PROGRAM and ABSTRACTS

Third
International
Conference
on Malignant Lymphoma
June, 10-13, 1987

Lugano, Switzerland

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Organizing Committee:

F. Cavalli (Bellinzona),
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Sponsored by Swiss Group for Clinical Cancer Research (SAKK) and Lega Ticinese Contro il Cancro

CONFERENCE SCHEDULE

WEDNESDAY, June 10, 1987

1:00 - 4:00 p.m. SATELLITE SYMPOSIUM (Room A)
STRATEGIES FOR THE INTEGRATION OF INTRON (INTERFERON ALFA 2B) INTO THE TREATMENT OF HEMATOLOGICAL MALIGNANCIES

4:00 - 5:00 p.m. MEET THE PROFESSOR (Rooms B,C,E,F)

4:30 - 6:00 p.m. POSTER SESSION I (Villa Ciani)

5:15 - 6:15 p.m. WELCOME PARTY (Room B)

6:15 - 7:30 p.m. Session 1 - OPENING CEREMONY (Room A)

HENRY KAPLAN MEMORIAL LECTURE (Room A)
MONOCLONAL ANTIBODIES: CURRENT STATUS AND RESEARCH AVENUES

THURSDAY, June 11, 1987

8:00 - 11:45 a.m. Session 2 - NEW ASPECTS IN THE BIOLOGY OF LYMPHOMA (Room A)

1:00 - 1:45 p.m. KEY NOTE LECTURE (Room A)
SPECIFIC CHROMOSOME ABERRATIONS IN NON-HODGKIN'S LYMPHOMA + LYMPHOID LEUKEMIA

1:50 - 2:50 p.m. Session 3 - HODGKIN'S DISEASE: OVERVIEW (Room A)

3:00 - 5:30 p.m. Session 4 - HODGKIN'S DISEASE IN ADULTS (Room A)

3:00 - 5:45 p.m. Session 5 - WORKSHOP ON NEW DIAGNOSTIC POSSIBILITIES IN LYMPHOMA (Room B)

3:00 - 6:10 p.m. Session 6 - LYMPHOMA IN CHILDHOOD (Room C)

5:30 - 6:30 p.m. POSTER SESSION II (Villa Ciani)

9:00 p.m. PERFORMANCE "ROMEO AND JULIET" THEATRE COMPANY: DEL CARRETTO (Room A)

FRIDAY, June 12, 1987

8:30 - 11:45 a.m. Session 7 - LYMPHOMA IN IMMUNODEFFICIENCY (Room A)

1:00 - 2:00 p.m. POSTER SESSION III (Villa Ciani)

2:00 - 3:00 p.m. Session 8 - NON HODGKIN'S LYMPHOMA: OVERVIEW (Room A)

3:10 - 6:00 p.m. Session 9 - TREATMENT OF NON HODGKIN'S LYMPHOMA IN ADULTS (Room A)

3:15 - 6:00 p.m. Session 10 - WORKSHOP ON THE CURRENT SITUATION OF BONE MARROW TRNSPLANTATION IN MALIGNANT LYMPHOMA (Room B)

3:05 - 6:00 p.m. Session 11 - PATHOLOGY AND CLINICAL-PATHOLOGICAL CORRELATIONS (Room C)

5:30 SATELLITE WORKSHOP (Room F)
INTERFERON ALFA 2A AND LYMPHOMAS

SATURDAY, June 13, 1987

9:00 - 12:00 a.m. Session 12 - NEW TREATMENTS-REPORTS ON CURRENT STATUS (Room A)
11:00 CONCLUDING LECTURE

12:00 ADJOURN

POSTER SESSIONS

VILLA CIANI

I - Wednesday, June 10, 4:30-6:00 p.m.
II - Thursday, June 11, 5:30-6:30 p.m.
III - Friday, June 12, 1:00-2:00 p.m.

LOCALISATION OF POSTERS

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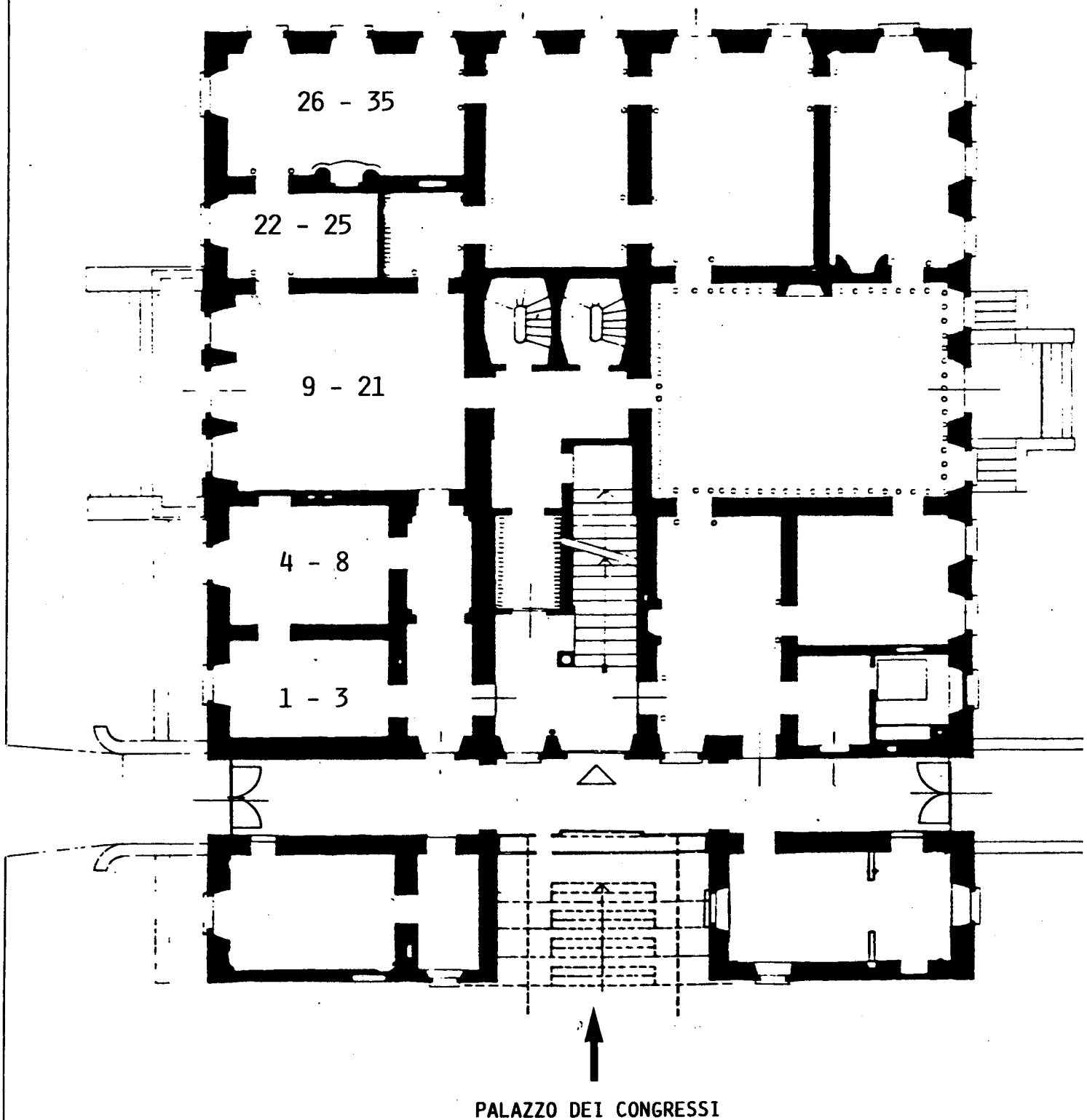

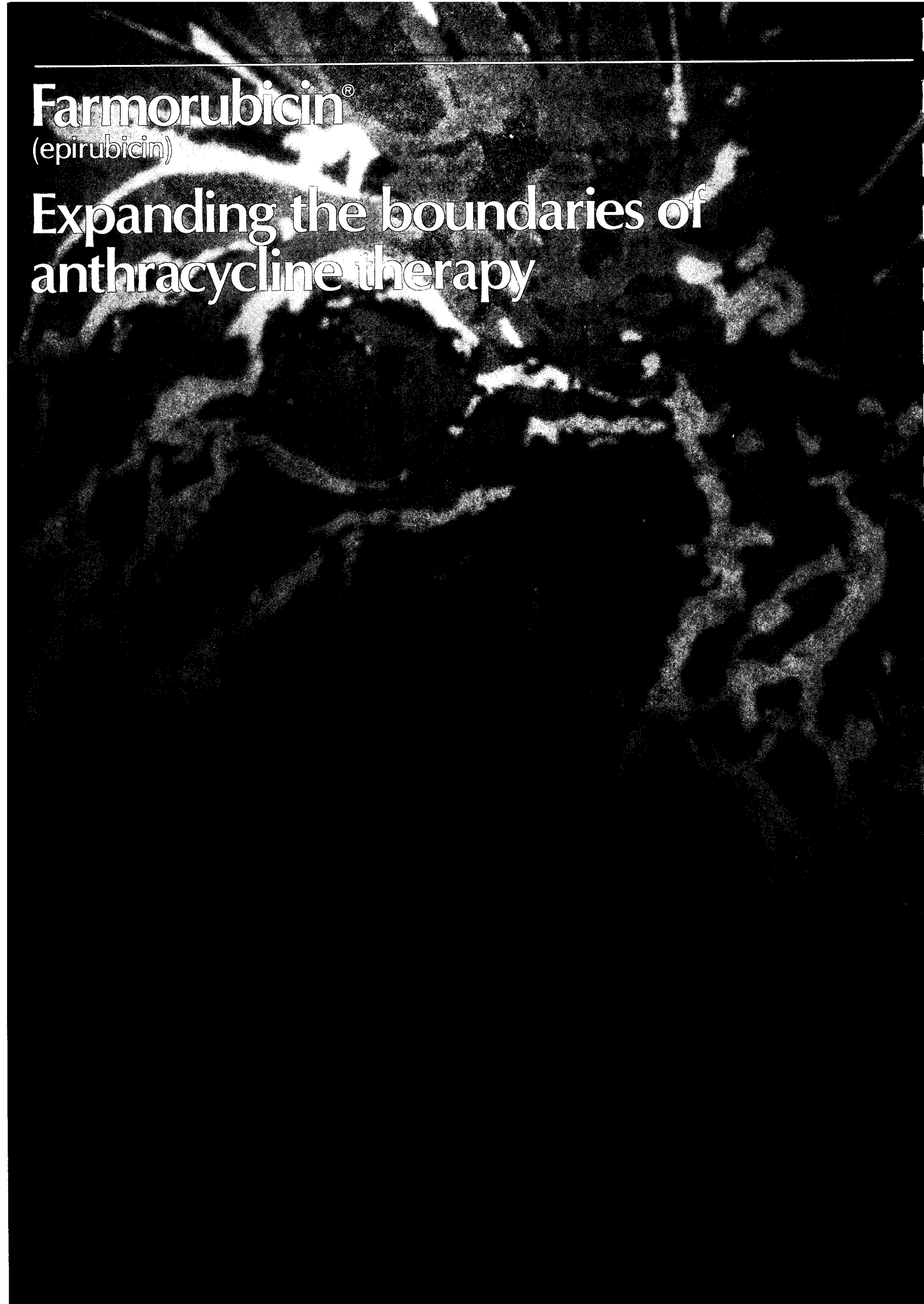
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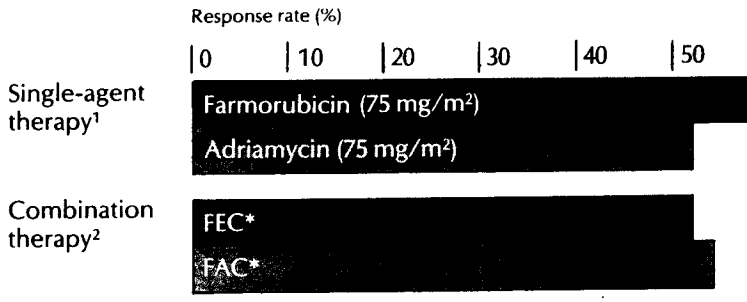
Farmorubicin matches Adriamycin®—milligram for milligram—in both single-agent[1] and combined chemotherapy regimens.[2,3]

Response of Farmorubicin and Adriamycin given at equimolar doses in single-agent or combination chemotherapy

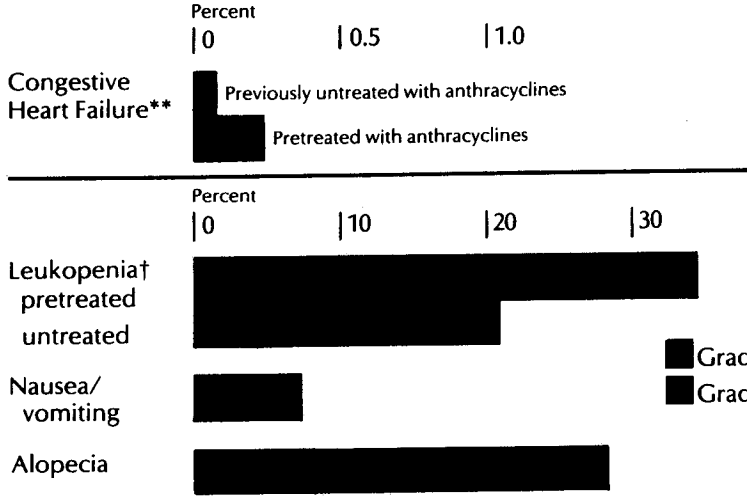


*Farmorubicin (FEC) or Adriamycin (FAC) 50 mg/m² combined with 5-fluorouracil (500 mg/m²) and cyclophosphamide (500 mg/m

Farmorubicin breaks the cardiotoxicity barrier and gives you more tolerable treatment

Farmorubicin cuts Adriamycin cardiotoxicity in half and allows cumulative doses up to 1,000 mg/m² with minimal risk of CHF.[3,4,5,6] In addition, Farmorubicin has shown less treatment-limiting myelosuppression[2] and fewer, less severe acute side effects.[3,5,6]

Percent of patients showing evidence of toxicity* (more than 1300 patients) (Farmorubicin dose: 75-90 mg/m² IV)[6]

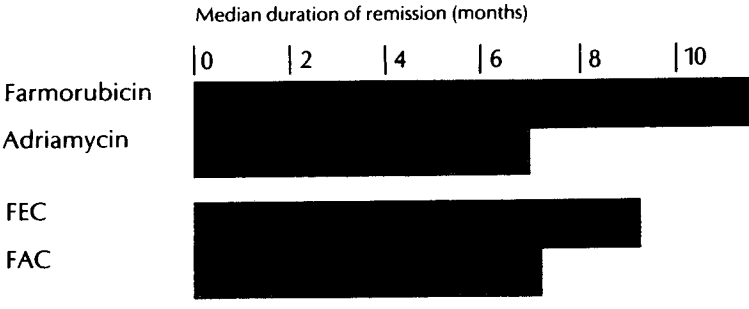


*WHO criteria
†Based on lowest WBC value recorded
**Total cumulative dose of anthracyclines ≤ 1000 mg/m²

Farmorubicin helps you sustain the remissions you achieve

Farmorubicin permits multiple additional courses of therapy at full therapeutic doses, undelayed by excessive or unpredictable hematologic toxicity.

Duration of remission in patients treated with Farmorubicin as a single agent* and in combined chemotherapy (FEC *vs* FAC)**



*Jain KK, *et al*
**Armand JP, *et al*, ECCO

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PHARMACOLOGY AND TOXICOLOGY

Experimental antitumor activity. Farmorubicin proved effective in a wide variety of experimental tumors, particularly leukemias L 1210, P 388, sarcomas solid and ascitic SA 180, melanoma B 16, mammary carcinoma, Lewis' lung carcinoma 38, as well as in human tumortransplanted into athymic nude mice (melanoma, breast, lung, prostatic and ovarian carcinomas).

Pharmacokinetic. In patients with normal liver and kidney functions, plasma levels of Farmorubicin exhibit a triexponential declining pattern, including a very fast early phase and a definitely slow end phase characterized by a half-life of about 30 hrs. Plasma levels of the main metabolite, namely the 13-OH derivative, are consistently lower and follow a similar curve pattern of the unchanged drug. Excretion predominantly occurs by biliary route. High plasma clearance values (1.4 l/min) indicate that the slow elimination is due to extensive tissue distribution. Farmorubicin does not surpass the blood-brain barrier (in rats).

Toxicology. Repeated administration (in rabbits and dogs) and cardiotoxicity studies (in rats and rabbits) showed that epirubicin (Farmorubicin) is less toxic than the parent compound, doxorubicin (Adriamycin).

Farmorubicin proved mutagenic in vitro and carcinogenic in vivo (in rodents).

CLINICAL INFORMATION

Farmorubicin proved to be active in breast, ovarian, gastric and hepatic carcinomas, malignant lymphomas, and soft tissue sarcomas. Preliminary evidence suggests that Farmorubicin may induce responses in small cell lung carcinoma, head and neck, pancreatic and rectal cancer, and acute lymphoblastic leukemia.

Contraindications. Myelosuppression, severe heart disease, previous treatments with maximal cumulative doses of Adriamycin or daunorubicin.

Side effects: Cardiac toxicity, alopecia, mucositis, gastrointestinal disorders, hematologic toxicity.

Precautions. Patients should be carefully monitored during the first course of Farmorubicin treatment. White and red blood cell and platelet counts should also be strictly monitored. At conventional dosage schedules, leukopenia is commonly transient, WBC nadir is reached between 10 and 14 days from start of treatment, and normal values are recovered within 21 days. Before, and possibly during treatment, liver function should be monitored by usual laboratory tests (SGOT, SGPT, AP, bilirubin).

In laboratory animals as well as in clinical settings Farmorubicin appeared associated to lower acute and chronic cardiotoxicity than Adriamycin. Although uncommon, left ventricular failure can occur, particularly in patients who have received a cumulative dose that exceed 1000 mg/m^2. However, cardiac decompensation can admittedly occur even several weeks after completion of treatment, proving sometimes unresponsive to specific medication. In case of simultaneous or previous irradiation to the mediastinal-pericardiac area, cumulative doses should be reduced accordingly. In any case, total Farmorubicin dose should be individualized on account of possible concomitant administration of potentially cardiotoxic agents. In addition, ECG is to be performed before and after every course. Appearance of ECG changes, such as T wave flattening or inversion, S-T depression arrhythmias (mostly transient and reversible), does not necessarily require treatment discontinuation.

Anthracycline-, and particularly Adriamycin- related cardiomyopathy appears associated with persistent reduction of QRS voltage, abnormally increased ratios of systolic intervals (PEP/LVET), and decrease of ventricular ejection fraction.

Cardiac monitoring of Farmorubicin-treated patients is of utmost importance. Heart function should be assessed by using multiple noninvasive techniques, such as ECG, echocardiography, and possibly ejection fraction as measured by myocardio scintiscanning.

Like other cytostatics, Farmorubicin can induce hyperuricemia from rapid lysis of neoplastic cells, therefore uricemia should be monitored accordingly to allow pharmacological control. Adequate information is still lacking as concerns drug influence on male and female fertility, or its teratogenic activity or fetal toxicity. Experimental data, however, suggest that Farmorubicin may harm the fetus.

Framorubicin may give a red color to the urine, up to 1-2 days after administration.

Drug interaction and incompatibility. Farmorubicin should not be mixed with heparin (chemical incompatibility). In combination regimens avoid mixing Farmorubicin together with other drugs into the same syringe.

Dosage and administration route. The recommended dose for single-agent Farmorubicin in adults is 75-90 mg/m^2 body surface, as 3-5 min. i.v. injections 3-weekly, when compatible with extant bone marrow function.

A lower dose is recommended for patients with reduced bone marrow reserve due to previous chemo- and/or radiotherapy, old age, or malignant bone marrow infiltration.

In this case, the total dose per course may be divided in 2 or 3 consecutive days.

In combination schedules, doses should be adequately reduced. Since the main elimination pathway is the hepatobiliary system, doses should also be reduced in patients with impaired liver function in order to prevent increased overall toxicity. In patients with serum bilirubin peaking at 1.4-3 mg/dL, a 50% reduction is recommended as well as a 75% reduction for higher values of serum bilirubin.

Moderately impaired renal function seems not to require dose reduction, due to low Farmorubicin excretion by renal route.

Modes of administration. Farmorubicin is to be administered i.v. It is inactive by oral route, and must not be given by i.m. or intrathecal routes.

Intravenous administration should occur via the tubing of a saline infusion (once proper needle placement has been verified). This minimizes the risk of extravasation while allowing washing of the vein or completion of injection. Drug extravasation is associated with serious tissue injury, up to necrosis. Venous sclerosis may be observed, particularly when small vessels are used or injections repeated in the same vein.

Freeze-dried preparation	Diluent added	Final concentration
10 mg	5 ml	2 mg/ml
20 mg	10 ml	2 mg/ml
50 mg	25 ml	2 mg/ml

The reconstituted solution is stable for 24 hrs at room temperature, and for 48 hrs in a refrigerator (4° - 10° C). It should be protected from direct light.

It is advisable that personnel handling this drug should wear protective gloves. Accidental contact of Farmorubicin powder or solution with skin or mucosa should be treated immediately by copious lavage with soap and water.

Package quantities. Each vial contains 10 mg or 50 mg of epirubicin hydrochloride as a freeze-dried powder.

Composition.

Epirubicin hydrochloride	10 mg	20 mg	50 mg
Excipient: Lactose	50 mg	100 mg	250 mg

CONFERENCE SCHEDULE

WEDNESDAY, June 10, 1987
4:00 - 7:30 p.m.

4:00 - 5:00 p.m.

MEET THE PROFESSOR (Rooms B,C,E,F)
(Entrance free)

SPECIAL SITUATIONS IN THE TREATMENT OF HD **(Room B)**
J.E. Ultmann, Chicago, USA

TREATMENT OF AGGRESSIVE NHL **(Room C)**
G. Bonadonna, Milan, Italy

LYMPHOMA IN CHILDREN **(Room E)**
S.B. Murphy, Memphis, USA

AUTOLOGOUS BONE MARROW TRANSPLANTATION IN THE TREATMENT OF LYMPHOMA **(Room F)**
J.O. Armitage, Omaha, USA

4:30 - 6:00 p.m.

POSTER SESSION I (Villa Ciani)
BASIC RESEARCH AND MISCELLANEOUS

Session 1 - OPENING CEREMONY (Room A)
Chairman: F. Cavalli

6:15 p.m.

WELCOME AND INTRODUCTORY REMARKS.
F. Cavalli, Bellinzona, Switzerland

6:30

HENRY KAPLAN MEMORIAL LECTURE
MONOCLONAL ANTIBODIES: CURRENT STATUS AND RESEARCH.
G. Köhler, Freiburg, West-Germany

THURSDAY, June 11, 1987
8:00 - 11:45 a.m.

Session 2 - NEW ASPECTS IN THE BIOLOGY OF LYMPHOMA (Room A)
Chairmen: G. Losa and C.W. Berard

Time	Abstract	Title, Authors
8:00 a.m.	2	Ki-1 LYMPHOMA: EXPERIMENTAL AND CLINICAL FINDINGS. H. Stein, et al, Berlin, West-Germany
8:20	3	RECEPTORS OF B CELL ACTIVATION AND DIFFERENTIATION ARE VARIABLY EXPRESSED ON EBV NEGATIVE AND POSITIVE CELL LINES. M.C. Favrot, et al, Lyon, France
8:35	4	B-CELL NEOPLASIA RECAPITULATES THE NORMAL HUMORAL IMMUNE RESPONSE. D.D. Weisenburger, et al, Omaha, USA
8:50	5	MULTICLONAL LYMPHOMAS. J. Sklar, Stanford, USA
9:15	6	PERIPHERAL BLOOD GENE REARRANGEMENT ANALYSES IN MALIGNANT LYMPHOMA. S.J. Horning, et al, Stanford, USA
9:30	7	REFRACTORINESS TO CHEMOTHERAPY AND POOR SURVIVAL RELATED TO ABNORMALITIES OF CHROMOSOMES 17 AND 7 IN LYMPHOMA. F. Cabanillas, et al, Houston, USA
9:45	8	CHROMOSOMAL ABERRATIONS IN CHRONIC B-LYMPHOCYTIC LEUKAEMIA - CONSISTENCY DURING PROGRESSION OF DISEASE. J. Gunnar, et al, Huddinge, Sweden
10:00		INTERMISSION
10:20	9	MIXED-LINEAGE LEUKEMIAS AND PHENOTYPIC SHIFTS OCCURRING IN RELAPSED CASES OF ACUTE T LYMPHOBLASTIC LYMPHOMAS. D. Delia, et al, Milan, Italy
10:35	10	COMBINATION THERAPY WITH CYTOKINES AND MONOCLONAL ANTIBODIES. B.F. Issell, Emeryville, USA
10:50	11	THE CLINICAL PHARMACOLOGY OF A RECOMBINANT HUMAN IL-2 ANALOG IN PATIENTS WITH CANCER. E.C. Bradley, et al, Emeryville, USA
11:05	12	DEVELOPMENT OF MONOCLONAL ANTIBODIES AGAINST HODGKIN-DERIVED CELL LINES. M. Pfreundschuh, et al, Cologne, West-Germany
11:20	13	LOW FIELD STRENGTH MAGNETIC RESONANCE IMAGING OF THE LIVER IN PATIENTS WITH MALIGNANT LYMPHOMA. M.A. Richards, et al, London, Great Britain
11:35	14	MALIGNANT LYMPHOMAS ASSOCIATED WITH ASBESTOS EXPOSURE. R. Jacobson, et al, Washington, USA
11:45		INTERMISSION
12:00 noon		LUNCH (Room B)

Thursday, June 11, 1987
8:00 a.m. - 1:45 p.m. (continued)

1:00 p.m.	15	**KEY NOTE LECTURE (Room A)** SPECIFIC CHROMOSOME ABERRATIONS IN NON-HODGKIN'S LYMPHOMA + LYMPHOID LEUKEMIA. J.D. Rowley, Chicago, USA
1:45 p.m.		INTERMISSION

Session 3 - HODGKIN'S DISEASE: OVERVIEW (Room A)
Chairman: A. Lister

1:50 - 2:50 p.m.

1:50 p.m.	16	HODGKIN'S DISEASE: THE MILAN CANCER INSTITUTE EXPERIENCE WITH MOPP AND ABVD. G. Bonadonna, Milan, Italy
2:10	17	HODGKIN'S DISEASE: NCI TRIALS ADDRESSING THE REMAINING CHALLENGES. R.C. Young, Bethesda, USA
2:30	18	THE CONTINUING CHALLENGE OF HODGKIN'S DISEASE. S.A. Rosenberg, Stanford, USA
2:50		INTERMISSION

Session 4 - HODGKIN'S DISEASE IN ADULTS (Room A)
Chairmen: R.C. Young and K.W. Brunner

3:00 - 5:30 p.m.

3:00 p.m.	19	HODGKIN'S DISEASE: IS PARA-AORTIC IRRADIATION NECESSARY IN ALL CASES OF SURGICALLY STAGED SUPRADIAPHRAGMATIC DISEASE? N.J.S. Voss, et al, Vancouver, Canada
3:15	20	RADIOTHERAPY VS CHEMOTHERAPY IN PATIENTS WITH EARLY STAGE HODGKIN'S DISEASE (PATH. ST. II AND IIA)) - REPORT AFTER 4.5 YEARS OF FOLLOW-UP. G.P. Biti, et al, Florence, Italy
3:30	21	THE CLINICAL STAGES I AND II HODGKIN'S DISEASE: THE EORTC LYMPHOMA GROUP EXPERIENCE OVER TWO DECADES. TOWARDS COMPREHENSIVE MANAGEMENT TAILORED TO PROGNOSTIC FACTORS. M. Tubiana, et al, Villejuif, France
3:45	22	RESULTS OF THE HD1 AND HD3 TRIALS OF THE GERMAN HODGKIN'S DISEASE STUDY GROUP. V. Diehl, et al, Cologne, West-Germany
4:00	23	MOPP VS ALTERNATING MOPP/ABVD IN ADVANCED HODGKIN'S DISEASE. R. Somers, et al, Amsterdam, The Netherlands
4:15	24	IMPROVED SURVIVAL WITH SEQUENTIAL BELO-MOPP FOLLOWED BY ABVD FOR ADVANCED HODGKIN'S DISEASE: 7-YEARS RESULTS. J.H. Glick, et al, Philadelphia, USA
4:30	25	RANDOMISED STUDY OF LOPP (LEUKERAN, ONCOVIN, PROCARBAZINE, PREDNISONE) AND LOPP ALTERNATING WITH EVAP (ETOPOSIDE, VELBE, ADRIAMYCIN, PREDNISONE) IN ADVANCED HODGKIN'S DISEASE - PRELIMINARY RESULTS. B.W. Hancock, Sheffield, Great Britain

Thursday, June 11, 1987
3:00 - 5:30 p.m. (continued)

4:45	26	PREDICTIVE VALUE OF EARLY RESPONSE TO MOPP IN "HIGH-RISK" STAGE II AND III HODGKIN'S DISEASE. A. Levis, et al, Torino, Italy
5:00	27	THE SIGNIFICANCE OF RESIDUAL MEDIASTINAL WIDENING FOLLOWING TREATMENT FOR HODGKIN'S DISEASE. J.A. Radford, et al, Manchester, Great Britain
5:15	28	SECONDARY MALIGNANCIES AFTER HODGKIN'S DISEASE IN THE NETHERLANDS CANCER INSTITUTE. R. Somers, et al, Amsterdam, The Netherlands

Session 5 - WORKSHOP ON NEW DIAGNOSTIC POSSIBILITIES IN LYMPHOMA (Room B)
Chairman: C.W. Berard - Co-chairman: F. Rilke

3:00 - 5:45 p.m.

3:00 p.m.	29	MAC (MORPHOLOGY-ANTIBODY-CHROMOSOME) METHOD IN THE CHARACTERIZATION OF THE CELLS IN LYMPHOMAS. S. Knuutila, Helsinki, Finland
3:20	30	MONOCLONAL ANTIBODIES IN THE DIAGNOSIS OF MALIGNANT LYMPHOMAS. H. Stein, et al, Berlin, West-Germany
3:40	31	REARRANGEMENTS OF ANTIGEN RECEPTOR GENE DNA IN MALIGNANT LYMPHOMA. J. Sklar, Stanford, USA
4:00	32	Ig GENE REARRANGEMENT IN NON-HODGKIN'S LYMPHOMA. R.A. Rudders, et al, Boston, USA
4:15	33	DETECTION OF LYMPHOMA CELLS IN PERIPHERAL BLOOD AND BONE MARROW BY DNA HYBRIDISATION. M. Brada, et al, Sutton, Great Britain
4:30	34	CORRELATION BETWEEN CELL SURFACE ANTIGEN EXPRESSION, AND IMMUNOGLOBULIN AND T-CELL RECEPTOR βCHAIN GENE REARRANGEMENT IN LYMPHOPROLIFERATIVE DISORDERS. Ph. Gaulard, et al, Creteil, France
4:45	35	THE p24 ANTIGEN RECOGNIZED BY CD9 MONOCLONAL ANTIBODIES IS RELATED TO A SUBUNIT OF THE CYTOADHESION RECEPTOR: BIOCHEMICAL COMPARISON AND DNA-MEDIATED GENE TRANSFER. S.C. Peiper, et al, Memphis, USA
5:00	36	PROGNOSTIC VALUE OF NUCLEIC ACID FLOW CYTOMETRY IN DIFFUSE LARGE CELL LYMPHOMA. P. M. McLaughlin, et al, Houston, USA
5:15	-	EVALUATION FROM THE CLINICIAN'S PERSPECTIVE. S.A. Rosenberg, Stanford, USA
5:30		DISCUSSION AND SUMMARY OF THE CHAIRMAN.

Thursday, June 11, 1987
3:00 - 6:00 p.m.

Session 6 - LYMPHOMA IN CHILDHOOD (Room C)
Chairpersons: S.B. Murphy and H.P. Wagner

3:00 p.m.	37	RISK-ADAPTED CHEMOTHERAPY, INVOLVED FIELD IRRADIATION WITH REDUCED DOSES AND SELECTIVE SPLENECTOMY IN CHILDHOOD HODGKIN'S DISEASE: UPDATE OF THE GERMAN MULTICENTER STUDY DAL-HD-82. G. Schellong, et al, Münster, West-Germany
3:20	38	PRIMARY CHEMOTHERAPY AND LOW-DOSE RADIATION IN INVOLVED FIELDS IN CHILDHOOD HODGKIN'S DISEASE. O. Oberlin, et al, Villejuif, France
3:40	39	HODGKIN'S DISEASE IN CHILDHOOD: THE EXPERIENCE OF THE ITALIAN ASSOCIATION OF PEDIATRIC HEMATOLOGY AND ONCOLOGY WITH PROTOCOL AIEOP-MH'83. V. Vecchi, et al, Bologna, Italy
3:50	40	CONTINUAL PROGRESS IN THE MANAGEMENT OF CHILDREN WITH HODGKIN'S DISEASE USING COMBINED MODALITY THERAPY. S.S. Donaldson, et al, Stanford, USA
4:00	41	LIMITED-FIELD AND LOW-DOSE RADIOTHERAPY + ABVD CHEMOTHERAPY FOR CHILDHOOD HODGKIN'S DISEASE. F. Fossati, et al, Milan, Italy
4:10	42	UPDATE RESULTS OF THE PROTOCOLS LMB OF THE FRENCH PEDIATRIC ONCOLOGY SOCIETY (SFOP) FOR B-CELL ADVANCED STAGE NON-HODGKIN'S LYMPHOMA. J.M. Zucker, et al, Villejuif, France
4:25	43	B-TYPE NON-HODGKIN'S LYMPHOMAS AND LEUKEMIA: THE BFM STUDY GROUP EXPERIENCE. St. Müller-Weihrich, et al, München, West-Germany
4:40	44	A DECADE OF PROGRESS IN CHILDHOOD NON-HODGKIN'S LYMPHOMA: THE CHILDRENS CANCER STUDY GROUP EXPERIENCE. S.E. Siegel, et al, Los Angeles, USA
5:00	45	HIGH CURE RATE WITH REDUCTION IN TOXICITY FOR CHILDREN WITH LOCALIZED NON-HODGKIN'S LYMPHOMA: RESULTS OF A RANDOMIZED STUDY OF THE PEDIATRIC ONCOLOGY GROUP. M.P. Link, et al, Palo Alto, USA
5:10	46	HIGH DOSE METHOTREXATE IN CHILDHOOD NON HODGKIN'S LYMPHOMA: ITS EFFICACY FOR CNS PROPHYLAXIS. C. Patte, et al, Villejuif, France
5:20	47	INTENSIVE SHORT-TERM CHEMOTHERAPY FOR ADVANCED CHILDHOOD BURKITT-TYPE NON-HODGKIN LYMPHOMA. M. Gasparini, et al, Milan, Italy
5:30	48	ADVANCED B CELL LYMPHOMA IN CHILDREN. WHO REMAINS THE HIGH RISK PATIENTS? T. Philip, et al, Lyon, France
5:40	49	MALIGNANT LYMPHOMAS UNDER 20 YEARS OF AGE IN A JAPANEASE DISTRICT (KAGOSHIMA) WITH PREVALENT ADULT T-CELL LEUKEMIA/ LYMPHOMAS. K. Hasui, et al, Kagoshima-shi, Japan

Thursday, June 11, 1987
3:00 - 6:00 p.m. (continued)

5:50	50	BURKITT'S LYMPHOMA IN KUWAIT. M. Samir Motawy, et al, Shuwaikh, Kuwait
6:00	51	ABDOMINAL NON-HODGKIN'S LYMPHOMA IN CHILDHOOD: MIDDLE EAST TYPE. Y. Sweed, et al, Haifa, Israel

5:30 - 6:30 **POSTER SESSION II (Villa Ciani)**
HODGKIN'S DISEASE IN ADULTS AND LYMPHOMA IN CHILDREN

FRIDAY, June 12, 1987
8:30 - 11:45 a.m.

Session 7 - LYMPHOMA IN IMMUNODEFFICIENCY (Room A)
Chairmen: C. Jasmin and H.J. Senn

8:30 a.m.	52	LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH IMMUNODEFICIENCY: TUMOR CHARACTERISTICS AND CYTOGENETIC ASSOCIATIONS. A.H. Filipovich, Minneapolis, USA
8:50	53	ADULT T-CELL LEUKEMIA/LYMPHOMA. K. Takatsuki, Kumamoto, Japan
9:10	54	PROGNOSTIC VALUE OF BLOOD AND BONE MARROW T-COLONY-FORMING CELLS IN PATIENTS WITH LYMPHADENOPATHY SYNDROME. C. Jasmin, et al, Villejuif, France
9:25	55	CLINICAL, MORPHOLOGIC, PHENOTYPIC, AND MOLECULAR GENETIC ANALYSIS OF AIDS/ARC-ASSOCIATED MALIGNANT LYMPHOID NEOPLASIA. D.M. Knowles, et al, New York, USA
9:40	56	EXPRESSION OF THE DEOXYNUCLEOTIDYL TERMINAL TRANSFERASE IN PERIPHERAL BLOOD CELLS OF INDIVIDUALS WITH ANTI HTLV-III/LAV ANTIBODIES. G.A. Losa, Locarno, Switzerland
9:55		INTERMISSION
10:15	57	MALIGNANT NON-HODGKINS LYMPHOMA IN PATIENTS WITH HIV INFECTION. P.S. Gill, et al, Los Angeles, USA
10:30	58	MALIGNANT LYMPHOMAS IN PERSONS AT HIGH RISK FOR AIDS IN ITALY: A REPORT OF 46 CASES. S. Monfardini, et al, Aviano, Italy
10:45	59	DIRECTIONS IN EXPERIMENTAL THERAPY OF AIDS AND INFECTION WITH HIV. P.A. Volberding, San Francisco, USA
11:15	60	HUMAN LYMPHOTROPIC VIRUSES (T&B CELL) AND THEIR ROLE IN MALIGNANCY, AIDS AND CENTRAL NERVOUS SYSTEM DISEASE. R.C. Gallo, Bethesda, USA
11:45		INTERMISSION
12 noon		LUNCH (Room B)

Friday, June 12, 1987
1:00 - 2:00 p.m.

POSTER SESSION III (Villa Ciani)
NON HODGKIN'S LYMPHOMA

Session 8 - NON HODGKIN'S LYMPHOMA: OVERVIEW (Room A)
Chairman: J.E. Ultmann

2:00 - 3:00 p.m.

2:00 p.m.	61	CURRENT STATUS OF NCI-TRIALS. R.C. Young, Bethesda, USA
2:20	62	CURRENT TRIALS IN THE UNITED STATES. J.H. Glick, Philadelphia, USA
2:40	63	CURRENT STATUS OF TRIAL IN EUROPE, ESPECIALLY UK. A. Lister, London, Great Britain
3:00		INTERMISSION

Session 9 - TREATMENT OF NON HODGKIN'S LYMPHOMA IN ADULTS (Room A)
Chairmen: P. Jacobs and G. Bonadonna

3:10 - 6:00 p.m.

3:10 p.m.	64	SURVIVAL OF GOOD PROGNOSIS DIFFUSE LARGE CELL LYMPHOMA PATIENTS TREATED WITH CHOP OR CHOP-VARIANTS. J.R. Anderson, et al, Boston, USA
3:25	65	CHOP IS CURATIVE IN THIRTY PERCENT OF PATIENTS WITH DIFFUSE LARGE CELL LYMPHOMA: A TWELVE YEAR SOUTHWEST ONCOLOGY GROUP FOLLOW UP. C.A. Coltman, et al, San Antonio, USA
3:40	66	CHOP-B ALTERNATED WITH CMED IN THE TREATMENT OF AGGRESSIVE LYMPHOMAS. W.S. Velasquez, et al, Houston, USA
3:55	67	MACOP-B, 12 WEEKLY TREATMENTS FOR AGGRESSIVE LYMPHOMAS: 6 YEARS OF EXPERIENCE. P. Klimo, et al, Vancouver, Canada
4:10	68	AGGRESSIVE LYMPHOMAS TREATED BY INTENSIVE CHEMOTHERAPY: UPDATED RESULTS OF LNH-80 PROTOCOL WITH A MEDIAN FOLLOW-UP OF 52 MONTHS. B. Coiffier, et al, Lyon, France
4:25	69	TREATMENT OF LYMPHOBLASTIC LYMPHOMA IN ADULTS. J.P. Colgan, et al, Rochester, USA
4:40	70	SOUTHWEST ONCOLOGY GROUP CLINICAL TRIALS FOR INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMAS. T.P. Miller, et al, Tucson, USA
4:55	71	PATTERNS OF RELAPSE IN LARGE CELL LYMPHOMA PATIENTS WITH MASSIVE BULKY DISEASE. M. Shipp, et al, Boston, USA

Friday, June 12, 1987
3:10 - 6:00 p.m. (continued)

5:05	72	FACTORS ASSOCIATED WITH RESPONSE, SURVIVAL AND TRANSFORMATION IN RECURRENT LOW GRADE FOLLICULAR LYMPHOMAS. J. Spinolo, et al, Houston, USA
5:20	73	INCIDENCE OF TRULY INDOLENT LYMPHOMA AND THE IMPACT OF A "NO TREATMENT" POLICY. R.C.F. Leonard, et al, Edinburgh, Great Britain
5:35	74	LONG-TERM OUTCOME WITH OR WITHOUT TUMOR PROGRESSION IN FOLLICULAR LOW GRADE NON-HODGKIN'S LYMPHOMA. J. Ersboll, et al, Copenhagen, Denmark
5:50	75	DOSE INTENSITY ANALYSIS FOR CHOP CHEMOTHERAPY IN UNFAVORABLE LYMPHOMA. R. Epelbaum, et al, Haifa, Israel
6:00		INTERMISSION

Session 10 - WORKSHOP ON THE CURRENT SITUATION OF BONE MARROW TRANSPLANTATION IN MALIGNANT LYMPHOMA (Room B)
Chairman: G.P. Canellos

3:15 - 6:00 p.m.

3:15	76	AUTOLOGOUS BONE MARROW TRANSPLANTATION IN HODGKIN'S DISEASE. J.O. Armitage, Omaha, USA
3:25	77	AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR NON HODGKIN LYMPHOMAS: PRESENT STATUS: RESULTS OF THE PARIS-SAINT ANTOINE TRANSPLANT TEAM AND 1987 SURVEY OF THE EBMTG. N.C. Gorin, et al, Paris, France
3:55	78	MARROW TRANSPLANTATION AS TREATMENT FOR MALIGNANT LYMPHOMA. F.R. Appelbaum, Seattle, USA
4:15		DISCUSSION
4:25	79	EBMT RESULTS OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN HODGKIN'S DISEASE. A.H. Goldstone, London, Great Britain
4:40	80	SEQUENTIAL HIGH-DOSE CHEMO-RADIOTHERAPY FOLLOWED BY AUTOLOGOUS BONE MARROW TRANSPLANTATION IN REFRACTORY OR RELAPSED HODGKIN'S DISEASE. A.M. Gianni, et al, Milan, Italy
4:55	81	ALLOGENEIC BONE MARROW TRANSPLANTATION FOR MALIGNANT NON HODGKIN'S LYMPHOMAS. P. Ernst, Copenhagen, Denmark
5:10	82	SELECTION CRITERIA IMPROVE DISEASE-FREE SURVIVAL IN PATIENTS WITH POOR PROGNOSIS NON-HODGKIN'S LYMPHOMA FOLLOWING AUTOLOGOUS BONE MARROW TRANSPLANTATION. T. Takvorian, et al, Boston, USA
5:25	83	ABMT IN BURKITT'S LYMPHOMA (50 CASES IN THE LYON PROTOCOL). T. Philip, et al, Lyon, France

5:40	84	CYTOXAN + TOTAL BODY IRRADIATION WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION IN ADULT LYMPHOBLASTIC LYMPHOMA IN FIRST COMPLETE REMISSION. A REPORT OF THE ITALIAN LYMPHOMA STUDY GROUP. G. Santini, et al, Genua, Italy
5:50		DISCUSSION AND SUMMARY OF THE CHAIRMAN

Session 11 - PATHOLOGY AND CLINICAL-PATHOLOGICAL CORRELATIONS (Room C)
Chairmen: H. Rappaport and K. Lennert

3:05 - 6:00 p.m.

3:05 p.m.	85	MALIGNANT HISTIOCYTOSIS: PHENOTYPIC AND GENOTYPIC HETEROGENEITY. F. Rilke, et al, Milan, Italy
3:20	86	THE CLINICAL AND PROGNOSTIC RELEVANCE OF A MODIFED "RYE" HISTOLOGICAL CLASSIFICATION OF HODGKIN'S DISEASE. M.H. Bennett, et al, Northwood, Great Britain
3:35	87	SINUSOIDAL B-CELL LYMPHOMA IS THE MALIGNANT LYMPHOMA OF SO-CALLED IMMATURE SINUS HISTIOCYTOSIS. C. Schilling, et al, Kiel, West-Germany
3:45	88	CLONALITY, PHENOTYPIC DIVERSITY NAD SURVIVAL IN 26 CASES OF ANGIOIMMUNOBLASTIC LYMPHADENOPATHY. A.C. Feller, et al, Kiel, West-Germany
4:00	89	THE CYTOLOGICAL APPEARANCES OF FOLLICULAR LYMPHOMA SMALL CELL TYPE AND THEIR RELATIONSHIP TO NATURAL HISTORY AND PROGNOSIS. K.A. MacLennan, et al, Nottingham, Great Britain
4:15	90	THE IMMUNO-PHENOTYPE OF NON-HODGKIN'S LYMPHOMA DOES NOT CORRELATE WITH CELL MORPHOLOGY. H.J. Schuurman, et al, Utrecht, The Netherlands
4:30	91	PRIMARY CUTANEOUS B CELL LYMPHOMAS: A MOLECULAR STUDY. D. Delia, et al, Milan, Italy
4:45	92	A NON PREVIOUSLY DESCRIBED, DIFFUSE, NON BLASTIC, NON BLASTOID B-MEDIUM CELL NON-HODGKIN'S LYMPHOMAS. G. Mathe, et al, Villejuif, France
5:00	93	PERIPHERAL T-CELL LYMPHOMAS: THERAPEUTIC ANALYSIS AND PROGNOSTIC FACTORS IN 54 PATIENTS. B. Coiffier, et al, Lyon France
5:15	94	PERIPHERAL T-CELL LYMPHOMA: A CLINICOPATHOLOGIC STUDY OF 74 CASES. A. Chott, et al, Vienna, Austria
5:30	95	PROGNOSTIC FACTORS IN STAGE III AND IV NON HODGKIN'S LYMPHOMA. M. Van Glabbeke, et al, Belgium, Brussels
5:45	96	AN ANALYSIS OF PROGNOSTIC FACTORS IN HIGH AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA. R.A. Cowan, et al, Manchester, Great Britain
6:00		INTERMISSION

SATURDAY, June 13, 1987
9:00 - 12:00 a.m.

Session 12 - NEW TREATMENTS - REPORTS ON CURRENT STATUS (Room A)
Chairmen: S.A. Rosenberg and M. Rozencweig

9:00 a.m.	97	TREATMENT OF LYMPHOMA IN JAPAN. N. Horikoshi, Tokyo, Japan
9:20	98	A PHASE I STUDY OF THE FEASIBILITY OF USING AUTOLOGOUS LYMPHOCYTES AS VECTORS TO TARGET RADIO-ACTIVE MATERIAL TO SITES OF DISEASE IN NON-HODGKIN'S LYMPHOMA. R.A. Cowan, et al, Manchester, Great Britain
9:35	99	DEOXYCOFORMYCIN: AN ACTIVE NEW DRUG IN LYMPHOID MALIGNANCIES. P.J. O'Dwyer, et al, Philadelphia, USA
9:50	100	COMBINATION OF CISPLATIN, HIGH DOSE ARA-C AND DECADRON IN RELAPSING LYMPHOMA. W. Velasquez, et al, Houston, USA
10:05	-	REPORT FROM THE WORKSHOP ON NEW DIAGNOSTIC POSSIBILITY IN LYMPHOMA (Session 5). C.W.Berard, Memphis, USA
10:25	-	REPORT FROM THE WORKSHOP ON BONE MARROW TRANSPLANTATION (Session 10). G.P. Canellos, Boston, USA
10:45	101	REPORT FROM THE CONFERENCE IN LYGON ARMS (November 1986). A. Lister, London, Great Britain
11:00	102	**CONCLUDING LECTURE** SUMMARY OF THE CONFERENCE AND FUTURE DIRECTIONS OF RESEARCH IN LYMPHOMA. J.E. Ultmann, et al, Chicago, USA
11:45	-	CLOSING REMARKS. F. Cavalli, Bellinzona, Switzerland
12:00		ADJOURN

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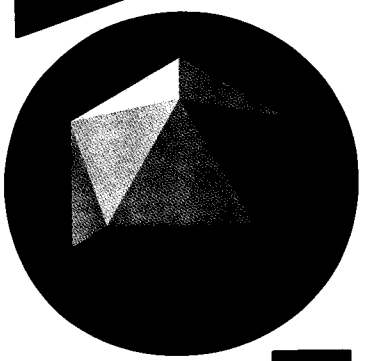

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ABSTRACTS

ORAL PRESENTATIONS

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

1 Cellular oncogenes have been identified by the biological activity of tumor DNAs in transfection assays and/or by homology to the transforming genes of retroviruses. In some tumors, the biological activity, organization or expression of these genes is altered, suggesting that such alterations contribute to the development of neoplastic disease. I will review experiments leading to the identification of cellular oncogenes and discuss our current understanding of the mechanisms by which they induce transformation of cells in culture and may contribute to the pathogenesis of neoplasms in vivo.

Geoffrey M. Cooper, Dana-Farber Cancer Institute, Boston, USA

2 POTENTIAL OF MONOCLONAL ANTIBODIES IN ONCOLOGY.

J.-C. Cerottini, Ludwig Institute for Cancer Research, Lausanne Branch, Epalinges, Switzerland.

The description by Köhler and Milstein of a reliable method for producing monoclonal antibodies has created a new era in the use of antibodies as research and diagnostic tools. The production of monoclonal antibodies is based on the fusion (or hybridization) in vitro of myeloma cells with antibody-producing lymphoid cells. While selected myeloma cell lines can be grown permanently in culture, antibody-producing cells usually undergo terminal differentiation after a few cell divisions and die. In the fusion product ("hybridoma"), the myeloma cell confers permanent growth, whereas the lymphoid cell contributes the capacity to produce specific antibody. Since a given antibody-producing cell is committed to the production of only one type of antibody molecule, the hybrid cell line obtained after fusion of this particular antibody-producing cell and a myeloma cell produces homogeneous antibodies of unique specificity. Thus, once a hybridoma has been developed, it is immortal and provides unlimited amounts of specific antibody.

While the use of monoclonal antibodies has already been extremely rewarding in basic research, there is increasing evidence that these reagents will have a profound impact on clinical medicine in the near future. In the field of oncology, monoclonal antibodies can be used to differentiate between normal and neoplastic cells and may be exploited for diagnostic and, ultimately, therapeutic gain. There is already evidence that monoclonal antibodies can facilitate accurate pathological diagnosis, classification of malignancies and early detection of micrometastases. Studies are in progress to determine their potential use in tumor localization (by immunoscintigraphy) and therapy.

3 OVERVIEW ON CURRENT TOPICS IN CLINICAL RESEARCH.

S. Rosenberg, Stanford University, Dep. of Medicine, Stanford, Ca., USA

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

4 HODGKIN'S DISEASE: FURTHER INFORMATION DERIVED FROM CELL-LINES.

Since 1978 we have established 4 cell-lines (L 428, L 538, L 540, L 591) from patients with Hodgkin's disease. The cell-lines are of malignant origin, as shown by several chromosomal aberrations. Morphological, cytochemical and immunological assays demonstrated the identity of the in vitro cells with Hodgkin (H)- and Sternberg-Reed (SR)-cells in vivo. Functional properties and surface characteristics are not in line with any known cell type of hematopoiesis or lymphoid tissue. The cell-lines produce factors involved in hematopoiesis and immunological response (CSF, IL 1, MIF). The in vitro Hodgkin-cells (L 428) are capable of presenting soluble antigen to lymphocytes.

A monoclonal antibody (Ki 1) produced against one of the cell-lines (L 428) reacts with H and SR cells in frozen sections of lymphoid tissue and with a so far unidentified cell-population in normal lymphnodes. Furthermore it binds to a minority of mononuclear cells in the peripheral blood of healthy individuals.

The established Hodgkin cell-lines may be of value in identifying the cell-markers of H and SR cells in vivo and may be helpful in eludicating the puzzle concerning the normal counterpart of H- and SR-cells.

The monoclonal antibody Ki 1 produced against L 428 is already being used in diagnosis of lymphomas in frozen sections of lymphoid tissue. It may be helpful for in vivo diagnosis of HD in man, since radiolabelled Ki 1 detects HD-tumors transplanted on nude mice.

V. Diehl, Universität Köln, Köln

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

5 ORIGIN AND BIOLOGIC FUNCTION OF REED-STERNBERG CELLS. Richard I. Fisher, Volker Diehl, Susan E. Bates, David J. Volkman, Toby T. Hecht, and Dan L. Longo. National Cancer Institute, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20205, and Medizinische Hochshule Hanover, Hanover, Germany.

Reed-Sternberg cells in biopsies from patients with Hodgkin's disease express Ia antigens yet lack other cell surface markers associated with mature B cells, T cells, or monocytes. We have utilized the L428 cell line to test the thesis that Hodgkin's disease is a tumor of antigen presenting cells. The L428 cells are potent stimulators of the human primary mixed lymphocyte cultures (J. Immunol. 6/83). Significant proliferation occurred when mononuclear leukocytes obtained from normal donors were stimulated with radiated L428 cells at responder:stimulator ratios varying from 200:1 to 20:1. Maximal proliferation occurred on day 5. These proliferative responses can be blocked by anti-Ia antibody. Antigen processing by responder monocytes was not required. The cells that proliferated were T cells, primarily of the helper subset. Under certain conditions the L428 cells are capable of producing IL-1. The L428 cells also function as accessory cells for mitogen-induced human T cell proliferative responses (J. Immunol. 5/84). Purified human T cells that are depleted of Ia-bearing cells and adherent cells do not proliferate in response to concanavalin A. The addition of as few as 1% radiated L428 cells restores the proliferative capacity of the T cells. The tumor cells were 30 times more potent than allogeneic mononuclear leukocytes as accessory cells. The T cells from patients with advanced stages of Hodgkin's disease have impared mitogen responses even in the presence of these potent accessory cells. The L428 cells are also capable of presenting soluble antigen to T cells in a genetically restricted fashion (AACR, 1984). T cell lines from HLA-DR5 normal donors, who had been immunized with tetanus toxoid, generated tetanus specific proliferative responses in the presence of the L428 cells. T cell lines from individuals with other DR phenotypes (DR 1, 2, 4, or 7) did not generate responses in the presence of tetanus and L428 cells. Thus the L428 cells possess all the characteristics of antigen presenting cells.

A murine monoclonal antibody termed HeFi-1 that selectively binds Reed-Sternberg cells in 18/18 tissue biopsies has been produced following immunization with the L428 cells. The antigen recognized by HeFi-1 is a 120 KD glycoprotein that does not modulate in vitro. HeFi-1 does not block the ability to the L428 cells to stimulate a mixed lymphocyte culture or function as an accessory cell. This antibody should prove useful not only for the diagnosis and treatment of Hodgkin's disease but also for determining the normal cell from which Hodgkin's disease originates.

6 RADIOIMMUNODETECTION OF HUMAN B-CELL LYMPHOMAS WITH A RADIOLABELED TUMOR-SPECIFIC MONOCLONAL ANTIBODY (Lym-1). A. L. Epstein, A.M. Zimmer, S.M. Spies, D. Mills, G. DeNardo, and S. DeNardo. Northwestern University, Chicago, Il 60611 and University of California at Davis, Sacremento, CA. 95817, USA.

A new monoclonal antibody, Lym-1, has been produced to a cell surface antigen expressed in normal lymph node B-cells and a subset of B-cell derived human lymphomas and leukemias. Specificity screens using a panel of human lymphoma and leukemia cell lines and biopsies have shown that Lym-1 is positive on a subset of diffuse histiocytic and Burkitt's lymphomas and B-cell CLL. On a panel of 18 normal human organs, Lym-1 was positive with B-cell zones of lymph nodes, a low % of peripheral blood B-cells, tissue macrophages, and colonic surface epithelium. Immunoprecipitation studies revealed that Lym-1 recognizes 4 polypeptides in the range of 31-35 kd. Because of its cell surface reactivity with a subset of B-cell tumors and its low reactivity with normal organs, Lym-1 was tested in a nude mouse animal system and in volunteer cancer patients for its radioimaging capabilities. Lym-1 (IgG2a) was purified from ascites fluid by ammonium sulfate precipitation and Protein-A affinity chromatography. Radiolabeling of whole antibody, $F(ab')_2$, and F(ab) fragments was achieved with I-131 using solid phase DPG, with I-123 using chloramine-T, and with Cu-67 using benzl EDTA bifunctional chelation. Athymic nude mice bearing right thigh Raji tumors were injected with 150-300 uCi of radiolabeled Lym-1 and imaged up to 7 days after injection at which time the animals were sacrificed and organ distribution performed. Highest tumor uptake was observed for radiolabeled whole antibody followed by $F(ab')_2$, and F(ab) fragments. These studies showed that specific and significant tumor uptake of radiolabeled Lym-1 could be achieved since 4-8% and 15-26% of the injected dose of I-131 and Cu-67 labeled Lym-1, respectively, localized to the tumor. With I-131, optimal tumor visualization for radioiodinated $F(ab')_2$ fragments and whole antibody was observed at 3 and 7 days after injection. At the present time, 5 volunteer breast cancer patients have been imaged with 1-5 mCi of I-123-Lym-1 in order to obtain biodistribution data in patients bearing Lym-1 negative tumors. Quantitative tomographic imaging using single photon emission computerized tomography revealed no abnormal uptake of radiolabeled antibody in the organs or tumors of these patients. These preliminary studies confirm the low reactivity of Lym-1 with normal tissues and opens the way for future studies with patients bearing antigen positive lymphomas. Therapeutic trials with I-131 and Cu-67 radiolabeled Lym-1 are anticipated upon the successful completion of these investigations.

7

THERAPEUTIC USE OF MONOCLONAL ANTI-IDIOTYPE ANTIBODIES AGAINST B-CELL LYMPHOMA. Annemarie Hekman, Elaine M. Rankin, Reinier Somers and Wim ten Bokkel Huinink, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam.

Five monoclonal antibodies have been made against the idiotype of the membrane immunoglobulin of the malignant lymphocytes of 4 patients with B-cell non-Hodgkin lymphoma. Two have been used for therapy in patients with advanced centrocytic lymphoma, antibody T2 for patient Top, and antibody K1 for patient Klos. Both antibodies were of the $IgG2_a$ subclass, were cytotoxic with rabbit but not with human complement, and did not modulate the antigen.

Patient Top had 10 x 10^9 malignant lymphocytes in the blood and these were used to determine the treatment schedule. There was a negligible amount of free idiotype. 3 different regimens were tried: escalation by doubling the dose daily from 5 mg to 160 mg, rapid escalation by doubling the dose hourly from 10 mg to 160 mg, and bolus dose 150 mg over 2 hrs followed by 20 mg/hr over 28 hours. There was a temporary fall in the lymphocytes after each treatment. At the end of the continous infusion, free antibody was detectable in the serum (10 µg/ml) and cells in the blood, bone marrow, lymph node and ascites were coated with T2. Two further infusions of T2, each lasting 42 hrs were given. The patient received a total of 3800 mg T2. ^{111}Indium oxine labelled lymphocytes[§] were used to demonstrate that malignant cells were rapidly cleared from the circulation which was repopulated with unlabelled cells. The S-phase cells in blood remained <2%. There was no alteration in spontaneous tritiated thymidine uptake in blood lymphocytes. Serial punch biopsies of lymph nodes showed an increase in the number of lytic cells, a sign of necrosis, during treatment from 0 to 25%. Monocyte activity as measured by chemiluminescence showed some improvement but remained below normal levels. Antibody dependent cellular cytotoxicity, negligible before treatment began, reached normal levels after the last infusion.

Patient Klos had a high level of free antigen before treatment. The dose was escalated until 400 mg over 2 hr which removed all free idiotype. This returned at a lower level the next day. 1200 mg K1 saturated the cells in the blood and lymph node with antibody and reached the cells in the ascites; excess K1 was detectable in the serum at 20 µg/ml. 5.9 gms K1 have been given, the lymph nodes are decreasing in size.

Neither patient has shown any toxicity; liver and renal function and complement status are unaltered. Neither patient has made antibodies to the mouse immunoglobulin. No modulation of the antigen was seen in either case. It is too early to assess tumour response, treatment stopped three weeks (patient Top) and one week (patient Klos) ago.

[§]see abstract number T-41

8

THE IMMUNOBIOLOGY OF B CELL LYMPHOMA, Ronald Levy, Medicine/Oncology, Stanford University, Stanford, CA, 94305

Human B cell lymphomas are considered to be monoclonal cell populations, i.e., derived from a single original transformed cell. This notion is based on analyses of karyotypes, X chromosome-linked enzymes, and immunoglobulin proteins. The cell surface immunoglobulin of each B cell tumor is idiotypically distinct. We have produced anti-idiotype antibodies for a series of 25 patients with B cell lymphomas. Each antibody is specifically reactive with the cell surface immunoglobulin of only one patient. These antibodies have been used as diagnostic monitoring reagents, as therapeutic agents, and as probes for the biology of the disease. Immunoassays have been performed on serum from a series of B lymphoma patients using the anti-idiotype antibodies. We find idiotypic protein in the serum with a wide variation in levels between patients but characteristic of each patient tumor. Within a patient, serial determinations of serum idiotype correlate well with tumor burden. The serum idiotype can be lowered to approximately 10% of initial level by plasmapheresis. Therapeutic trials are underway with anti-idiotype antibodies and these will be discussed. Obstacles to therapeutic effect have been identified. These include serum idiotype, anti-mouse immune response, antigenic modulation, and tumor heterogeneity. Recently, we have determined that some B cell lymphomas are composed of two clones differing in cell surface idiotype and in immunoglobulin gene rearrangements. The incidence of this phenomenon may be as high as 10% of cases of follicular lymphomas.

9 T-CELL DIFFERENTIATION: IMPLICATIONS FOR THE ONCOLOGIST AND BIOLOGIST. S. F. Schlossman. Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115.

Recent advances in both the cloning of antigen specific human T lymphocytes and the production of monoclonal antibodies against cell surface structures has permitted the identification of cell surface glycoproteins involved in antigen-recognition. Analysis of the functional role of both polymorphic or clonotypic structures on human T cells as well as nonpolymorphic structures has allowed the construction of a model for the human T cell antigen receptor. This receptor is a cell surface complex comprised of a clonotypic (Ti) 90 KD heterodimer and the monomorphic 20/25 KD T3 molecule. Approximately 30-40 x 10^3 Ti and T3 molecules exist on the surface of the human T lymphocyte and these cell surface glycoproteins are fully expressed during late thymic ontogeny at the time of development of immunocompetence. The Ti antigen is made up of α and β chains both containing variable and constant regions. It is now clear that the β chain of the T cell receptor has distant homology to immunoglobulins as defined by protein structure and molecular probes. Triggering of the T3/Ti molecular complex results in clonal T cell proliferation utilizing an IL2 dependent autocrine pathway. The associative recognition structures defined by the 76 KD T8 and 62 KD T4 glycoproteins clearly allows for the subsetting of human T lymphocyte. More importantly, from a functional point of view, the T8 lymphocyte and the T8 glycoprotein itself appears to restrict the response of these cells to antigens presented in association with HLA-A, B or C antigens (Class I) whereas T4 glycoprotein and its corresponding subset views antigen in association with HLA-Dr, DS or SB (Class II). The precise role of the T4 and T8 antigens in imposing MHC restrictions on T cells is still not entirely clear. Nevertheless, T4 and T8 in association with the T3/Ti complex appear to provide a critical set of structures which can account for both T cell specificity and MHC restriction. The applications of this new technology of cellular characterization is still in its infancy but is expected to have a profound impact on our understanding of clinical diseases. It is believed that the structures involved in cell-cell interactions and triggering the human T cell should provide the strategies with which to manipulate the immune response for the benefit of the host.

10 IMMUNOLOGIC PHENOTYPES OF NON-HODGKIN'S LYMPHOMAS: CORRELATION WITH MORPHOLOGY AND FUNCTION. E.S. Jaffe, M.D., J. Cossman, M.D., L.M. Neckers, Ph.D., R.M. Braziel, M.D., and C. Simrell, M.D. NCI, Bethesda Md., USA

Modern immunology has been instrumental in the delineation of distinct clinicopathologic entities within the heterogenous non-Hodgkin's lymphomas. The low grade B cell lymphomas; i.e. follicular lymphomas (FL), intermediately differentiated lymphocytic lymphomas (IDL), and well-differentiated lymphocytic lymphomas (WDL), each have a unique immunologic phenotype which may represent specific and possibly sequential stages of B cell differentiation (1). All cases expressed monoclonal surface immunoglobulin (SIg) and HLA-DR and stained with B1 and BA-1, but differed in reactivity with Leu 1 (p65), BA-2 (p24), and J5 (CALLA). All FL were Leu 1-, BA-2 -, and were + with J5 in $\sim$ 50% of cases. IDL were + with all three of the above reagents, whereas WDL were Leu 1+, BA-2 - and variably J5 +. Fluorescence intensities observed for SIg, BA-1 and B-1 showed a sequential decrease; i.e., FL>IDL>WDL.

Correlative studies were also performed to study the interrelationship of function, i.e., immunoglobulin secretion, with morphologic and immunophenotypic characteristics. WDL were readily induced to secrete monoclonal Ig after exposure to the phorbol ester TPA. Ig secretion did not require the addition of allogeneic T lymphocytes (2). In contrast, most FL did not readily secrete Ig, either in the presence or absence of TPA. Depletion of autologous T-lymphocytes and the addition of allogeneic T-cells produced maximal Ig secretion, but the readdition of autologous T-cells reduced levels of Ig secretion (3). These findings suggest a suppressor function for the T-cells found in FL. No correlation with helper: suppressor ratios was observed.

Six FL that histologically progressed to diffuse lymphomas were found to contain a predominance of T-lymphocytes (mean 69%). However, residual monoclonal B-cells could be identified in 4/6 cases by SIg staining and in one case by Southern blot analysis which demonstrated clonally rearranged heavy and light chain genes (4). The T cells, although numerically predominant, were phenotypically normal, and may represent a beneficial host response, since an indolent clinical course was maintained in 5/6 patients despite histologic conversion (5).

Post thymic T-cell malignancies are heterogenous clinically and morphologically and represent a spectrum from low grade (T-CLL) to high grade (large cell, immunoblastic) malignancies. Most post-thymic lymphomas express a helper antigenic phenotype, but correlations between phenotype and function are not consistently observed (6). Cells from angiocentric immunoproliferative lesions (lymphomatoid granulomatosis) and the T-cell angiocentric lymphomas that supervene secrete a phagocytosis-inducing lymphokine, which may lead to an erythrophagocytic syndrome mimicking malignant histiocytosis clinically and pathologically (7,8).

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11 FUNCTIONAL INTERACTIONS OF MALIGNANT CELLS DURING B CELL LYMPHOMAGENESIS. Carol L. Reinisch, Dept. of Comparative Medicine, Tufts University School of Veterinary Medicine, 136 Harrison Avenue, Boston, Massachusetts, U.S.A.

Immune regulation of B cell lymphomagenesis is not well understood, primarily because few predictive animal models exist. Recently we have developed a murine model of Waldenströms macroglobulinemia induced by the retrovirus MSV-MuLV-M. In these mice, plasmacytoid-lymphocytic tumors develop in the mesenteric lymph node two or more years following infection with virus.[1]

Cells isolated from the tumor cell population, which consists primarily of mu^+ B cells, have been repeatedly cloned in vitro. These cloned cells express the lymphocyte differentiation antigens Thy1.2, Ly1 and Qa1 and are T cells. Functionally these T cells 1) promote the differentiation of granulocytes and erythrocytes and 2) enhance antigen-independent and dependent lymphocyte differentiation and function.[2] When injected into (syngeneic) B6 mice, the T cells induce rapidly proliferating immunoblastic sarcomas which kill the recipient in 7-10 days.

These results show that there is an intimate association between mu^+ B cells and $Ly1^+$ $Qa1^+$ T cells during B cell lymphomagenesis, and suggest that there may be two malignant cells which interact during tumorigenesis. Given these data, we would emphasize that understanding the pathogenesis of non Hodgkins lymphomas in either the animal or human model necessitates the isolation and functional characterization of all the subpopulations within a tumor cell population.

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12 BLOOD LYMPHOCYTE SUBPOPULATIONS AND MITOGEN RESPONSIVENESS IN RELATION TO PROGNOSIS IN PATIENTS WITH NON-HODGKIN LYMPHOMA.

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Non-Hodgkin lymphomas (NHL) are mostly of B cell type. Non-leukemic NHL patients often have blood lymphocytes with an abnormal ratio between κ- and λ-bearing lymphocytes (normal range 1.0-3.3) with an increase in lymphocytes with the same light chain phenotype as lymph node tumour cells. Lymphocytes having specificity for the same antigenic determinant carrying the same light chain isotype with identical antigenic combining sites belong to the same clone. Thus, a blood κ:λ ratio outside the normal range with a selective increase of lymphocytes of the same light chain type as in tumour lymph nodes may suggest a "leukemic" spread of the disease. Lymphocytes from untreated NHL patients are poorly stimulated to DNA-synthesis by mitogens but the mitogenic proliferative response of the lymphocytes is restored in complete remission (CR) (Eur. J. Cancer 19, 747, 1983; Scand J Hematol 30, 68, 1983). To evaluate the prognostic information of blood lymphocyte subpopulations at diagnosis and the lymphocyte DNA-synthesis after stimulation with mitogens in CR 127 untreated and 58 CR patients were studied. Blood T lymphocyte subpopulations were identified by monoclonal OKT antibodies. B ($smIg^+$) lymphocytes were stained by direct IFL using $F(ab')_2$ fragments of antibodies. Lymphocyte response to ConA and PWM stimulation was measured after incubation with C^{14}-thymidine.

Forty per cent of the untreated patients had a ratio between κ- and λ-bearing blood B lymphocytes outside the normal range. Most of the patients were in clinical stage III-IV (76%) and had low grade malignant lymphomas identified as B-CLL, IC, CB/CC and CC (68%). Patients with CB/CC lymphomas and normal κ:λ ratios survived significantly longer than those with abnormal ratios ($p < 0.01$). The mean total number of $OKT3^+$ (PAN-T) and $OKT4^+$ (helper/inducer) T lymphocytes were significantly reduced in patients compared to controls ($p < 0.001$). The reduction was not related to clinical stage or histopathology. $OKT8^+$ (suppressor/cytotoxic) T lymphocytes were not significantly different from controls.

The majority of patients in CR were tested 6 months or more following termination of radio/chemotherapy. Patients with a normal response (= median value - 1 SD of healthy controls) to ConA 20 μg/ml had a significantly longer duration of first clinical remission time than those with a subnormal response.

It is concluded that an abnormal lymphocyte κ:λ ratio at diagnosis is a predictor of poor prognosis and the reduced blood lymphocyte response to ConA in clinical remission is associated with early relapse.

13 CELLULAR INTERACTIONS REGULATING T-CELL COLONY FORMATION IN THE ABSENCE OF ADDED GROWTH FACTORS IN PATIENTS WITH T-CELL MALIGNANCIES.

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Peripheral blood T-cell colony forming cells(T-CFC) from patients with T-cell malignancies can generate T-cell colonies in methylcellulose in the absence of added growth factors.In 13 out of 25 patients,less spontaneous colonies were obtained from $E^-OKT_3^-$ cells than from unseparated peripheral blood lymphocytes(PBL).Irradiated autologous but not E^+cells from normal subjects enhanced the plating efficiency of $E^-OKT_3^-$ precursors in co-culture experiments either in methylcellulose or in separate agar/methylcellulose.Conditioned media prepared from leukemic blasts(98%E^+ cells) was able to induce T-cell colony growth from normal mature(E^+) and immature($E^-OKT_3^-$) T-CFC.Depletion of PBL by plastic adherence resulted in a decrese of colony number in 4 out of 4 patients.Accessory adherent cells were $HLA\text{-}DR^-$(as determined by treatment with a pool of 4 anti-DR monoclonal antibodies and complement).Irradiated adherent cells enhanced the plating efficiency from adherent-depleted PBL in co-culture experiments in methylcellulose but not in the two layers system.Media conditioned by adherent cells alone or supplemented either with IL1 or IL2 did not enhance colony growth from patients' PBL,A^- cells.These results demonstrate that E^+ and adherent cells have an accessory role for the spontaneous T-cell colony formation which is mediated both by diffusible factors and cellular contact.

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TREATMENT OF NATURAL MURINE NON-HODGKIN'S LYMPHOMA USING IMMUNOREGULATORY CELL TYPES AND IL2. R.H. Keller, S. Swartz, C.W. Patrick, G. Steven, N. Torke, The Wood VAMC Marcus Center, Medical College of Wisconsin, 5000 West National Avenue, Milwaukee, Wisconsin, USA 53193.

We have previously reported the natural development of nodular (Blood 60:114A, 1982) and diffuse (Blood 58:313A, 1981) non-Hodgkin's Lymphoma in Aged Balb C Mice. We elected to examine the effect of adoptive transfer of syngeneic normal T cells, activated macrophages and natural killer cells and purified lymphokines on the evolution of the disease process in murine NHL. One hundred Balb C mice between the ages of 16-18 months were divided into three groups. All animals were hemisplenectomized on day -1, given either 1 x 10^8 enriched T cells (T), 1 x 10^8 enriched activated peritoneal macrophages (M); or .4 x 10^7 enriched natural killer cells (NK) once, or 10 units IL2 every 3 days IP; or saline (controls). The mice monitored weekly for Kappa/Lambda ratios, PBT cell % and automated CBCs and sacrificed at 36 days. Histologic evaluation was performed at the time of hemisplenectomy and sacrifice. 40% of the M C group and 70% of the M group demonstrated NHL on initial evaluation. All of the C group and 42% of the M group demonstrated progression of disease activity (SCCL+WDLL). Similar results occurred in short term experiments employing purified IL2. The results of these studies suggest that T cell imbalances are associated with alterations of disease activity in NHL and suggest that immunoregulatory T cells and/or immunochemically purified lymphokines from these cells may prove beneficial in the treatment of NHL.

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HTLV IN LYMPHOID LEUKEMIAS AND LYMPHOMAS: R. C. Gallo, Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA

As discussed elsewhere at these meetings HTLV is a generic name for what are now known to be a wide family of closely and distantly related human and primate exogenous retroviruses which have the following properties in common: (1) T-lymphotropic, (2) are usually specifically T4 lymphotropic, (3) contain a reverse transcriptase of 100,000 Daltons which is Mg^{++} preferring for its catalytic activity, (4) have unusually large long terminal repeat sequences (LTRs), (5) abrogate normal T-cell functions, (6) sometimes can transform normal primary T cells *in vitro* into cells with neoplastic properties, and (7) have cytopathogenic effects including the ability to produce T-cell death after infection. As of this writing there are more than 40 isolates in our laboratory and more than 70 in the world.

There are different major subgroups. Most belong to the group we have termed HTLV-I. A few are less than 10% homologous to HTLV-I and are called HTLV-II. They were obtained from a hairy cell leukemia and an AIDS patient. Numerous additional isolates have been obtained from HTLV-I and HTLV-II patients with AIDS. The analyses of them is in progress.

HTLV-I is the subgroup closely linked to the cause of a certain T-cell malignancy. This disease covers a spectrum of histopathologically defined lymphoreticular neoplasms which HTLV-I now defines as a distinct clinical entity, usually of $T4^+$, $T8^-$, Ia^+, TAC^+, mature T-cells. The patients usually have an aggressive disease usually exhibiting systemic manifestations, often (50%) skin involvement and frequent hypercalcemia (50%). The disease clusters in various parts of the world, and where it clusters HTLV-I is prevalent. The virus is apparently transmitted only by close contact or by blood products. The epidemiological data, the *in vitro* transformation, the numerous animal models of leukemias and lymphomas caused by retroviruses, the presence of integrated HTLV nucleic acid sequences in the DNA of the neoplastic T-cells, and several other results from molecular biological experiments make HTLV, in my view, the best example of a virus caused human malignancy, and perhaps the clearest example we have of the cause of any human cancer.

HTLV-I may also be involved in the cause of a fraction of mycosis fungoided and Sezary cases and *indirectly* in some B-cell neoplasias as will be discussed. Finally, variants of these retroviruses may be important in AIDS.

16 THE CURRENT STATUS OF NCI TRIALS IN HODGKIN'S DISEASE.

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The development of effective therapies for all stages of Hodgkin's disease represents one of the most remarkable achievements of modern cancer treatment. Despite these achievements, there remain a number of areas where improvements in the management of Hodgkin's disease are needed and three of these areas have been the central focus of the ongoing clinical trials at the National Cancer Institute (USA). In early stage disease as many as 25% of patients relapse from radiation-induced complete remissions and although many can be salvaged by chemotherapy, this is accomplished at some risk of induced second malignancy. Furthermore, successful radiotherapeutic management of early stage disease demands considerable technical expertise and access to sophisticated equipment not always widely available to all patients. Because combination chemotherapy is curative in advanced disease and can salvage many patients who relapse after radiation therapy and because trials with MOPP in early stage Hodgkin's disease in Uganda showed considerable promise, we are comparing MOPP alone to radiation therapy as initial treatment of early stage disease. Important parameters for comparison include not only complete remission frequency, survival, and disease-free survival but also acute and chronic toxicities and effectiveness of salvage.

One subset of patients which has consistently had a substantial relapse rate regardless of initial stage are those patients with massive mediastinal disease at presentation. We are treating such patients with alternating monthly cycles of MOPP-ABVD after radiation ports are designed by simulation to include the entire original extent of disease. After six cycles of chemotherapy, patients receive 1050 rads to the original extent of disease, followed by another 2500-3500 r to a reduced mediastinal volume. The rationale for such an approach for mantle irradiation is to minimize the marginal and pulmonary relapses so frequent in this subset of patients.

Although the treatment of advanced Hodgkin's disease with MOPP has dramatically altered the prognosis for these patients, further progress is still needed. Nearly half of patients with advanced disease still die prematurely. Salvage therapy for those patients who fail initial induction or relapse within one year of intial treatment continues to be suboptimal. The current NCI trial for advanced disease patients (Stages IIIA, IIIB and IV) is aimed at testing the Goldie-Coldman hypothesis that early exposure of the tumor to two combinations of non-cross resistant drugs is more likely to result in cure than conventional cyclic four-drug treatment. The study compares MOPP to MOPP alternating with CABS (CCNU, Adriamycin, Bleomycin, Streptozotocin) chemotherapy. Seventy-nine patients have been randomized and complete remission rates are similar for both regimens at this point with median survivals in both groups exceeding 80% at 4 yrs for either treatment.

17 CURRENT STATUS OF STANFORD HODGKIN'S DISEASE TRIALS.

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Randomized clinical trials designed to evaluate various treatment programs for patients with Hodgkin's disease were initiated at Stanford University in 1962. These continuous studies involving 838 patients, as of March 1, 1984, have undergone four major revisions during the past two decades.

Between 1962-1967, 132 patients with CSI, II and III were enrolled on various radiation trials. Patients with CSIII disease were treated for the first time with total lymphoid irradiation (TLI) with approximately 40 % of these patients remaining continuously free of disease. Between 1968-1974, 367 patients were enrolled on studies primarily evaluating the role of adjuvant MOPP chemotherapy. Laparotomy and splenectomy was used routinely and patients with all stages of the disease were included. Adjuvant MOPP resulted in significant improvement in disease free survival for some stages of the disease, but the survival advantage was minimal, except for patients with PSIIIA disease. Between 1974-1980, 237 patients were enrolled on studies evaluating an alternative to the MOPP adjuvant, PAVe chemotherapy, and variations of the combined modality treatment plans. PAVe has proved to be as effective as MOPP in these studies without producing acute leukemia to date. An alternating treatment plan, beginning with chemotherapy, appears superior to previous programs, for patients with advanced disease (IIIB and IV).

Current studies, initiated in 1980, have enrolled 102 patients to date. A relatively mild adjuvant, VBM (vinblastine, bleomycin and methotrexate) is being studied for favorable patients, staged with laparotomy. The ABVD regimen is being evaluated in combined modality and alternating chemotherapy regimens. The major emphasis of current protocols is to reduce acute and long term morbidities, without compromising excellent survival results and to further improve the results in patients with the poorest prognoses.

The rationale, design and results of these trials will be presented.

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ALTERNATING CHEMOTHERAPY WITH MOPP/ABVD IN HODGKIN'S DISEASE: UPDATED RESULTS. G. Bonadonna. Istituto Nazionale Tumori, Milano 20133, Italy.

From 1974 to 1982, 88 patients with PS IV were randomized to receive either MOPP for 12 cycles or MOPP/ABVD for 12 cycles. Details on this study were previously reported (New Engl. J. Med. 306: 770, 1982). The updated 7-year results with a median follow up in excess of 60 mos are as follows:

	MOPP (%)	MOPP/ABVD (%)	P
Progression	20.9	4.4	<0.05
Freedom from progression	35.1	68.1	0.001
Complete response	74.4	88.9	0.14
Bulky disease	57.1	88.9	0.10
Non bulky	82.8	88.9	0.78
"A" symptoms	76.9	85.7	0.92
"B" symptoms	73.3	90.3	0.16
NS histology	76.0	87.5	0.50
Others	72.2	90.5	0.20
≤ 40 yrs	78.6	82.8	0.94
> 40 yrs	66.7	100	0.04
Relapse-free survival	44.4	76.8	0.004
Bulky disease	37.5	75.7	0.04
Non bulky	48.7	76.6	0.04
"A" symptoms	50.0	65.5	0.36
"B" symptoms	44.5	79.5	0.006
NS histology	55.9	88.9	0.01
Others	30.8	59.9	0.10
≤ 40 yrs	43.5	75.9	0.004
> 40 yrs	51.5	70.2	0.50
Survival of CR_s	73.2	90.3	0.038
Overall survival	61.1	82.3	0.043

MOPP/ABVD was superior in all proghostic subgroups and less myelotoxic than MOPP. Acute leukemia was observed in 1 patient in each treatment group. Both patients had received chemotherapy after relapse from prior RT. In August 1982, a new randomized study was started in PS IIA (bulky), IIB, III and IV comparing MOPP/ABVD (MM/AA) vs half cycle of either regimen within a month period (MA/MA). Low dose RT (2500 rads) was limited to the site(s) of previous bulky disease. With a minimum follow up of 6 mos, the preliminary results are as follows:

	MM/AA	MA/MA
Complete response	88.9% (32/36)	92.5% (37/40)
Still in complete remission	84.4% (27/32)	91.9% (34/37)

Present data confirm the favorable impact of alternating chemotherapy vs MOPP alone. However, the optimal sequence remains to be clarified by the ongoing study.

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COMBINED MODALITY THERAPY FOR HODGKIN'S DISEASE.
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The integration of intensive multi-agent chemotherapy and radiotherapy for the management of Hodgkins disease is predicated on a major appeal, i.e., patients who failed chemotherapy are most likely to fail in sites of overt involvement, whereas patients who fail radiotherapy are most likely to fail outside the field of radiation. When these modalities are put together for the management of Hodgkins disease, it is unclear how much of either is truly required, in contrast to the use of either modality alone. Optimal timing in integrating these two modalities also remains to be defined. In addition, the actual technique of treatment remains very important.

This presentation will review the results of combined modality approaches published in various medical centers with special emphasis on the long term outcome. In addition, it will review the available information on secondary oncogenesis. At the present time, the results of combined modality therapy in terms of sterilizing Hodgkins disease appear to be excellent. However, the long range toxicity is such that its use should probably be restricted to those patients who have an expected cure rate less than 65 % with either modality alone. This arbitrary figure reflects a) the detectable risk of leukemia related to treatment with the combined modality approach and b) the "salvage" achieved with combination chemotherapy in patients who relapse following radiotherapy.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

20 CURRENT STATUS OF THE CURABILITY OF CHILDREN WITH HODGKIN'S DISEASE (HD): AN ASSESSMENT OF THE RISK:BENEFIT RATIO OF MODERN THERAPY. S.B. Murphy, St. Jude Children's Research Hospital, Memphis, TN USA.

Major improvement in the disease-free survival (DFS) rates of children with HD has occurred in the last 10-15 years. Because of appropriate concern over growth disturbances in irradiated areas, treatment policies at most large centers and cooperative groups treating children have shown a trend away from high-dose, large volume radiotherapy. In view of the effectiveness of chemotherapy in controlling advanced stages of HD, combined modality approaches, incorporating four-drug chemotherapy combinations (e.g., MOPP, CVPP, COPP, OPPA, ABVD) plus low-dose (2000-2500 rads) involved or extended field irradiation, have now become the standard treatment policy for most children (except favorable CS or PSIA). As a result of these trends, reported overall 5-year-DFS rates for children with HD are currently 85-90%. The implications of these data are profound. Since 9 out of 10 children with HD carefully staged and treated with a modern approach will become long-term survivors, there is an imperative need to better define curative therapy associated with minimal acute and long-term morbidity (infectious deaths in remission, sterility, hypothyroidism, growth failure, non-lymphocytic leukemias and other second malignant neoplasms). Further improvements in the therapeutic index of combined modality approaches for children with HD will require large, well-planned and controlled clinical trials,incorporating pretreatment stratification according to a precise estimation of the relapse hazard, testing further reductions in the dose and volume of radiotherapy (? elimination altogether) and further improvements in drug doses, scheduling, and combinations, coupled with extended follow-up, to include long-term observations on the quality of life of survivors. Due to the relative rarity of pediatric cases of HD, such studies obviously require coordination of national effort, and will take years, even decades, to complete. It is likely that there will be no threshold below which therapy can be reduced to achieve complete freedom from side effects while maintaining high rates of curability (90%). Recognizing this reality, the primary therapy for each child with HD must currently be based on curative intent, eschewing any reliance on later salvage approaches.

21 LATE EFFECTS OF CHEMOTHERAPY IN HODGKIN'S DISEASE

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It has now been clearly demonstrated that approximately fifty per cent of patients treated for advanced Hodgkin's Disease with combination chemotherapy will be free of recurrence ten years later. There are two major organic long-term side effects of the treatment most frequently used (cyclical therapy with Mustine, Vinblastine, Prednisolone and Procarbazine or variants), infertility and the development of second malignancy. Azoospermia is invariable following the first two cycles of therapy and recovery is very rare, although has been observed. A premature menopause occurs in more than half the women treated, increasing in frequency with age. The gonadal damage in both men and women has been shown to be due to 'End organ failure'. Second malignancy has been reported as occurring with a considerably greater frequency than is expected in the normal population, with acute myelogenous leukaemia being the commonest.

22 SECONDARY ACUTE NONLYMPHOCYTIC LEUKEMIA (ANLL) AND DYSMYELOPOIETIC SYNDROME (DMPS): A MODEL OF LEUKEMOGENESIS WITH IMPLICATIONS IN THE PRIMARY TREATMENT OF LYMPHOMAS.

K.S. Albain, M. M. Le Beau, J. W. Vardiman, J. D. Rowley, H.M. Golomb, and J. E. Ultmann. University of Chicago, IL.

Patients (pts) receiving chemotherapy (CT), radiotherapy (RT), or both are at an increased risk for developing DMPS or ANLL, either of which is associated with consistent chromosome abnormalities (chr abn) of No. 5 and/or 7. We describe clinical and cytogenetic analyses of 63 pts with previously treated diseases: 23, Hodgkin's disease; 10, non-Hodgkin's lymphoma; 6, other lymphoproliferative; 21, solid tumors; and 3, renal transplant. The median age was 55 years. Eleven pts had RT only, all but 2 with pelvic ports; 21 had CT only, with either prolonged alkylating agent therapy (alk ag tx) or methyl CCNU. The other 31 pts had both CT and RT, usually with standard doses. Nineteen pts developed DMPS; 15, ANLL; and 29, DMPS followed by ANLL. The median time to bone marrow dysfunction (BMD) was 56 mo, with no difference by type of primary tx. Mean time from DMPS to ANLL was 5 mo. Clonal chr abn were identified in 61/63 pts (97%), compared to 75/140 pts (54%) with ANLL de novo. Abn of No. 5 and/or 7 were seen in 55/61 (90%) secondary DMPS/ANLL pts, a higher frequency than in ANLL de novo (35%). Only 1 pt had 5q- as the only abn. Deletion analyses of 5 and 7 showed that (7)(q34→35) and (5)(q31→32) were consistently lost. The oncogene c-fms has been localized to 5q34. Chr abn were unrelated to age, sex, initial disease, or mode of primary tx. However, abn of 5 or 7 were associated with DMPS whether or not followed by ANLL, rather than with the occurrence of ANLL without DMPS (45/48 or 94% DMPS ± ANLL v. 10/15 or 67% ANLL; p=.02). Median survival from BMD was 7.8 mo and was unrelated to initial disease, treatment, or chr abn. Most pts with DMPS died of infectious or hemorrhagic complications. Eleven pts with ANLL died shortly after diagnosis without therapy. Of the 29 pts who received a standard Ara-C-based induction regimen, only 6 pts achieved a CR (4/6 did not have prior DMPS; none had loss of No. 5); 4 are alive in remission at 6-43 mo follow-up. Two pts received low dose subcutaneous Ara-C and 2 pts, retinoic acid, during the DMPS phase without response. There were no CRs in 4 pts treated with high dose Ara-C. From this analysis we suggest the following conclusions: 1) pelvic portals are causatively implicated in the pts who only had primary RT; 2) all but 1 CT only pt had high dose alk ag tx or MeCCNU given over a prolonged period; 3) the presence of DMPS, not ANLL, was most strongly associated with abn of 5 or 7; 4) the critical region of 5 and 7 were defined for the first time in this group of pts; 5) the response rate to modern induction regimens was lower than in pts with de novo ANLL, even with high dose Ara-C, in our group of pts with mostly complex abn of 5 and 7. The implications of this data for designing future up-front lymphoma treatment programs will be discussed.

23 SECOND CANCERS AFTER TREATMENT IN TWO SUCCESSIVE COHORTS OF PATIENTS WITH EARLY STAGES OF HODGKIN'S DISEASE

M. HENRY-AMAR for the EORTC Radiotherapy-Chemotherapy Group.

Two successive cohorts of patients with HD clinical stages I-II (H1 trial : 1964-71, 334 pts ; H2 trial : 1972-76, 300 pts) were prospectively followed. Thirty-four second cancers (SC) were registered, 21 in the H1 trial and 13 in the H2 trial, including 6 leukemias (4+2), 4 non-Hodgkin lymphomas (3+1) and 24 solid tumors (14+10). Initial treatments were : a) in the H1 trial : regional radiotherapy (RT) at 40 Gy with or without vinblastine (VLB) for two years ; b) in the H2 trial : regional RT at 40 Gy plus paraaortic and spleen RT at 40 Gy or the same RT after laparotomy+splenectomy. Moreover, patients with mixed cellularity or lymphocytic depletion histological types were randomised between VLB or a combination of VLB + procarbazine (PCZ) for two years. For the present study, three treatment groups were distinguished : patients without relapse (No Rel.), relapsing patients treated without combination chemotherapy (No poly-CT) and those treated by a combination chemotherapy (Poly-CT) for relapse. In both trials, in the "No Rel." groups, the occurence of SC did not differ regardless of whether the patients received CT or not, and, in the H2 trial, whether or not they received VLB or VLB+PCZ. A time-dependant covariate analysis was used to assess the contribution of each type of therapy on occurence of SC. Time lapse to SC ranged from 2 to 16 years (H1) and from 3 to 9 years (H2) after initial treatment, and from 0 to 12 years (H1) and from 2 to 6 years (H2) after retreatment for relapse. The relative risk (RR) of leukemia in the "Poly-CT" groups was 300 in the H1 trial ($p<0.001$) relative to the general population incidence rates and 200 in the H2 trial ($p<0.001$) while it was not significantly increased in the "No Rel." groups. In the H1 trial, RR of solid tumors was 26 ($p<0.001$) in the "Poly-CT" group, 3.67 ($p=0.027$) in the "No Poly-CT" group and not significantly increased in the "No Rel." group. RR of secondary solid tumors in the H2 "No Rel." group, was 3.14 ($p<0.001$). Comparison of occurence of solid tumors between the two H1 and H2 trials showed, in the "No Rel." group, that the difference observed was due to a shorter delay between initial treatment and secondary solid tumor in the H2 trial. At 7 years, the cumulative proportion of all SC in the "No Rel. group was less than 1% in the H1 trial, while it was greater than 3% in the H2 trial ($p=0.016$). In the H2 trial, extensive RT to paraaortic and spleen regions may be responsible for the excess of solid tumors (bowel and kidney) observed. The most important factors for developping an SC were combination chemotherapy and age over 40 years. The data suggest that combination chemotherapy may be responsible for leukemias in the two cohorts, and for other second tumors only in the H1 trial.

24 LACK OF CORRELATION OF ANN ARBOR CLINICAL PARAMETERS AND BIOPSY DETERMINATION OF LIVER INVOLVEMENT IN STAGE III AND IV HODGKIN'S DISEASE: A SOUTHWEST ONCOLOGY GROUP (SWOG) STUDY.

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We reviewed the clinical and pathological staging of 273 eligible patients (pts) with pathologic stage III or IV Hodgkin's disease receiving induction chemotherapy +/- involved field radiotherapy consolidation as part of SWOG 7808. Pre-study forms plus the actual pathology and radiology reports were reviewed. Of 197 pts that had liver biopsies (BX), 24% (47) were positive (pos) by percutaneous (percut) BX or by BX obtained at laparotomy (lap), of those 150 determined negative (neg), 37% (55) had only a percut BX while 63% (95) had a liver BX at lap +/- a percut BX. The Ann Arbor (AA) clinical criteria for liver involvement, i.e. 1) hepatomegaly + ↑ alk phos; and/or 2) ↑ 2 different liver function tests (SGOT and alk phos); and/or 3) abnormal liver scan and 1 abnormal liver function test, were correlated with BX results.

45% (21/47) patients with a pos liver BX had negative AA clinical criteria for liver involvement. Conversely 20% of pts with lap neg liver BX had pos AA criteria for liver involvement. 21% (10/47) pts with a pos liver BX were clinical stage IIIA or less, whereas 11% (7/66) of all pts stage IIIA or less eligible for the study had a pos percut or lap liver BX. None of the pts with clinical stage IIIA or less rendered pathologic stage IV by liver BX had pos bone marrows or any other pathologic evidence of stage IV disease. 64% (26/41) of pts with a pos liver BX had a neg liver scan. 80% (16/20) of pts with a pos liver BX had a neg CT of the liver. 26 pts had a lap liver BX following a neg percut BX. The false neg rate was 31%.

155/197 pts were response evaluable (32 too early, 10 not evaluable). The CR rate for 23 pts who were AA clinical criteria neg but liver BX pos (AA-BX+) was not different from the 95 pts who were criteria and BX neg (AA^-BX^-) (65 vs 70%). The CR rates were similar despite the fact that only 15% of the AA^-BX^- group as opposed to 100% of the AA^-BX^+ group were pathologic stage IV.

We conclude that (1) AA clinical criteria are not useful in predicting liver involvement; (2) percut liver BX is not useful when neg; (3) pts with clinical stage IIIA or less should have an open liver BX before receiving non-systemic therapy; and (4) pathologic liver involvement without clinical signs of liver involvement is not a poor prognostic variable.

25 LONG TERM FOLLOW-UP OF PATIENTS WITH CLINICAL STAGES I.II HODGKIN'S DISEASE : COMPARISON OF INITIAL SPLENECTOMY AND SPLEEN IRRADIATION.

A controlled clinical trial (H_2 trial) was carried out in patients with clinical stages I and II Hodgkin's disease (H.D.) by the EORTC Radiotherapy-Chemotherapy group from 1972 to 1976. The aim of this H_2 trial was (a) to compare the efficacy of spleen irradiation and of splenectomy; (b) to assess the prognostic significance of the information provided by laparotomy. For this purpose, all patients with pathological stages (PS) I, II and III received the same radiotherapy (mantle field and para-aortic lymph nodes). (c) to compare for these patients with poor histological subtypes [mixed cellularity, (MC) and lymphoid depletion, (LD)] two schedules of long term chemotherapy : either Vinblastine (VLB) alone or VLB + Procarbazine (PCZ). The results of the trial including 300 patients with at least 8 years follow-up for the last patients randomised are presented.

Fourty-eight patients (30%) relapsed out of 156 patients registered in the group treated by splenic irradiation, and 35 patients (24%) relapsed out of 144 in the group treated by splenectomy. The difference is not statistically significant. The overal survival at 10 years is 84% and there is no difference in the two groups. It is noticeable that among the 53 deaths observed only 26 (49%) were due to H.D. The main other causes of death were sequellae of treatment (5 cases), intercurrent disease (12 cases) and secondary cancer or leukemia (6 cases). Non-lethal complications of the treatment were mainly complications of the digestive tract. In the group treated by laparotomy and radiotherapy (144 patients) we observed 25 digestive complications (9 small bowel obstructions, 16 ulcers) i.e. 17% versus only 4 ulcers in the group of 156 patients treated by radiotherapy alone (2,5%). The difference is highly significant ($p < 0.001$).

The patients who received chemotherapy had a significant higher disease free survival (DFS) even after adjustment for initial treatment : splenectomy or spleen irradiation.

A multivariate analysis was performed to study the prognostic factors and showed that high-risk parameters are : spleen involvement at laparotomy; erythrocyte sedimentation rate (ESR) higher than 50 mm; presence of systemic symptoms, bulky mediastinal involvement and a higher number of lymph nodes areas involved (more than 2). The delineation of clinical stages I and II H.D. between "high risk" and "low risk" group is now possible without laparotomy. For the former group, chemotherapy is the main treatment while a lighter treatment with radiotherapy alone may be adequate in "low risk patients".

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26 STAGING LAPAROTOMY WITH SPLENECTOMY IN STAGE I AND II HODGKIN'S DISEASE. NO THERAPEUTIC BENEFIT.

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In a prospective randomized study of treatment for early stage Hodgkin's disease, of 104 patients with presentation above the diaphragm, 76 patients had staging by exploratory laparotomy with splenectomy and 28 had staging by closed techniques. Treatment consisted of involved field radiation alone (44 patients), involved field radiation followed by chemotherapy (38 patients), total nodal radiation alone (15 patients) and total nodal radiation followed by chemotherapy (7 patients). Both groups had similar clinical features on presentation, and both had similar treatment distribution.

With similar median followup (87 months) a trend for longer remission and survival was observed in the group of patients staged by closed staging (68% and 92% respectively) compared to the group staged by exploratory laparotomy with splenectomy (59% and 74% respectively). These differences however were not statistically significant (p 0.27 and 0.09 respectively). There were more patients presenting multiple areas of relapse among patient staged by exploratory laparotomy with splenectomy compared to the group staged by closed techniques (11/32 relapses vs. 0/9 relapses, respectively p 0.082). Relapse in the abdomen alone or as part of disseminated relapse was observed in 12% (9 patients) in the group of patients who had staging by exploratory laparotomy as compared to 3% (1 patient) in the group staged by closed techniques (p 0.28). Two patients (7%) staged by closed techniques died with Hodgkin's disease. Thirteen patients (17%) staged by laparotomy died: 7 of Hodgkin's disease, the other 6 died in complete remission of: non-Hodgkin's lymphoma (1 patient), leukoencephalopathy (1 patient), sepsis during chemotherapy (2 patients), myocardial infarction (1 patient) and cerebrovascular accident (1 patient). Three other patients in this Group had other secondary malignancies successfully controlled: histiocytic lymphoma, squamous cell carcinoma of cervix and malignant schwanoma. No secondary malignancies were observed in the group staged by closed techniques.

Staging laparotomy with splenectomy in early stage Hodgkin's disease did not improve the duration of remission or survival or decrease the number of relapses in the abdomen as compared to closed staging.

27 SURGICAL RESTAGING AFTER 3 OR 6 COURSES OF MOPP CHEMOTHERAPY IN HODGKIN'S DISEASE (HD). UPDATED RESULTS.

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121 patients (pts) with HD, clinical staged, were treated by two different, successive protocols. 68 pts, I B 7 pts, II A 17 pts, II B 27 pts, III 17 pts, were treated from 4.72 to 12.76. 66 pts underwent surgical restaging (SR) with splenectomy after 6 courses of MOPP and Vinblastine monthly x 4. 53 pts, I B 1 pt, II A 10 pts, II B 26 pts, III 16 pts, were treated from 3.77 to 9.79. 52 pts underwent SR after 3 courses of MOPP. All pts received mantle irradiation (RT). CS III and CS I-II with persistent disease at SR received additional inverted Y or para aortic field irradiation. The clinical complete remission rate (CR), partial response (PR) and failure was respectively 80 %, 14 %, 6 % after 6 MOPP and 83 %, 15 %, 2 % after 3 MOPP. Upon SR, 83 % of pts (55/66) after 6 MOPP, 92 % of pts (48/52) after 3 MOPP, were free of residual disease. Persistant splenic disease at laparotomy in pts clinically restaged as CR was not significantly different after 6 MOPP (2/54) and after 3 MOPP (1/44). The incidence of false negative clinical restaging (clinical CR with pathologic SR) was respectively 3.5 % and 2 %. CR rate was 94 % (64/68) after 6 MOPP and RT, 96 % (51/53) after 3 MOPP and RT. The actuarial survival at 66 months is respectively 94 % and 86 % after 6 or 3 courses of MOPP followed by RT. The relapse free survival at 66 months is respectively 96.6 % and 88 %. We conclude that 3 courses of MOPP are as efficient as 6 to treate splenic occult disease in CS II A, I B, II B with supradiaphragmatic presentation and to achieved CR when combined with RT.

28 THE MANAGEMENT OF LOCALISED, INFRADIAPHRAGMATIC HODGKIN'S DISEASE: EXPERIENCE OF A RARE CLINICAL PRESENTATION AT ST. BARTHOLOMEW'S HOSPITAL.

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Between 1969 and 1982, 23 previously untreated patients with Hodgkin's disease (HD) confined to infradiaphragmatic sites were treated at St. Bartholomew's Hospital. The distinguishing clinical characteristics of the patient population were a male:female ratio of 20:3 and a mean age of 39 years which was significantly (p 0.05) older than the mean age, 32 years, of patients with supradiaphragmatic HD, referred during the same time period. Sixteen patients were surgically staged and the final pretreatment stages were PS +A: 5; PS IIA: 11; CS IIA: 1; PS IIB: 1; CS IIB: 5. Splenic involvement correlated closely with the number of lymph node sites involved, being detected in 8/9 (89%) CS IIA and 1/7 (14%) CS IA patients (p 0.001).

Complete remission (CR) was achieved in 21 (91%) patients: 13/13 following 'inverted Y' radiotherapy and 8/10 following combination chemotherapy. Twenty patients remain alive and 18 continue without recurrence of HD between 15 months and 12 years. All patients who failed to enter CR or who relapsed had presented with 3 or more sites of involvement or with constitutional ('B') symptoms. These results confirm the generally good prognosis of this uncommon presentation of HD and also suggest that prognosis is determined by the bulk of disease rather than its precise anatomical localisation, provided that appropriate therapy is administered.

29 STRATEGIES FOR MANAGEMENT OF CHILDHOOD NON-HODGKIN'S LYMPHOMAS (NHL) BASED UPON STAGE AND IMMUNOPATHOLOGIC SUBTYPE: RATIONALE AND CURRENT RESULTS.

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Childhood NHL is heterogenous in its clinical presentation and relapse hazard with modern therapy. It follows that not all children are equally benefited by a uniform treatment policy. Instead, alternative treatment strategies are appropriate for subgroups of patients, based upon pretreatment staging and determination of immunopathologic subtype. Using a simple clinical staging system, we and others have shown that children with Stages I and II, localized disease, regardless of histopathologic subtype, have an excellent prognosis (90% curability) when treated with combined modalities. Consequently, with the objective of reducing acute toxicity and adverse long-term consequences of treatment, current trials aimed at lessening the intensity of therapy for children with Stage I or II disease are underway in many centers and cooperative groups. Optimal management of advanced stages, III and IV, requires categorical separation of lymphoblastic (T) from non-lymphoblastic (B) cases. Lymphoblastic lymphomas, primarily mediastinal, should be treated like high-risk acute lymphoblastic leukemia, with multiple drugs and CNS prophylaxis, without mediastinal radiation. Using such a strategy, the 3-year disease-free survival rate of advanced stages of lymphoblastic lymphomas in our experience and others is approximately 75%. Advanced stages III and IV of Burkitt-type NHL have been treated successfully with intensive combination chemotherapy protocols of short duration (6 months) incorporating high doses of cyclophosphamide, high dose methotrexate, cytosine arabinoside, and other agents in combination with intrathecal prophylaxis. Using such a strategy, several groups (SJCRH Total Therapy 'B', SFOP LMB-01-02, and BFM 81-83) have reported major improvements (to 65-75%) in the curability of Stage III-IV Burkitt-type NHL, though Burkitt's lymphoma in a leukemic phase (B-ALL) remains grave. 5-10% of all cases of childhood NHL are either nodular, mixed, pleomorphic peripheral T-cell type, mediastinal non-lymphoblastic, or essentially unclassifiable and require an individualized approach to management. In summary, using a modern strategy for treatment, the majority of children with NHL are curable.

30 RESULTS OF THE BFM THERAPY FOR CHILDHOOD NON-HODGKIN'S LYMPHOMA. IMPROVEMENT OF PROGNOSIS BY ADAPTION OF CHEMOTHERAPY TO STAGE AND TYPE.

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Treatment of childhood NHL has been increasingly aggressive, but mostly did not take into account the heterogeneity of these diseases. In the BFM study 1975/81, childhood NHL was treated uniformly with a chemotherapeutic regimen, which has been proven to be very effective in childhood ALL. Results depended primarily on clinical stage and histologic/immunologic type. In disseminated disease (stage III and IV according to Murphy), the probability of continuous complete remission (CCR) after 8 years is excellent for Non-B-NHL (78%, n=42), but poor for B-NHL (34%, n=29). B-NHLs relapsed exclusively within 7 months after diagnosis.

Therefore, in 1981 a new therapeutic regimen was developed for B-NHL and B-ALL, while the therapy of Non-B-NHL underwent no maior changes. Two slightly different, alternating chemotherapy blocs were given in B-Neoplasias: Bloc 1: Cyclophosphamide 200 mg/m2 daily day 1-5; Methotrexate 500 mg/m2 with leucovorin rescue day 1; i.th. Methotrexate day 1; VM 26 165 mg/m2 and ARA-C 300 mg/m2 day 5. Bloc 2: As bloc 1, but ADR 50 mg/m2 instead of VM 26/ARA-C day 5. Patients with stage I and resectable stage II B-NHL (stage "II-R", mostly intraabdominal) received 4 of these blocs within 8 weeks, disseminated and not resectable intraabdominal B-NHL (stage "II-NR") 8 blocs within approximately 20 weeks. No continuation therapy was given. Second look laparatomy was performed in most patients with initially non resectable intraabdominal B-NHL. Prophylactic cranial irradiation was given to patients with disseminated B- or Non-B-NHL only.

3 years after initiation of this stage- and type-adapted regimen, the probabilities of CCR are: All NHL-patients (n=99): 80%; Non-B-NHL, stage I/II (n=9): 89%; Non-B-NHL, stage III/IV (n=33): 79%; B-NHL, stage I/II-R (n=19):100%; B-NHL, stage II-NR/IV (n=37): 67%. B-ALL (n=22): 49%. In conclusion, our results indicate, that treatment of B-NHL and B-ALL has to be different from treatment of Non-B-Neoplasias. The prognosis of B-NHL and even B-ALL has been greatly improved by the BFM therapy designed for more specific treatment of these diseases.

31 IMPROVEMENT OF SURVIVAL OF STAGE IV B-CELL NON HODGKIN LYMPHOMA (NHL) AND B ACUTE LEUKEMIA (B-ALL). A STUDY OF THE FRENCH PEDIATRIC ONCOLOGY SOCIETY (SFOP)

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Advanced stage (st.) diffuse B-cell NHL and moreover B-ALL are known to be of very bad prognosis. For these (extended head and neck st. II, all st. III, IV and B-ALL), a new protocol, called LMB, was designed in February 1981. The protocol was as follows : A. Induction with : 1) "COP-COPAD-M" course : CPM : 0,5 g/m2 Day (D) 0 and 1 g/m2 D6, 7, 8 ; VCR : 2 mg/m2 D0, 5, 10 ; PRED : 2 mg/kg/d from D0 to D10 ; ADR : 60 mg/m2 D6 ; HD-MTX : 3 g/m2 D5 ; IT-MTX : 15 mg/m2 D0, 5, 10. 2) "COPAD-M" course as before from D5 to D10. 3) "CAMAD" course : ARA-C : 100 mg/m2/d in continuous infusion D1 to D5 ; L-ASP : 1000 U/kg D2 to D6 ; HD-MTX : 3 g/m2 D0 ; ADR : 45 mg/m2 D5 and 6 ; IT-MTX : 15 mg/m2 D1 ; IT-ARA-C : 30 mg/m2 D6. 4) "MINI-BACT" course : BCNU : 60 mg/m2 D0 ; ARA-C : 100 mg/m2 D0 to 4 ; CPM : 0,5 g/m2 D1, 2, 3 and 6-TG : 150 mg/m2 D0 to 4. B. No radiotherapy at all. C. Maintenance made of two monthly alternative courses : 1) HD-MTX : 3 g/m2 D0 ; CPM : 0,5 g/m2 D0, 1 ; ADR : 60 mg/m2 D1 ; VCR : 2 mg/m2 D2 ; PRED : 2 mg/kg D0 to 4 and IT-MTX : 15 mg/m2 D1. 2) BCNU : 60 mg/m2 D0 ; ARA-C : 100 mg/m2 D0 to 4 ; IT-ARA-C : 30 mg/m2 ; L-ASP : 1000 U/kg D1 to 4 ; 6-TG : 150 mg/m2 D0 to 3. The treatment was to be completed within one year.

Due to toxicity, this protocol was modified after the first 32 patients in November 1981 : CPM was diminished and delayed in COP-COPAD-M : 0,3 g/m2 D0 and 0,5 g/m2 D8, 9, 10. ADR was removed from CAMAD.

From February 1981 to October 1983, 123 patients from 17 centers in France have been included in a non randomised study. According to Murphy's staging (st. IV being defined by less than 25 % blast cells in bone marrow), there were : 10 st. II, 79 st. III, 13 st. IV (6 CNS involvement) and 20 B-ALL (8 had CNS involvement and 10 blast cells in blood). Actuarial survival for all patients is 74 %, 100 % for st. II, 78 % for st. III, 54 % for st. IV, 53 % for B-ALL.

Thus, according to these criteria, there is no difference in survival between st. IV and B-ALL. In fact, with this treatment, the critical prognostic factor is the initial CNS involvement in both st. IV and B-ALL. The actuarial survival is 80 % for the 17 st. IV and B-ALL patients without CNS involvement and 30 % for the 16 with CNS involvement.

In conclusion, this protocol has considerably improved survival for st. IV NHL and B-ALL. For a next study, we consider to diminish lenght of protocol for all patients without CNS involvement and to intensify it for patients with CNS involvement.

32 THERAPY OF UNDIFFERENTIATED (INCLUDING BURKITT'S) AND LYMPHOBLASTIC LYMPHOMAS IN CHILDREN AND YOUNG ADULTS.

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Seventy five patients with diffuse non-Hodgkin's lymphomas, aged 2-35 years have been treated according to an intensive protocol in which a 42 hour infusion of methotrexate (total 2.7 gm/m^2) with leukovorin rescue is administered 10 days (first 6 cycles) or 14 days (last 9 cycles) after a combination of cyclophosphamide (1.2 g/m^2, given alone in the first cycle), vincristine (1.4 mg/m^2), adriamycin (40 mg/m^2) and prednisone (40 mg/m^2 daily x 5). Intensive intrathecal therapy is given as CNS prophylaxis. Radiation is used only in exceptional circumstances (e.g., paraplegia). Approximately 70% of patients had advanced stage disease. All patients have been followed for at least one year. Overall complete response rate was approximately 90% and continuous disease-free survival (DFS) for all patients was approximately 60% at 3 years. Patients with extensive bone marrow involvement, regardless of histology, had the worst prognosis (less than 20% DFS at 3 years), and patients with lymphoblastic lymphoma (without marrow involvement) or completely resected abdominal undifferentiated lymphoma had the best prognosis (over 85% DFS at 3 years). The latter patients are treated with only 6 cycles of therapy. Patients without bone marrow involvement had a DFS of approximately 70% at 3 years. Patients classified as Murphy stage III had a DFS of over 60% at 3 years. No differences in prognosis were observed in patients less than 16 yrs or greater than 17 yrs, regardless of histology, but all partial responders were 16 or more years old. The best predictor of response was tumor burden, as measured by clinical stage, or biochemical parameters such as serum LDH and uric acid levels. Relapse in the CNS was the commonest site of recurrence in children, but 4 such relapses occurred prior to the introduction of intrathecal prophylaxis, which appears to be effective. In adults, the commonest site of relapse was the bone marrow. These results are of interest since a) this protocol is effective in both lymphoblastic and undifferentiated lymphomas in the absence of bone marrow involvement; b) radiation is not used; and c) patients with completely resected disease do well with only 6 cycles of therapy.

33 EVOLUTION OF THE THERAPEUTIC APPROACHES OF NON-HODGKIN'S LYMPHOMA OF CHILDHOOD - Cl. JACQUILLAT, D. KHAYAT, M. WEIL

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During the past decades, a huge improvement has been made concerning the understanding and the prognosis of pediatric (ped.) non-hodgkin's lymphoma (NHL). Until the late sixties, the NHL of childhood were considered as non different from the adults NHL and were treated very slightly, mainly with radiotherapy and/or surgery. The results obtained with those historical controls were of about 10 % (extended forms) to 40 % (localized forms) long term survival. The bone marrow involvement led to classify some NHL as leukemias and therefore were not included in thoses series. During the seventies, a better understanding of the disease led to separate the ped. NHL from the adult NHL. Some features appeared very characteristic of the ped. NHL : 1°) A very rapid and agressive clinical course which has to be opposed by a vigourous induction treatment ; 2°) A high incidence of central nervous system (CNS) involvement justifying a systematic CNS prophylaxis ;- 3°) The better accuracy of the Murphy's staging (st) than the Ann Arbor st system. During this period, all of us pointed out the great value of the histological features of the ped. NHL : 1°) being almost always of the diffuse histologic pattern ;2°) with about 40 % of them originated from B-lymphocytes (most of them classified as Burkitt type) with proeminant abdominal symptomatology ;3°) and most of the rest with T-lymphocytes lineage features (lymphoblastic) explaining the occurence of mediastinal extension in about one third of the children. The therapeutic approach became therefore more specific with immediate and heavy treatment, systematic CNS prophylaxis, giving 85 % overall long-term survival in localized form and about 50 % in non-localized NHL, using chemotherapeutic regimens such as "LSA_2-L_2" and "COMP". This study of Wollner and others studies pointed out the different therapeutic approaches that should be done according to the B or T-lymphocyte origine of the proliferation, on which are based now most of the up to date treatments : non localized lymphoblastic type NHL should be treated agressively, almost like acute leukemias with regimens which include Cytosine Arabinoside and Asparaginase, such as the "VIRCALL" or the "LSA_2-L_2",. The results of such treatments in this indication reach probably now a better than 75 % cure rate. The treatment of non-localized B-lymphocyte type NHL can be slightly less agressive with regimens such as "COMP" which should include Methotrexate and Cyclophosphamide, those two drugs highly improving the results in non-differentiated or Burkitt NHL with about 60 % long-term survival. Except perhaps for some very localized non-lymphoblastic forms, CNS prophylaxis is always imperative but skull irradiation may not be mandatory.

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CHILDHOOD HODGKIN'S DISEASE: TREATMENT WITH ABVD CHEMOTHERAPY AND LIMITED FIELD RADIOTHERAPY. F.Fossati-Bellani, R.Kenda, F.Lombardi, C.Gianni, M.Gasparini, P.Pizzetti, R.Musumeci, and G.Bonadonna. Istituto Nazionale Tumori, Milan 20133, Italy.

With the objective of reducing acute and late complications from surgical diagnostic procedures and from extensive radiation therapy (RT), since 1979 a new therapeutic approach has been devised and applied to children and adolescents with nodal extent of Hodgkin's disease admitted and treated at our Institute. Laparotomy with splenectomy was omitted, and staging procedures utilized lymphangiography, CA scan, bone marrow biopsy and laparoscopy to evaluate the extent of disease. The initial treatment for all patients, regardless of stage and histologic subtype, consisted of three monthly cycles of ABVD (ADM 25 mg/m^2, BLM 10 mg/m^2, VLB 6 mg/m^2, DTIC 375 mg/m^2). Subsequently, RT was delivered according to the type of clinical response induced by chemotherapy: 30-35 Gy to involved area(s) in complete and partial responders, respectively; 25 Gy to the adjacent area(s). Three additional courses of ABVD were then given only to children with stage IIB and IIIA and B. Thirty-four consecutive children (age 3.4 to 15.4 yrs, median 10 yrs) were staged as follows: IA 12, IIA 7, IIB 6, IIIB 2, IIIS A+B 7. According to histology patients were classified into the following subtypes: LP 2, MC 12, NS 20. Following initial ABVD, CR was achieved in 16 of 19 patients (84%) with stage I and IIA, and PR >50% in 3 patients. Stage IIB and IIIA and B attained CR in 6 of 15 (40%) and PR >50% in 9 cases. After a median follow-up of 30 months (range 15-51) 33 of 34 children remain alive and progression-free. Only one child with stage IIIB relapsed with disseminated disease two months after completion of therapy. Nausea and vomiting represented the only immediate toxic effect of this treatment program and were almost always severe. No patient showed either cardiac or respiratory abnormalities. In children followed for more than 2 years growth as well as endocrine and gonadal function were uneffected. Although this combined approach appears very effective in inducing high remission rates and durable CR, a longer follow-up is needed to establish the actual cure rate and treatment-related late sequelae.

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COMBINED TREATMENT MODALITY WITH REDUCED CHEMO- AND RADIOTHERAPY IN HODGKIN'S DISEASE: RESULTS FROM 300 CHILDREN IN 2 CONSECUTIVE STUDIES

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Since 1978 two consecutive therapy studies for Hodgkin's disease in children are in progress in Germany and Austria. Between June 1978 and Nov 1981 170 protocol pts from 47 hospitals were enrolled in the 1st study HD-DAL 78 (age 1 - 16 yrs, median 12;2 yrs, male/female ratio 1.79). Laparotomy was done in 164 pts and splenectomy in 159 pts. Chemotherapy consisting of 2 OPPA cycles (Oncovine, Procarbazine, Prednisone, Adriamycine) were administered to all pts prior to irradiation. Additional 4 COPP cycles (C = Cyclophosphamide) were given after irradiation to stage IIB to IV pts. All involved fields (IF) were irradiated with 36 - 40 Gy. To the extended fields (EF) 36 - 40 Gy (group I) or 18 - 20 Gy (group II) were given in a randomised manner. Projected disease free survival rates after 5 yrs are 91 % in the total group and 89 % (I) and 94 % (II) in the 2 randomisation groups. Thus, radiation dose to EF can be reduced, if a combined treatment modality is used.

In Dec 1981 the non-randomised 2nd study HD-DAL 82 was started. Pts are stratified into 3 groups with different chemotherapy duration: stage I/IIA 2 x OPPA, stage IIB/IIIA 2 x OPPA plus 2 x COPP, stage IIIB/IV 2 x OPPA plus 4 x COPP. Irradiation is limited to IF, the dose depending on extent of chemotherapy (35, 30 or 25 Gy). Laparotomy is done in all children, but splenectomy is performed only in selected cases (approx. 36 %) following a new intraoperative strategy, which was developed on the basis of an analysis of 154 pts of the study HD-DAL 78 [Klin. Pädiat. 194 : 242 - 250 (1982)]. Until Dec 1983 130 protocol pts from 46 hospitals entered the study (age 3 - 6 yrs, median 12 yrs, male/female ratio 1.82). All pts achieved complete remission. Until now 1 child (stage $IV_{L,B}$) had a relapse in its lungs. 2 pts (stage IIIB) died of infections. Projected disease free survival rates after 2 yrs are 100 % for stage I/IIA (n=64) as well as for stage IIB/IIIA (n=36) and 86 % for stage IIIB/IV (n=30).

36 HODGKIN'S DISEASE (HD) IN CHILDHOOD : TREATMENT WITH CHEMOTHERAPY AND LOW-DOSE RADIATION. RATIONALE AND FEASIBILITY

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For the FRENCH CHILDHOOD HD COOPERATIVE GROUP

Dramatic improvement in survival and relapse free survival (RFS) has been obtained in childhood HD employing extended fields radiotherapy (RT) alone or in conjunction with multiagent chemotherapy (CT). Nevertheless it is everyone concern to minimize the side effects of such treatment while maintaining good RFS.

With this aim, 4000 rads radiation was first limited to involved fields (IF) and chemotherapy lowered to 3 cycles of MOPP as the first step. In 65 clinically staged patients (CS IA-CS IVB) the overall 5 years survival was 93 % and RFS was 83 %.

Based upon these data and those of other published series on low-dose radiation, the French Society of Pediatric Oncology associated with Hôpital Saint-Louis (Paris) started in 1982 a new study as a second step of the therapeutic decrease. It aims at answering to 2 questions : 1) effectiveness of ABVD alone compared to alternating MOPP-ABVD in remission induction ; 2) effectiveness of 2000 rads in IF when associated to CT. No staging laparotomy is performed. Treatment is based on CT followed by RT. Thus, according to the disease extent and systemic symptoms, 2 different schemes of CT and RT are used : 1) CSI-IIA : randomized CT : 4 ABVD vs alternating 2 MOPP-2 ABVD then RT 2000 rads to IF (stages I upper neck disease are excluded from randomization but given 4 ABVD before RT). 2) CSIB-IIB-III-IV : alternating 3 MOPP-3 ABVD then RT 2000 rads to IF and lomboaortic and splenic fields in all the cases.

The RT dose is not randomized but remission is evaluated at the end of CT. Patients (pts) who do not attain "good remission" (defined as complete remission or at least reduction of tumor $\geq$ 70 % at the end of CT) are given the previous dose of 4000 rads.

In December 1983, 50 pts have been included in the study : 28 CSI-IIA, 7 CSI-IIB, 8 CSIII, 7 CSIV. 37 pts completed CT : 29 pts achieved CR and 5 pts good remission, these pts were given 2000 rads. 1 patient had partial remission ($<$ 70%) after 4 ABVD but attained CR with MOPP. Only 2 pts (IIIB-IVA) were considered as CT failures for they presented early relapse before RT and had 4000 rads RT. All the pts in the study are still now in first CR with follow-up from 1 month to 20 month (median 11 months).

37 HODGKIN'S DISEASE (HD) IN CHILDHOOD AND ADOLESCENCE.RESULTS OF CHEMOTHERAPY-RADIOTHERAPY (CT-RT) IN CLINICAL STAGES (CS) IA-IIB.

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From 4/1972 to 5/1980, 72 children and adolescents (age, range 5-19 years, median 16) with HD, CS IA-IIB (IA:18, II2 A, 2 areas involved on the same side of the diaphragm : 23, II3 + A, 3 areas or more : 16, IIB : 15) were prospectively treated by 2 successive clinical trials (H72 and H77). CS IA and II2A received 3 MOPP and supradiaphragmatic RT (40 gy) ; no laparotomy was performed. CS II3 + A and IIB received 6 MOPP (H72), 3 MOPP or 3 CVPP (CCNU, Vinblastine, Procarbazine, Prednisone) (H77) and had a subsequent laparotomy followed by supradiaphragmatic RT with a lumboaortic field if positive laparotomy. Patients (pts) without evidence of mediastinal involvement did not have mediastinal RT. At completion of therapy, 70/72 pts were in complete remission (CR) (1 failure, 1 death under treatment). Eight pts relapsed (in situ : 1, marginal : 1, non irradiated subdiaphragmatic area : 6) after 3 to 57 months of CR (median 20 months) ; 1 pt died after relapse. There were 3 deaths in CR (infection : 2 ; AML : 1, actuarial risk : 1.8 %). In 11/1983 median follow-up was 75 months (range 27-132 months) ; actuarial probabilities for survival and freedom from relapse for all pts were respectively 91.6 % and 87.3 %. There was no statistical difference according to CS, age ($>$ 15 or $\leq$ 15 years), sex, 6 or 3 cycles of CT. Bone growth defects related to RT could be reduced particularly in the 29 pts who did not receive mediastinal RT (none of them had a mediastinal relapse). Azoospermia was the rule for studied male pts, but CT allowed small girls and young women to retain reproductive integrity. The 38 non splenectomized pts were subtracted to the infection risk of splenectomy

38 TREATMENT OF CHILDHOOD HODGKIN'S DISEASE STAGE I AND II WITHOUT RADIOTHERAPY

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Radiotherapy is the major modality in the treatment of Hodgkin's Disease stage I and II in adults, while chemotherapy is mainly used as an adjuvant before or after radiotherapy. However, combination chemotherapy has become the main modality for patients with advanced stages of Hodgkin's Disease, and at least half of the patients with stage III and IV can be cured with chemotherapy alone. Because good results are obtained with this strategy, children with Hodgkin's Disease have been treated in most centres as if they were small adults. However, during the past decade it has become more apparent that the late sequelae from radiotherapy are more serious in children. With decreasing age the late effects from radiotherapy, such as growth disturbances in irradiated areas, hypoplasia of breasts in pubertal girls, hypothyroidism, pericardial fibrosis, radiation pneumonitis and aspermia are increasingly prominent; in addition radiation-associated tumours can be expected. Consequently radiotherapeutic management of children with early stage Hodgkin's Disease has been adapted in several treatment centres. Extended fields have been reduced to involved fields, and it has been shown that the 4000 Rad dose can be decreased to 2500 Rad if the radiotherapy was sandwiched between periods of chemotherapeutic treatment.
In 1975 we decided to select from our patients with Hodgkin's Disease CS I and II a group of children who presented with only small lymphnode swellings, i.e. lymphnode tumours with a diameter less than 4 cm. These patients were treated with six MOPP-cycles at monthly intervals, without radiotherapy. The other children with CS I and II, having tumour masses with a diameter of more than 4 cm, were also treated with six cycles of MOPP, to which involved field radiotherapy was added after the third MOPP cycle. The radiation dose was 2500 Rad, given over a period of 3 weeks. From 1975 to 1982 18 consecutive children aged 5-14 years with CS I and II were treated according to the above mentioned programme. No child underwent staging laparotomy with splenectomy, but the other usual stage-screening methods were completely performed, including lymphangiography. Nine patients had small tumours with a diameter less than 4 cm, and they were treated with six cycles of MOPP without radiotherapy. Complete remission was easily obtained in all patients and up until now no relapse have occurred. These patients are followed for 11-103 months (median 59.6 months). Nine patients, having tumour masses in excess of 4 cm, received bimodal treatment with MOPP and involved field radiotherapy. From this group one child developed a relapse outside the irradiated area after 26 months, and he died of progressive disease in spite of agressive treatment with full dose radiotherapy and heavy chemotherapy. No relapses were seen in the other eight patients of this group, and they are followed for 22-72 months (median 49.9 months).
The data derived from this study, although preliminary, indicate that stage I and II of childhood Hodgkin's Disease can be successfully managed with chemotherapy alone. This was also the conclusion of dr. Olweny et al. based on their experience with the treatment of 48 children with Hodgkin's Disease in Uganda, where no radiotherapeutic facilities were available. However, much more consideration must be given to the late complications of this type of treatment. The risk of infertility in boys, who are treated with alkylating agents during or after puberty is subtantial. Second malignancies are also to be expected in the group of patients who are treated with MOPP, especially in those cases where chemotherapy was combined with radiotherapy.
It is not only our task to define the minimum effective therapy for children stage I and II Hodgkin's Disease, but also to treat them without damaging late effects. Although by far the majority of these patients can be cured by the MOPP-combination without radiotherapy, we must look for other chemotherapeutic combinations which do not contain alkylating agents, but have the same curative properties without its potentially injuring sequelae.

39 SELECTIVE SPLENECTOMY IN CHILDREN WITH HODGKIN'S DISEASE: PROSPECTIVE USE OF A NEW INTRAOPERATIVE STRATEGY IN 109 CHILDREN.

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By means of an analysis of 154 splenectomised children with Hodgkin's disease (study HD-DAL 78) we tried to find out a method to predict splenic involvement (IS) on the basis of clinical and/or intraoperative findings. 6 out of 17 pre- and intraoperative findings showed significant correlation to IS: B-symptomatology, palpable spleen, mediastinal enlargement, nodular changes of the splenic surface (SS+), enlarged lymphnodes of the hilus of spleen and/or the tail of pancreas (SH/TP+), enlargement of other upper-abdominal lymphnodes. Multivariat analysis showed, that the two most evident findings SS+ and SH/TP+ gave almost the entire information which can be obtained about IS. All other parameters were no longer significant when combined with these two.
Based on these results an intraoperative strategy has been developed. Splenectomy is restricted to those pts, which present the criteria SS+ and/or SH/TP+ (expected incidence 36 %). If abdominal lymphnode biopsies are positive in non-splenectomised children, irradiation will include the spleen, because the probability for IS in these cases is 70 %. In an additional 9 % of the non-splenectomised pts an IS remains undetected, i. e. our strategy of selective splenectomy has to be used in combination with chemotherapy.
Until Nov 1983 the new method was applied prospectively in 109 children of the therapy study HD-DAL 82. Pts receive 2, 4 or 6 cycles of chemotherapy (depending on the stage of HD) followed by involved field irradiation. 39/109 pts (36 %) were splenectomised, 26 pts by the criteria SS+ and 13 pts by SH/TP+. The spleen was involved in 28 of the 39 pts (72 %). 4 non-splenectomised pts received irradiation of their spleen due to positive abdominal lymphnode biopsies. These figures correspond very well with the expectations from the retrospective analysis. After a median observation time of 12 mths (range 1 - 24 mths) only 1 pt has relapsed (lungs). These results confirm the usefulness of our new strategy making it possible to omit splenectomy in about two thirds of pts and still to obtain detailed information about infradiaphragmatic spread.

40 ENZYMES INVOLVED IN ADENOSINE METABOLISM, IN NORMAL OR LEUKEMIC LYMPHOCYTES

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Enzymes involved in adenosine metabolism and adenine nucleotide catabolism are particularly important in lymphocytes, as compared to other cell types, mainly because lymphocytes are almost devoided of *de novo* purine synthesis. Moreover adenosine appears to be involved in lymphocyte differentiation and function. Deficiencies in some of these enzymes are correlated with abnormal maturation levels, abnormal lymphocyte function, and it was unambiguously shown that inherited deficiencies of some adenosine metabolizing enzymes led to immunodeficiencies.

We studied several of these enzymes both in human and mouse, in normal lymphocyte sub-populations, in leukemic cells and in lymphoblastoid cell lines.

For several enzymes, no significant differences were found among various populations: adenosine kinase, deoxyadenosine kinase, AMP kinase, S-adenosyl-homocysteine hydrolase, S-adenosyl-homocysteine synthesis, cytosolic 5'nucleotidase.

On the opposite, ecto-5'nucleotidase, ecto-ADPase, ecto-ATPase, AMP-deaminase were found higher in mature than in immature cells. Adenosine deaminase was found lower in mature than in immature cells.

In human lymphoblastoid cell lines also, low 5'N/ADA ratios and low AMP-deaminase activities seemed to be correlated with high TdT (Terminal deoxynucleotidyl Tranferase) levels and immature character, while high 5'N/ADA and high AMP-deaminase activities were found in mature cells with low TdT levels.

In lymphocytes from patients with some B-cell type leukemias we found low activities for both adenosine deaminase and ecto-5'nucleotidase, while in T-ALL patients low ecto-5'nucleotidase and normal adenosine deaminase activities were observed.

41 PURINE NUCLEOTIDE METABOLISM IN NORMAL AND PATHOLOGICAL LYMPHOID CELL DIFFERENTIATION.

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A normal purine metabolism is necessary for proper functioning of lymphoid cells. For *normal lymphoid cell differentiation*, lymphocytes in various maturation stages differ considerably in make-up of enzymes of purine metabolism. E.g., within the T-cell lineage, the activity ratio adenosine deaminase (ADA) / purine nucleoside phosphorylase (PNP) is twofold higher in small immature lymphocytes in the thymus cortex than in medium-sized cells in the thymus medulla, and blood T-cells reveal a value 20-fold lower than thymocytes. The variation in enzyme make-up is related with cell function. E.g., for thymocyte subpopulations there is a significant correlation between the activity ratio ecto-5'-nucleotidase (ecto-5'NT) / deoxycytidine kinase (which ratio determines the net capacity of the cell to convert (deoxy)nucleosides to toxic (deoxy)ribonucleotides) and the capacity of (deoxy)nucleosides to inhibit proliferative responses of the cell.
For *pathological lymphoid cell differentiation*, especially lymphoreticular malignancies (leukemia and lymphoma), immunological phenotyping has proved to be of value in addition to histopathology in assessment diagnosis and prognosis. The evaluation of purine enzymes has revealed considerable differences between various forms of leukemia. E.g., childhood T-cell acute lymphoblastic leukemia (T-ALL) distinguishes from other forms of ALL by a relatively high ADA and low ecto-5'NT enzyme activity. Within one type of leukemia subgroups can be discerned, e.g. in B-cell chronic lymphocytic leukemia, cells from patients with paraproteinemia have higher ecto-5'NT and lower ADA activities than cells from patients without paraproteinemia.
Apart of being markers in diagnosis, the assessment of purine enzyme make-up shares with immunological phenotyping the possibility to relate pathological lymphoid cells with normal lymphoid cell differentiation. In this, the enzyme make-up of T-ALL resembles that of immature T-cells found in the thymus. From its relation with cell function, the purine enzyme make-up (by giving insight in privileged pathways in purine nucleotide metabolism) may open possible ways of treatment, which include either inhibition of enzyme activities (e.g., ADA by deoxycoformycin) or therapy with purine analogues which are easily converted in pathological cells to toxic compounds. The variable succes of deoxycoformycin treatment of ALL may be based on variation in enzyme make-up, especially in ecto-5'NT activity (which dephosphorylates toxic ribonucleotides accumulating due to blocked ADA activity).

Most studies on purine nucleotide metabolism have been performed on leukemia and need extension to lymphoma. The detailed analysis of purine enzyme make-up in pathological cells in lymphoma may add to a better classification and prognosis of the disorder, and may open putative approaches of treatment by enzyme-directed chemotherapy.

42 EXPRESSION OF AN ECTOENZYME-CASCADE ON HUMAN LEUKEMIC AND LYMPHOBLASTOID CELLS. BIOCHEMICAL AND IMMUNOLOGICAL STUDIES AND CLINICAL SIGNIFICANCE.

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Earlier observations of Silber et al. on differential expression of the ectoenzyme 5′-nucleotidase (5′-N) on peripheral blood lymphocytes of normal subjects and patients with CLL were extended into the field of acute leukemias. Here a remarkable correlation of high activities of this enzyme with the expression of the common ALL antigen was found. The two surface antigens are not identical and plasmamembrane subfractionation studies with the cell line Nalm 1 show, that they are not closely associated on the membrane level. Further ectoenzymes like ATPase, ADPase and a nucleoside-diphosphate-kinase were characterized in their membrane orientation and enzymatic properties in lymphoblastoid B-cell-lines. ATPase, ADPase and 5′-N seem to be organized in form of an enzyme-cascade, since all three members are enriched in specific plasmamembrane subfractions. A coordinate expression of ATPase and 5′-N is found in a series of different B-cell-lines, but this does not apply to T-cell-lines or blast cells in different forms of acute leukemias. A number of findings in this investigation could be substantiated or extended using inhibiting polyclonal or monoclonal antibodies against 5′-N. Ecto-5′-N as a biochemical diagnostic marker is especially useful for the distinction of lymphoid and myeloid blast crisis in CML. Its clinical significance was further evaluated within a prospective study on acute leukemias. Our own data on ectoenzyme-expression in malignant lymphomas do not yet allow any general conclusions.
By virtue of their distinct differences in the patterns of surface expression lymphocytes and lymphoblastoid cells are regarded as good models for the study of the normal physiological function of ectoenzyme-cascades.

43 ENZYMATIC AND ULTRASTRUCTURAL PROPERTIES OF THE PLASMA MEMBRANE IN HUMAN LEUKEMIAS, NON-HODGKIN'S LYMPHOMAS AND IN HUMAN LYMPHOBLASTOID CELLS.

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The cellular plasmalemma is an effective organelle which enables many physiological events to be carry out through the involvement of associated enzymes, antigens and other macromolecular constituents.Their characteristic levels may undergo changes during pathological onset, following stimulation, perturbation of homeostasis or by adaptation to the various stages of cell differentiation and maturation.

The amplitude of variations of enzymatic and ultrastructural markers was investigated in the plasma membrane of cells with acute lymphoblastic leukemia or isolated from NH lymphomas and in human leukemic cell lines assigned to a definite stage of the B cell lineage.The enzymatic analysis of membranes obtained by discontinuous isopycnic centrifugation revealed not only characteristic enzymatic make-up in the various leukemic cell lines but also different activity profiles of each enzyme within a given cell population. At the opposite, a freeze-fracture analysis of intact cells revealed normal particle density distributions on the plasma membrane with a minor scattering of the particle density between the various cell lines.

These findings may reflect a continuous rearrangement of those constituents located on the outer leaflet of the plasma membrane while integral entities ensuring the intimate architecture of the cell envelope distributed more uniformly in proliferating cells. Membrane dynamics partially explains activity variations and should be ascribed to cell proliferation and maturation rather than to pathogenic events. It could also elucidate the shedding off of membrane fragments enriched with single membrane enzyme and antigen, which have been identified in cell culture supernatants and in sera of leukemic patients.

Resting human blood lymphocytes and more mature lymphoid cells express a more uniform distribution of their membrane constituents.

44 ENZYME PATHWAYS IN MALIGNANT LYMPHOMAS. A.V. Hoffbrand, Department of Haematology, Royal Free Hospital and School of Medicine, London, U.K.

Recent biochemical studies have shown close similarities between normal lymphoid cells and the leukaemias and lymphomas which are thought to arise by clonal expansion from them. The enzymes found to be of particular value diagnostically are adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP) and 5'-nucleotidase (5'NT) which are concerned in purine degradation, terminal transferase (TdT), ecto-ATPase, thymidine kinase (TK) and lactate dehydrogenase (LDH). Normal thymic cortical "blasts" and most Thy-ALL cases and some T lymphomas show high ADA, low PNP and 5'NT and raised TdT. In comparison to normal B cells, poorly or well differentiated B lymphomas and myeloid cells, early T cells show a highly efficient multienzyme complex for DNA synthesis but the ability of early T cells to degrade DNA precursors is low, endogenous production of deoxyadenosine is low and early T cells are susceptible to toxicity by deoxyribonucleosides, or to the ADA inhibitor deoxycoformycin (dCF). Thus, dCF and deoxyadenosine or deoxyguanosine plus PNP inhibitors could be used to selectively kill T tumour cells in bone marrow prior to autologous transplantation. More mature normal T cells and mature T cell tumours (e.g. Sezary, some T lymphomas, T-CLL) show higher PNP and 5'NT levels with low ADA and absent TdT. Although normal OKT_8 cells show higher 5'NT levels than OKT_4 cells, this pattern is not clearly reproduced in chronic T cell disorders. The LDH isoenzyme pattern changes as T cells mature and this pattern is also reproduced in the corresponding "early" and "late" T cell tumours.

The earliest recognisable B cell tumours e.g. c-ALL and pre B-ALL and the normal equivalent cells show the presence of TdT. It is possible that TdT has a role in the generation of diversity during immunoglobulin gene rearrangements in these early B cells. These cells have intermediate levels of ADA, PNP and 5'NT, the ADA:PNP ratio being higher than in more mature B cells or B cell tumours. TdT is absent from SIg secreting B cells and the B cell lymphomas derived from them. CLL shows low levels of all three purine degradative enzymes, absent TdT, but higher ecto ATPase levels than in mature B or T cells. TK is of fetal (TK_1) type in less well differentiated non-Hodgkin's lymphomas but of normal adult (TK_2) type in diffuse well-differentiated lymphomas. In CLL, TK_2 occurs except in clinically aggressive cases but in hairy cell leukaemia, TK_1 surprisingly dominates.

45 LYMPHOCYTE UROPORPHYRINOGEN SYNTHASE ACTIVITY IN LYMPHOPROLIFERATIVE DISORDERS - A VALUABLE DIAGNOSTIC TEST. +*M. Lahav, +O. Epstein, +N. Schoenfeld, "M. Shaklai and +*A. Atsmon. +The Laboratory of Biochemical Pharmacology, *Department of Internal Medicine B and "The Hematology Unit, The Beilinson Medical Center, Petah Tiqva, Israel.

Patients with lymphoproliferative diseases (LPD) were shown to have a significantly elevated activity of lymphocyte uroporphyrinogen synthase (1-URO-S). The mean values of 1-URO-S activity of a control group (n=70) and of LPD patients (n=70) were 24.7 (SD=5.2) and 87.2 (SD=44.0) pmol porphyrins/mg protein/hr, respectively. There was almost no overlap in the 1-URO-S activity of patients with LPD and of the control group. L-URO-S activities of patients with other malignant diseases and with viral and bacterial infections were within the normal range. The specifity of the determination of 1-URO-S activity in the diagnosis of LPD was 98% and the sensitivity was 97%. The positive predictive value of the test was over 90%. L-URO-S activity was determined in 49 patients clinically suspected of harboring LPD. In 45 of them a final diagnosis was established. In 15 of the latter the test was positive and the diagnosis was subsequently confirmed by other means such as a lymph node biopsy. In 27 patients the test was negative and other causes for the symptoms were established. In three patients, suffering from diseases other than LPD, the values obtained were slightly above the highest value of the controls. These data indicate that the determination of lymphocyte uroporphyrinogen synthase activity may be of considerable assistance in the diagnosis of lymphoproliferative diseases.

46 BIOCHEMICAL MARKERS IN NON-HODGKIN'S LYMPHOMA STAGES III AND IV AND PROGNOSIS - A MULTIVARIATE ANALYSIS.

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The prognostic value of different pretreatment laboratory and clinical findings at diagnosis was analyzed in a series of 141 patients with generalized non-Hodgkin's lymphoma. Univariate and multivariate survival analysis (Cox's regression model) was performed using serum analysis of deoxythymidine kinase (S-TK), β_2-microglobulin (S-β_2m), lactic dehydrogenase (S-LDH), α-1-acid glycoprotein = orosomucoid (S-α_1 AGP), haptoglobin and ferritin. In addition hemoglobin and erythrocyte sedimentation rate were measured. The clinical variables were age, presence or absence of B-symptoms, histopathology ("low-grade"; "intermediate grade" and "high-grade" malignancy, respectively), and bone-marrow involvement. Among the eight biochemical markers all were found to relate significantly to survival except hemoglobin and sedimentation rate. Among the clinical variables, B-symptoms and histopathology were found to relate significantly to survival. Using a multivariate analysis to all variables, S-TK was found to be the best factor predicting duration of survival. The only significant additional information was given by S-α_1 AGP. When only the clinical variables were taken into account it was found that histopathology contributed significant information to B-symptoms in the prediction of the survival time. If the biochemical variables were added to this model only S-TK gave significant additional prognostic information.

TK is an enzyme involved in the DNA synthesis. It converts deoxythymidine to deoxythymidinemonophosphate (dTMP). The activity of TK is high in dividing cells and very low in resting cells. When measuring S-TK we used a very sensitive method recently described (Gronowitz et al. Int. J. Cancer, January 1984).

We conclude that S-TK seems to be the most important prognostic biochemical marker in NHL.

47 PURINE DEGRADATIVE ENZYMES IN THE MALIGNANT CELLS OF PATIENTS WITH B-CELL LEUKEMIA.

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Previous studies have shown that investigations of the purine degradative enzymes adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP) and 5'-nucleotidase (5'-NT) are of value in defining subsets of lymphoid malignancies of T-cell origin. The significance of these enzymes in B-cell derived malignancies is still unknown. We have studied the activities of these enzymes in the circulating malignant cells of 13 patients with B-chronic lymphatic leukaemia (B-CLL), 15 patients with leukaemic immunocytoma (IC), 4 patients with centrocytic lymphomas (CC), 3 patients with B-prolymphocytic leukaemia (B-PLL). Diagnosis was established by morphology (cytology or histology) according to Kiel classification, immunologic marker analysis with monoclonal antibodies against B-cell differentiation antigens (HD-6, HD-21, HD-28, HD-39), and studies of surface and intracytoplasmic immunoglobulins.

Malignant cells of B-CLL were characterised by low activities of ADA (mean ± SD = 1.62 ± 1.04 U/10^8 cells), PNP (mean = 65.8 ± 31.9 U/10^6 cells), and 5'NT (mean = 1.97 ± 1.67 U/10^6 cells). In malignant cells of IC, low activity of ADA (mean = 1.64 ± 1.40 U/10^8 cells) was also observed, but the activities of PNP (mean = 99.9 ± 30.5) and 5'NT (mean = 22.6 ± 13.4) were relative high. The differences in PNP ($p < 0.05$) and in 5'NT ($p < 0.001$) between B-CLL and immunocytoma were significant. In CC, ADA activity was again low (mean 0.95 ± 0.85 U/10^8 cells), but PNP (mean = 86.9 ± 21.3 U/10^6 cells) and 5'NT (mean = 13.6 ± 9.7 U/10^6 cells) activities were moderately high. Circulating cells of PLL were shown to have low levels of ADA (mean = 1.59 ± 1.09 U/10^8 cells), PNP (55.9 ± 36.0 U/10^6 cells) and 5'NT (mean 1.43 ± 1.36 U/10^6 cells). These findings suggest that quantitation of purine degradative enzymes can be useful in classifying subsets of B-cell malignancy. In IC, for example, the enzyme activities were comparable to those measured in normal peripheral B-cells. These results support the conception that immunocytoma cells are well-differentiated whereas the B-CLL cells are immature with respect to the B-cell axis. Studies of these enzymes may be also of importance in defining maturation stages of B-cell malignancies.

48 TRANSFERRIN RECEPTOR EXPRESSION IN NON HODGKIN LYMPHOMAS (NHL). AN IMMUNOHISTOCHEMICAL STUDY.

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The monoclonal antibody OKT9 is directed at a transferrin receptor, which is present on the cytoplasmic membrane of proliferating cells, while it is not expressed by resting elements. Recently Habeshow et al. found that the percentage of OKT9 positive cells in lymphomatous nodes was related to disease activity and survival, showing that the low grade lymphomas of the Kiel classification had significant fewer positive elements than the high grade ones. These Authors, however, studied cell suspensions, which do not permit any correlation between the immunological analysis and structural characteristics of the examined tissues. Therefore, in order to get more reliable, information, we tested by an immunoperoxidase - ABC - method the expression of OKT9 on lyophilized frozen section of 24 lymph nodes from patients with different types of NHL diagnosed according to Kiel . Our results confirm a well defined OKT9 reactivity pattern, which corresponds to the grade of malignancy. Moreover, within the low grade lymphomas, a group of cases dysplaied higher number of positive cells; this support the view that, between low and high grade lymphomas, a third group of tumors with an intermediate behaviour could be defined. Finally according to the results obtained in the cases of centroblastic centrocytic lymphoma in centroblastic trasformation, it must be outlined that the recognition of areas with a higher content of OKT9 positive cells might have prognostic relevance, expecially in low grade cases with an initial evolution into a more aggressive form.

49 BANDED CHROMOSOME ABNORMALITIES IN NON-BURKITT'S, NON-HODGIN'S LYMPHOMA. CORRELATIONS WITH MORPHOLOGY AND IMMUNOLOGIC PHENOTYPE.

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The malignant lymphomas were among the first human neoplasms to be studied systematically when the new banding techniques became available. When appropriate techniques are used, clonal chromosome abnormalities can be found in the neoplastic tissue of almost all cases. We initially studied involved lymph nodes or other tumor masses in 94 patients with malignant lymphoma (Cancer Research 43:2975, 1983). Clonal chromosome abnormalities were identified in 91, including all 81 B-lymphomas, but only 6 of 9 T-lymphomas. Many recurring chromosome abnormalities were found. Most common numerical alterations involved gains of chromosome 12 (19% of patients), chromosome 18 (13% of patients), chromosome 7 (12% of patients), and chromosome 21 (10% of patients). Structural abnormalities were more frequent than numerical alterations. Most commonly involved chromosome regions were 14q (71% of patients), 18q (36% of patients), 6q (31% of patients), 1p (24% of patients), and 8q (19% of patients). Seven recurring translocations were identified and all except one involved 14q32. The most frequent were t(14;18)(q32;q21), t(8;14)(q24;q32) and t(1;14)(q42;q32). Deletions most frequently involved the long arm of chromosome 6 at band q21 or q23.

The common recurring chromosome abnormalities were correlated with histology, using the International Working Formulation for Clinical Usage, and with immunologic phenotype. Four abnormalities were significantly associated with specific histologies. Eighty-two percent of patients with t(14;18)(q32;q21) were follicular. Similarly, 82% of patients with del(6)(q21) had large cell lymphoma. Lymphomas with trisomy 7 were either diffuse, large cell or follicular. Patients with t(8;14)(q24;q32) were primarily diffuse, large cell; one patient had malignant lymphoma small lymphocytic type. A significant association with immunologic phenotype was seen for t(14;18) only. All patients with this translocation had either B or C' lymphomas, and the heavy chain was more commonly γ and less frequently δμ than among the total B-lymphoma population. Interestingly, both cases with t(3;14)(p21;q32) expressed μ heavy chain and both cases with t(14;19)(q32;q13) expressed δμ. Finally, preliminary analysis in our lymphomas indicates that recurring chromosome abnormalities are frequently in areas to which oncogenes have been localized.

50 CHROMOSOMAL ABERRATIONS IN LOW-GRADE MALIGNANT B-CELL LYMPHOPROLIFERATIVE NEOPLASIAS.

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Forty-seven patients with low-grade malignant B-cell lymphoproliferative neoplasia were studied. According to the Kiel classification 20 patients had classical CLL, 23 immunocytoma, 2 prolymphocytic leukemia (PLL) and 1 centroblastic-centrocytic lymphoma (CBCC). One patient could not be subclassified. Chromosome analysis was made after stimulation of separated peripheral blood lymphocytes and/or cells from lymph nodes with lipopolysaccharide from E. coli (LPS) or Epstein-Barr virus (EBV). The Q-banding technique was used for chromosome identification.

A sufficient number of metaphases, adequate for chromosome analysis, was found in 36 patients. Of these 24 had clonal aberrations, 14 had an extra chromosome 12, either alone or together with aberrations. Five patients had a 14q+ abnormality, and 3 patients had deletion of chromosome 11. Three patients had abnormalities of chromosome 6. Five patients had 3 or more clonal aberrations. Both patients with prolymphocytic leukemia had aberrations on chromosome 3. Other aberrations were found in all subgroups without clear differences in frequency.

One patient had a partial duplication of chromosome 12. An extra segment, q13 → q22, was attached to one chromosome 12. This abnormality had probably arisen through chromatide exchange.

Patients with 3 or more clonal aberrations had the shortest survival. Patients with +12 alone or together with other aberrations had a shorter probability of therapy-free survival than patients with a normal karyotype or than patients with too few metaphases for cytogenetic analysis. The shortest therapy-free survival was found in patients who had immunocytoma with +12.

In conclusion, chromosomal aberrations occur in more than 50% of patients with low-grade malignant B-cell lymphoproliferative neoplasias. More than 50% of patients with aberrations have an extra chromosome 12 which is the most specific abnormality. The genes that tend to be duplicated during leukemogenesis leading to these types of B-cell disorders characterised by trisomy of chromosome 12 are probably located on the segment q13 → q22. Multiple aberrations and an extra chromosome 12 signify a less favourable prognosis, particularly in the immunocytomas.

51 CHROMOSOME ABNORMALITIES IN BURKITT'S LYMPHOMA .

A. De La Chapelle, University of Helsinki, Helsinki, Finland

The breakpoints involved in recurrent structural chromosome abnormalities associated with Burkitt's lymphoma (BL) are close to the cellular myc oncogene on the one hand, and the structural genes for immunoglobulins on the other. Molecular studies have shown structural rearrangements in these genes that may alter their functions. These events may play a key role in the mechanisms leading to malignant transformation of B lymphocytes. It is believed that this may serve as a model for a better understanding of the mechanisms that lead to malignancy in other system as well. For this reason the current interest in chromosome abnormalities associated with BL goes well beyond the scope of BL itself.

In this presentation a critical review is given of chromosome abnormalities reported to occur in BL. It is shown that in addition to the 3 typical reciprocal translocations in each of which band 8q24 is involved, other structural abnormalities occur as well, whereas numerical abnormalities are rarer. The significance of these other abnormalities will be evaluated. Since many studies were made on established BL cell lines rather than on tumor material, an attempt is made to distinguish between primary and secondary abnormalities.

52 TLYM-1, A STAGE SPECIFIC TRANSFORMING GENE FROM T CELL LYMPHOMAS.

M.A. Lane, Chief, Laboratory of Molecular Immunobiology, Dana Farber Cancer Institute, Dep. of Pathology, Harvard Medical School

Transfection of NIH 3T3 cells with foreign DNA has facilitated the identification of a variety of activated cellular transforming genes from human and rodent neoplasms. Ras genes which are transcribed by every cell at every stage of differentiation have been found to be activated in 10-20 % of all tumors tested, while such genes as Blym-1 and T-lym1 are found to be activated only in cells of specific lineages at specific stages of differentiation.

TLym-1 has been found to be activated in 3 out of 4 human T-cell lymphomas and 7/8 rodent T-cell lymphomas. These neoplasms represent an intermediate stage of normal T-lymphocyte differentiation and the gene activated in these tumors differes by restriction endonuclease sensitivity from the gene activated in T-lymphoid neoplasms representative of a more mature stage of differentia - tion. TLym1 was isolated by molecular cloning and is about 2kb in size. The gene shares homology with genes encoded within the MHC1 region, and is somewhat novel in that it behaves as a secreted protein. Our current speculation is that TLym1 represents the transforming allele of a gene located within the TL/Qa region of the major histocompatibility locus and we further speculate that this may account for its highly stage specific expression in T-lymphoid tumors.

53 Prognostic Groups for Management of Clinical Stage (C.S.) I and II Hodgkin's Disease (H.D.) by Radiation Therapy.

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

Radiation therapy for localised H.D. has conventionally been applied following staging laparotomy and with the use of prophylactic abdominal irradiation fields. Given increasing awareness of upper abdominal involvement despite supradiaphragmatic presentation, and the necessity for upper abdominal radiation despite negative laparotomy, an analysis has been undertaken to establish the circumstances whereby curative irradiation can be applied solely by resort to clinical parameters.

Two hundred fifty-two patients with C.S. I and II H.D. received radical radiotherapy between 1968-1977 at P.M.H. The actuarial overall survival, cause-specific survival (death from disease end point) and relapse-free rates at 10 years were 79%, 84% and 61% respectively.

A multivariate analysis to define prognostic factors indicated that age, stage and histology were of independent significance in determining survival and relapse. Disease bulk was predictive only of relapse.

Supra versus infradiaphragmatic presentation and mediastinal involvement were not of independent prognostic importance.

Radiation volume as a univariate determinant of relapse indicated higher relapse rates for "involved" or "mantle" fields compared with fields incorporating abdominal nodal sites of risk.

Three patient groups were defined retrospectively by relapse rate according to age, stage and histology.

<table>
<tr><th></th><th></th><th>IA</th><th>IA</th><th>IIA</th><th>IB&IIB</th></tr>
<tr><th>Age</th><th>Histology</th><th>Upper Cervical</th><th>Other Sites</th><th colspan="2"></th></tr>
<tr><td><50</td><td>LP/NS</td><td rowspan="3">Group I
Relapse
Rate 1/12 (8%)</td><td colspan="2" rowspan="2">Group II
Relapse Rate
63/187 (36%)</td><td rowspan="2">Group III</td></tr>
<tr><td></td><td>MC/LD</td></tr>
<tr><td>>50</td><td>LP/NS</td><td colspan="2">Relapse Rate 17/23 (74%)</td></tr>
<tr><td></td><td>MC/LD</td><td colspan="3"></td></tr>
</table>

Subsequent analysis of Groups I, II and III according to radiation volume indicated that the relapse rate for Group II could be reduced to approximately 25% by use of abdominal radiation.

Although mediastinal involvement was not of prognostic significance, those with massive mediastinal involvement (>10 cm T.D. on P.A. chest radiograph) had a significantly higher intrathoracic failure rate and a high resultant mortality.

A comparison of theoretical expectation of control for clinically staged patients with that achieved following surgical staging indicates that the proportion of patients cured by radiation alone is similar for both groups. In addition, categorisation by multiple clinical prognostic factors permits identification of patients with a similar expectation of control by radiation therapy as has been achieved following surgical definition of stage.

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CHEMOTHERAPY AND LOCALIZED IRRADIATION IN THE MANAGEMENT OF CLINICAL STAGES IA AND II2A HODGKIN'S DISEASE : F. Teillet, F. Teillet-Thiebaud, B. Asselain, Ch. Miot, G. Philippe, Ch. Fermé, J. Bernard. Groupe d'Etudes sur la maladie de Hodgkin -Hôpital Louis Mourier, 92700 Colombes, Hôpital Saint-Louis, 75010 Paris.

Between May 1977 and May 1980, 73 consecutive previously untreated patients, clinical supradiaphragmatic stages IA and II2A biopsy-prooved Hodgkin's disease, were included in a therapeutic trial. All patients received 3 cycles of MOPP. Then they were randomized into 2 series for irradiation 1) classical supradiaphragmatic extended-field irradiation (S), 2) localised irradiation of areas initialy involved (F). No spleno-lumbar irradiation was performed in any of the two series.

	(F)	(S)	
male	25	24	73
female	11	13	
IA	21	20	73
II2A	15	17	

The Complete Remission Rate was 98,5% (1/73). At 5 years, actuarial survival rate was : 98% in both series; disease-free survival rate was 85% in (F) and 80% in (S) series. In the (F) series, no patient relapsed in non-irradiated adjacent areas. 2 patients in (F) and 1 patient in (S) series relapsed in spleno-lumbar areas (4% of all patients). 2 of these 3 patients achieved a second complete remission. Up to now we have observed only one "second malignancy" in the (S) series : a cancer of the oesophagus, 3 years after completion of treatment in a 60 years-old patient. In order to reduce the therapeutic procedure in favorable clinical stages of Hodgkin's disease we evaluated the efficiency of a prior relatively slight chemotherapy in terms of prophylaxy by comparison betwen localised versus extended field irradiation. Thurthermore we evaluated the efficiency of such a chemotherapy on subdiaphragmatic occult disease from a clinical point of vue that is the incidence of relapses in infradiaphragmatic areas. From our data, it seems possible to assume that 1) when such a prior chemotherapy is used, reduction of irradiated field is possible, 2) the risk of infra-diaphragmatic relapses is low -less than 5%- and in such relapses salvage therapy is very efficient.

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MOPP VS RADIOTHERAPY/MOPP FOR EARLY-STAGE HODGKINS DISEASE (HD)- A SIX YEAR FOLLOW-UP. Peter J. O'Dwyer, Michael B. Stewart, Peter H. Wiernik. Baltimore Cancer Research Center Investigational Drug Branch NCI and Albert Einstein Cancer Center, New York, NY 10461, USA.

Thirty-six patients (pts) with previously untreated HD stages IB to IIIA were randomized to treatment with extended field radiotherapy followed by MOPP (RT+C) or MOPP (C) alone. Distribution of histologic subtype, age and sex were similar in both groups. Two pts in each group were inevaluable: 1 died before treatment began, 1 had a non-Hodgkin's lymphoma, and 2 did not complete therapy. The 17 evaluable pts in the RT+C group included 1 stage IB, 7 IIA, 4 IIB, and 5 IIIA. Sixteen achieved complete remission (CR); one had a good partial remission (PR). Five pts relapsed from 18 to 66 months later, of whom 4 have died, 2 of progressive disease, 1 of sepsis, and 1 of squamous cell lung cancer. The median duration of CR is 63+ months, and of survival, 74+ months. Among the 15 evaluable pts in the C group, there were 8 stage IIA, 1 IIB, and 6 IIIA. There were 12 CR, 1PR and 2 non-responders (NR). The PR and 1 NR subsequently achieved CR with radiotherapy: neither has relapsed, though the former has now developed a secondary leukemia. Three pts relapsed 11-24 months later: one responded to and one failed subsequent radiotherapy, while one responded to retreatment with MOPP. The median duration of CR is 64.5+ months, and of survival 75+ months. The median follow-up for all evaluable pts is 75 months. There is no difference between the groups in terms of actuarial freedom from first relapse or actuarial survival. Late infectious disease morbidity was more prevalent in the RT+C group, and two pts are disabled by constrictive pericarditis following mantle radiation. Second neoplasms and hypothyroidism were observed in both groups. These results with chemotherapy alone in stage II and III patients are comparable to those of any previously-reported radiotherapy series. They continue to suggest that MOPP alone may be as effective and less toxic than combined modality therapy, and that restriction of radiation therapy for incomplete responders to chemotherapy may result in equal survival.

56 RANDOMIZED STUDY OF CHEMOTHERAPY ALONE VS CHEMOTHERAPY PLUS RADIOTHERAPY IN CLINICAL STAGE IA-IIA.

S. Pavlovsky, J. Dupont, E. Jiménez, F. Sackmann Muriel, C. Montero, G. Garay. From Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) and Grupo Latinoamericano de Tratamiento de Hemopatías Malignas (GLATHEM), Buenos Aires, Argentina.

From September 1977 to December 1983 a total of 90 patients with previously untreated Hodgkin's Disease in clinical stage IA-IIA (without staging laparotomy) were randomly assigned to chemotherapy alone (CT) for 6 cycles or 3 cycles of the same chemotherapy followed by radiation therapy (3000 rads) to the involved area at diagnosis and with 3 more cycles of chemotherapy (CT-RT). Chemotherapy consisted of monthly cycles of cyclophosphamide 600mg/m^2/iv day 1; vinblastine 6mg/m^2/iv day 1; procarbazine 100mg/m^2/po day 1 to 14 and prednisone 40mg/m^2/po day 1 to 14 (CVPP). A total of 31 patients were $\leq$ 15 years old and 59 were older. Forty-seven were treated with CT and 43 with CT-RT.

The median time of treatment completion was 6 months for CT and 8 months for CT-RT. None of the patients received maintenance treatment.

The rate of complete remission (CR), duration of complete remission (DCR) and overall survival (OS) at 48 months are:

Treatment	No.Pts.	CR		DCR	OS
		No.	%		
CT	47	42	89	86%	94%
CT-RT	43	39	91	85%	84%

Five patients obtained partial remission with CT alone. All had mediastinal involvement, received further treatment with RT and remain alive. Of the four patients in CT-RT who failed to obtained CR one died of sepsis at 5 months and 3 died of progression of diseases at 9, 10 and 11 months.

Five patients relapsed in CT and 3 in CT-RT, while, among all the patients entered in the study, 2 and 6 died respectively.

We can concluded that combination chemotherapy CVPP produces a similar rate of CR, duration of CR and survival as CVPP plus radiation therapy in clinical stages IA-IIA of Hodgkin's Disease.

This study was supported in part by the Cooperative Cancer Treatment Research Program which is a project of the PAHO and NCI, Contract No. NO1-CM-27391.

57 COMBINED MODALITY THERAPY (CHEMOTHERAPY PLUS RADIOTHERAPY) IN HODGKIN'S DISEASE, CS IA TO IIIB.

II.- RESULTS OF THE H77 TRIAL (1977-1980). J.M. Andrieu*, Y. Coscas, P. Cramer, C. Julien, M.Weil, G. Tricot.

* Hematology, Hospital Laennec - 75340 Paris, France.

From january 1977 to april 1980, 173 patients (pts) with Hodgkin's disease (HD), clinical stages (CS) IA to IIIB were prospectively treated at hôpital Saint-Louis (Paris). Their initial characteristics were : - sex : males 102, females 71 ; - age : 5 to 65 years, median 28 ; - CS : IA 42, IIA 63, IB IIB 48, IIIA 9, IIIB 11 ; - histological type : I 28, II 71, III 55, IV 6, unclassif. 13). The 79 pts with CS IA and II_2A (only 2 areas involved on the same side of the diaphragm) followed the H 7701 trial which consisted in 3 MOPP cycles plus radiotherapy (40 Gy) which was randomized in 2 groups ; the first one received a focal irradiation only whereas the other one had a mantle, a mantle excluding mediastinium or an inverted Y plus spleen radiotherapy according to initial presentation. The 74 pts with CS_3II A (3 or more areas involved), IB, IIB followed the randomized H 7702 trial : the patients received at random 3 cycles of MOPP or CVPP (CCNU, Vinblastine, Procarbazine, Prednisone) ; partial and complete responders underwent a laparotomy with splenectomy followed by supradiaphragmatic irradiation (a lombo-aortic field was added in case of positive laparotomy). The 20 pts with CS III followed the H 7703 trial : 3 cycles of MOPP or CVPP (at random) were first given ; a splenectomy was then performed followed by total or subtotal nodal irradiation. At completion of therapy, 167 pts (96.5%) were in complete remission (CR). Twenty pts relapsed (in situ or marginal 3, non irradiated lymph nodes 14, visceral areas 3) after 3 to 60 months of CR (median 12) ; after individual retreatment 12 of them are alive (8 in second CR). Eighteen pts died (initial failures : 4 ; complications of chemotherapy : 2 ; relapsing pts : 8 ; deaths in first CR : 4 including 2 acute leukemias, 1 oesophagus cancer and 1 overwhelming infection). In january 1984 the median follow-up was 53 months (min 32, max 84). Actuarial probabilities (7 years) of survival (calculated from diagnosis) and disease free duration (calculated from completion of therapy) of the whole goup of patients are 87.5% and 85.2% respectively (IA:91.8% and 88%; IIA:92.1% and 89%; IB,IIB:82.6% and 78.7%; IIIA:88.9% and 88.9%; IIIB:76% and 88.9%. No differences were found between focal and more extended irradiations (trial H7701) and between 3 MOPP and 3CVPP (trials H7702 and H7703). Survival (but not disease free duration) is significantly lower in pts over 40 years of age ($P<0.05$).

58 COMBINED MODALITY TREATMENT OF HODGKIN'S DISEASE CONFINED TO LYMPH NODES. Janice P. Dutcher, MD and Peter H. Wiernik, MD
Albert Einstein Col of Med and Montefiore Med Cent, Bx, NY USA

Eighty-seven patients (pts) with newly diagnosed Hodgkin's disease (HD) pathologic stages IA, IIA, IIA_E, IIB, IIB_E, IIIA, $IIIA_E$, were randomized to receive either extended field radiotherapy alone (RT) or RT followed by 6 courses of MOPP chemotherapy (RT+C). All E Stage of lung patients had large mediastinal masses. Pts were entered into study from January 1970 to January 1974. 13 pts were excluded from long-term follow-up. Pts with stages IA, IIA, IIB were randomized and evaluated separately from pts with stage IIIA disease. Of 16 evaluable pts with less than stage IIIA, 29 received RT only and 17 received RT+C. Of 28 evaluable pts with stage IIIA, 12 received RT only and 16 received RT+C. After a minimum of 10 years follow-up, 55% of early stage pts treated with RT only are in continuous remission, compared to 90% of pts who received RT+C (p=0.053). 8 pts treated with RT only have relapsed: 2/2 pts with IIA_E lung (both dead of HD) and 2/2 pts with IIB_E (both dead of HD); 6/18 pts with stage IIA disease have relapsed (2 dead), including one at 94 months in nodes previously included in the RT port. One of 17 pts who received RT+C has relapsed and is alive at 113+ mos. Survival between groups is not statistically different (p=0.27). After a minimum of 10 years follow-up, 41% of pts with stage IIIA HD treated with RT only are in continuous remission, compared to 95% of pts treated with RT+C (p=0.006). Seven pts who received RT only have relapsed including 5 with IIIA (2 late relapses at 112 and 118 mos.) and 2/3 with $IIIA_E$ lung (both dead of HD). One pt treated with RT+C has relapsed and is alive at 118+ mo. If deaths due to all causes are included, there is no statistical difference in survival between groups (p=0.53). No deaths from HD have occurred in pts treated with RT+C. Deaths from other causes in pts with stage IIIA treated with RT+C include 3 cardiac, 2 lung Ca, and 1 early leukemia. No pts with IA, IIA, IIB treated with RT+C have died. 5 pts with IIIA treated with RT alone have relapsed and died of HD. 3 pts with early stage disease treated with RT only have died, 1 of fibrosarcoma in the RT port, 1 suicide, and 1 leukemia after relapse and re-treatment of HD. Combined modality therapy of pts with early HD may be superior to RT alone, especially in subgroups with large mediastinal masses and/or pulmonary extranodal extension, or generalized abdominal nodal involvement.

59 CHEMOTHERAPY ALONE VS. COMBINED MODALITY THERAPY FOR STAGE III HODGKIN'S DISEASE: A FIVE-YEAR FOLLOW-UP OF SOUTHWEST ONCOLOGY GROUP (SWOG) STUDY #7518. P.N. Grozea, E.J. DePersio, C.A. Coltman, Jr., C.J. Fabian, F.S. Morrison, D.O. Dixon and S.E. Jones. University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, P.O. Box 26901, Oklahoma City, OK, 73190, and the Southwest Oncology Group, San Antonio, TX, 78229.

The SWOG initiated in October 1975 a clinical trial in pathological (laparotomy) stage III Hodgkin's disease with randomization to chemotherapy alone consisting of ten courses of MOPP plus low dose Bleomycin (LDB) vs. combined modality program of three courses of the same chemotherapy followed by total nodal irradiation (TNI). Systematic restaging has been performed with additional cycles of MOPP plus LDB administered for residual disease. All cases have been reviewed by the Lymphoma Pathology Panel. From the 137 patients registered until the closing date (April 1980) 117 are fully evaluable. With 59 months median time on the study of the surviving patients the results are as follows:

	MOPP + LDB	MOPP + LDB + TNI	P	
CR rate	89%	96%	0.27	(2 sided Chi square)
5-yr. relapse free survival	77%	81%	0.30	
5-yr. survival rate	86%	91%	0.48	Gehan test of significance

No statistically significant differences in CR rate by baseline characteristics or by A vs. B symptoms is detected (and not expected because of the large number of patients entering CR). Comparison of the relapse free survival (RFS) curves for the subset of nodular sclerosis shows a strong statistical trend (P = 0.051) in favor of the combined modality limb while the same comparison for the subset of mixed cellularity reveals only a trend to more relapses on the combined modality limb (P = 0.17). Toxicities of the two regimens were comparable with respect to immediate side effects and complications. Hematological toxicities, generally, allowed 59% of the patients on the chemotherapy alone limb to complete the ten cycles of MOPP + LDB and 66% of the patients on the combined modality limb to complete the full XRT (33% have low doses for the inverted Y). While survival curves are not statistically significantly different, more patients on the chemotherapy alone limb died of disease and more patients on the combined modality died of toxicities, including one AML and one late marrow failure. These results suggest that for the initial therapy of stage III Hodgkin's disease chemotherapy alone or combined modality could be similarly effective except for the histological type of nodular sclerosis for which combined modality treatment should be considered - presumably with reduced dose of TNI or involved field XRT to original sites of involvement (in order to decrease the risk of second malignancies while increasing the probability of relapse free survival).

60 A STUDY OF CHEMOTHERAPY (MVPP) FOR PATIENTS WITH STAGES IIIB AND IV HODGKIN'S DISEASE (HD) WITH AN ASSESSMENT OF PROGNOSTIC FACTORS.

W.P.Steward*, J.Wagstaff*, I.Todd# & D.Crowther,*Department of Medical Oncology, Christie Hospital, Manchester M20 9BX, #Department of Radiotherapy, Christie Hospital.

118 patients with previously untreated stages IIIB and IV HD were entered into a prospective study of treatment with chemotherapy, using Mustine, 6mg/m^2 i.v. days 1 & 8, Vinblastine, 6mg/m^2 i.v. days 1 & 8, Procarbazine, 100mg/m^2 orally daily, days 1-14 and Prednisolone, 40mgs. orally daily, days 1-14 (MVPP), repeated every six weeks to six courses beyond complete remission (CR) followed by radiotherapy to sites of previous bulk disease.

32 patients had stage IIIB, 20 patients, stage IVA and 66 patients, stage IVB disease. The bone marrow was involved in 16 patients (13%), the liver in 44 patients (37%) and lung parenchyma in 22 patients (19%). Median follow up was 62 months.

The overall CR rate was 74%, 71% of patients with stage IV disease achieved a CR. No factors predicted response. The overall relapse-free survival (RFS) was 86%. No factors predicted the duration of RFS.

Overall five year survival was 73%. Log rank analysis showed that survival was adversely affected by failure to achieve a CR ($p < 0.0001$), increasing age ($p = 0.0002$), high LDH ($p = 0.004$), stage IV disease ($p = 0.008$), high alkaline phosphatase ($p = 0.008$) and high AST ($p = 0.031$). A Cox's multivariate analysis was carried out and showed survival to be adversely affected by failure to achieve a CR ($p < 0.001$), increasing stage ($p < 0.001$), raised serum LDH ($p = 0.013$), increasing age ($p = 0.036$) and raised serum alkaline phosphatase levels ($p = 0.039$).

MVPP is a useful alternative to MOPP and is without associated neurotoxicity. Groups of patients have been identified with a poor prognosis using this regimen for whom alternative therapy should be considered in future.

61 STAGING AND TREATMENT WITH CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE (CVP) IN ADVANCED CUTANEOUS T-CELL LYMPHOMAS(CTCL).

U.Tirelli,A.Carbone,A.Veronesi,E.Galligioni,M.Roncadin,M.G. Trovò,S.Tumolo,F.Brema,E.Grigoletto.Div. of Radiother.& Med. Oncology General Hospital, Pordenone;Centro di Riferimento Oncologico, Aviano, Pordenone, Italy.

The purposes of the study are to evaluate the staging of CTCL and the treatment with CVP of patients(pts) with advanced disease.Twenty-three consecutive pts with histologically confirmed CTCL underwent staging evaluation between Jan'75 and Nov'83.The routine staging procedures included chest x-ray,peripheral blood count and cytomorphology,bone marrow aspirate and biopsy,lymphangiogram,peritoneoscopy with multiple spleen and liver biopsies.Lymphnodal biopsy and/or cytology were performed in selected pts. After the staging was completed,pts were classified(most retrospectively) according to TNM system.Sixteen pts (7 males,9 females,median age 61 yrs,range 24-77)had advanced disease:2 pts had stage IIB for skin tumors;1 pt stage III for generalized erythroderma and 13 pts stage IV for lymphnodal histological involvement(9 pts) and/or visceral histological involvement(5 pts).Among pts with stage IV,6 pts had skin tumors and 7 pts generalized erythroderma. Bone marrow was involved in 3 pts,liver and spleen in 1 pt each.Peripheral blood involvement was present in 9 pts.All 16 pts but three were previously untreated with drugs.CVP was given for at least 3 cycles prior to the evaluation of response and for at least 6 cycles to CRs.Only 14 pts are evaluable for response,since 2 pts are still receiving their first cycles of CVP. CVP induced a 57% overall objective response rate with 4 CR of 43+,19,19,14+ mos duration.The overall median survival was 22.5 mos.Median survival for pts attaining CR vs PR and NR was 44+ vs 16 mos(p=.02).Five pts died of disease.Toxicity was quite acceptable.We conclude that:1)pts with CTCL,if properly staged,often present with advanced (stage IIB-III-IV)or extracutaneous (stage IV) disease(69% and 56% respectively in our series),in agreement with NCI data when only light microscopy was used (63% and 51%respectively in the 49 pts reported by Bunn Jr et al:Ann Int Med 1980; 93:223).In addition,bone marrow was involved in 13% of our pts compared to 2% of Bunn Jr et al series;2)The experience with combination chemotherapy alone in CTCL is limited(approximately 80 pts reported in the literature),the largest series reporting only 12 pts.CVP employed in 14 consecutive pts with advanced CTCL at our institution is an effective combination chemotherapy regimen.

62 TREATMENT OF CUTANEOUS T-CELL LYMPHOMAS (CTCL) WITH BIOLOGIC RESPONSE MODIFIERS: RECOMBINANT LEUKOCYTE A INTERFERON (IFL-rA) and T101 MONOCLONAL ANTIBODY. P.A. Bunn, K. Foon, D. Longo, D. Ihde R. Oldham, R. Schroff, J. Minna, E. Glatstein. National Cancer Institute Bethesda, MD.

CTCL (mycosis fungoides and Sezary syndrome) patients refractory to standard therapy were treated with $50X10^6$ units/m^2 of IFL-rA IM three times weekly (20 pts) or 1-100 mg of T101 monoclonal antibody 8 patients via an intravenous infusion over 2-24 hr to determine the effectiveness and toxicities of these therapies. The patients had advanced stages (13 with cutaneous tumors, 9 with erythoderma, 6 with generalized plaques; 13 with histologic lymph node involvement, 12 with peripheral blood involvement, and 5 with visceral organ involvement) and extensive prior therapy (topical HN_2 in 26, PUVA in 17, whole skin electron beam irradiation in 17, and systemic chemotherapy in 21). After IFL-rA there were partial responses in 9/17 evaluable patients (3 too early for response evaluation), minor or mixed responses in 3/17 patients, and no response in 5/17 patients. Partial responses lasted a median of 5+ mo with 5 continuing responses of 5+ to 19+ mo. duration. Toxicity consisted of a flu-like syndrome consisting of fatigue, anorexia, weight loss, malaise, and decreased performance status sometimes accompanied by mental confusion requiring dose reductions in all patients. All patients had transient fevers which became less pronounced with continued therapy. Reversible elevations in liver function tests (6 patients), nephrotic syndrome with renal failure, (1 patient) and modest decreases in WBC and platelet counts were noted. One patient previously treated with alkylating agents developed acute monocytic leukemia. T101 produced improvement in skin lesions in 2 patients, one of whom also had objective improvement in lymph nodes and peripheral blood. There were no complete or partial responses. Toxicity consisted of shortness of breath (3 patients given >10 mg over 2 hrs), mild fever (3 patients) and cutaneous purpura (1 patient). Shortness of breath was not observed with less rapid infusions. Lack of anti-tumor response may be due to absence of tumor localization with low doses, antigen modulation, inhomogeneous tissue uptake, development of anti-murine antibodies or lack of direct cytotoxicity. We conclude: IFL-rA has definite activity in CTCL, but new doses and schedules should be explored to reduce toxicity and achieve complete responses; T101 is relatively non-toxic but new approaches such as radio/drug-labeling are necessary to enhance cytotoxicity.

63 ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS): BASIC FINDINGS. Dan L. Longo, Ronald G. Steis, Anthony S. Fauci, H. Clifford Lane, Henry Masur, Edward P. Gelmann, National Institutes of Health, Bethesda, MD 20205

The AIDS syndrome is an almost uniformly fatal,transmissable new disease characterized by profoundly depressed cellular immunity and manifested clinically by serious, life-threatening opportunistic infections and neoplasms. Recently, a new strain of human retrovirus (HTLV-III) has been isolated as a putative etiologic agent. A variety of neoplasms have been noted among AIDS patients, particularly Kaposi's sarcoma (KS), an endothelial cell tumor, and a variety of lymphomas including diffuse large cell lymphoma, immunoblastic sarcoma, lymphoblastic lymphoma, and Hodgkin's disease. Neoplasms develop in about 40% of all AIDS patients; 36% develop KS and about 4% develop malignant lymphoma. The incidence of KS is nearly 50% in the male homosexual risk group and is less than 10% in the other major risk groups. Unlike the Kaposi's sarcoma endemic to Africa and most common in elderly Jewish and Italian men (which is localized to skin and curable by local irradiation in the vast majority), the KS in AIDS patients spreads to visceral organs, particularly the GI tract and lymph nodes, in nearly 3/4 of patients. Efforts to treat the KS in AIDS patients have included various preparations of interferons, interleukin-2, single agent and combination chemotherapy, and radiation (x-ray and electron beam). Trials of recombinant interferons (recombinant leukocyte A interferon; Hoffman-LaRoche used at Memorial-Sloan Kettering: recombinant alpha-2 interferon; Schering used at USCF) have yielded objective response rates of nearly 40%. Patients usually required at least 10 weeks of therapy and relapsed if interferon was discontinued. Responding patients tend to have disease limited to skin, no history of opportunistic infection, and T4/T8 ratios >0.5. We used 3 different doses of human lymphoblastoid interferon (Burroughs-Wellcome) in 29 AIDS patients with Kaposi's sarcoma. The response rate was 14%. During therapy most patients had a 30-50% decrease in lymphocyte count that returned to pre-therapy levels when treatment was stopped. Interleukin-2 has been used in about 15 patients without significant antitumor effect. X-radiation can quickly shrink masses in critical locations and election beam therapy is effective against skin lesions. Chemotherapy has the highest response rate (86%) and is effective at controlling life-threatening disease. However, the majority of patients die within a few months of opportunistic infection. No therapy has been shown to alter survival but selective use of radiation and chemotherapy can usually prevent death from KS. Patients who develop malignant lymphoma almost always die of lymphoma, therefore, attempts at remission induction with regimens effective in the individual histologic subtypes seem warranted. The ultimate success in controlling AIDS-associated neoplasia probably depends on reversing the underlying immune defect.

64 MALIGNANT LYMPHOMA IN HOMOSEXUAL MEN: CLINICAL FEATURES AND RELATIONSHIP TO ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS).

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Since the recognition of AIDS, the medical community has become increasingly aware of other medical conditions emerging among homosexual men. From March 1982 to March 1984, 18 homosexual males, ages 20-74, have been seen at NYU with lymphoma. Of these, 5 had epidemic Kaposi's sarcoma (EKS) and 4 had opportunistic infections (OI) 0-10 months (mos) prior to the diagnosis of lymphoma. In one patient with prior OI, EKS and lymphoma were both diagnosed on autopsy. Clinical data are summarized in the table.

Pathology	Stage/Site	Therapy	Outcome (Time From DX)	Associated Disease
DHL	IE(Thigh)	Local RT	Died(2mos)	No
DHL	IE(Small Bowel)	Resection	Relapse(3mos)	OI
		COPBLAM	Died(7mos)	
DHL	IV(Small Bowel)	None	Died(1week)	No
DHL	IV(Small Bowel)	CHOP	Died(10mos)	OI
DHL	IV(Lung)	None	DX on Autopsy	OI/EKS
Burkitt's	IV(CNS)	M-BACOD	Relapse(4mos)	No
		CHOP	Died(7mos)	
Burkitt's	IV	M-BACOD	Relapse(5mos)	No
			Died(7mos)	
Burkitt's	IV	Lost to follow up		
Burkitt's	IV	High dose CTX	PR(4mos)	No
PDL	IV	Local RT	Died(2mos)	No
PDL	IV	VP16/Bleo	Died(4mos)	EKS
PDL	IV	VP16/Bleo	PR(24mos)	EKS
Hodgkin's-NS	IIA	Total nodal RT	CR(2mos)	EKS
Hodgkin's-NS	IE(Tonsil)	Local RT	NED(5mos)	No
Hodgkin's-NS	IIIB	MOPP/ABVD	NED(11mos)	No
Hodgkin's-MC	IA(Axilla)	Local RT	Relapse(5mos)	No
Undifferentiated	IV	None	Died(2days)	EKS
Unclassified	1°CNS	Local RT	Died(2mos)	OI

The occurrence of 18 cases of lymphoma in male homosexuals in 24 mos in a single institution, and the association with EKS and OI suggest that lymphomas in this group may be a manifestation of AIDS. Unusual features of the non-Hodgkin's lymphomas are extra nodal presentation (14/14) and extremely poor prognosis (median survival = 4 mos) despite aggressive chemotherapy and a high initial response rate. In addition, 4 cases of Hodgkin's disease (1 with EKS) were seen. Interestingly, no cases of concomitant EKS and Burkitt's were seen. One patient presented with Burkitt's of the mandible with monoclonal markers showing IgG. Further characterization including mononuclear cell surface markers, other markers, such as Beta-2-microglobulin, cytogenetic evolution and serology is in progress.

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65 DIFFUSE LYMPHOMAS IN PATIENTS (PTS) AT HIGH RISK FOR ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS).

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Prisoners are a group well-recognized to be at high risk for AIDS. The incidence of AIDS in this population is approximately 120/100,000 per year and AIDS is now the leading cause of natural death in the New York State correctional system. Intravenous drug abuse has been identified as the most important risk factor for AIDS in this population. The Westchester County Medical Center (WCMC) serves as a referral center for approximately 10,000 New York State prisoners or one-third of the entire New York State prison population. Since November 1981, 36 prisoners have been diagnosed to have AIDS at this hospital. Although Kaposi's sarcoma is widely regarded as the most common malignancy associated with AIDS, this tumor was seen in only 2 (5%) of the 36 patients. Since patients who are immunosuppressed are known to be at increased risk for lymphomas, we retrospectively reviewed the pathology records of prisoners seen at WCMC over the same period of time. During the study interval, 6 prisoners were diagnosed to have diffuse non-Hodgkin's lymphoma (NHL), 1 had Hodgkin's disease and 1 had malignant histiocytosis. No patient with nodular lymphoma was seen. All patients with NHL met the criteria of the "Working Formulation" for high grade lymphomas. Among the 6 patients with NHL, only 1 was considered to have AIDS; this patient had a primary brain lymphoma. Our findings suggest that the incidence of NHL among prisoners is 30/100,000 per year, a 15-fold increase compared to the general population where the incidence has remained relatively constant at 2.2/100,000 per year. In addition, at least two other I.V. drug users who were not prisoners were diagnosed to have NHL over the same period. We conclude that diffuse lymphomas may represent yet another facet in the spectrum of the syndrome of acquired immune deficiency and may well be a more common expression of this syndrome among I.V. drug users/prisoners than Kaposi's sarcoma.

66 NON-HODGKIN'S LYMPHOMAS IN HOMOSEXUAL MALES. S. Riggs, S. Kalter, F. Cabanillas, F. Hagemeister, W. Velasquez, B. Barlogie, P. Salvador, P. Mansell, A. Rios, E. Hersh, J. Butler, M.D. Anderson Hospital & Tumor Institute, Houston, Tx. 77030.

Over the last two years, an increased incidence of lymphomas in homosexual males has been noted in several cities in the United States. During the period 1981-1983 we have evaluated & treated 14 homosexual males with advanced stage lymphomas. Ages ranged from 20 to 45 yrs. Five pts had diffuse large cell (DLCL), 5 had diffuse undifferentiated (DUL) of either Burkitt's (3) or non-Burkitt's (2) type, 2 had nodular poorly differentiated lymphocytic (NPDL), 1 had well differentiated lymphocytic (WDLL), & 1 had unclassifiable lymphoma. All were morphologically consistent with B cell neoplasms. All 5 pts with DLCL had focal brain lesions, with 2 of these presenting as primary CNS lymphoma. In contrast, only 1 of the DUL pts had CNS involvement, which was meningeal. Three of the DLCL pts had concomitant pulmonary lymphoma & extensive Kaposi's sarcoma. Pts with DUL tended to have the common abdominal & marrow involvement, but 1 also had bilateral tonsillar lesions. Only 1 of the DUL pts had Kaposi's sarcoma which was minimal. Three of the DUL pts had a history of fluctuating histologically proven reactive lymphadenopathy prior to the clinical onset of the lymphomas. B cell markers on the DUL tumor cells confirmed IgGK (3), IgGλ (1), & IgMK (1). All 3 DUL pts tested had the 8 to 14 chromosomal translocation in lymphoma tissue, & 2 of the 3 also had an XO abnormality in the malignant cells. A bizarre finding in the WDLL pt was extensive bilateral lymphoma of the earlobes. All pts tested had T lymphocyte helper/suppressor ratios less than 1 & decreased skin test delayed hypersensitivity, with the most marked abnormalities occurring in the DLCL pts. Antibody titers for cytomegalovirus & Epstein-Barr virus were positive in 10/11 & 11/11 pts tested, respectively. Antibodies to the human T leukemia-lymphoma virus were present in the sera of 2 DLCL & 1 DUL pt. Four of the 5 DLCL pts had severe prechemotherapy opportunistic infections, including Pneumocystis, Candida, & Toxoplasma. No pts had autoimmune hemolytic anemia or thrombocytopenia. Responses to treatment & survivals have been poor in all 5 DLCL pts, with 4 deaths & median survival of 3 mos. Four of the 5 DUL pts achieved a complete remission (CR), & 3 of these remain in CR at 7, 7, & 23 mos; none have died. The NPDL & WDLL pts all responded to treatment & are alive at >18 mos. In contrast to some earlier reports that immunosuppressed homosexual males cannot tolerate intensive chemotherapy, it continues to be our experience that the subsets of undifferentiated & indolent lymphoma pts may respond well to various adriamycin-containing regimens with minimal or no secondary infections. Increased awareness of the potential for development of CNS large cell lymphomas in homosexual males will hopefully lead to earlier diagnostic evaluations to distinguish these brain lesions from those caused by Toxoplasmosis & other opportunistic infections, & thus increased potential for successful treatment.

67 OVERVIEW ON CURRENT STRATEGY OF THE TREATMENT OF NON HODGKIN'S LYMPHOMAS. J.E. Ultmann, E.R. Gaynor, University of Chicago Cancer Research Center, 5841 S. Maryland Avenue, Chicago, IL 60637

Research of the past decade has provided substantial insight into the pathogenesis and treatment of the malignant lymphomas.

Using hybridoma technology, monoclonal antibodies have enabled us to probe the cell surface of both benign and malignant lymphocytes. What were previously known to be a group of diverse diseases from a clinical standpoint are now known to be diverse in their cellular origin and in their stage of differentiation. Probing into the nucleus of the cell, we now know that certain lymphomas are characterized by specific chromosomal abnormalities. Perhaps as in the case of chronic myelogenous leukemia and the acute leukemias, these chromosomal abnormalities will be found to correlate with and predict clinical characteristics including presentation, pathophysiology, and response to therapy. Further probing on a molecular level has begun to unravel abnormalities of the genetic code itself and has revealed the presence of oncogenes associated with specific chromosomal abnormalities suggesting a possible role for these DNA sequences in the neoplastic process. What the presence of the oncogene means and whether its presence is causal to the malignant process are questions of intense interest at the present time.

While we have made great strides in our understanding of the malignant lymphomas on a cellular and molecular basis, we continue to pursue effective therapy for these diseases. New drugs, new analogs of already available drugs, new combinations of drugs and new immunoregulatory approaches must be developed to improve on what has already been accomplished.

What then is the challenge which is before us? The challenge is threefold: to continue to expand our knowledge of the cellular and molecular nature of the malignant lymphomas, to synthesize these newly acquired insights into a meaningful model which will have prognostic and therapeutic significance, and to continue our search for ever more effective and ever less toxic treatment approaches to these malignant diseases.

68 UPDATE OF FAVORABLE (LOW GRADE) NON-HODGKIN'S LYMPHOMA.

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The favorable or low grade non-Hodgkin's lymphomas (NHL) include three major subtypes, small lymphocytic (SL), follicular, small cleaved cell type (FSC), and follicular, mixed small cleaved and large cell type (FM). The follicular subtypes are the most common type of NHL in major U.S. centers but is apparently less common in Europe and Japan. These lymphomas usually affect older indivi - duals (average age 55-60 yrs) and are usually widespread (stages III & IV) at the time of diagnosis.

Randomized trials of various treatment programs including combination chemotherapy, irradiation, combined modality therapy and single agent chemotherapy have revealed high response rates (65-80 % CR's), but also continuous high relapse rates without evident cure. Overall survival, however, is good with median of 6-10 years. A selected group of 83 asymptomatic patients with advanced low grade NHL have been followed without initial therapy (NIT) at Stanford. Median survival is 11 years. Median time to requiring therapy was 36 months, longer for FSC (48 months) than FM (16.5 months). Spontaneous regression occurred in 20 % of all patients, including 30 % of FSC group.

Histologic transformation tho higher grade NHL is a problem and occurs in treated and NIT groups equally, reaching 40-50 % at 10 years after diagnosis. These studies and interesting biologic observations will be reviewed.

69 WATCH AND WAIT VERSUS AGGRESSIVE COMBINED MODALITY THERAPY FOR ADVANCED FAVORABLE PROGNOSIS NON-HODGKIN'S LYMPHOMAS.

Dan L. Longo, Vincent T. DeVita, Jr., Eli Glatstein, Louis A. Matis, Richard I. Fisher, Robert C. Young. National Cancer Institute, Bethesda, MD 20205.

The management of advanced stage favorable prognosis non-Hodgkin's lymphomas, which generally include nodular poorly-differentiated lymphocytic (NPDL), nodular mixed (NML), diffuse well-differentiated lymphocytic (DWDL), diffuse intermediately differentiated lymphocytic (DIDL), and diffuse small cleaved cell lymphoma (DPDL-SC), is controversial. Until now the outcomes of the various treatment approaches have been roughly comparable. Randomized prospective clinical trials of single-agent chemotherapy, combination chemotherapy, systemic radiotherapy, and combined modality treatments have shown no significant differences in overall survival. In addition, with the possible exception of NML, the survival of favorable prognosis lymphoma patients treated to obtain complete response is not very different from the survival of a selected group of patients seen at Stanford who received no initial therapy. Therefore, it is not clear whether it is better to treat aggressively or conservatively. Another feature of the favorable lymphomas is their propensity to evolve into aggressive histologic subtypes, a conversion that may occur in 40% or more of patients. Treatment of the aggressive lymphomas has advanced to the point that a majority of such patients appear to be curable with combination chemotherapy. Thus, patients with favorable lymphomas may do best when they convert to aggressive lymphomas that may be cured with available therapies. To determine the best treatment approach to favorable lymphomas, we are randomizing patients with stages III and IV disease to receive no initial therapy or an aggressive attempt at remission induction with ProMACE-MOPP flexitherapy followed by low dose total lymphoid radiation. Patients randomized to no initial therapy may receive low dose palliative radiation to symptomatic masses, however, if they develop widespread symptomatic disease or disease in a site not adequately treatable with 2500 R, or if they undergo histologic conversion to an aggressive lymphoma subtype, they cross over to aggressive therapy. This study design allows us to address some of the unanswered questions in the treatment of favorable lymphomas. Are conservative and aggressive treatment approaches comparable in terms of survival? How frequent is histologic conversion in minimally treated patients? Are patients who convert to aggressive histology as responsive to therapy as patients with de novo aggressive lymphoma? Can an improvement in combination chemotherapy and the addition of total lymphoid radiation result in prolonged disease-free survival in favorable lymphoma patients? The answers to these questions are needed through the study of patients with favorable lymphoma. The consignment of such patients to palliative therapy outside a clinical trial setting delays the development of better treatment approaches.

70 TREATMENT OF DIFFUSE LARGE CELL NON-HODGKIN"S LYMPHOMAS.

Richard I. Fisher, Vincent T. DeVita, Dan L. Longo, Daniel C. Ihde, and Robert C. Young, National Cancer Institute, Bethesda, MD 20205.

Until the mid-1960's the advanced stage, high grade non-Hodgkin's lymphomas were rapidly progressive, fatal diseases with few patients remaining alive at 5 years. Studies conducted at the NCI then demonstrated that 47% of all patients with advanced stages of diffuse mixed, large cell, and undifferentiated non-Burkitt's lymphoma could achieve a complete remission documented by re-evaluation of all initially involved sites following treatment with either the C-MOPP or BACOP combination chemotherapy regimens. Furthermore, 70-80% of these complete responders had long-term disease-free survival tantamount to cure. Although histologic diagnosis did not determine the prognosis of these patients, clinical factors such as male sex, B symptoms, advanced stage, bone marrow disease, huge gastrointestinal masses, hepatic disease, low hemoglobin, and high LDH were all associated with a poor prognosis. By the mid-1970's, studies conducted at several institutions had also demonstrated that 30-40% of all these patients could be cured by combination chemotherapy. The third generation of NCI studies, termed the ProMACE-MOPP flexible induction program, significantly improved these results and has been recently published (Ann. Int. Med., 3/83). The ProMACE regimen includes cytoxan, adriamycin, VP-16, prednisone, and high dose methotrexate at 1.5 gm/m^2 followed by leucovorin rescue. This dose of methotrexate requires hospitalization for intravenous hydration, alkalinization, and monitoring of serum methotrexate levels. Patients received induction therapy with ProMACE, consolidation with MOPP, and late intensification with ProMACE. The duration of each phase of therapy was determined by the patient's rate of tumor response. Complete remissions were achieved in 74% of all patients and 73% of these complete remittors remain disease-free in excess of 3 years. Myelosuppression was dose limiting with a 10% septic death rate. Improved results were seen in all patient groups. The fourth generation of NCI studies randomizes patients to receive either the day 1 ProMACE drugs with the day 8 MOPP drugs and a lower methotrexate dose on day 15 vs. ProMACE on day 1 and CytaBOM on day 8 (cytarabine, bleomycin, oncovin, and methotrexate) (ASCO, 1984). Both of these regimens are given entirely in the outpatient clinic. Preliminary analysis suggests complete remission rates comparable to the original ProMACE-MOPP study although follow-up is still too short to know the durability of these complete remissions. There were no septic deaths. However, diffuse interstitial pneumonitis has been the major toxicity with an increased incidence of pneumocystis carinii pneumonia in the ProMACE-CytaBOM arm. All ProMACE-CytaBOM patients now receive prophylactic trimethoprim sulfamethoxazole. Further follow-up is required to determine whether these new regimens can provide durable complete remissions with less cost and toxicity.

71 THE USE OF CHEMOTHERAPY FOR LOCALIZED LARGE CELL LYMPHOMA; UPDATED RESULTS FROM THE UNIVERSITY OF ARIZONA.

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Historically, radiotherapy alone has been used to treat lymphoma of unfavorable histology with limited spread (stages I, IE, II, IIE) but this has proven curative in only carefully selected patients with the most limited disease (stages I or IE). The majority of patients with stage II or IIE disease recur after radiotherapy and many succumb to their disease. Because current multi-drug chemotherapy programs, particularly those containing doxorubicin, are curative for patients with large cell ("histiocytic") lymphoma of more advanced stage (III or IV) we have been evaluating the use of initial chemotherapy alone (CT) or with adjuvant involved field radiotherapy (CT + RT) after achievement of complete response (CR). Early results have been published (Lancet 1:358, 1979; Blood 62:413, 1983). In this presentation we will update our experience. Forty-nine patients have received CT alone (30 patients) or CT + RT (19 patients). Histologic subtypes include diffuse large cell (47 patients) and follicular large cell (2 patients). Chemotherapy consisted of the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in 48 patients and C-MOPP in another patient with heart disease. Potentially adverse patient characteristics included stage II or IIE disease in 63%, age > 65 years in 33%, gastrointestinal tract involvement in 14%, and bulky disease in 35% of patients. The CR rate is 98% (48 of 49). At a median follow-up time of 41 months, 84% of all patients remain continuously free of disease. Eight relapses have occurred: 6 of 30 receiving CT and 2 of 19 receiving CT + RT. Five of 8 patients with recurrence have achieved a second CR. Forty-five patients (92%) remain alive. None of the potential adverse prognostic factors listed above affected outcome of therapy including age > 65 (2 relapses in 14 patients). Our experience with rapid clinical staging and immediate combination chemotherapy for apparently localized lymphomas of unfavorable histology appears to be a valid strategy. The optimal amount of chemotherapy and the role for involved field radiotherapy remain to be defined.

72 CELL OF ORIGIN OF HODGKIN'S DISEASE.
C.W. Berard, Div. of Pathology, St. Jude Children's Hospital, Memphis, USA

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

73 **Reactive Lymphadenopathy Simulating Malignant Lymphoma**
R.F. Dorfman, Stanford University, Stanford, California

This presentation will comprise a discussion of certain lesions/disorders frequently referred to me in consultation, in addition to others recently described. Reference will be made to the importance of avoiding technical errors in the preparation of lymph node biopsies which unquestionably lead to many of the problems encountered in their evaluation. The method of evaluation is based on an assessment of both architectural and cytologic features. The discussion on follicular lesions will include distinction between follicular hyperplasia and follicular lymphoma; Castleman's disease with emphasis on the recently described multicentric form and its association with lymphomas and Kaposi's sarcoma; progressive transformation of germinal centers and the provocative proposal that this phenomenon is histogenetically related to the nodular form of Hodgkin's disease; and persistent lymphadenopathy in homosexual males characterized mainly by florid follicular hyperplasia with "folliculysis".

Histiocytic lesions/disorders include histiocytosis X (Langerhans cell granulomatosis) and its distinction from sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Criteria for the distinction of these disorders from malignant histiocytosis and from sinusoidal large cell lymphoma will be presented. Immunoblastic proliferations and disorders include consideration of angioimmunoblastic lymphadenopathy and its distinction from "abnormal immune reactions" and from peripheral T cell lymphomas. Finally mention will be made of the newly described disorder, "Kikuchi's necrotizing lymphadenitis" and its distinction from other necrotizing lesions of lymph nodes.

The presentation will conclude with a discussion of the place of frozen sectioning in the evaluation of lymph node biopsies.

74 LYMPHOCYTE DEPLETED HODGKIN'S DISEASE - DOES IT EXIST?

Elaine S. Jaffe, M.D., Jeffrey A. Kant, M.D., Ph.D., Susan M. Hubbard, B.S., Dan L. Longo, M.D., Richard M. Simon, Ph.D., and Vincent T. DeVita Jr., M.D. National Cancer Institute, Bethesda, Md., USA.

Lymphocyte depleted Hodgkin's disease (LDHD) has been regarded by many as the poorest prognostic group of patients with Hodgkin's disease. Others have suggested that LDHD may be a distinct clinicopathologic entity and have questioned its relationship to Hodgkin's disease. Of 198 patients who received MOPP treatment at the NCI for Hodgkin's disease between 1964 and 1976, 43 (22%) were originally classified as LDHD. The initial diagnostic biopsies from 39 of these patients were rereviewed and revealed 10 with non-Hodgkin's lymphomas, 9 with LDHD, 13 with nodular sclerosing Hodgkin's disease, lymphocyte depleted subtype (NSLD), and 7 with Hodgkin's disease lacking a lymphocyte depleted component. The non-Hodgkin's lymphoma patients were further subclassified as diffuse, large cell (2 cases) and large cell, immunoblastic (8 cases). In many cases the pleomorphic character of the neoplastic infiltrate and/or inflammatory background was suggestive of peripheral T-cell lymphoma, but due to the retrospective nature of the study, no immunologic phenotyping could be performed. The pathologic review was done without knowledge of clinical features which were examined after review in the three major subgroups. Of 10 patients with non-Hodgkin's lymphoma only 3 had a complete remission (30%), and median survival was 7 months. A number of these patients presented with clinical features unusual in Hodgkin's disease such as bulky abdominal disease, epitrochlear lymphadenopathy and hypercalcemia. In contrast to the non-Hodgkin's lymphomas, complete remissions were attained by 67% and 85% of patients in the LDHD and NSLD groups, respectively; median survival had not been reached in either group with a minimum of 81 months followup. Mediastinal masses greater than one-third of the chest diameter were seen in three of these patients; none were observed in the non-Hodgkin's lymphoma group. The median age of patients was 46.5 years in the non-Hodgkin's lymphoma group compared with 23 and 29 years in the LDHD and NSLD groups. Lymphocyte depleted Hodgkin's disease, adequately treated, is in our experience no worse than other histopathologic subtypes of Hodgkin's disease. The erroneous inclusion of patients with high grade non-Hodgkin's lymphomas into this subtype of Hodgkin's disease may be one reason for literature reports of its more aggressive nature. The diagnosis of LDHD should be made cautiously, particularly in patients with clinical features unusual for Hodgkin's disease at presentation.

75 IMMUNO-ELECTRON MICROSCOPIC STUDY OF IMMUNOGLOBULIN PRODUCTION BY NON-HODGKIN'S MALIGNANT LYMPHOMAS.

L. Lombardi, G. Della Torre, R. Giardini, F. Rilke, Istituto Nazionale Tumori, 20133 Milan, Italy.

Sixteen selected cases of non-Hodgkin's lymphomas (NHL), representing different steps of B-cell morphofunctional modulation, were studied by an avidin-biotin complex technique modified for electron microscopy. Mechanically isolated tumor cells were fixed with 0.4% glutaraldehyde in 0.01 M hypotonic buffer, incubated with biotinyl goat anti-human IgG heavy and light chains and with avidin-peroxidase conjugates in saponin-containing solutions, fixed again with 2.5% glutaraldehyde, treated with diaminobenzidine and H_2O_2, and processed for electron microscopy. Control cells were incubated with biotinyl goat anti-mouse IgG. Unstained ultrathin sections were observed. A large number of cells of those lymphomas which reflect the early stages of modulation toward plasma cells, namely chronic lymphocytic leukemia (2 cases) and centrocytic (2 cases) and centroblastic (1 case) NHL, showed labelling of immunoglobulins on the membranes of the perinuclear and rough endoplasmic reticulum cisternae with scarce immunoglobulin accumulation within the cisternae. Only a few centrocytes of centroblastic-centrocytic NHL (3 cases) showed a weak labelling of intracytoplasmic membranes. The cells with an evident plasmablastic differentiation of lymphoplasmacytoid NHL (3 cases) and of 2 cases of immunoblastic NHL showed immunoglobulins on the membranes and within the cisternae of the rough endoplasmic reticulum. However, the centrocytes of one of the cases of lymphoplasmacytoid NHL, which revealed features of a follicular center cell lymphoma with plasmacytic differentiation, showed immunostaining of intracytoplasmic membranes without immunoglobulin accumulation. The third case of immunoblastic NHL showed labelling of the intracytoplasmic membranes and of the periphery of Russell bodies, whereas diffuse intracisternal immunoglobulin accumulation was not observed. As regards Burkitt's lymphoma (2 cases), most cells of one case showed labelling of intracytoplasmic membranes, whereas a few cells with a large central nucleolus accumulated immunoglobulins in the rough endoplasmic reticulum cisternae. Numerous cells of the second case showed immunoglobulins within vesicles of a large Golgi complex.

76 FLOW-CYTOFLUOROMETRIC DNA ANALYSIS IN NON-HODGKIN'S LYMPHOMAS.

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209 lymphomas were analyzed with respect to proliferative activity (S-phase frequency) and ploidy (DNA content) in relation to histopathological classification according to the Kiel and Rappaport classifications. Low grade malignant lymphomas according to the Kiel as well as the Rappaport classifications had significantly lower proliferative activity than the high grade malignant lymphomas. However, there was a marked variation in the proliferative activity between individual cases, especially among follicle centre cell derived and high grade malignant lymphomas. Approximately 30 per cent of the lymphomas were considered aneuploid (according to DNA content). Aneuploid lymphomas were most frequent among CB/CC and lB lymphomas. Interestingly, a considerable proportion of the aneuploid CB/CC lymphomas had a DNA content in the near tetraploid range, while most of the other aneuploid lymphoma types had relatively small variations in the DNA content. There was no significant difference in the proliferative activity between aneuploid and "diploid" non-Hodgkin's lymphomas (NHL) with the same diagnosis. By stepwise discriminant analysis, S-phase frequency, not DNA content, was found to significantly discriminate between low and high grade malignant lymphomas, both according to the Kiel and the Rappaport classifications. Discriminant analysis showed that 94 per cent of the low grade malignant lymphomas could be identified as such on the basis of their proliferative activity, whereas only 63 per cent of the high grade malignant lymphomas could be identified as malignant according to the proliferative activity. Very similar results were obtained with respect to proliferative activity using the Kiel and the Rappaport classifications as the basis for the division of lymphomas into high and low grade malignancy groups. These results indicate that the Kiel and Rappaport classifications equally well identify highly proliferative lymphomas and that proliferative activity analyzed by flow-cytofluorometry seems to be a marker of malignancy partly independet of the histopathological classification.

77 THE PROGNOSTIC SIGNIFICANCE OF CYTOLOGICAL SUBDIVISION OF NODULAR SCLEROSING HODGKIN'S DISEASE: ANALYSIS OF 1156 PATIENTS.

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We have histologically reviewed 1156 cases of nodular sclerosing Hodgkin's disease which were entered into the clinical trials of the British National Lymphoma Investigation during the period between 1970 and 1980. Cases have been categorised according to the cytological appearances of the cellular nodules into the low and high grade malignancy groups which have been termed Grade 1 and 2 respectively. 71.6% were histologically classified as Grade 1 and 28.4% as Grade 2. When patients presenting at all stages are analysed together, there is a large difference between the survivals of the Grade 1 (84.3% five year survival) and Grade 2 (59.9% five year survival) types of nodular sclerosing Hodgkin's disease. This difference is statistically highly significant ($X^2 = 73.79; p<0.001$). 884 patients either underwent a staging laparotomy or had evidence of stage IV disease. Within this group, large differences in survival are present between the two grades when patients with stage I and II disease are examined ($X^2 = 44.41; p<0.001$) and when patients with stage III and IV disease are studied ($X^2 = 39.82; p<0.001$). Stage is an important prognostic factor in the Grade 1 histological group, patients presenting at stages I and II having a superior survival (93.5% five year survival) to those presenting at a more advanced stage (79.6% five year survival) and this difference is statistically highly significant ($X^2 = 26.0; p<0.001$). The prognostic significance of stage is less marked in the Grade 2 histological group ($X^2 = 5.55; p<0.025$). It therefore appears that cytological subdivision is of great value in predicting prognosis.

78 BURKITT'S LYMPHOMAS: MORPHOMETRIC ANALYSIS OF 55 CELL LINES WITH GEOGRAPHICAL, VIRAL, IMMUNOLOGIC, AND CYTOGENETIC CORRELATIONS.

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Fifty five cell lines derived from endemic and non-endemic Burkitt's tumors (established by G. LENOIR, IRCC, LYON) were characterized by morphometric means using a Leitz ASM semi-automatic quantitative analysis system on plastic embedded cell suspension pellets. Nuclear parametric discriminators computed on line were: size (with 13 Log nuclear area classes previously defined), shape, area dispersion. General characteristics including geographical origin, EBNA status and caryotype were available for the great majority of the cell lines.

The Burkitt's lymphomas are usually mapped in a discrimination zone defined by classes 3 and 4, with a low value for shape & area dispersion discriminator. The histomorphometrical classification emphasizes the cytological polymorphism of Burkitt's cell lines, in the size, shape, and shape & area dispersion of the nuclei. 24 cell lines are mapped in the zone of large cell lymphomas (size class $\geq$ 5). Nuclear shapes differed from case to case, with frequently irregular nuclei. Finally, a morphological continuum seems to extend from typical small noncleaved cell lines to polymorphous large cell lines.

Simultaneously, a cytological and cytomorphometric study was done on cytospin preps with analysis of the following parameters: (1) cytology : chromatin pattern, size and number of nucleoli, mitosis number, plasmacytic transformation, (2) cytomorphometry : nuclear area, whole cell area, cytoplasm to nucleus ratio, shape. A linear relationship exists between histomorphometrical and cytomorphometrical results, especially for nuclear areas.

The comparison of the morphometric data with immunological, viral, geographical data shows some interesting points: EBV + cell lines are significantly larger than EBV - ones, a pre-B phenotype ($c\mu$ +) and an East African origin are significantly associated with largest cells; there is a strong relationship between African origin, pre-B phenotype, EBV + character, and large cells. Moreover, we were able to compare in some cases the cytologic and morphometric findings in the cell lines with morphology and morphometry of the original tumors.

Finally, this study points out (1) the transforming role of EBV, especially in the cases of massive contamination, (2) the possibly different target cell in Burkitt's lymphomas, (3) the large spectrum of morphological pictures from small noncleaved to large cleaved, noncleaved and immunoblastic types.

79 NON-HODGKIN LYMPHOMA WITH MULTILOBATED NUCLEI; A DISTINCT PATHOLOGIC ENTITY?

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We previously documented cutaneous T-cell lymphoma, multilobated type, and subsequently found lymphoid cells with multilobated nuclei (MC) in Non-Hodgkin Lymphoma (NHL) of lymph node. This prompted us to evaluate whether NHL with MC is a specific morphologic and immunologic entity, or is part of a spectrum of various subtypes of NHL. NHL with a conspicuous component of MC and in which a full-scheme immunological, enzymehistochemical and electronmicroscopical analysis was possible were investigated. Apart from two cases of cutaneous T-cell lymphoma, one case of atypical Sezary's Syndrome with early immunoblastic transformation with large and small MC was found. A wide spectrum of B-NHL contained MC. It included one case of B-CLL with small MC, and four cases of ML Centroblastic Centrocytic (ML CbCc). Much more (21/48) cases of ML Polymorphic Immunocytoma (ML Pl) and ML CbCc contained low numbers of MC. Even more, we observed MC in follicle centres of several benign reactive lymph nodes. Five extranodal B-NHL (maxilla, mandible, elbow, retroperitoneum) contained MC and were classified as ML CbCc or ML Cb. One mediastinal NHL, diffuse undifferentiated large cell (DUL), which lacked immunological markers for B or T lymphocytes contained numerous very large MC. However, MC are not specific for NHL as we encountered one case of undifferentiated carcinoma and of myelomonocytic leukemia, both disseminated into lymph nodes, with this nuclear feature. We concluded that the occurrence of MC does not warrant a T lymphocytic origin or even a lymphoid origin of tumour cells.

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80 TREATMENT OF AGGRESSIVE LYMPHOMA IN JAPAN

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A total of 100 patients with advanced non-Hodgkin's lymphoma (NHL) were treated with a combination chemotherapy consisting of vincristine, cyclophosphamide, prednisolone and adriamycin (VEPA) in a cooperative study group involving 5 major institutions. Of 41 patients with T-cell lymphoma, there were 15 complete remissions (36.6%); however, only 3 (16.7%) of 18 patients either with adult-T-cell leukemia or with pleomorphic T-cell lymphoma obtained complete remission.

On the other hand, VEPA produced complete remission rates of 58.5% and 72.2% in 41 patients with B-cell lymphoma and in 18 patients with surface markers undetermined but defined to be B-cell lymphoma by morphology, respectively.

Median durations of complete remissions were 4 months for T-cell and 16 months for B-cell type, while 10 of 13 patients with cell lineage-undetermined are still in remission of more than 2 years.

Thus, the result has indicated that cell-lineage is an important prognostic factor for HNL and T-cell lymphoma; especialy, ATL and pleomorphic type are the worst histology, because none of conventional drugs used in the treatment of NHL appears to be sufficiently active for these two tumors.

In several new drugs tested recently, Human Lymphoblastoid Interferon and VP-16 seem to have some activity against T-cell lymphoma.

81 MODERATE DOSE METHOTREXATE (m) COMBINED WITH BLEOMYCIN (B), ADRIAMYCIN (A), CYCLOPHOSPHAMIDE (C), ONCOVIN (O) AND DEXAMETHASONE (D), m-BACOD, IN ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA (DHL). A.T. Skarin, G.P. Canellos, D.S. Rosenthal, D.C. Case and J.M. MacIntyre. Dana-Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, MA. 02115. The use of high dose methotrexate (M=3g/m^2) requires critically important urinary alkalinization and hydration to avoid serious renal and other complications. In addition, assay of blood MTX levels must be measured and the drug expense can be prohibitive. The M-BACOD program (Skarin et al, J. Clin. Oncol. 1:91-98, 1983) was therefore modified by employing moderate dose MTX (m) at 200mg/m^2 IV on days 8 and 15 of each 3-week cycle. Leucovorin factor rescue, 10mg/m^2 was given at 24 hrs q 6h x 6 to prevent toxicity; B (4mg/m^2 IV), A (45mg /m^2 IV), C (600mg/m^2 IV) and O (1.0mg/m^2 IV) were given on day 1 along with D (6mg/m^2 qd x 5) for a total of 10 cycles. The m-BACOD program has been completed in 53 evaluable patients (median age 43, range 17-73 yrs), with Stage I, II, II_E (10 pts), III (9 pts) or IV (34 pts) DHL. Only 4 patients had prior therapy, while 29 patients (55%) had B-symptoms. Sites of extranodal disease included marrow - 7 patients (13%); effusion - 7 patients; bone, GI - 6 patients each; lung, liver - 6 patients each; soft tissue - 3 patients; skin - 2 patients; other - 10 patients. A CR was achieved in 40 patients (75%): Stage I, II, II_E 7/10 (70%), Stage III 7/9 (78%), and Stage IV 26/34 (76%); a PR in 8 patients (15%), while 5 patients (10%) had NR. The median follow-up time in CR patients is 13 mo. (range 5-27 mo.) from time of CR. 9 patients (23%) have relapsed (8/26 Stage IV) all within 1 year except for 2 (15 and 16 mo.). All PR patients relapsed within 3-9 mo. While m-BACOD was not designed for CNS prophylaxis, CNS relapse occurred in 1 CR and 1 PR patient. All 5 NR patients and 5/8 PR patients died from progressive disease, compared to only 3 CR patients (7.5%). The median follow-up of the remaining CR patients is 17^+ mo. after start of therapy (range 7^+ - 28^+ mo.). Of the entire study group, 40 patients (75%) are alive with 31 (58%) are relapse-free. Toxicity included mucositis mainly after day 8 MTX in 21 patients, representing 6% of courses, but no significant renal complications occurred. Leucopenia with fever occurred in 13 patients (24%) but was fatal in only 1 patient (2%). Bleomycin was discontinued due to fever/chills in 3 patients and reversible pulmonary infiltrates in 6 patients (11%). Moderate dose MTX in the m-BACOD program results in a CR rate and durability comparable to high dose MTX (M-BACOD) but use of m on day 8 and 15 results in increased mucositis. The latter may be improved by increased hydration. Before recommending m-BACOD for general use, further patient accrual and longer follow-up are required, to determine whether a relapse-free survival comparable to M-BACOD ($\sim$ 65%) can be achieved.

82 A RANDOMISED COMPARISON OF ADJUVANT VAP + M vs CMOPP IN RADIOTHERAPY TREATED CLINICAL STAGES I & II HIGH GRADE LYMPHOMA (NHL).

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Sixty patients with histologically confirmed (centrally reviewed) clinically staged (including bone marrow aspirate and trephine; CAT scanning of the abdomen and pelvis) high grade NHL (DPDL, DH, DM, DU) were treated with involved field radiotherapy (XRT). Post-XRT randomisation was to either six weeks VAP (Vincristine, 2 mgs.i.v. wkly x 6; Adriamycin, 50mgs/m² i.v. every 2 wks x 3; Prednisolone, 40mgs p.o. daily for 6 wks) followed by two years oral maintenance(M) (6MP, 50mgs/m² p.o. daily; Methotrexate, 10mgs/m² p.o.wkly and Cyclophosphamide, 200mgs/m² p.o.wkly: all for 2 years) or six cycles of CMOPP (Cyclophosphamide, 650mgs/m² i.v. days 1 & 8; Vincristine, 2 mgs i.v. days 1 & 8; Procarbazine, 100mgs/m² p.o. days 1-14; Prednisolone, 40mgs p.o. days 1-14) at three weekly intervals.

Two patients failed to achieve CR (3%). Both developed disease outside the irradiated field, either before or shortly after starting adjuvant chemotherapy. The overall CR rate was 97% (VAP = 96%; CMOPP = 97%). The six week VAP programme was much better tolerated than CMOPP.

	RFS%		Survival %	
	2yrs	5yrs	2yrs	5 yrs
XRT + VAP + M	83	74	80	68
	No signif.diff.		No signif.diff.	
XRT + CMOPP	90	82	89	89

Ten deaths have occurred (VAP = 7, CMOPP = 3), five of these from intercurrent causes (Ca.ovary (VAP), melanoma (CMOPP), astrocytoma (VAP), coronary artery disease (VAP) and pneumocystis carinii (VAP)). A further patient died from respiratory failure with pulmonary shadowing (CMOPP) but no postmortem was performed (?lymphoma/infection). Two patients died with CNS lymphoma and two with generalised disease. One patient relapsed in an XRT field and achieved a CR with further XRT and remains disease-free at six years.

Histology and age did not affect RFS or overall survival.

Seven patients with bulky disease (>5cm) have died versus three without it, but the RFS is the same for both groups.

We conclude that six weeks of VAP + M is well tolerated and produces as good results as the more intensive CMOPP, but that chemotherapy might be more appropriate alone or prior to XRT.

83 A RANDOMIZED TRIAL OF C-MOPP vs BACOP FOR THE TREATMENT OF DIFFUSE MIXED AND HISTIOCYTIC (DHL) LYMPHOMAS.

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There is enough evidence that combination of cyclophosphamide, vincristine, procarbazine and prednisone (C-MOPP) and bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) can each produce long-term complete remission (CR) in patients with DHL. We have assessed the relative efficacy of these regimens in a randomized trial. As of November 1983, 102 patients have been entered and 88 are evaluable (BACOP 48, C-MOPP 40). Both groups are comparable in age, stage and distribution of histology. Seventy six percent were stages III and IV. There were 25/48 (52%) with BACOP and 19/40 (48%) in C-MOPP that achieved CR (P=N.S.). At 48 months, 60% of BACOP patients and 35% of C-MOPP patients who achieved CR are expected to continue in first CR ($P < 0.05$). No relapse has been observed after 18 months. The percent remaining in CR at 48 months of patients treated with BACOP and C-MOPP according to stages are: I-II: 71% and 66% (P:N.S.), III-IV: 58% and 24% ($P < 0.05$). There have been 25 deaths in each group, with 32% in BACOP and 25% in C-MOPP alive at 48 months. Complete responders have 53% of possibility of continuining alive at 48 months, compared to 12 and 6 months of median survival of partial and null responders ($P < 0.005$). Pattern of relapse was the original site of disease in 72% of patients; 19% of relapses were in CNS but only 7% were isolated CNS first relapses. Toxicity of BACOP has not been markedly greater in terms of myelosupression or clinically evident cardiac or lung toxicity. BACOP showed a higher duration of CR than C-MOPP only in stages III-IV, although this difference does not have a significant impact in overall survival. More intensive combinations and schedules are needed for the treatment of this aggressive disease. (Supported by the Collaborative Cancer Treatment Research Program, a project of the Pan American Health Organization and US National Cancer Institute, Contract NO1-CM-27391).

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84 LYMPHOBLASTIC LYMPHOMA IN ADULTS: A STUDY ON 30 PATIENTS TREATED WITH TWO DIFFERENT PROGRAMS ACCORDING TO BONE MARROW FINDINGS. C. Bernasconi, E. Brusamolino, M. Lazzarino, L. Salvaneschi, P. Isernia. Divisione di Ematologia, Ospedale Policlinico San Matteo, Istituto di Ricovero e Cura a Carattere Scientifico, 27100 Pavia, Italy.

A study was done on thirty previously untreated adult patients affected with lymphoblastic lymphoma with two different therapy programs according to bone marrow findings. The pathologic diagnosis was done on lymph node biopsies (24 cases), on bone marrow biopsies (3 cases), on tonsil, skin and testis in one case, respectively. The classification criteria were according to the Working Formulation for clinical usage (NCI, 1982). The median time of follow-up was of 18 months (range 6-65+ mos). Patients with bone marrow involvement were given an ALL-like program, consisting of vincristine 1.4 mg/m^2, daunorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, i.v., once a week for 6 weeks, and prednisone 40 mg/m^2 per os, a day, during all the induction time. Patients in complete remission after 6 cycles had CNS prophylaxis, with cranial irradiation with ^{60}Co (24 Gy) and five doses of intrathecal methotrexate (12 mg/m^2). Maintenance therapy consisted of 6-mercaptopurine 50 mg/m^2 per os, daily and of methotrexate 15 mg/m^2, i.v. once a week for three weeks a month. The fourth week was covered by a reinduction course with vincristine 1.4 mg/m^2 and prednisone 40 mg/m^2. Every three courses, daunorubicin was added, up to the total dose of 450 mg/m^2. Chemotherapy was withheld after 3 years of continuous disease-free survival. Bone marrow negative patients were given a program consisting of cyclical polychemotherapy and radiotherapy on bulky mediastinum (lymphoma program). The regimen was CHOP-Bleo for 6 cycles of induction therapy every 4 weeks and 2 adjunctive cycles of consolidation without further maintenance regimen or CNS prophylaxis. Bulky mediastinum was delivered an involved field high-energy radiotherapy. The CR rate per whole group was 54% (67% for ALL-treated versus 40% for lymphoma-treated patients; p=0.05), with a median survival for remitters of 28.5 mos. ALL-treated patients had a median survival of 16.5 versus 10 months of lymphoma-treated ones (p=0.05). The 3-yr survival was 24 and 10% for the two groups, respectively. Relapse-free survival for whole group was 65% at 12 and 25% at 24 mos. Nine out of 15 patients who achieved CR relapsed in a 24-months interval from remission; three cases relapsed in new sites of disease (mediastinum, CNS, bone marrow with leukemia), five in both previous and new sites and a single in previous sites only (bone marrow and CNS). Bone marrow involvement at diagnosis and therapy program did not significantly influence the duration of relapse-free survival. Central nervous system involvement was diagnosed in 8 out of 30 patients (27%). No patients who underwent CNS prophylaxis had neurological complication or developed later CNS relapse. The better prognosis of ALL-treated patients, in spite of bone marrow positivity, argues in favor of an ALL-like therapy in all adult lymphoblastic lymphomas, in term of CR rate, overall survival, and absence of CNS relapse: this therapy should be adopted irrespective to bone marrow findings, and no matter how localized the lymphoma appears to be.

85 RESULTS OF IFOSFAMIDE - VP-16 SALVAGE COMBINATIONS FOR PATIENTS WITH RECURRENT OR REFRACTORY AGGRESSIVE LYMPHOMA. F. Cabanillas, F.B. Hagemeister, S. Riggs, P. Salvador, W. Velasquez, P. McLaughlin. M.D. Anderson Hospital & Tumor Institute, Houston, Texas 77030.

Primary refractoriness to induction chemotherapy or relapse from remission usually carries a dismal prognosis for patients with intermediate or high grade ("aggressive") lymphomas. During the past six years we have used Ifosfamide - VP-16 based salvage regimens to treat 154 pts with recurrent or refractory aggressive lymphoma & an additional 7 pts who were partially refractory to front line therapy. Partial refractoriness was defined as achievement of a PR as the maximum response after a minimum of six courses of front line adriamycin containing combinations. These partially refractory pts were crossed over to the Ifosfamide - VP-16 based regimen before relapse occured on front line therapy. The salvage regimens used consisted of the following combinations: IMVP-16 (Ifosfamide, MTX, VP-16), AIVP-16 (AMSA, Ifosfamide, VP-16) & MIME [Methyl Gag, Ifosfamide, MTX & Etoposide (VP-16)]. Response rates in patients with recurrent or refractory disease were:

Regimen	N	CR(%)	PR(%)	Median RFS of CR's	P Value
IMVP-16	33	11 (33)	11 (33)	9 Mos.	
AIVP-16	25	12 (48)	2 (8)	9 Mos.	> .05
MIME	96	33 (34)	29 (30)	16 Mos.	
TOTAL	154	55 (36)	42 (27)		

Of 48 CR's who have been at risk >1 yr, 15 (31%) are still in CR. Response according to histological type was as follows:

	N	CR(%)	PR(%)
Large Cell	119	39 (33)	33 (28)
Lymphoblastic	13	6 (46)	2 (15)
Diffuse Small Cleaved (DPDL)	15	7 (47)	5 (33)
Diffuse Small Non-Cleaved (DUL)	7	3 (43)	2 (29)

In addition there were 7 partially refractory patients treated with these regimens & 6 (86%) achieved CR. Three of these 6 are still in CR >2 yrs. Ifosfamide - VP-16 based salvage combinations are effective in producing responses in pts with recurrent lymphoma. The quality of the CR's in the MIME regimen appears to be slightly superior although this hasn't reached statistical significance. The early use of these regimens in partially refractory pts (before relapse occurs) results in a high % of CR's of long duration. Toxicity consists mostly of infection (28%), and hemorrhagic cystitis in 20% of pts. A modest fraction of pts with recurrent or refractory lymphoma and a high fraction of partially refractory lymphomas appear to be potentially curable with these salvage regimens.

86 METHOTREXATE PLUS HIGH DOSE CYTARABINE IN ADVANCED REFRACTORY LYMPHOMA. R. Opfell*, J. Schottinger+, N. Schlutz+, H. Ballard°, and S. Armentrout+. *New York University, New York, NY, +Univ. of California, Irvine, CA, °Manhattan Veterans Administration Hospital, New York, NY.

Methotrexate and Cytarabine are reportedly synergistic. Eight patients with advanced refractory lymphoma were treated with Methotrexate 40 mg/M2 x 1 dose followed in one hour by Cytarabine 3gm/M2 x 4 doses q 12 h. The regimen was repeated q 21 days. Patients included 2 Hodgkins, 1 DUL, 2 DHL, 1 NPDL, 1 plasmacytoid lymphocytic, and 1 T cell prolymphocytic leukemia; ages 24-71 (median 46). All were heavily pretreated, had progressed on adriamycin containing regimens, and 3/8 had received prior radiotherapy. Prior chemotherapy consisted of 4-10 drugs (median 7) and 5-18 cycles of therapy (median 9). There were 6/8 major responses with 4 CR and 2 PR. One patient had MR with relief of abdominal pain and pedal edema. The patient with DUL had CNS involvement, no measurable disease, expired of cardiac arrest apparently unrelated to toxicity after two cycles. One patient with Hodgkins was in CR after 2 cycles, relapsed after no therapy and responded with a PR after 2 cycles. 6 of 8 patients survive for 4-12 months. Therapy was well tolerated: the major toxicity was myeloid, without CNS toxicity or mucositis. Granulocyte nadirs below 1,000 and platelet nadirs below 35,000 were seen in every patient. There was rapid recovery with return of leukocyte count to at least 3,500 and platelet count to at least 100,000 within 21 days in 90% of the cycles. This combination produced rapid responses in the majority of this group of heavily pretreated patients. De-escalation of the dose of cytarabine will be done to determine whether similar antitumor responses can be obtained with less myeloid toxicity.

87 A NEW COMBINATION REGIMEN OF EXPERIMENTAL DRUGS FOR THE TREATMENT OF RELAPSED LYMPHOMA: GALLIUM NITRATE, METHYLGLYOXAL BIS(GUANYLHYDRAZONE) AND ETOPOSIDE.
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Current combined modality treatment with chemotherapy and radiation can produce complete remission (CR) and prolonged survival in ≥ 50% of patients (pts) with advanced-stage Hodgkin's disease (HD) and diffuse large-cell ("histiocytic") lymphoma. However, the prognosis for most pts who fail to respond or who relapse from such aggressive therapy remains extremely poor. Previously, we found that both methylglyoxal bis(guanylhydrazone) (MGBG) and gallium nitrate (GN) had major anticancer activity as single agents in pts with malignant lymphoma. We have combined these non-myelosuppressive drugs with etoposide (VP-16-213) in a new regimen for the treatment of patients with advanced, relapsed lymphoma. In this protocol, GN was administered by continuous infusion for 7 days (d) at a dose of 300 mg/sq m/d. MGBG was given on days 1 and 10 (600 mg/mq m) and etoposide was given daily x 3 days (100-125 mg/sq m/d) on days 2, 3 and 4. Subsequent cycles were given every 3-4 weeks.

To date, 29 pts are evaluable. Each pt had received extensive prior chemotherapy (median of 2 combination regimens (range 1-4) and 6 drugs (range, 4-12). Eighteen pts had also received radiotherapy, of the 29 evaluable pts 15 (52%) had major responses (4 CR, fully restaged; 11 PR). Response according to Rappaport classification was: 9/13 DHL, 3/3 Hodgkin's; 2/5 DPDL; 0/3 NPDL; 1/5 other NHL. Median response duration exceeds 4 months. The major toxic reaction to this regimen has been myelosuppression (leukocytes 1000/cu mm in 39% of pts, platelets 40,000/cu mm in 30%). Twenty percent of pts developed an increase in serum creatinine ≥ 1.0 mg/dl. Four pts developed optic neuritis which was associated with substantial reduction of visual acuity in 2 pts.

This new drug regimen has major activity in patients with relapsed lymphoma. The individual drugs do not share mechanisms of action or toxic effects which are similar to other agents conventionally used for the treatment of lymphoma. Therefore, this regimen may not be cross-resistant with standard chemotherapy and may prove useful as an alternating regimen for the therapy previously untreated patients.

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88 CLINICAL INTERFERON (IFN) STUDIES IN LEUKAEMIA AND LYMPHOMA

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The potential clinical relevance of the antiproliferative effect of the α interferons initially demonstrated in murine leukaemia models, has been investigated in patients with lymphoma and leukaemia.

Phase I studies with leucocyte lymphoblastoid and recombinant DNA have shown that the maximum dose given over a prolonged period compatible with a normal ambulatory existence is less than $10x10^6$ IU daily and that the maximum dose given over a short period is $100x10^6$ IU daily. The dose limiting side effects are central nervous system toxicity and metabolic disturbance.

The Phase II results available at present may be summarised as follows: Responses, although rarely complete, have been observed in lymphoma treated at doses between $2x10^6$ IU/m^2 to $50x10^6$ IU twice weekly. The highest response rate 16/25 (64%) has been reported in low grade Non Hodgkin's lymphoma (NHL), treated with $50x10^6$ IU/m^2 thrice weekly and IFN-αA, confirming early experience with IFN-α at lower doses. Less impressive responses of short duration have also been achieved in chronic lymphatic leukaemia (9/28), high grade NHL (4/19) and Hodgkin's disease (4/12).

A clear demonstration of the antiproliferative activity of IFN-α (leucocyte) has been made in chronic myeloid leukaemia with indefinite administration of 3 to 9 $x10^6$ IU daily. The peripheral blood count returned towards normal in 22/25 (88%) patients, although splenomegaly frequently persisted, and the Philadelphia chromosone remained. Very high doses of IFN-α_2 given by continous intravenous infusion reduced the white blood count more rapidly, but the effect was only transient in 4/4 patients. Preliminary results suggest that complete remission can be achieved with this dose of IFN-α in patients with hairy cell leukaemia (3/7). No benefit has been shown for any patient (0/23) with acute myelogenous leukaemia, receiving either high dose continuous infusion of lymphoblastoid IFN-α or recombinant DNA IFN in spite of an in vitro evidence of activity at the serum levels achieved.

Studies are currently in progress to evaluate the differentiation effect of IFN- in leukaemia, and the possible synergistic action of α IFN with cytotoxic chemicals in lymphoma.

89 NEW DRUGS IN MALIGNANT LYMPHOMAS.

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Malignant lymphomas are sensitive to a broad range of chemotherapeutic agents and a number of highly active regimens have been tested and found to be clinically useful. The search for new chemotherapeutic agents with useful activity against malignant lymphomas is becoming increasingly more difficult because patients suitable for phase II studies have received extensive prior therapy with radiation therapy and/or a variety of different drugs, resulting in increased likelihood of their tumors possessing multiple cross-resistance phenotypes and a high probability of reduced bone marrow reserve in the majority of subjects. The consequence of this is that successful new agents must possess reasonable inherent anti-lymphoma activity and safety AND be relatively non-cross resistant with drugs the patient has already received AND in many cases have either a different spectrum of toxicities from other drugs or at least have minimal toxic impact on the bone marrow. These considerations make impractical suggestions that lymphomas might be used as a clinical model for screening anticancer agents prior to their use in solid tumors.

In spite of these difficulties new agents continue to be tested in lymphomas. Using the 1983 edition of the Compilation of Experimental Cancer Therapy Protocol Summaries prepared by the International Cancer Research Data Bank as a representative collection of cancer studies throughout the world, 105 study protocols were reviewed. Fifty three of the 105 trials (50%) utilize one or more new agents for some phase of treatment and 40 trials (38%) are specific for previously treated patients. The most common used new agents include: etoposide (VP-16), teniposide (VM-26), MeGAG, spirogermanium, ifosfamide, amsacrine, and deoxycoformycin. Of the 53 trials using new agents, 41 (77%) use one or more of these seven agents. In addition, a smaller number of trials (7 studies) introduce the use of biologic response modifying agents and immunological manipulations. These agents include BCG and Interferon. Six of the 7 trials using these agents allow entry of patients with no prior systemic therapy, and it is notable that 4 of the 7 trials are randomized and that 3 of these 4 trials have untreated control groups.

Additional agents about to enter early trials in lymphomas include: a pair of platinum analogs, carboplatin, and iproplatin; a bleomycin analog, tallysomysin S10b; a pair of antimetabolites, FAMP and fludarabine; and a number of other agents. Interest in developing new agents remains high and this is reflected in the surprisingly high percentage of studies utilizing new agents for the treatment of lymphomas.

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SELF-RECOGNITION MECHANISM AND IMMUNE REACTIVITY IN H-2 INCOMPATIBLE BONE MARROW RADIATION CHIMERAS. G.JM Maestroni[1], W. Pierpaoli[2], G. Losa[1]. 1: Laboratory of Cellular Pathology, Istituto Cantonale di Patologia, 6604 LOCARNO, Switzerland. 2: Institute for Integrative Biomedical Research, 8123 EBMATINGEN, Switzerland.

Timed administration of urmanipulated donor (P1) bone marrow cells suspended in a solution of recently identified microenvironmental components of the bone marrow into lethally irradiated recipients (P2) makes for the induction of complete, GVHD-free and stable allochimerism. Depending on the donor-recipient combination, P1→P2 allochimeras may or may not show depressed primary immune responses against T-dependent antigens. Conversely, alloreactivity was perfectly normal in all combination used. Chimerism of established (>3-4 months after bone marrow transplantation, BMT) P1→P2 allochimeras cannot be adoptively transferred to new irradiated recipients. This fact denies existence of suppressive mechanisms in chimeric bone marrow or spleen cells in contrast with the unresponsiveness shown in vitro in mixed lymphocyte cultures of chimeric lymphocytes against normal P1 or P2 lymphocytes. However, established P1→P2 chimeras are able to "suppress" passively transfused immunocompetent P1 and/or P2 lymphocytes. Large amounts ($80\text{-}90 \times 10^6$) of P1 and/or P2 immunocompetent leukocytes (spleen cells) passively transfused into established and GVHD-free P1→P2 allochimeras failed to show effector functions. Normal, immunocompetent P1 spleen cells inoculated into P1→P2 chimeras did not reconstitute primary responses against T-dependent antigens nor elicited GVHD, while normal immunocompetent P2 spleen cells failed to reverse chimerism. In both cases the transfused chimeras remained healthy and retained their chimerism. Moreover, GVHD-free P1→P2 allochimeras showed the surprising ability to reject P2 skin grafts. Both these phenomena are dependent upon the age (time after BMT) of the established chimeras. Preliminary ultrastructural studies of chimeric spleens have revealed an abnormal number of cells with plasmocytoid features. These findings pointed to the existence of an "unknown suppression-rejection principle" operating in the chimeras. In other words, a principle that mediates P1 lymphocyte suppression and possibly P2 lymphocytes rejection. Furthermore, the impairment of primary responses against T-dependent antigens seems not to depend on thymus directed H-2 restricted T-B cells recognition mechanisms. In fact, normal immunocompetent P1 lymphocytes did not reconstitute those P1→P2 allochimeras showing reduced primary responses against T-dependent antigens. All together, these data open fundamental questions about the mechanisms of self-recognition and their effect on the immune reactivity of allogeneic bone marrow chimeras.

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APPLICATION OF IMMUNOTOXINS TO AUTOLOGOUS BONE MARROW TRANSPLANTATION. F.Uckun, S.Ramakrishnan, L.L.Houston and M.Aksoy. Dep. of Hematology, University of Istanbul and Dept. of Biochemistry, University of Kansas, USA.

Current strategies for effective autologous bone marrow transplantation(ABMT) in leukemia and high grade malignant lymphoma include the in vitro use of immunotoxins-monoclonal antibodies covalently bound to a toxin such as ricin or a hemitoxin such as pokeweed antiviral protein (PAP),a potent inactivator of ribosomes.The present study was performed to assess the selective clonogenic lymphoma cell elimination from human marrow by in vitro use of an immunotoxin of pan-B-IgG1(κ) monoclonal antibody B43 linked to PAP and to define optimal conditions for application of B43-PAP to ABMT.PAP was purified from spring leaves of Phytolacca americana and linked to B43 by a disulfide bond using N-succinimidyl-3-(2-pyridyldithio) propionate(SPDP).The molar ratio of PAP to antibody was estimated to be 2:1 by a specific homologous radioimmunoassay.To quantify the target cell selective cytotoxicity of B43-PAP,we applied a highly sensitive clonogenic assay which can measure elimination of almost 6 logs of clonogenic lymphoma cells from human marrow.The stem cell toxicity of B43-PAP was evaluated by conventional in vitro clonal assays using highly purified stem cell suspensions. Treatment with B43-PAP under standard assay conditions (8h at 37°C) selectively inhibited protein synthesis in target lymphoma cells by more than 95% eliminating some 4 logs of clonogenic lymphoma cell contamination from a 100-fold excess of normal bone marrow.In contrast to this very high anti-tumor activity,less than 50% of pluripotent stem cells(CFU-GEMM) were lost.Chloroquine,an agent that raises lysosomal pH,specifically enhanced the rate of protein synthesis inhibition by B43-PAP at concentrations not affecting the growth of clonogenic lymphoma cells or pluripotent human hemopoeitic progenitors in culture and extended the final level of kill more than 1,5 logs compared to its absence.The almost 6 logs of selective lymphoma cell elimination achieved with B43-PAP in the presence of chloroquine suggests that in future clinical trials,B43-PAP or other PAP conjugates of monoclonal antibodies can be effectively used to eliminate residual clonogenic tumor cells from autologous stem cell grafts.

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92 IN VITRO PURGING WITH HYDROPEROXYCYCLOPHOSPHAMIDE (4-HC) AND ITS EFFECTS ON HEMATOPOIETIC AND STROMAL ELEMENTS OF HUMAN BONE MARROW. Salvatore Siena, Hugo Castro-Malaspina, Subhash Gulati, Li Lu, Teresa Cartagena, Richard J. O'Reilly, Bayard D. Clarkson, and Malcolm A.S. Moore. Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.

Transplantation of 4-HC purged autologous bone marrow(ABMT) after high-dose chemoradiotherapy is a promising approach to the treatment of lymphoma and leukemia. This is based on the assumption that the dose of 4-HC employed selectively kills malignant cells without eliminating the cellular progenitors responsible for the hemopoietic reconstitution of the host. Recent clinical observations indicate that 4-HC purging techniques while depleting the graft of granulomonocytic (CFU-GM) and erythroid (BFU-E) committed stem cells, do not affect its capacity to repopulate the host hemopoietic system. In this respect the role of marrow stromal cells (MSC) and pluripotential stem cells (CFU-GEMM) has not been defined. The purpose of this investigation was to analyze the effects of 4-HC on MSC and CFU-GEMM. MSC were quantitatively studied by the marrow fibroblast colony-forming cell (CFU-F) assay and functionally by the long-term marrow culture assay (LTMC). The 4-HC toxicity on MSC and hemopoietic progenitors was dose and cell concentration dependent. The following ID_{50} (μM 4-HC) were found:

Clonal Assay	Cell Concentration	
	20×10^5/ml	10×10^5/ml
CFU-F	235	115
CFU-GEMM	31	n.d.
BFU-E	41	n.d.
CFU-GM	89	22

Treatment of marrow cells with 100 μM 4-HC, which is the dose we currently use for ABMT, resulted in depletion of hemopoietic progenitors (CFU-GEMM 0%, BFU-E 3.2 %, CFU-GM 26.6%). All 6 patients with NHL transplanted after supralethal chemoradiotherapy with autologous 100μM 4-HC purged marrow showed full hemopoietic recovery. This suggests that the CFU-GEMM may not represent the stem cell responsible for hemopoietic reconstitution in the transplanted host. In contrast, the MSC progenitor CFU-F was relatively resistant to the in vitro action of 4-HC. Moreover, 4-HC treated bone marrow in LTMC gave raise to stromal layers composed of fibroblasts, endothelial cells, adipocytes, and macrophages similarly to controls, although a higher number of cells per inoculum was required. Coculture of these heterogeneous stromal layers with freshly isolated autologous hemopoietic cells demonstrated that the stroma grown from 4-HC treated marrow sustained the long-term production of CFU-GM similarly to controls. Thus, MSC are relatively resistant and not functionally affected by 4-HC. This is sharp contrast with the high sensitivity of hemopoietic progenitors. Taking into account the notion of transplantability and radiosensitivity of MSC, the relevance of MSC in the area of bone marrow transplantation will be discussed. Furthermore, an in vitro ABMT model employing a coculture system in LTMC will be presented.

93 INDICATION FOR BONE MARROW HARVESTING AND PURGING IN BURKITT LYMPHOMA : A 3 YEARS EXPERIENCE. I. Philip[1], T. Philip[1], M. Favrot[1], P. Biron[1], G.M. Lenoir[2]. 1. Centre Léon Bérard - Bone Marrow Transplant Team - 28 rue Laënnec 69008 LYON - FRANCE. 2. International Agency for Cancer Research - 175 Cours Albert Thomas - LYON - FRANCE.

Between 1980 and 1983 317 bone marrow aspirates from 63 Burkitt lymphoma were studied with an in vitro liquid culture monitoring system.

1. BL cell line was obtain in culture from 14 out of 15 patients studied with cytologically positive marrow. The in vitro monitoring system was shown to be usefull regardless of EBV status (7 EBV ⊕ - 8 EBV ⊖), patient status (9 at relapse, 6 at diagnosis) and cytogenetic anomalies (8 t(8;14) - 2 t(8;22) - 2 t(8;2) in 12 patients studied).

2. When bone marrow was cytologically normal or suspect (i.e. less than 5 % BL cells) the in vitro monitoring system was shown to be more sensible than cytologic examination in 25/56 i.e. 44 % of the cases. The sensitivity of the test is of 1/100.000 i.e. 3 logs inferior to cytology.

3. If bone marrow will be harvested for all patients in CR after 2 months of chemotherapy purging marrow will not be necessary (38/38 negative culture) but 7/10 patients will be harvested for nothing (30 % of indication for ABMT).

4. If bone marrow will be harvested at relapse or in PR purging procedure was shown to be necessary in 9/16 cases i.e. 56 % of the cases.

94 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR RELAPSED NON-HODGKIN'S LYMPHOMA (NHL): ANTI-B_1 MONOCLONAL ANTIBODY TREATED AUTOLOGOUS BONE MARROW. L. Nadler, T. Takvorian, R. Finberg, R. Bast, L. Botnick, S. Hellman, G.P. Canellos, S.F. Schlossman, Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA

Five patients with relapsed B-cell NHL were treated with intensive chemo-radiotherapy and reconstituted with autologous bone marrow (BM) rendered free of tumor by in vitro treatment with the B cell specific monoclonal antibody anti-B_1 and rabbit complement. Median age was 46 years (range 43-57) and histology at relapse included diffuse mixed (1), diffuse large cell (3) and diffuse poorly differentiated (1). These patients had relapsed one to six times on conventional therapy with BM involvement in 4 of 5. They were re-induced into a minimal disease state, with $\leq$ 5% BM involvement, utilizing chemotherapy alone (3 patients) or with radiation therapy and chemotherapy (2 patients). The marrow in remission was harvested, treated in vitro with anti-B_1 and complement, and cryopreserved. Patients then received Cytoxan at 60mg/kg on days 1 and 2, followed by 3 days of fractionated whole body irradiation (200 rads twice daily), followed by re-infusion of the treated autologous bone marrow on day 6. All patients achieved a complete response with engraftment of the treated marrow by 4 weeks. Acute toxicity included self-limited nausea, vomiting and mucositis; culture negative low grade fever developed in 4 of 5 patients which responded to antibiotics. B_1 positive B cells were first detected at 1 month and achieved normal levels at 2-3 months whereas circulating levels of immunoglobulin did not return to normal until 6 months. Late toxicity included atypical pneumonia at 3 1/2 months and herpetic conjunctivitis at 7 months in one patient. One patient had localized Herpes zoster at 7 months. No other late toxicity has been seen. Three of 5 patients are presently disease free in an unmaintained remission at 13, 12 and 1 months. One patient with 6 relapses prior to autologous transplantation relapsed at 2 months with extensive disease and died of lymphoma. A second patient relapsed at 6 months at the site of former bulk disease but not in the bone marrow which was previously involved, and is being palliated. The present study suggests that anti-B_1 treated autologous BM can rescue the aplasia of intensive chemo-radiotherapy. Moreover, autologous BM transplantation with tumor cell depletion has relatively little toxicity compared to allogeneic transplantation, and preliminary evidence to date suggests that this approach may be useful in the future treatment of NHL, especially during the initial induction of high risk patients.

95 AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR POOR PROGNOSIS LYMPHOMA. S.Gulati, L.Gandola, R.Vega, B.Shank, D.Straus B.Koziner, B.Lee, R.Mertelsmann, S.Kempin, M.Andreeff, R. Dinsmore, T.Gee, J.Yopp, R.O'Reilly and B.Clarkson. Memorial Sloan-Kettering Cancer Center, New York, NY 10021.

Patients with poor prognosis lymphoma,identified as having bulky mediastinal or abdominal disease and/or high serum lactic dehydrogenase level ($>$500 units/ml),even though initially responsive to conventional therapy have poor survival rates. Sixteen such patients with diffuse histiocytic lymphoma (DHL) had their bone marrow (BM) cryopreserved after induction chemotherapy consisting of cytoxan , adriamycin, vincristine and prednisone (L-17M protocol). At the time of transplant, radiation to the site of residual disease was followed by TBI (total 1320 rads) 11 doses over 4 days; then cytoxan 60mg/M^2/day x 2 days with ASCT rescue. Seven patients had ASCT soon after induction therapy (in CR or PR) ;all seven patients are doing well with follow-up of 22,16,12,11,7,7 and one months. Five patients progressed after L-17M induction and were then treated with ASCT protocol, Two of them have died of peritransplant complications;one has relapsed but is alive at 9 months and the other two are disease-free with follow-up of 4 and 2 months. Four patients were heavily pretreated before ASCT. One of these patients died few days after transplant; one patient relapsed but is alive at 4 months and the other two are doing well with 15 and 4 months of follow-up. Five of the above patients with initial BM involvement (2 progression on L-17M , 3 heavily pretreated) received 4-hydroperoxycyclophosphamide (4-HC) purged BM and all had good hematopoietic reconstitution. Two of these patients relapsed , but all are still alive. From these results, it appears that "superconsolidation" with TBI and cytoxan followed by ASCT has promise in improving the management of patients with poor prognosis lymphomas.Methods of purging bone marrow will also be discussed. (Support CA-08526;19117;20194) .

96 MASSIVE THERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION AS RESCUE PROTOCOL FOR BURKITT LYMPHOMA (EXPERIENCE OF 18 CASES). T. Philip, P. Biron, I. Philip, M. Favrot, G. Souillet, P. Hervé, E. Plouvier, J.L. Bernard, C. Raybaud, D. Frappaz, F. Freycon, B. Crozet, M. Brunat-Mentigny. Centre Léon Bérard - Bone Marrow Transplant Unit and France Autogreffe Study Group.

Overall survival for children with Burkitt lymphoma raised from 42 % to 80 % in our group in a 3 years period. During the same period massive therapy (i.e. BACT) was investigated by us in two different groups of patients.

- In the first group 10 patients treated by the former protocol (i.e. CHOP) were selected for ABMT because of relapse (cases 1,3,4,5,6,7,9), PR after 3 months of CHOP (case 2), or long delay to reach CR (cases 8 and 10). 3 of the 7 relapses are still alive 930 ⊕ , 894 ⊕ and 410 ⊕ post ABMT. Patient 2 in PR is alive NED 990 ⊕ and one of the two long delay to CR is alive NED 184 ⊕ . 5/10 patients are alive NED (4 more than 2 years post ABMT).

- The second group is made of 8 patients aggressively treated during the period 1981-1983. 43 patients were treated by our group during this period and 8 selected for massive therapy and ABMT i.e. 1/7 localized disease because of early relapse → alive NED 163 ⊕ , 4/28 stage III because of PR (1), progression (2) or long delay to reach CR (1) → 1 alive NED 186 ⊕ , 3/8 stage IV because of PR or for consolidation of initial CNS involvement → 1 alive NED 260 ⊕ . A total of 3/8 patients are alive NED.

In this group of very bad prognosis BL 8/18 are alive NED 163 to 990 days post ABMT. 4 of the 10 relapsed patients are alive NED including 3 with more than one year survival (i.e. cure for BL). This report shows ① The BACT efficacy in BL. ② ABMT will concerned a maximum of 30 % of BL cases. ③ Necessity to purge at least some bone marrow. ④ Feasibility of purging marrow (5 cases).

97 TREATMENT OF REFRACTORY NON-HODGKIN'S LYMPHOMA WITH INTENSIVE CHEMORADIOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION. G. Santos, A. Yeager, H. Braine, H. Kaizer*, M. Colvin, L. Munoz, and R. Levy**, The Johns Hopkins Oncology Center, Baltimore, MD, *Rush Medical College, Chicago, IL, and ** Stanford University, Palo Alto, CA.

The long-term survival is poor in patients with refractory or relapsing non-Hodgkin's lymphoma (NHL). We examined the efficacy of intensive chemotherapy and total body irradiation (TBI) followed by autologous bone marrow transplantation (auto BMT) with "purged" cryopreserved marrow in refractory or relapsing NHL. Sixteen patients, ages 3-39 years, received a preparative regimen consisting of cyclophosphamide, 50 mg/kg/day x 4, and TBI (300 rad/day x 4 or 180 rad B.I.D. x 8); 4 patients also received adriamycin, 30 mg/M^2/day x 3. Marrow was treated in vitro with 40-100 ug/ml of 4-hydroperoxycyclophosphamide (4HC) or, in patients with T-cell NHL, one or two monoclonal antibodies (Leu-1 + Leu-9) plus complement (C'). As of January 15, 1984, we have obtained these results:

In Vitro Rx	No. Pts.	No. Relapses (days post BMT)	No. in Remission (days post BMT)
4HC	7	3 (33,60,75)	4 (17+,122+,781+,797+)
Leu-1	4	2 (49,75)	2 (696+,1198+)
Leu-1 + Leu-9	5	3 (48,91,405)	2 (10+,52+)

We conclude that the combination of intensive chemoradiotherapy and auto BMT with pharmacologically or immunologically "purged" marrow may provide a significant opportunity for disease-free survival in relapsing or refractory NHL.

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98 Lymphoproliferative Diseases with Monoclonal Gammopathy

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In the past decade malignant lymphomas have been recognized and characterized as tumors of the immune system, with the neoplastic cells often manifesting morphologic and functional characteristics that mimic those of their normal benign counterparts. Lymphoproliferative diseases with monoclonal gammopathy result usually from the neoplastic transformation of clones of B-cells at or near the terminal stages of B-cell differentiation. To understand the morphology, pathogenesis, and clinical manifestations of these disorders, however, one must have an overview of the physiology and interrelationships of B-cells, T-cells, and cells of the mononuclear phagocytic system. In this presentation such an overview will consider initially both the normal immune system and selected congenital and acquired immunodeficiency states. In this context, it will become apparent that neoplastic lymphoproliferative disorders with monoclonal gammopathy arise from the milieu of the immune system and retain to variable degrees functional attributes demonstrable in terminally differentiated normal B-cells. Attention will focus mainly on multiple myeloma, macroglobulinemia of Waldenstrom, and the heavy chain diseases, with emphasis on their clinical, morphologic, and immunologic manifestations. A comprehensive review of the subject is available in the following reference:

Callihan, T.R., Holbert, J.M. and Berard, C.W.: Neoplasms of terminal B-cell differentiation: the morphologic basis of functional diversity. In Malignant Lymphomas: A Pathology Annual Monograph, pp. 169-268, Appleton-Century-Crofts, Norwalk, Connecticut, 1983.

99 ANGIOIMMUNOBLASTIC LYMPHADENOPATHY: CLINICAL COURSE, IMMUNOLOGICAL CHARACTERISTICS AND TREATMENT RESULTS IN 25 PATIENTS.

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We observed 25 patients with Angioblastic Lymphadenopathy (AILAP) between 1972 and 1983. Diagnosis was established by lymphnodebiopsy. Patients without histologically proven diagnosis from lymphnodes were excluded from this study. Median age was 50,4 years. 60% were male, 42% female. Initial clinical symptoms occurred 3 months before diagnosis: lymphnode enlargement (80%), fewer (60%), weight loss and nightsweat (44%), hepato-splenomegaly (48%), exanthema like erythroder mia and generalized pruritus (20%). Laboratory investigations at the time of diagnosis: rapid blood sedimentation rate (60%), thrombocytope nia < 100.000/mm^3 (52%), anaemia: Hb <12 g% (48%), leucopenia < 3000/mm^3 (24%) with > 10% eosinophilic granulocytes, liver enzyme - alterations (20%). Immunological characteristics during the active phase of AILAP: polyclonal gammopathy, increase of immune-complexes, cold haemagglutinins, antibodies against smooth muscles and EBV. Cellular analysis: T-lymphocyte depletion with low helper and high suppressor cell activity, normal NK-cell activity. B-lymphocyte - proliferation with high num ber of terminal mature B-cells. Reactivity with mitogens normal or low.

Treatment decision was based on clinical symptoms and progression of AILAP. If tolerable to the patient we waited 4 weeks for spontaneous regression which was observed in 4/25 cases (16%). If AILAP was continuously progressing, therapy consisted either of Prednisone (slow progression: group A) or polychemotherapy (rapid progression: group B).
A: Prednisone 60 mg/m^2 p.o. daily for 4 weeks, subsequent stepwise reduction to maintenance level; if CR: therapy-stop after 4 months.
B: Cyclophosphamide 100 mg/m^2 p.o. daily, Vincristine 2 mg i.v. weekly, Prednisone 60 mg/m^2 p.o. daily ± Procarbacine 100 mg/m^2 p.o. daily (Cy and Pred: day 1-28, Vcr day 1,8,15,22, Pro day 1-14; q day 29)
After CR: Pred-maintenance. Patients not responding to A switched to B.
Results: Only A: 2 CR, 2 PR, 1 NC, 2 P (n = 7)
Only B: 0 CR, 0 PR, 0 NC, 6 P (n = 6)
B after A: 0 CR, 4 PR, 1 NC, 3 P (n = 8)
Median survival of all patients was 36,4 months. Median survival of non-responders was 9,4 months. Median observation time was 34,5 months. 7/25 patients showed a malignant transformation of AILAP: 4 Hodgkin's diseases, 3 Non-Hodgkin-Lymphomas (28%). 2/25 patients had synchronous secondary malignancies: AML and Cervical-Carcinoma. 13/25 patients died (52%), 12 are alive, 9 with no evidence of AILAP.
Conclusions: 1. There are three prognostically different clinical courses of AILAP: spontaneous regression, good response to Prednisone, poor response to either Prednison or polychemotherapy. There is no clear relationship to the stage of the disease or other characteristics like immunological malfunctions. 2. Further analysis of immunological impairments might help to develop new, more efficient kinds of therapy. 3. In many cases AILAP precedes malignant transformation or secondary malignancies.

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100 A CONTINUUM OF ALL AND NHL TYPES ACCORDING TO THE DIFFERENTIATION STEPS DETERMINED BY MONOCLONAL ANTIBODIES. CORRELATION WITH WHO, FAB AND NCI CLASSIFICATIONS.

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We have in a double blind fashion categorized according to WHO, FAB and NCI classifications all ALL and NHL after having characterized their immune types with monoclonal antibodies. Patients with ALL of which all OKT, cμ and sIg were negative had a WHO microblastic ALL , FAB L1. Patients OKT10+, OKT6, 3, 4 and 8-, B1, cμ, sIg- had a WHO prolymphoblastic T and FAB L2-3 ALL. Patients with all OK, cμ and sIg- but B1+ had the WHO prolymphoblastic of the B series ALL FAB L2-3. Patients with large cells OKT10 and OKT6+, OKT3, OKT4 and OKT8-, B1, cμ and sIg-correspond to the WHO T macrolymphoblastic ALL or NHL (cortico-thymocytic) and to the FAB-L2-3. Patients with large cells all OKT and B1-, cμ+ and sIg- correspond to the WHO pre-B-macroblastic ALL and to the FAB L2-3. Patients with OKT10 and OKT6, OKT3+, cμ-, sIg-, B1- correspond to the WHO T mixed lymphoblasto-prolymphocytic ALL or NHL and to the FAB L1-2. Patients with mixed-size cells all OKT-, cμ+ and sIg- and B1- correspond to the WHO pre-B mixed lymphoblasto-prolymphocytic ALL and to the FAB 1-2. Patients with all OKT-, $c\mu^{\pm}$ and sIg+ correspond to the WHO Burkitt'sleukemia and lymphoma or to FAB L3. All NHL of the B types are $c\mu^{\pm}$, this positivity being of various qualitative and quantitative types. The B lymphocytic NHL is sIgM+. The lymphoplasmocytic NHL is sIgM+. The small non cleaved nucleus cell type is sIgM+++, sIG+++. The small cleaved nucleus cell type is sIgM+, sIgG+. The large non cleaved nucleus cell type is sIgM++. The large cleaved nucleus cell type is sIgM+, sIgG+ and sIgG+. The B immunoblastic NHL (with convoluted or no nuclei) is sIgM+++ and sIgG+++. The T lymphocytic NHL is OKT4+ or OKT8+, OKT10 and OKT6-. Mycosis fungoide and Sezary disease (with cerebroid nuclei) are OKT4+, OKT10 and 6-. The Watanabe immunoblasto-pleiomorphic type is usually OKT4+, OKT8, OKT10, OKT6-. We have also observed cases of OKT8+, OKT4, OKT10, OKT6- NHL.

101 COMPARISON OF THE WORKING FORMULATION (WF) OF NON-HODGKIN'S LYMPHOMA (NHL) WITH THE RAPPAPORT (R), KIEL (K), AND LUKES & COLLINS (L&C) CLASSIFICATIONS. TERMINOLOGICAL CORRELATIONS AND PROGNOSTIC VALUE.

Jens Ersbøll, Henrik Schultz, Nis I Nissen, Philip Hougaard and Klaus Hou-Jensen. The Finsen Institute, Copenhagen, Denmark.

658 cases of NHL seen 1970-79 were reviewed and classified according to the R, K, L&C classifications and the WF. Each classification proved equally effective in separating patients into subgroups with prognoses ranging from a median survival of 1 year to 7 years. The R, K, L&C systems were compared one by one against the WF following the translation guidelines of the NCI-sponsored Study (Cancer 1982;49, 2112). The WF was more similar to the R and L&C systems than to the K system, since 82 %, 89 % and 75 % of the cases respectively were translatable according to the above-mentioned Criteria. The greatest similarities among the 4 systems were observed in FCC-lymphomas composed of predominantly small lymphocytes (93-98% accordance), in lymphomas of CLL type (80-100% accordance), and in FCC-lymphomas of small non-cleaved cytology (82-100% accordance). The greatest differences were seen in lymphomas composed of large lymphoid cells or of mixed cellular subpopulations. (58-90% accordance). The uncertain relation between the U-cell subtype of the L&C system and the lymphoblastic lymphomas of non-convoluted subtype accounted for the defective translation of this subtype (38-100 % accordance).
The Cox proportional hazards model was used to assess the prognostic effect of histologic subtype within each system after adjusting for the relative effect of age, sex, stage and symptoms. The following hazards are all compared to the F-SC subtype of the WF: SL (1.61,P=0.07 F-SC = 1, F-M (1.43,P=0.27), F-L (4.22,P <.0001), D-SC (1.68, P=0.06), D-M (2.61,P= .0002), D-L (3.28, P <.0001), IB (3.89, P<.0001), LB(5.0 P=<.0001), SNC (3.56,P <.0001). The intermediate malignancy grouping of the WF was prognostic heterogeneous, the SL and D-SC subtype had similar survivals (median 3.4 years), and the D-M,D-L and F-L subtypes had survivals similar to subtypes of the high grade grouping. By the use of the Cox model including two classifications simultaneous (WF compared one by one with the R,K, L&C systems) it was shown that the WF can substitute any of the established classifications in terms of prognostic value.

102 CLINICAL AND PROGNOSTIC RELEVANCE OF THE KIEL CLASSIFICATION OF NON-HODGKIN LYMPHOMAS (NHL): RESULTS OF A PROSPECTIVE MULTICENTER STUDY

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From 1975 to 1980, 1127 patients (pts.) with NHL entered a prospective multicenter observation study of the Kiel Lymphoma Study Group. During the first 3 to 4 years overall survival of the 782 pts. with low-grade malignant NHL (lymphocytic lymphomas, predominantly B-CLL: 23.1 %; LP immunocytoma = LP-IC: 18.9 %; centrocytic = CC lymphoma: 7,7 %; centroblastic-centrocytic = CB-CC lymphoma: 13,9 %) exceeded that observed in the 341 pts. with high-grade malignant NHL (centroblastic = CB lymphoma: 13,9 %; immunoblastic = IB lymphoma: 7,4 %; lymphoblastic = LB lymphoma: 5,3 %). Survival curves of pts. with low-grade malignant NHL declined with a flat slope without evidence of plateau. Prognostic superiority of CB-CC lymphoma and B-CLL over LP-IC and CC lymphoma could be recognized only after 2 years of followup. Survival curves of pts. with high-grade malignant NHL showed a rapid decline during the first 1 to 1 1/2 years and a subsequent plateauing. Intermediate course of survival curves of pts. with advanced stages of LP-IC, CC lymphoma and CB lymphomas between those of pts. with B-CLL and CB-CC lymphoma and those of pts. with IB and LB lymphomas suggest the existence of a group of NHL of "intermediate"-grade prognosis.
At presentation, 81 % of pts. with CC lymphoma showed stage IV disease. Only in pts. with stage I stable complete remissions (CR) could be achieved by radiotherapy. Survival curve of pts. with advanced stages showed a linear decline without evidence of plateauing. - Results of radiotherapy in pts. with stages I to III of CB-CC lymphoma support the concept that this NHL may remain restricted to the lymphatic system for a prolonged period of time. Strategy of "watchful waiting" for advanced CB-CC lymphoma is challenged by the unsatisfactory results obtained in this study and by improvement of prognosis observed in pts. achieving CR.
The high-grade malignant IB lymphoma was less favorable than CB lymphoma with respect to both clinical and prognostic features. Initial stages I and II were diagnosed in as many as 30 to 40 % of pts. with CB and IB lymphomas. Most of these pts. were treated by radiotherapy alone. However, only in stage I of CB lymphoma a sufficient proportion (80 %) of pts. achieved stable CR. Prognosis of patients with advanced CB, IB and LB lymphomas could only be improved by induction of CR but not of partial remission.
Poor risk factors for the individual NHL entities as evidenced by multiple regression analysis are discussed.

103 BONE MARROW AND BLOOD INVOLVEMENT BY NON-HODGKIN'S LYMPHOMA: CLINICOPATHOLOGIC FEATURES AND PROGNOSTIC SIGNIFICANCE IN RELATIONSHIP TO THE WORKING FORMULATION.

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One hundred and thirty-seven consecutive patients with malignant non-Hodgkin's lymphoma(ML) classified according to the Kiel system, who underwent routine bone marrow(BM) biopsy and peripheral blood examination as part of their initial evaluation, were reviewed according to the Working Formulation(WF). Patients with CLL, as well as cases with lymphoblastic lymphoma with blood and BM disease indistinguishable from acute lymphoblastic leukemia were excluded from this study. The median time of follow-up was 21 months (range 3-67+ mos). The overall incidence of BM involvement at diagnosis was 38%(52/137). The frequencies of BM disease in the three major prognostic groups of the WF were the following: 51%(28/55) for low grade (LGML); 32%(18/56) for intermediate grade (IGML) and 23%(6/26) for high grade malignant lymphomas (HGML). As regards the prognostic significance of BM involvement, the survival curves obtained grouping patients into low grade, intermediate grade and high grade malignancies were not significantly affected by the presence or absence of marrow disease at presentation. In fact, the lymph node histology proved to be the most important prognostic factor. Nevertheless, among patients with BM infiltration at diagnosis, a focal pattern of proliferation and a low extent of marrow disease (<30% replacement) discriminated groups with better prognosis.

Peripheral blood involvement by lymphoma was found at diagnosis in 42% (22/52) of cases with marrow disease; 17 cases showed leukemic spread during clinical course. As concerns prognostic significance of the leukemic spread, peripheral blood involvement at diagnosis in LGML appeared to have no important effect on the outcome of the disease, whereas late leukemic conversion heralded a rapid change to a more aggressive disease (median survival from the onset of leukemic phase 13mo). In fact, a shift to a less differentiated lymph node histology was documented in five patients with late leukemic spread. In patient with IGML, either initial or subsequent blood involvement was correlated with significantly worse prognosis (median survival 11,5 mo in leukemic patients; median not reached at 67 mo in non leukemic cases, $P<0.005$).As regards HGML, the median survival of leukemic and non leukemic cases did not differ statistically. Two major conclusions can be drawn. First, the presence of BM infiltration per se within each of the three major prognostic groups seems not to affect survival. Second, leukemic presentation in IGML and late leukemic conversion in LGML are associated with a worse prognosis.

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

104 PATTERNS OF SURVIVAL IN NON-HODGKIN'S LYMPHOMA (NHL). T. Reichert, R. Christensen, A. Bartolucci, C. Walker, J. Moore. Duke University Medical Center, Durham, NC 27710, Entropy Limited, Lincoln, MA 011773, and SECSG Statistical Center, Birmingham, AL 35294.

NHL is a heterogeneous group of diseases which are often separated into two groups (favorable versus unfavorable) based on little more than the presence or absence of a nodular pattern of growth within the tumor. Refinements in description based on light microscopic criteria and even cell surface phenotype determinants have not yet provided information of additional prognostic utility. 334 previously untreated patients with advanced stage NHL were enrolled in a Southeastern Cancer Study Group (SECSG) clinical trial of cyclophosphamide, vincristine and prednisone (COP) versus the same regimen plus BCNU. No response or survival differences were noted between the regimens. Using a computer method which constructs constellations of patient characteristics and evaluates them for their ability to predict survival in a complete and exhaustive fashion*, we have divided the entire population of NHL patients into three groups. Those patients with performance status greater than 75%, "A" symptoms, and a normal value for the serum transaminase (SGOT) have a prolonged survival independent of disease histology and of their initial response to therapy. Those patients not so defined are also homogeneous in survival and in complete response rates except for a group having either low performance status (less than 70%) or night sweats at presentation. This latter sub-group is comprised almost entirely of patients with unfavorable histology disease. These patterns were discovered using 2/3 of the patients (224), were used to predict the survival of the remaining 110 patients in the study; and were then further validated on a dataset including all patients treated similarly at Duke University Medical Center. Nearly identical patterns were found analyzing favorable and unfavorable histology patients separately; and in other subsets of the data such as responders only. These patterns speak for the dominance of clinical heterogeneity over histologic diversity. They may well explain the wide variation in response and survival experiences reported by different institutions with similar treatment regimens (37-81% CR rate in favorable histology disease). They provide unambiguous guidelines for the deferral of treatment in a group of patients much larger than that suggested by earlier reports; and appear to explain the paradoxical survival gain reported in some series for patients with favorable histology disease who attain a complete response to therapy.

*Entropy Minimax: SWAPDP algorithm

105 PRIMARY INTESTINAL LYMPHOMA OF ADULTS IN THE MIDDLE EAST- COMPARATIVE STUDY OF IPSID VS NON-IPSID. L Hashimi, E Anaissie, C Allam, M Khalyl, P Salem. American University of Beirut Medical Center (AUBMC) Beirut, Lebanon.

Seventy five cases of primary intestinal lymphoma were diagnosed in adults at AUBMC during the period 1961-1980. Two additional cases with the pre-malignant phase of Immunoproliferative Small Intestinal Disease (IPSID) were also studied. 41.5% of patients had IPSID and 35% non-IPSID. In the remaining 23.5% it was difficult to distinguish IPSID from non-IPSID. IPSID differed from non-IPSID in the following: (1). Age: median age in IPSID was 25 yr while in non-IPSID 37 yr. (2). Clinical features: while chronic diarrhea and emaciation were the prominent clinical features at presentation in IPSID, the presence of abdominal mass and/or complications like obstruction, bleeding and perforation were the prominent features in non-IPSID. (3). Pathological features: a. IPSID was shown to involve the entirety of the small intestine as a diffuse cellular infiltrate predominantly confined to mucosa and submucosa, and in 36% of patients it was associated with tumoral masses. Non-IPSID on the other hand presented as one or more intestinal tumors in the absence of diffuse mucosal infiltrate. b. Gross pathological findings in IPSID were most conspicuous in the upper third of the small intestine while those of non-IPSID occurred primarily in the ileo-cecal region. c. The most frequent lymphoma in non-IPSID according to the Kiel classification was immunoblastic (45%), while in IPSID it was lymphoplasmacytic (41%). The cellular mucosal infiltrate in IPSID was usually lymphoplasmacytic or plasmacytic. In non-IPSID the mucosa distant to the site of tumor was free of infiltrate. (4). Immunological abnormalities: IPSID was associated with the synthesis and secretion of an abnormal IgA immunoglobulin free of light chains (α heavy chain protein). Like Burkitt's lymphoma, IPSID is a newly described disease which provides us with an opportunity to study the etiopathogenesis of lymphoproliferative disorders.

LO6 OVERVIEW: "THE IMPORTANCE OF VIRUSES IN LYMPHOMA"

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1. As "tools" in animal laboratory experiments to learn basic mechanisms of lymphomagenesis. Viruses of different forms cause different types of lymphoid neoplasias in many different animals. Sometimes this is limited to laboratory experiments, yet even in these instances more can be learned about mechanisms involved in the genesis of these lymphomas than from other causes because virus antigens and nucleic acids can be detected and the causative agent thereby can be followed. Moreover, the genes able to do this, contained in the viral genome, are packaged positive by the virus. This provides investigators with the opportunity of learning much about the genetic information which can cause lymphomas and mechanisms for their control. Some examples of such systems include the Herpes saimairi virus which apparently does not cause neoplasias in its natural host but can induce lymphomas upon inoculation of certain other monkeys and some retroviruses also by inoculation into heterologous species, e.g., lymphomas of sheep induced by bovine leukemia virus.

2. As "tools" to identify genes (onc-genes) in human DNA which may be critical to lymphomagenesis. Those animal retroviruses which cause cancers (often lymphomas) very rapidly contain a cellular derived gene, called an onc gene which codes for a protein leading to direct transformation of the cell. By using techniques of molecular biology these onc genes genes can be isolated and analyzed. Since the homologous genes in normal cells are conserved throughout evolution, they are also present in human DNA. Therefore, the isolated viral onc gene (v-onc) can be used to detect and isolate the corresponding cellular onc gene (c-onc) from DNA of normal human cells. This gene can be compared to the same gene from DNA obtained from human lymphomas to see if an important reproducible abnormality in the lymphoma gene can be found. The level of expression (transcription to mRNA) of the various c-onc genes from normal and lymphoma tissue can also be compared. We have been involved in a few studies like this which have led to interesting results, e.g., we have cloned several human onc genes, determined their chromosomal localization, and found the translocation of c-myc in Burkitt lymphoma in collaboration with C. Croce. Other approaches (DNA transfection) were chiefly made by G. Cooper and his colleagues, have led to the discovery by these investigators of new genes (e.g., B-Lym and T-Lym) which, like some other c-onc genes, may not only be involved in some lymphomas but quite likely in some aspects of normal lymphoid growth and differentiation. This technique and the above described work in animal retroviruses has opened up a new era of lymphoma research which offers us our first glimpse at the nature of genes important to lymphomagenesis and may lead to new ways to sub-classify and possibly to treat these diseases in the future.

3. As causes of naturally occurring animal and human lymphomas. In addition to producing lymphomas in the laboratory with various types of viruses (see #1), viruses are by far the most important known causes of naturally occurring lymphomas. This, of course, was first known from field animal studies and include, for example, the avian DNA virus (MDV) (a herpes virus) in Marek's disease of chickens and numerous animal lymphomas caused by RNA tumor viruses (retroviruses). Thus, avian leukosis virus, mouse amphotrophic leukemia virus, feline leukemia virus, bovine leukemia virus, and gibbon ape leukemia virus are the etiological agents of naturally occurring lymphomas of chickens, mice, cats, cows, and gibbon apes respectively. Viruses are now known to also be involved in the cause of human lymphomas. Thus, it has been suspected for some time that EBV plays a role in the early abnormalities which later due to several required additional factors leads to African Burkitt's lymphoma. The role of EBV, therefore, appears to be indirect.

In view of the known numerous animal retroviruses directly causing animal lymphomas, it was reasonable to believe that similar human retroviruses could be discovered. Thus, since Rous' discovery of the first retrovirus shortly after the turn of the century, numerous intense searches were made for this kind of virus in man. Work in this direction was greeted by pessimism and cynicism by the 1970s because of all the earlier failures. However, technological advances leading to very sensitive assays for retroviruses combined with our discovery of T-cell growth factor (IL-2), which enabled us to grow appropriate target cells for sufficient time, led us to isolate the first human leukemia/lymphoma retroviruses. Elsewhere, we have discussed the manner of isolation, nature of the HTLV positive lymphoid cell, characteristics of the disease, types of retrovirus isolated, and touched upon the epidemiology. Here I will expand on the epidemiology, and summarize some of the biological effects of these viruses and what is known or thought about the mechanism(s) involved in their induction of lymphomas. I will also describe the probable role of related retroviruses in the cause of AIDS.

4. Conclusion and Future. Work on tumor viruses has provided the beginning insights into the cause and pathogenesis of human lymphomas and already helped in lymphoma categorization. I anticipate that additional new isolates of such viruses will be found in the future and causatively linked to some other lymphomas and that work on c-onc genes will lead to new ideas of disease pathogenesis.

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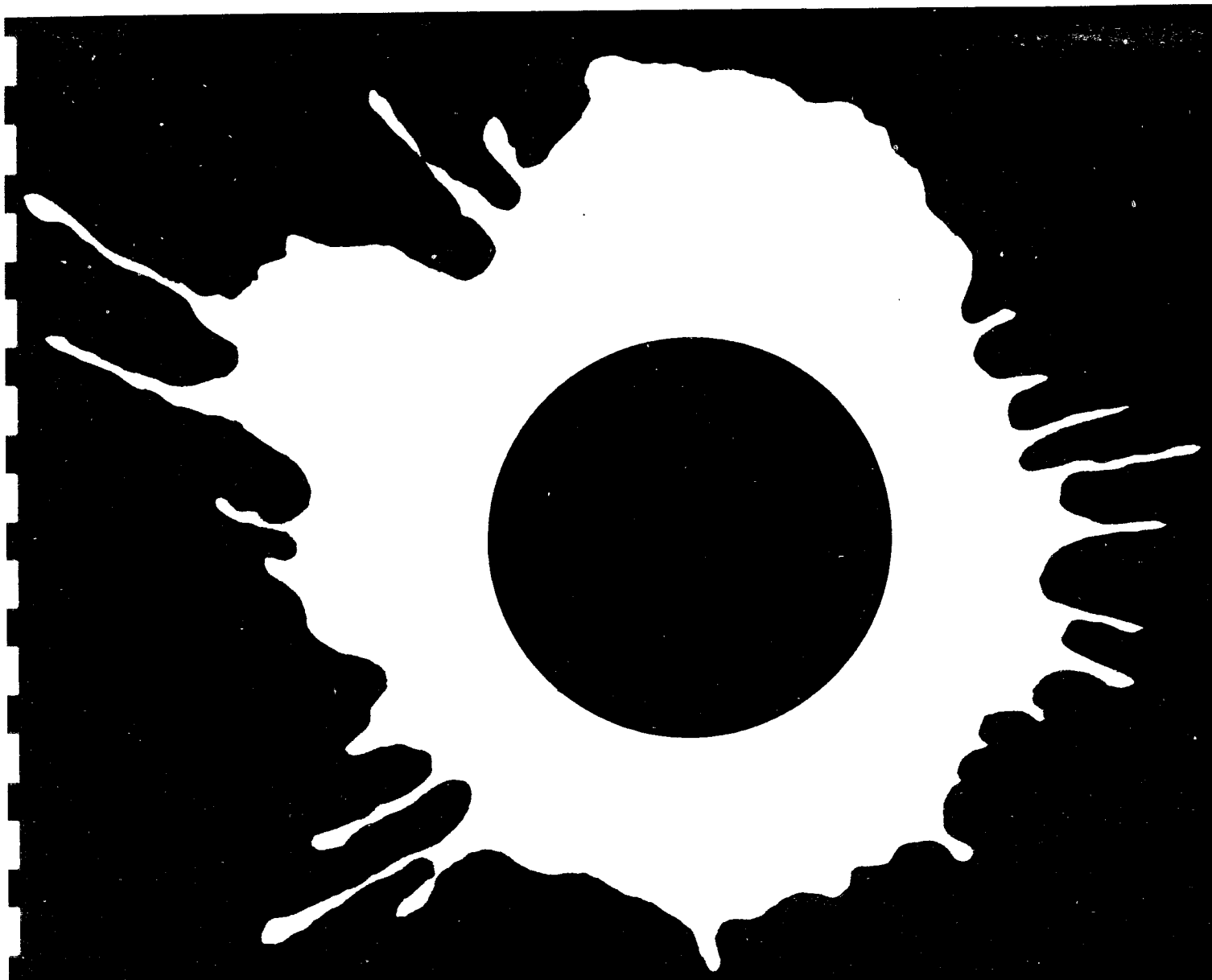

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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2. Pathologisches Institut der Universität Kiel, F.R.G.

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

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

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

P 4 UTILIZATION OF MONOCLONAL ANTIBODIES FOR PHENOTYPING OF LYMPHOPROLIFERATIVE DISORDERS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

V. Diehl, H. Burrichter, H.C. Rossbach, P. Gillow, M. Schaadt.

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

P 22 ENZYME ACTIVITIES IN HUMAN LYMPHOMAS.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

P 26 Q-LACKING TRANSFER RNA IN MALIGNANT LYMPHOMAS.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

P 31 DENDRITIC RETICULUM CELL; A GIANT CELL?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References
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P 40 MONOCLONAL GAMMOPATHY: CLINICOPATHOLOGIC AND CYTOGENETIC FINDINGS.

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

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

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

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

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

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

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

P 43 PRIMARY HISTIOCYTIC LYMPHOMA OF SKIN AND SUBCUTANEOUS TISSUES.

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

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

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

Low grade: -diffuse small lymphocytic 3

Intermediate grade:

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

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

High grade:

Immunoblastic 4 Burkitts 23 lymphoblastic 6

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

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

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

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

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

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

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

P 47 ROLE OF RESTAGING LAPAROSCOPY IN MALIGNANT LYMPHOMAS.

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

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

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

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

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

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

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

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

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

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

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

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

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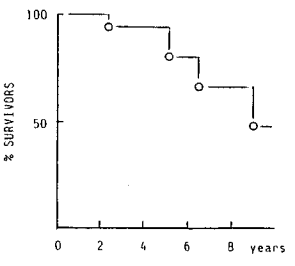
Bone involvement during first staging for HD is not unusual. However a symptomatic bone disease due to HD as initial presentation is rather rare. From Jan.1970 to Dec.1983 14 patients (pts) were referred to our institution from medical or ortopedics dep.ts because of symptomatic cancerous bone disease,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



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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

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

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

Results:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reference:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE 1 Failures According to Treatment Method and Stage

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

* Three patients excluded because they died of surgical complications.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Participating clinics: see part I.

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

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

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

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

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

Updated results on a larger series will be presented.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACTS

PRESENTATION BY TITLE ONLY

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

The authors studied inherent affinity in children with malignant lymphoma.

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

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

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

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

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

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

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

T 2 PERSISTENT LYMPHADENITIS AS A PRODROME OF ACQUIRED IMMUNE DEFICIENCY SYNDROME.
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In the present epidemic of opportunistic infections associated with the acquired immune deficiency syndrome (AIDS), persistent, often generalized lymphadenopathies are frequently observed. We have studied the histopathology and immunopathology of 54 biopsied lymph nodes in male homosexual patients and correlated the findings with the clinical presentation and immunological data. Repeat biopsies were also performed and correlated with follow-up. The lesions most commonly seen consisted of extreme hyperplasia of germinal centers showing extensive cellular destruction and phagocytosis of nuclear debris. In addition, there were focal hemorrhages, aggregates of clear cells of monocytic origin and accumulations of neutrophiles. These lesions diagnosed as acute lymphadenitis preceded in most cases by 6 to 20 months the opportunistic infections AIDS, Kaposi sarcoma or non-Hodgkin's lymphoma while in some cases the lesions were concomittant. A minority of cases were characterized by lymphocyte depletion , vascular hyperplasia and fibrosis, possibly representing the late phase of lymphadenitis. It is suggested that the systemic, persistent lymphadenitis of homosexual males is produced by a lymphotropic virus, resulting in the destruction of a certain class of lymphocytes leading to the induction of the acquired immune deficiency syndrome.

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

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

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

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

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

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

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T 5

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

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

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

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

T 6

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

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

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

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

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

T 7

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

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

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

T 8

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

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

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

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

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

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T 9

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

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

T 10

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

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

T 11

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

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

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

T 12

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

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

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

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

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

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

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

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Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, USA and Loyola University Stritch School of Medicine, Maywood, IL, USA.

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

T 15 WALDENSTROM'S MACROGLOBULINEMIA AND CHROMOSOMES

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

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

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

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T 17

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

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

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

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

T 18

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

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

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

T 19

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

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

T 20

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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T 24 T-CELL LEUKEMIAS WITH MATURE PHENOTYPE.

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

T 25

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

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

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

T 26

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

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

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

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

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

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

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

T 27

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

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

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

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

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

T 28

NON-SPECIFIC IMMUNOLOGICAL MECHANISMS AT PATIENTS WITH HODGKIN DISEASE.
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The mechanism of immunological reactivity in 47 untreated patients with Hodgkin Disease (HD) was studied by investigating the reactivity of peripheral lymphocytes to phytohemagglutinin (PHA) and by detection of the sera inhibitory factors on xenogeneic test cells.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

T 35

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

T 41

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

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

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

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

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

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

[§]see abstract number 7

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

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

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

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

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

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

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

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

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

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

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

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

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

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

T 48 NODULAR SCLEROSIS HODGKIN'S DISEASE

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

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

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

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

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

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

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

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

T 51 Subtypes of cutaneous T-cell lymphomas.

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 53 LYMPHOBLASTIC LYMPHOMAS/LEUKEMIAS IN THEIR BIMODAL DIFFERENTIATION.

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

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

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

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

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

T 55 EXCISION BIOPSIES FROM THE SPLEEN BY ULTRASOUND GUIDANCE.

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

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

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

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

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

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

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

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

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

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

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

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

T 58 PRIMARY GASTRIC LYMPHOMA IN THE MIDDLE EAST

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

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

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

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

T 65

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

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

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

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

T 66

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

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

T 67

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

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

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

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

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

T 68

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

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

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

T 70

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

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

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

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

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

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

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

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T 73

CHILDHOOD ABDOMINAL LYMPHOMAS IN THE MIDDLE EAST

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

T 74

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

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

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

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

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

T 75

SECONDARY IMMUNODEFICIENCY OF CHILDHOOD MALIGNANT LYMPHOMAS

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

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

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

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

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

T 76

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

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Baker Al-Awamy, M.D.

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

Results of a cooperative pilot study

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

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

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

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

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

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

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

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

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

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

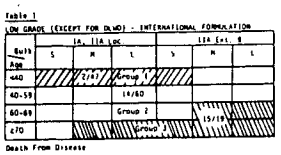
Prognostic factors determining cause-specific survival were derived from 716 patients (≥17 years) with clinical stage (CS) I and II NHL referred between 1967-1978. Significant independent prognostic factors ranked by Cox Regression were disease bulk, age, stage and histology.

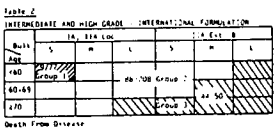
The effect of XRT was determined by analysis of 496 patients receiving XRT as first therapy. As relative rates of death from disease differed markedly for low-grade (LG) versus IG/HG histologies, cause-specific mortality was analysed using multiple prognostic factors for LG and IG/HG histologies separately.

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

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

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





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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

Participating clinics: see part I.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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

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

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

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

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

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

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

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

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

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

T 95

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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T 101

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

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

T 102

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

T 103

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

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

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

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

T 104

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

T 109

Late Complications after treatment of Hodgkin's disease.
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Since 1974 we have treated 512 HD and observed three major types of late complications: 1) ANLL induced
2) Failures in genital functions
3) Persistent chronic hepathitis

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

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

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

T 110

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

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

T 111

HODGKIN'S DISEASE (HD) AND PREGNANCY

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

T 112

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

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

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

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

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

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

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

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

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

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

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

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

T 117

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

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

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