. of cases	actuarial risk %	RR	p
RT alone	53	0	0	0		2	3.7	4.1	ns
CT alone	160	3	2.1	75	.0001	3	2.7	1.2	ns
RT+adj. CT	109	8	11.1	266	.0001	4	4.5	3.2	.05
RT+salv. CT	107	3	6.4	100	.0001	5	10.9	3.9	.025

No cases of leukemia were documented in patients given RT alone: the risk of ANLL was 11.1% and 6.4% in the RT+CT groups. No positive correlation was noted between age over 40 and increased risk of ANLL. The 10-year actuarial risk of ST ranged between 2.7 (CT alone) and 10.9% (RT and salvage CT). However, the relative risk was significant only for the combined modality groups. No excess risk was observed for lung cancer and melanoma, whereas the risk for soft tissue sarcomas (including Kaposi sa.), non Hodgkin's lymphomas (NHL) and endometrium carcinoma was significantly raised. From 1975 to 1985, 450 patients were treated for NHL. RT alone was given to 7%; monochemotherapy with chlorambucil and/or cyclophosphamide to 17% of total patients; polychemotherapy with and without doxorubicin to 24 and 32% of total. RT+CT was adopted in 20% of cases. Within a 7-year median follow-up, 18 new malignancies (4%) were documented (2 ANLL and 16 ST). The RR was highly significant ($p < 0.001$) for the group of men with low-grade malignancy NHL, whereas it was not for low-grade malignancy women and for high-malignancy NHL. The RR was significant ($p < 0.025$) for the group given long-term chlorambucil and/or cyclophosphamide. Excess risk was observed for ANLL, Kaposi sa. (1 case) and skin basalioma.

P 28 SECOND MALIGNANCIES IN BRITISH NATIONAL LYMPHOMA INVESTIGATION HODGKIN'S DISEASE STUDIES.

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In the series of over 2,300 evaluable patients with Hodgkin's Disease entered into British National Lymphoma Investigation Studies since 1970, second malignancies have so far been reported in 68 patients: 14 acute leukaemia, 11 non Hodgkin's lymphomas and 43 solid tumours.

Of the 14 cases of leukaemia, 12 were acute myeloblastic and 2 acute lymphoblastic. The overall actuarial risk of leukaemia in the whole group at 10 years was 1.2%. No patient developed leukaemia who received radiotherapy alone. In the patients receiving chemotherapy alone the risk at 10 years was 2.6%. The patients who developed leukaemia received significantly more courses of chemotherapy than a case control group. The risk of leukaemia was related to the cumulative drug dosage given, with CCNU appearing to be particularly leukaemogenic. For patients receiving CCNU the overall risk of leukaemia was 12% and this rose to 18.5% when used for salvage treatment.

43 cases of solid tumours were reported, of which the commonest was carcinoma of the bronchus, occuring in 20 patients, 6 of whom were under 50 years of age. In 11 of the 43 patients the tumour developed in a previously irradiated area.

In contrast to the 14 cases of leukaemia which arose in multiply-treated patients who were unlikely to be cured of their disease, 29 of the 43 who developed solid tumours had been free of Hodgkin's disease, some of them for many years.

P 29 MYELITIS FOLLOWING CENTRAL NERVOUS SYSTEM IRRADIATION AND CHEMOTHERAPY: A REPORT OF TEN CASES FROM A SINGLE INSTITUTION.

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Ten cases of myelitis occurred following treatment of central nervous system (CNS) leukaemia/lymphoma with radiation and intrathecal chemotherapy. Radiation doses were within normally accepted tolerance levels. Several factors were common to all cases.

1) All had CNS involvement or parameningeal disease at diagnosis.
2) They had a segment of the craniospinal axis irradiated.
3) They received combined systemic and intrathecal chemotherapy.
4) All had negative cerebrospinal fluid (CSF) and negative myelograms at the onset of myelitis.

Patient Characteristics: 9 male, 1 female, age 6-61, average 33 years Acute lymphatic leukaemia 3; acute promyelocytic leukaemia 1; non-Hodgkin's lymphoma 6 - stage IE extradural 1, stage IIE 2, IIIE 1, stage IV 2. One patient had CNS disease at diagnosis, 6 developed CNS relapse after inadequate prophylaxis and 2 relapsed in the CNS after adequate prophylaxis. One had extradural involvement only. All patients received systemic chemotherapy. Nine patients received intrathecal methotrexate with or without cytosine arabinoside and hydrocortisone. One patient received intrathecal cytosine arabinoside. Nine patients received cranial irradiation and the tenth patient received intraventricular chemotherapy via an Ommaya reservoir. Two patients received craniospinal irradiation and 2 patients received total body irradiation. The total number of intrathecal chemotherapy doses varied from 3 to 30. All patients developed typical transverse myelitis at a time when there was no evidence of recurrence of disease including negative myelography and CSF cytology. Despite this, 3 patients were mistakenly assumed to have recurrence of disease and were retreated. Only 3 of the patients are alive, all with permanent neurological deficits. Autopsy material was available on 4 cases. There was evidence of diffuse demyelination, fibrinoid necrosis and thickened meninges. The anatomical distribution was variable, one showing scattered peripheral focal lesions in the spinal cord with a secondary ascending degeneration. Two patients exhibited marked sclerosing arachnoiditis whilst the 4th patient had changes more typical of radiation myelitis.

Meningeal disease and/or CNS irradiation may predispose to the development of myelitis by increasing the neurotoxic effects of intrathecal and systemic therapy. Conversely, methotrexate or cytosine arabinoside administered intrathecally or systemically may lower the tolerance of the spinal cord to irradiation. Iatrogenic etiology of myelitis should be considered when CSF cytology and myelography are normal.

P 30 Favourable prognosis in childhood T-cell lymphomes

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From August 1981 until April 1984 19 consecutive children aged 2-17 yrs, with mediastinal T-cell lymphoma were treated in our Institute. Ten children had initial bone marrow involvement. These 19 children were treated as follows:

Induction: Vincristine, i.v. x6, Nitrogen Mustard i.v.x2
Procarbazine p.o. for 2 weeks, prednisolone p o for 5 weeks
L-asparaginase i.v. for 2 weeks

CNS-prophylaxis: 25 Gy to the cranium and 6 intrathecal injections with cytosine-arabinoside

Maintenance: BACOP during 18 months

With this regimen 18 children have achieved complete remission. One child had a partial remission and was treated with an autologous bone marrow transplantation. This boy remains disease-free, 63^{+}months after diagnosis. Four children have relapsed in the bone marrow and they died. No relapse occured in the mediastinum. The remaining 15 patients are free of disease from 33^{+} to 65^{+} months, providing a disease-free survival rate of 79%.

This DFS belongs to the highest survival rates published so far. According to these results one should consider the possibility of reducing the aggressiveness of the therapy.

P 31 CHILDHOOD ADVANCED HODGKIN'S DISEASE TREATED WITH SIX CYCLES OF ABVD AND REGIONAL LOW DOSE IRRADIATION: A PILOT STUDY.

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Sixty-six patients with pathologically staged advanced Hodgkin's disease (IIIA.M.-macromediastinum, IIIA.S.-macrospleen, III_2A, IIIB, IVA, IVB) were entered onto a pilot study consisting of six cycles of ABVD (adriamycin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2, bleomycin 10 units/m^2 q. 2 weeks x 12) followed by low dose (2100 cGy in 12 fractions) regional irradiation. Patient characteristics: ineligible 2; III_1A.S. 7; IIIA.M. 4; III_2A 6; IIIB 20; IVA 10; IVB 17; staging laparotomy and splenectomy 42; laparotomy without splenectomy 4; partial splenectomy 1; no laparotomy 17. Eight of fourteen (57%) with proven paraaortic node disease had concomitant pelvic node involvement compared to one of 21 (5%) with negative paraaortic disease. The event free survival was 89% with a median follow-up of 13 months. Three patients relapsed, two of whom died. One patient developed acute leukaemia and died of complications following bone marrow transplantation.

Toxicity on 62 evaluated patients using CCSG criteria was as follows:

	0	1+	2+	3+	4+	Unknown
Pulmonary	38	3	3	2	2	15
Haematological	0	2	7	18	35	0
Gastrointestinal	25	3	24	8	2	0
Hepatic	33	17	11	1	0	0
Peripheral Neuropathy	55	4	3	0	0	0

Of the four patients with grade III-IV pulmonary toxicity (decrease in DLCO of > 35%) one was fatal and one necessitated stopping therapy after five cycles of ABVD.

Analysis of 49 patients completing six cycles of ABVD revealed the following percentage of drugs delivered: adriamycin 94%, bleomycin 95%, vinblastine 94%, dacarbazine 95%. Five patients had reduced bleomycin dosage. Carbon monoxide diffusing capacity appeared to be an early predictor of bleomycin related pulmonary toxicity. A prospective randomized trial is underway comparing this regimen with alternating MOPP/ABVD.

P 32 KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) TUMOR REGISTRY: DISPLAY OF MALIGNANT LYMPHOMAS IN CHILDREN UNDER THE AGE OF 15 YEARS.

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The KFSH & RC Tumor Registry, the first to be created in Saudi Arabia, maintains a complete database of all cancer patients diagnosed and/or treated at the Hospital from 1 June 1975 to 31 December 1985. It registered a total of 1415 patients < 15 years of age, or 12.6% of the total number of cases. Ninety-eight % of patients were Arabs (88% Saudis). Of these 1415 patients, 222 (15.7%) had Non-Hodgkin's Lymphoma (NHL): 162 boys (73%) and 60 girls; and 112 (7.9%) had Hodgkin's Disease (HD): 90 boys (80%) and 22 girls.

HISTOLOGIC TYPES

NHL (222 CASES)			HD (112 CASES)		
Type	No/%	Sex Boy/Girl	Type	No/%	Sex Boy/Girl
Undifferentiated	107/48		Mixed Cellularity	62/55	49/13
A. Non-Burkitt	70	55/15	Nodular Sclerosis	23/20	16/7
B. Burkitt	37	27/10	Lymphocyte Predom.	11/10	11/0
Lymphoblastic	59/26	40/19	Lymphocyte Depletion	4/4	4/0
Histiocytic	12/6	10/2	Unspecified	12/11	10/2
Unspecified	44/20	30/14			

INCIDENCES ACCORDING TO SEX AND AGE
Number of Cases Per Each Year Of Age

Age (yrs)		1	2	3	4	5	6	7	8	9	10	11	12	13	14
NHL (222:162 BOYS, 60 GIRLS) RATIO 2.7/1.0															
Sex:	Boy	1	7	26	33	25	19	9	9	7	4	2	13	4	3
	Girl	0	5	10	11	11	6	1	4	2	1	4	3	2	0
Total		1	12	36	44	36	25	10	13	9	5	6	16	6	3
HD (112:90 BOYS, 22 GIRLS) RATIO 4.0/1.0															
Sex:	Boy	0	0	2	10	10	11	12	9	5	9	5	10	3	4
	Girl	0	0	1	1	0	1	3	1	4	0	2	3	1	5
Total		0	0	3	11	10	12	15	10	9	9	7	13	4	9

NHL and HD revealed a marked predominance for boys: 2.7 to 1.0 and 4.0 to 1.0, respectively. Two-thirds of NHL patients were < 8 years of age, and near half of HD patients > 8 years of age. In the NHL group there was a marked incidence of Burkitt's lymphoma, and in the HD group there was a marked incidence of the mixed cellularity type. These features appear unique. The national geographical distribution of the tumors has been determined, and the survival information on each patient is an ongoing process. The KFSH & RC Tumor Registry is a valuable source of information to study childhood tumors in the Middle East, since it deals with a homogeneous Arab population (98% of the cases).

P 33 RESULTS OF TREATMENT OF ADVANCED STAGE B-CELL NON-HODGKIN'S LYMPHOMA IN CHILDREN WITH SJCRH-TOTAL B2 THERAPY.

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Since January 1984 pts with non-Hodgkin's lymphoma (NHL) observed in our institution have been treated with different chemotherapeutic regimens depending on stage and histo-immunological subtype. Pts with stage III and IV B-NHL and B-Acute Lymphoblastic Leukemia (B-ALL) were treated with "Total B-2" protocol, an intensive chemotherapeutic regimen based upon appreciation of rapid tumor growth kinetics as adopted at St.Jude Children's Research Hospital. Treatment consists of a fractionated schedule of cyclophosphamide (300 mg/mq q12 h X 6 doses) followed immediately by adriamycin (50 mg/mq) and vincristine (1.5 mg/mq) with combined intrathecal methotrexate (it MTX) and cytarabine (ARA-C). Immediately upon hematologic recovery, i.v.high-doses MTX (1,000 mg/mq over 24 hours) followed by i.v. ARA-C (400 mg/mq over the next 48 hours) is administered with leucovorin rescue and repeated intrethecal treatments. The treatment sequence described is repeated 4 times, with the dose of ARA-C doubled in succeeding courses, up to 3200 mg/mq. The entire planned therapy requires aproximately 24 weeks.

Since 1984 to december 1986 we treated 11 children with this approach. According to initial extent of disease, 8 were classified as stage III (7 of whom had massive unresectable intra-abdominal tumor and 1 had lymphonode and mediastinal involvement), 2 as stage IV NHL and 1 as B-cell ALL. 1 stage IV pt had initial involvement of the CNS.

Ten evaluable pts attained a complete remission (CR) (100%) (1 pt was excluded from analysis because too early to evaluation) . 7 out of10 pts are alive in CCR. All but one stage III NHL pts (6/7=85.7%) remain disease-free for periods ranging from 3 to 35 months; at present time 3 of them are off-therapy after 1+, 27+, 30+ months respectively. The stage IV NHL pt with initial CNS disease is off-therapy in CCR after 13 months; the 2 remaining pts (B-ALL, stage IV NHL) presented CNS-relapse after 3 months from diagnosis and 1 month after completion of therapy respectively, and eventually died. Major toxicity consisted of severe hematopoietic suppression and febrile episodes with neutropenia, generally 7-14 days after the completion of each chemotherapeutic phase which required very intensive supportive care and hospitalization.

According to the results reported in the literature, our previous experience showed a poor outcome in advanced stage B-cell NHL pts when LSA_2-L_2 protocol was employed ; on the contrary the results obtained with Total-B2 protocol appear to be very satisfactory. This chemotherapeutic approach represents an effective therapy for stage III B-NHL. On the contrary, as our preliminary results suggest, pts with stage IV B-NHL or B-ALL may need alternative regimens such as more intensive CNS prophylaxis.This approach might be of benefit to patients with CNS involvement at diagnosis, who present a very poor outcome, as referred by Murphy.

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