ABSTRACTS

ORAL PRESENTATIONS
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.
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OVERVIEW ON CURRENT TOPICS IN CLINICAL RESEARCH.

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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 elucidating 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 radiolabeled Ki 1 detects HD-tumors transplanted on nude mice.

V. Diehl, Universität Köln, Köln
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ORIGIN AND BIOLOGIC FUNCTION OF REED-STERNBERG CELLS. Richard J. Fischer, Volkert Diehl, Susan S. 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 Hochschule Hannover, Hannover, Germany.

Reed-Sternberg cells in biopsies from patients with Hodgkin's disease express la 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 reaction (J. Immunol. 89:3). Significant proliferative occurred when mono-nuclear 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-la 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 la-bearing cells and adherent cells do not proliferate in response to concanavalin A. The addition of as few as 1 x 10^5 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 impaired 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 manner (AACR, 1984). T cell lines from MA-D85 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 toxoid. Thus the L428 cells possess all the characteristics of antigen presenting cells.

A murine monoclonal antibody termed Hef-1 that selectively binds Reed-Sternberg cells in 10/18 tissue biopsies has been produced following immunization with the L428 cells. The antigen recognized by Hef-1 is a 120 KD glycoprotein that does not reside in vitro. Hef-1 does not block the ability to the L428 cells to stimulate a mixed lymphocyte culture or function as antigen presenting 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.

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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 areas of lymph nodes, a low 10 peripheral blood B-cells, tissue macrophages, and colonic surface epithelium. Immunoprecipitation studies revealed that Lym-1 recognizes a polypeptide in the range of 31-35 kD. Western blotting of cell surface reactivity with a subset of B-cell tumors and its low reactivity with normal organs. Lym-1 was reacted in a nude mouse animal system and in volunteer cancer patients for its radiolabeled capabilities. Lym-1 (IgG2a) was purified from ascites fluid by ammonium sulfate precipitation and Protein A affinity chromatography. Radio labeling of whole antibody, F(ab')2, and F(ab')2 fragments was achieved with I-131 using solid phase DCC, with I-123 using chloramine-T, and with Cu-67 using benal DTPA bifunctional chelation. At 48 h mice bearing right thigh Raji tumors were injected with 150-300 wCi of radiolabeled I-131 and imaged up to 7 days after injection at which time the animals were sacrificed and distribution performed. Highest tumor uptake was observed for radiolabeled whole antibody followed by F(ab')2, and F(ab')2 fragments. These studies showed that specific and significant tumor uptake of radiolabeled I-131 could be achieved since 4-8 days and 15-26% of the injected dose of I-131 and Cu-67 labeled Lym-1, respectively, was localized to the tumor. With I-131, optimal tumor visualization for radiolabeled 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 I-123-131-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.
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THE ANTIDIOTYPE THERAPY OF MALIGNANT LYMOPHYAL INTRAPARENCHYMAL ANTIBOIES

against B-cell lymphomas

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Five monoclonal antibodies have been made against the idiotype of the
malignant lymphoma 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 IgG2a 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 negligible amount of free idiotype. 3 different regimens were tried:
escalation by doubling the dose every 2 days from 5 mg to 160 mg, rapid
escalation by doubling the dose every 2 days from 5 mg to 160 mg, and bolus
injections at a constant infusion. Free antibody levels in the serum (10
ng/ml) and in the blood, bone marrow, lymph nodes, and blood.

In patient Top, the response was delayed by 2 weeks and the number of
lymphocytes dropped to 5 x 10^9. In patient Klos, the response was
immediate and the number of lymphocytes dropped to 2 x 10^9.

Neither patient has shown any toxicity, liver or renal function
and complement status are unaltered.

5 see abstract number T-41

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THE IMMUNOLOGY OF B-CELL LYMPHOMA

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Human B cell lymphomas are considered to be monoclonal cell populations,
which are derived from a single original transformed cell. This notion is based on
analyses of karyotypes, chromosome-linked enzymes, and immunglobulin
proteins. The cell surface immunoglobulin of each B cell tumor is idio-
typically distinct. We have produced anti-idiotype antibodies for a series of 25
patients with B cell lymphomas. Each antibody is specific reactive with
only one patient. These antibodies have been used as diagnostic monitoring reagents, as therapeutic agents, and as
probes for the biology of the disease.

Immunosassays have been performed on serum from a series of B lymphoma patients using the anti-idiotype antibody
between patients but characteristic.

Serial determinations of serum idiotypic correlate well with tumor burden.
The serum idiotype can be lowered.

Therapeutic trials and these will be discussed. Obstacles to therapeutic effect have been
identified. These include serum anti-idiotype antibodies 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 nonpolymorphic 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 immunglobulins as defined by protein structure and molecular probes. Triggering of the T3/ft molecule complex results in clonal T cell proliferation utilizing an IL2 dependent autocrine pathway. The associative recognition structures defined by the 76 KD ti 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 Ti 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, DQ or BQ (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 LYMPHOMA: CORRELATION WITH MORPHOLOGY AND FUNCTION. T. S. Jaffe, M.D., J. Gossman, M.D., L. H. Lock, Ph.D., R. M. Brasile, M.D., and C. Simeri, M.D. NCI, Bethesda MD, USA.

Modern immunology has been instrumental in the delineation of distinct clinicopathologic entities within the heterogeneous non-Hodgkin's Lymphomas. The low grade B cell lymphomas; Bcellular 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 (Sg) in association with HLA-DR and with either B1 or B2, but differed in reactivity with Leu 1 (p65), B2-2 (p50), and J5 (GAL). All FL were Leu 1+, B2-2-, and were + with J5 in 50% of cases. IDL were all three of the above reagents, whereas WDL were Leu 1+, B2-2+ and variably J5+. Fluorescence intensities observed for St, B1- and B2-2 showed a sequential decrease; i.e., FL>IDL-WDL.

Correlative studies were also performed to study the interrelationship of function, i.e., immunglobulin secretion, with morphologic and immunophenotypic characterization. WDL were readily induced to secrete monoclonal Ig after exposure to the phorbol ester TPA. Ig secretion did not require the addition of autologous 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 autologous 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 ratio 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 Ig 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, 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 heterogeneous clinically and morphologically and represent a spectrum from low grade (T-CLL) to high grade (large cell, immunoblastic) malignancies. Post-post-thymic lymphomas express a helper antigenic phenotype, but correlations between phenotype and function are not consistently observed (6). Cells from angiocentric immunoproliferative lesions (lymphoma-toid granulomas) and the T-cell angiocentric lymphomas that supervene secrete a phagocyte-inducing lymphokine, which may lead to an erythropagocytic syndrome mimicking malignant histiocytosis clinically and pathologically (7,8).
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REFERENCES


11 FUNCTIONAL INTERACTIONS OF MALIGNANT CELLS DURING B CELL LYMPHOMAGENESIS. Carol L. Reinsch, Dept. of Comparative Medicine, Tufts University School of Veterinary Medicine, 116 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 Waldenström 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.

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, Lyt1 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. 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 Lyt1, Qa1 T cells during B cell lymphomagenesis, and suggest that there may be two aspects of tumor progression. Emphasize that understanding the pathogenesis of non-Hodgkin 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 MITOKIN RESPONSIVENESS IN RELATION TO PROGNOSIS IN PATIENTS WITH NON-HODGKIN LYMPHOMA

Lindemura, C., Bamberfeld, P., Bjorkholm, M., Christensen, B., Hola, G., Johansson, B., Mellstedt, H. Radumondem and Dept. of Radiotherapy, Dept. of Pathology, Karolinska Hospital, Dept. of Medicine, Danderyd Hospital, Dept. of Immunology, Huddinge Hospital, Stockholm, Sweden.

Non-Hodgkin lymphomas (NHL) are mostly of B cell type. Non-lymphoid NHL patients often have blood lymphocytes with an abnormal ratio between K- and A-bearing lymphocytes (normal range 1.0-3.3) with an increase in lymphocytes with the same light chain phenotype as lymph node tumor cells. Lymphocytes having specificity for the same antigenic determinant carrying the same light chain isotype of the clinical antigenic combining sites belong to the same clone. Thus, a blood K:A ratio outside the normal range with a selective increase of lymphocytes of the same light chain type as in tumor 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) (Cancer 1979, 757, 1983; Scand J Hematol 30, 66, 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 IF using Fab' fragments of antibodies. Lymphocyte response to ConA and PWM stimulation were measured after incubation with ACTH.

Forty per cent of the untreated patients had a ratio between K- and A-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 IC (6%). Patients with CB/CC lymphomas and normal K:A ratios survived significantly longer than those with abnormal ratios (p < 0.01). The mean total number of OKT3+ (PAN-I) 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 - 1.50 of healthy controls) to ConA 20 μg/ml had a significantly longer duration of clinical remission time than those with a subnormal response.

It is concluded that an abnormal lymphoeyte K:A 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. V. Georgoulas and C. Joxinin, Laboratoire d'Oncogenese Appliquee, INSERM USO5, Hospital Paul Brousse, Villejuif 94800, Paris, France.

Peripheral blood T-cell colony forming cells (T-CFC) from patients with T-cell malignancies can generate T-cell colonies in methycellulose in the absence of added growth factors. In 13 out of 25 patients, less spontaneous colonies were obtained from EOKT3+ cells than from unseparated peripheral blood lymphocytes (PBL). Irradiated autologous but not E cells from normal subjects enhanced the plating efficiency of EOKT3+ precursors in co-culture experiments either in methycellulose or in separate agar/methylcellulose. Conditioned media prepared from leukemic blasts (98B plus E cells) was able to induce T-cell colony growth from normal mature(E) and immature(EOKT3+) T-CFC. Depletion of PBL by plastic adherence resulted in a decrease of colony number in 4 of 4 patients. Accessory adherent cells were HLA-DR+ (as determined by treatment with a pool of 4 anti-HLA monoclonal antibodies and complement). Irradiated adherent cells enhanced the plating efficiency from adherent-depleted PBL in co-culture experiments in methycellulose 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. E 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.

We have previously reported the natural development of nodular (Blood 60;11A, 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 neoplastic process in murine NHL. One hundred Balb C mice between the ages of 16-18 months were divided into three groups. All animals were hemiplegic over the right side. All animals were treated with either 1 x 10^6 enriched T cells or 1 x 10^8 enriched activated peritoneal macrophages (M) or 4 x 10^7 enriched natural killer cells (NK) once, or 10 units ILL once with 10 units ILL once or saline (controls). The mice were monitored weekly for Karp/Lambtha ratio, PBT cell % and automated CBCs and sacrificed at 36 days. Histologic evaluation was performed at the time of hemiplegia and sacrifice. 40% of the T cell group and 70% of the NK group demonstrated NHL on initial evaluation. All of the T cell group and 42% of the NK group demonstrated progression of disease activity (SGCL-MKLL). Similar results occurred in short term experiments employing purified ILL. The results of these studies suggest that T cell imbalances are associated with alteration of disease activity in NHL and suggest that immunoregulatory T cells and/or immunocytogenically purified lymphokines from these cells may prove beneficial in the treatment of NHL.

This work is supported in part by VA Research Service; NIH Grans RO8105, CA20660, HL23290; a VA Clinical Investigatorship, the American Lung Association and the Marcus Foundation.

15 HLV IN LYMPHOMA LEUKEMIAS AND LYMPHOMAS: R. C. Gallo, Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

As discussed elsewhere at these meetings HLV 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 lymphotrophic, (3) contain a reverse transcriptase of 100,000 Daltons which is Mg^2+ preferring for its catalytic activity, (4) have unusually large long terminal repeat sequences (LTR), (5) abrogate normal T-cell function, (6) sometime 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 HLV-I. A few are less than 10% homologous to HLV-I and are called HLV-II. They were obtained from a hairy cell leukemia and a AIDS patient. Numerous additional isolates have been obtained from HLV-I and HLV-II patients with AIDS. The analyses of them is in progress.

HLV-I is the subgroup closely linked to the cause of a certain T-cell malignancy. This disease covers a spectrum of histologically-defined lymphoreticular neoplasms which HLV-I now defines as a distinct clinical entity, usually of T4*, T6*, 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 HLV-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 HLV nucleic acid sequences in the DNA of the neoplastic T-cells, and several other results from molecular biological experiments make HLV, 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.

HLV-I may also be involved in the cause of a fraction of mycosis fungoided and Sézary cases and indirectly in some B-cell neoplasias as will be discussed. Finally, variants of these retroviruses may be important in AIDS.
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16 THE CURRENT STATUS OF NCI TRIALS IN Hodgkin's DISEASE.
Robert C. Young, Dan L. Longo, Eli Glasstein, Pat L. Daffey, Charles F. Winkler, Peter H. Wiernik, and Vincent T. DeVita, Jr., NCI, Bethesda, MD & Univ. of MD Hospital, Baltimore, MD

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 1500 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 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 the patients who fail initial induction or relapse within one year of initial 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 therapy. The regimen substitutes two chemotherapy drugs for the radiotherapy in the Goldie-Coldman sequence.

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 CS1, 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 PSIII A 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, followed by 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 patients with mediastinal 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/ABV0 IN HODGKIN’S DISEASE:
UPATED RESULTS. C. Bondanini, 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/ABV0 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 (X) MOPP/ABV0 (%) P
Progression 30.6 4.6 <0.001
Freedom from progression 75.7 88.9 0.14
Bulky disease 57.1 88.9 0.10
Non bulky 84.6 88.9 0.77
"A" symptoms 76.9 87.5 0.16
"B" symptoms 73.3 90.3 0.10
NS histology 76.0 90.5 0.20
Others 72.2 90.5 0.10
< 40 yrs 78.6 82.8 0.94
> 40 yrs 58.7 100 0.06
Relapse-free survival 56.4 76.8 0.004
Bulky disease 75.7 76.8 0.06
Non bulky 68.7 76.6 0.04
"A" symptoms 60.0 63.5 0.36
"B" symptoms 64.5 75.5 0.006
NS histology 55.9 86.7 0.01
Others 30.8 56.7 0.10
< 40 yrs 85.3 75.9 0.004
> 40 yrs 51.3 70.2 0.50
Survival of C1 71.2 90.3 0.028
Overall survival 81.1 82.3 0.063
MOPP/ABV0 was superior in all prognostic 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
IT (Bulky), IIb, III and IV comparing MOPP/ABV0 (MM/MA) vs half
of either regimen within a month period (MM/MA). Low dose RT
(1500 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/MA
MM/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.

19
COMBINED MODALITY THERAPY FOR HODGKIN’S DISEASE.
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The integration of intensive multi-agent chemotherapy and radio-
therapy for the management of Hodgkin’s disease is predicated on
a major appeal, i.e., patients who failed chemotherapy are most
likely to fail in sites of prior involvement, whereas patients
who fail radiotherapy are most likely to fail outside the field
of radiation. When these modalities are put together for the man-
gement of Hodgkin’s 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 re-
mains very important.

This presentation will review the results of combined modality
approaches published in various medical centers with special em-
phasis 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 steri-
izing Hodgkin’s 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.
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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 rad) 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 estimate 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 invariably 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.
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22

SECONDARY ACUTE NONLYMPHOCYTIC LEUKEMIA (ANLL) AND DISSEMINATED
LYMPHATIC SYNDROME (DMPS): A MODEL OF LEUKEMOGENESIS WITH IM-
PLICATIONS IN THE PRIMARY TREATMENT OF LYMPHOMAS.

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: 33 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 CT only, all but 2 with pelvic ports; 21 had CT only, with
either prolonged alkylating agent therapy (alk ag tx) or mech 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 7
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 65/61 (10%) secondary DMPS/ANLL pts. A higher frequency than in
ANLL de novo (35%). Only 1 pt had sq- as the only abn. Deletion
analyses of 5 and 7 showed that (5) (q34-35) and (7) (q31-32) were con-
sistently lost. The oncogene c-myc has been localized to Sq34. Chr
abn were unrelated to sex, age, 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 vs. 10/73 or 6% ANLL, p = .02). Median sur-
vival 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 Chs in 4 pts treated with high dose Ara-C. From this analysis
we suggest the following conclusions: 1) pelvic portals are causa-
tively implicated in the pts who only had primary RT; 2) all but 1 CT
only pt had high dose alk ag tx or mech CCNU 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
modem 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 ORTC Radiotherapy-Chemotherapy Group.

Two successive cohorts of patients with HD clinical stages I-II (HI
trial : 1964-71, 334 pts; H2 trial : 1977-78, 300 pts) were prospect-
ively followed. Thirty-four second cancers (SC) were registered, 21
in the HI trial and 13 in the H2 trial, including 5 leukemias (4+2),
4 Hodgkin lymphomas (1+3) and 24 solid tumors (14+10). Initial
treatment were a) in the HI trial : regional radiotherapy (RT) at
40 Gy with or without vinblastine (VBL) for two years; b) in the H2
trial regional RT at 40 Gy plus para aortic and spleen RT at 40 Gy
or the same RT after laparotomy+splenectomy. Moreover, patients
with mixed cellularity or lymphocyte depletion histological types were
randomised between VBL or a combination of VBL + procabazine (PCZ)
for two years. For the present study, three treatment groups were dis-
tinctly: patients without relapse (No Rel.), relapsing patients
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 occurrence of SC did not differ
regardless of whether the patients received CT or not, and, in the
H2 trial, whether or not they received VBL or VBL+PCZ. A time-
dependent covariate analysis was used to assess the contribution of
each type of therapy on occurrence of SC. Time lapse to SC ranged from
2 to 16 years (HI) and from 3 to 9 years (H2) after initial treatment,
and from 0 to 12 years (HI) and from 2 to 6 years (H2) after retreat-
ment. The relative risk (RR) of leukemias in the "Poly-CT"-group was 3.00 in the HI trial (p=0.001) relative to the general popu-
lation incidence rates and 2.00 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 25 (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 5.14 (p=0.001). Comparison of occurrence 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 ini-
tial 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 35% in the H2 trial
(p=0.016). In the H2 trial, extensive RT to para aortic and spleen re-
gions may be responsible for the excess of solid tumors (bowel
and kidney) observed. The most important factors for developing 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 HI trial.
24 LACK OF CORRELATION OF ANN ARBOR CLINICAL PARAMETERS AND IV HODGKIN'S DISEASE: A SOUTHWEST ONCOLOGY GROUP (SWOG) STUDY. C. Fabian, R. Denny, C. Menfield, D. Dixon, University of Kansas Medical Center, Kansas City, KS 66103, and SWOG Biostatistical Office, Houston, TX 77030.

We reviewed the clinical and pathological staging of 273 eligible patients (pts) with pathologic stage I-II or IV Hodgkin's disease receiving induction chemotherapy +/- involved field radiotherapy consolidation as part of SWOG 7802. Pre-study forms gathered clinical pathology and radiology reports were reviewed. Of 197 pts that had liver biopsies (BK), 24% (47) were positive (pos) by percutaneous (percu) BK or by BK obtained at laparotomy (lap), of those 150 determined negative (neg), 37% (55) had only a percu BK while 63% (95) had a BK at lap (+- a percu BK). 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 abnormal liver function test, were correlated with BK result.

45% (21/47) pts with a pos liver BK had negative AA clinical criteria for liver involvement. Conversely 20% of pts with a lap neg liver BK had pos AA criteria for liver involvement. 21% (10/47) pts with a pos liver BK were clinical stage IIIA or less, whereas 11% (7/66) of all pts stage IIIA or less eligible for the study. None of the pts with clinical stage IIIA or less rendered pathologic stage IV by liver BK had pos bone marrow or any other pathologic evidence of stage IV disease. 64% (26/41) of pts with a pos liver BK had a neg liver scan. 50% (16/32) of pts with a pos liver BK had a neg CT of the liver. 26% had a lap liver BK following a neg percu BK. The false neg rate was 31%.

152/197 pts were response evaluable (32 too early, 10 not evaluable). The CR rate for 123 pts who were AA clinical criteria neg but liver BK pos (AA-BK+) but were not different from the 95 pts who were criteria and BK neg (AA-BK-) (65 vs. 70%). The CR rates were similar despite the fact that only 15% of the AA-BK+ group as opposed to 100% of the AA-BK- group were pathologic stage IV.

We conclude that (1) AA clinical criteria are not useful in predicting liver involvement; (2) percu liver BK is not useful when neg; (3) pts with clinical stage IIIA or less should have an open liver BK 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 SPLENOLOGY.

A controlled clinical trial (H 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 trial was to compare the efficacy of splenic irradiation and of splenectomy. (b) to assess the prognostic significance of the information provided by laparotomy. For this purpose, a schedule with pathological stages (P) I, II and III received the same radiotherapy (mantle field and para-aortic lymph node); (c) to compare for these patients with poor histological subtypes (mixed cellularity, nodular sclerosis, lymphoma depletion, etc.) two schedules of long term chemotherapy: either Vinblastine (VL) alone or VL + Procarbazine (PC); the results of the trial including 300 patients with at least 8 years follow-up for the last patients randomised are presented. Forty-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 overall 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 sequelae of treatment (5 cases), intercurrent disease (12 cases) and secondary cancer or leukemia (4 cases). Non-lethal complications of the treatment were mainly complications of the digestive tract. In the group treated by laparotomy and radiotherapy (124 patients) we observed 25 digestive complications (9 small bowel obstruction, 16 ulceri, i.e. 1.7% 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 (initial treatment: splenectomy or splenic irradiation).

Multivariate analysis was performed to study the prognostic factors and showed that high-risk parameters were: 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 dismalation 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 allow may be adequate in "low-risk patients".

N. Hayat, Villejuif, France
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 (66% 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 0.002). 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 0.26). 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), leukemonephropathy (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 schwannoma. 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 MOFF CHEMOTHERAPY IN HODGKIN'S DISEASE (HD). UPDATED RESULTS.


121 patients (pts) with HD clinical staged, were treated by two different, successive protocols. 66 pts, 1 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 a 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 were 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.

Persistent 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 1.5 % and 2 %. CR rate was 94 % (66/69) 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 treat splenic occult disease in CS I-II, I B, II B with supradiaphragmatic presentation and to achieved CR when combined with RT.
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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 1960 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 characteristic of the patient population was 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 IIA 5; PS IIB: 1; PS III: 1; CS IIA: 5; CS IIB: 1; CS III: 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 V' 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 (CM) 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 (B) from non-lymphoblastic (A) 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 (SCHN Total Therapy 'B', SFOP LMB-01-D2, and FM 81-B) have reported major improvements (to 65-75%) in the cureability 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.
RESULTS OF THE BPM THERAPY FOR CHILDHOOD NON-HODGKIN'S LYMPHOMA. IMPROVEMENT OF PROGNOSIS BY ADAPTATION OF CHEMOTHERAPY TO STAGE AND TYPE.


Treatment of childhood NHL has been increasingly aggressive, but mostly did not take into account the heterogeneity of these diseases. In the BPM study 1979/81, childhood NHL was treated uniformly with a chemotherapy regimen, which has been shown 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 Hug, the probability of continuous complete remission (CCR) after 8 years is excellent for Non-B-NHL (70%, n=42), but poor for B-NHL (34%, n=29). B-NHL was 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 major changes. Two slightly different, alternating chemotherapy blocks were given in B-Neoplasias: Block 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. Block 2: As block 1, but ADR 50 mg/m² instead of VM 26/ARA-C 50 mg/m² day 5. Patients with stage I and resectable stage II B-NHL (stage "II-R") mostly received 4 blocks of these blocks within 8 weeks, disseminated and not resectable intraabdominal B-NHL (stage "II-NR") 8 blocks in absence of approximately 20 weeks. No continuation therapy was given. Second look laparotomy 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 (n=19) of: 90% Non-B-NHL, stage I/II (n=9); 100% Non-B-NHL, stage III/IV (n=33); 75% B-NHL, stage I/II-R (n=9); 60% B-NHL, stage II-NR/IV (n=3): 65%. B-ALL (n=2): 49%.

In conclusion, our results indicate, that treatment of B-NHL and B-ALL has to be different from treatment of Non-B-Neoplasias, and even B-ALL has been greatly improved by the BPM therapy designed for more specific treatment of these diseases.

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)

C. Patte, Th. Philip, A. Bernard, E. Bent-Lemoine, F. Demedico, Ch. Rodary, P. Bryon, J. Lemerle

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 stage IV B-NHL (st. III, IV and B-ALL), a new protocol, called LMN, was designed in February 1981. The protocol was as follows:

A. Induction with 1) COP-COPAD-M: CPN: 0.5 g/m² Day (1) OR (2); 5 mg/m² D2, 7, 8; MTH: 2 mg/m² D2, 5, 10; PREM: 2 mg/kg D1 to D10; ADR: 60 mg/m² D1, 5, 10, 21; MMTX: 15 mg/m² D0, 5, 10; "COPAD-M" courses as before from D5 to D31; "CAMAD" courses: ARA-C: 100 mg/m² D1 to D5 in continuous infusion (CI) D1 to D5; L-ASP: 1000 U/kg D2 to D5; MTH: 3 g/m² D5; 45 mg/m² D5 and 6 D; MMTX: 15 mg/m² D1; IT-ARA-C: 30 mg/m² D2; 4) "MINI-BACT" course: BOCN: 60 mg/m² D0; ARA-C: 100 mg/m² D0 to 4; CPN: 0.5 g/m² D1, 2, 3, and 4 TG: 150 mg/m² D0 to 4.

B. No radiotherapy at all.

C. Maintenance mode of two monthly alternative courses: 1) COP-MTX: 3 g/m² D0; CPN: 0.5 g/m² D0; ADR: 60 mg/m² D1; VCR: 2 mg/m² D3; MTH: 2 mg/kg D0 to 4 and D3, MMTX: 15 mg/m² D1; BOCN: 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 to 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: CPN 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 randomized study. According to the Rung'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 CMS involvement) and 20 B-ALL (8 had CMS involvement and 10 blast cells in blood). Actuarial survival for all patients is 74.5, 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 CMS involvement in both st. IV and B-ALL. The actuarial survival is 80% for the 17 st. IV and B-ALL patients without CMS involvement and 30% for the 16 with CMS involvement.

In conclusion, this protocol has considerably improved survival for st. IV NHL and B-ALL. For a next study, we consider to diminish length of protocol for all patients without CMS involvement and to intensify it for patients with CMS involvement.
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32 THERAPY OF UNDIFFERENTIATED (INCLUDING BURKITT'S) AND LYMPHOMASTIC 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 4-hour infusion of methotrexate (total 2.7 mg/m²) with leukovorin rescue is administered 10 days (first 6 cycles) or 14 days (last 9 cycles) after a combination of cyclophosphamide (11.2 g/m², given alone in the first cycle), vincristine (1.4 mg/m²), Adriamycin (40 mg/m²), and prednisone (40 mg/m² daily x 9). Intensive intrathecal therapy is given as CNS prophylaxis. Radiation is used only in exceptional circumstances (e.g., paraplegia). Approximately 90% of patients have 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 lymphomas (without marrow involvement) or completely resected abdominal undifferentiated lymphomas 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 10% at 2 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 of age. 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 common 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.


During the past decade, a large improvement has been made concerning the understanding and the prognosis of pediatric (ped.) non-Hodgkin’s lymphoma (NHL). Until the late sixties, 90% 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 these historical cases were about 10% extended forms) to 40% (localised forms) long-term survival. The bone marrow involvement led to classify some NHL as leukemias and therefore were not included in those 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 aggressive clinical course which has to be opposed by a vigorous 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 (s) than the Ann Arbor’s staging system. During this period, all of us pointed out the great value of the histological features of the ped. NHL: 1) 1) being almost always of the diffuse histologic pattern; 2) With about 40% of them originated from B-lymphocyes (most of them classified as Burkitt type) with prominent abdominal symptomatology; 3) 3) and most of the rest with T-lymphocytes lineages (lymphoblastic) explaining the occurrence of mediastinal extension in about one third of the children. The therapeutic approach become therefore specific with immediate and heavy treatment, systematic CNS prophylaxis, giving 55% overall long-term survival in localized form and about 50% in non-localized NHL, using chemotherapy regimens such as LSA-L, and "COMB." This study of Muller and others (1980) pointed out: i) The different therapeutic approaches that should be done according to the B or T-lymphocytes of the proliferation, on which are based now most of the up to date treatments: non-localized lymphoblastic type NHL should be treated more aggressively, almost like acute leukemias with regimens which include Cytoxane, Ara-C, and Ara-A, as such as the "Vincant" or the "LSA-L." The results of such treatments, in this indication reach probably now a better than 75% cure rate. The treatment of non-localized B-lymphocytes type NHL can be slightly less aggressive with regimens such as "COMB" which allows to use Methylprednisolone and Cyclophosphamide, those two drugs highly improving the results in non-differentiated or Burkitt NHL with 85% long-term survival. Except perhaps for some very localized non-lymphoblastic forms, CNS prophylaxis is always imperative but sterilization may not be mandatory.
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With the objective of reducing acute and late complications from surgical diagnostic procedures and from extensive radiation therapy, since 1979 a new therapeutic approach has been devised and applied to children and adolescents with nodal extent of Hodgkin's disease. The initial treatment for all patients, regardless of stage and histologic subtype, consisted of three monthly cycles of ABVD (vinblastine 25 mg/m², adriamycin 40 mg/m², DTIC 375 mg/m²). Sequentially, RT was delivered according to the type of clinical response induced by chemotherapy: 30-35 Gy to involved areas (IA) in complete and partial responders, respectively; 25 Gy to the adjacent area(s). Three additional courses of ABVD were then given only to patients with stage IIB and II A1 and B. Thirty-four consecutive children (age 3 to 15 yrs) were staged as follows: A; 7, B; 7. According to histology, patients were classified into the following subtypes: LP 2, ECG 12, CM 20. Following initial ABVD, CR was achieved in 16 of 19 patients (84%) with stage I and II A1 and in 4 of 5 (80%) in 3 patients. Stage IIB and II A2 and B attained CR in 6 of 15 (40%) and PR in 9 cases. After a median follow-up of 30 months, 33 of 34 children remain alive and progression-free. Only one child with stage IIB relapsed two months after completion of the treatment program and were almost always severe. No patient showed either cardiac or respiratory abnormalities. In children followed for more than 2 years the results as well as endocrine and genitourinary function were unaffected. 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 CHEMOTHERAPY 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 to 16 yrs, median 11 yrs; 55% males, 45% females; 15% ECG, 79% LP). Laparotomy was done in 164 pts and splenectomy in 159 pts. Chemotherapy consisting of 2 OPPA cycles (Oncovine, Procarbazine, Prednisone, Adriamycin) 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 (PI) 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 years are 91% in the total group and 89% (1) 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/II A 2 x OPPA, stage I/II A 2 x OPPA plus 2 x COPP, stage IIB/IV 2 x OPPA plus 4 x COPP. Irradiation is limited to EF, 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 [R. C. R. Pham. Pediat. 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, B) had a relapse in its lungs. 2 pts (stage I/II A) died of infections. Projected disease free survival rates after 2 yrs are 100% for stage I/II A (n=64) as well as for stage IIB/IIIA (n=36) and 86% for stage IIB/IV (n=30).
36 HODGKIN'S DISEASE (HD) IN CHILDHOOD: TREATMENT WITH CHEMOTHERAPY AND LOW-DOSE RADIATION. RATIONALE AND FEASIBILITY

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Dramatic improvement in survival and relapse-free survival (RFS) has been obtained in childhood HD employing extended field 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 results.

With this aim, 4000 rads radiation was first limited to involved fields (IF) and chemotherapy lowered to 3 cycles of MOPP on the first step. In 65 clinically staged patients (CS IA-CS III B) the overall 5 years survival was 93% and RFS was 85%.

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 on 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) CSII-1IA - randomized CT; 2) ABVD vs alternating 2 MOPP-2 ABVD then RT 2000 rads to IF (stages II upper neck disease are excluded from randomization but given 4 ABVD before RT), 2) CSIIH-1IB-IIIA-1IV alternating 3 MOPP-3 ABVD then RT 2000 rads to IF and lumboaortic 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 obtain "good remission" (defined as complete remission or at least reduction of tumor by 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 CSII-1IA, 7 CSII-1IB, 8 CSIIH, 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.


From 4/1972 to 5/1980, 72 children and adolescents (age, range 5-19 years, median 16) with HD, CS IA-IIB (IA:18, IIA:2, II:15, areas involved on the same side of the diaphragm: 25, IIA + A, 3 areas or more: 16, IIB:15) were prospectively treated by 2 successive clinical trials (HT2 and HT7). CS IA and IIA received 3 MOPP and supradiaphragmatic RT (40 Gy); no laparotomy was performed. CS IIA + A and IIB received 6 MOPP (HT2), 3 MOPP or 3 CVPP (CCNU, Vinblastine, Procarbazine, Prednisone) (HT7) 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, 71/72 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 ≤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). Azospermia 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 splenectomized
TREATMENT OF CHILDHOOD HODGKIN'S DISEASE STAGE I AND II WITHOUT RADIOTHERAPY


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 I and II 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 adults. However, during the past decade it has become clear that the late sequelae from radiotherapy are more serious in children. With demonstrable reduced growth, endocrine disorders, thyroid and bone changes, and increased risks of second malignant neoplasms, it is increasingly important to avoid radiation-associated damage. Consequently, radiotherapeutic treatment of children with early stage Hodgkin's Disease has been abandoned in several treatment centres. Extended fields have been replaced by involved field irradiation, and it has been shown that the 4000 cGy dose can be decreased to 2500 cGy if the radiotherapy was combined with periods of chemotherapy treatment. In this study 28 patients with Hodgkin's Disease stage I and II were treated in a group of 38 patients who presented with only small lymphnode swellings, i.e. lymphnode tumours with a diameter under 4 cm. These patients were treated with 6 cycles of MOPP every 3 months, without radiotherapy. The other children with stage I and II, having tumour masses with a diameter of more than 4 cm were also treated with 6 cycles of MOPP, to which involved field radiotherapy was added after the third MOPP cycle. The radiation dose was 2500 cGy, given over a period of 3 weeks. From 1976 to 1984 contraceptive children aged 15-19 years with stage I and II were treated according to the above mentioned programme. No child underwent staging laparatomy with splenectomy, but the criteria for staging laparatomy were reassessed. After a follow-up period of 2 years, most patients were treated with 6 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 11-25 months (median 19.6 months). Nine patients, having tumour masses of 4 cm, received combined treatment with MOPP and involved field radiotherapy. From this group one child developed a relapse outside the irradiated area after 16 months, and he died of progressive disease in spite of aggressive treatment with full dose radiotherapy and heavy chemotherapy, he relapsed seen in the other eight patients of this group, and they are followed for 12-30 months (median 26.9 months). The data derive from this study, although preliminary, indicate that stage I and II of childhood Hodgkin's Disease can be successfully managed with this strategy. Further follow-up will give the conclusion of a study by all, based on their experience with the treatment of 38 children with this regimen. In the perspective of the development of radiotherapy facilities were available. However, much more consideration will 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 substantial. Secondary malignancies are also to be expected in the group of patients who are treated with MOPP, especially in those centres 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 at other chemotherapeutic combinations which do not contain alkylating agents, but have the same curative properties without its potentially injuring sequelae.

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 splenecetomised children with Hodgkin's disease (study HD-DAL 78) we tried to find out a method to predict splenic involvement (SI) on the basis of clinical and/or preoperative findings. 6 out of 17 pre- and intraoperative findings showed significant correlation to SI: 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 the top of the upper-abdominal lymphnodes. Multivariate analysis showed, that the most evident findings SS+ and SH/TP+ gave almost the entire information which can be obtained about SI. All other parameters were not 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+, while patients without any of these criteria are splenecetomised, when required. 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 received 2, 4 or 6 cycles of chemotherapy (depending on the stage of HD) followed by involved field irradiation. 36 pts (33%) were splenecetomised. 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-splenecetomised pts received irradiation of their spleen due to positive abdomanal lymphnode biopsies. These figures correspond very well with the expectations from the retrospective analysis. After a median observation time of 12 months (range 1-24 months) only 1 pt has released (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 infra-diaphragmatic spread.
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40 ENZYMES INVOLVED IN ADENOSINE METABOLISM, IN NORMAL OR LEUKEMIC LYMPHOCYTES
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Enzymes involved in adenosine metabolism and adenosine nucleotide catabolism are particularly important in lymphocytes, as compared to other cell types, mainly because lymphocytes are almost devoid 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 hydrodase, S-adenosyl-homocysteine synthetase, 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'S/ADA ratios and low AMP-deaminase activities seemed to be correlated with high TdT (Terminal deoxynucleotyl Transferase) levels and immaturity character, while high 5'S/ADA and high AMP-deaminase activities were found in mature cells with low TdT levels.

In lymphocytes from patients with some B-cell type leukemia 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. H.J. Schuurjann1, J.O.R. van Laarhoven1, and G.K. de Groot2. Div. Immunopathology and Immunohaematology, University Hospital, Utrecht, and Dept. Human Genetics, University Hospital, Nijmegen, The Netherlands

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)/deoxycytidylate kinase (which ratio determines the net capacity of the cell to convert (deoxynucleosides 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 paraproteinemias have a higher ecto-5'-NT and lower ADA activities than cells from patients without paraproteinemias. 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 deoxycytidylate (deoxycytidylate kinase) or therapy with purine analogues which are easily converted in pathological cells to toxic compounds. The variable success of deoxycytidylate 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.
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Earlier observations of Silver et al. on differential expression of the ectoenzyme 5'-nucleotidase (5'-N) on peripheral blood lymphocytes of normal subjects and patients with CML 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 Nam 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 LYMHPHOMAS 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 NHL 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.
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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 leukemias and lymphomas which are thought to arise by clonal expansion from them. The enzymes found to be of particular value diagnostically are adenine deaminase (ADA), purine nucleoside phosphorylase (PNP) and 5'-nucleotidase (5'-NT) which are concerned in purine degradation, terminal transferase (TdT), ecto-ATPase, chymidine kinase (TK) and lactate dehydrogenase (LDH). Normal chronic 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 multizym 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 deoxynucleosides, 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. Swazy, some T lymphomas, T-ALL) show higher PNP and 5'-NT levels with low ADA and absent TdT. Although normal OKT8 cells show higher 5'-NT levels than OKT3 cells, this pattern is not clearly reproduced in chronic T cell disorders. The LHR isoenzyme pattern changes at 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 (TK1) type in less well differentiated non-Hodgkins lymphomas but of normal adult (TK2) type in diffuse wall-differentiated lymphomas. In Cll, TK1 occurs except in clinically aggressive cases but in hairy cell leukaemia, TK1 surprisingly dominates.

45  LYMPHOCYTE UROPHORPHINGEN SYNTHESE ACTIVITY IN LYMPPHOBLASTIC DISORDERS - A VALUABLE DIAGNOSTIC TEST. **M. Lahav, 40, Epstein, H., Schoenfeld, 1', Shakal, and **A. Atmon, The Laboratory of Biochemical Pharmacology, "Department of Internal Medicine B and the Hematology Unit, The Belinson Medical Center, Petah Tikva, Israel.

Patients with lymphoblastic lymphomas (LDP) were shown to have a significantly elevated activity of lymphocyte urophorphirinogen synthase (1-URO-S). The mean values of 1-URO-S activity of a control group (n=70) and of LDP patients (n=70) were 24.7 (SD=5.2) and 87.2 (SD=44.0) nmo 1 phorphyrins/mg protein/hr, respectively. There was almost no overlap in the 1-URO-S activity of patients with LDP and of the control group. 1-URO-S activities of patients with other malignant diseases and with viral and bacterial infections were within the normal range. The specificity of the determination of 1-URO-S activity in the diagnosis of LDP was 98% and the sensitivity was 97%. The positive predictive value of the test was over 90%. 1-URO-S activity was determined in 49 patients clinically suspected of harboring LDP. 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 LDP, the values obtained were slightly above the highest value of the controls. These data indicate that the determination of lymphocyte urophorphirinogen synthase activity may be of considerable assistance in the diagnosis of lymphoblastic diseases.
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46 BIOCHEMICAL MARKERS IN NON-HODGKIN'S LYMPHOMA STAGES III AND IV AND PROGNOSIS - A MULTIVARIATE ANALYSIS. H. Hagberg, A. Killander, B. Gimelius. Departments of Medicine and Oncology, University Hospital, Uppsala, Sweden.

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-microglobulin (S-βm), lactate dehydrogenase (S-LDH), α1-acid glycoprotein = orosomucoid (S-n, 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-βm, 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.

S-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.


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 chronic lymphatic leukemia (B-CLL), 15 patients with leukemic immunocytoma (IC), 4 patients with centrocytic lymphomas (CC), 3 patients with B-prolymphocytic leukemia (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 (CD-19, CD-21, CD-28, CD-39), and studies of surface and intracytoplasmic immunoglobulins.

Malignant cells of B-CLL were characterized by low activities of ADA (mean 9.5 ± 0.25 ± 1.06 U/10^9 cells), PNP (mean 65.8 ± 31.9 U/10^9 cells), and 5'-NT (mean 1.37 ± 0.17 U/10^9 cells). In malignant cells of IC, low activity of ADA (mean 1.64 ± 1.60 U/10^9 cells) was also observed, but the activities of PNP (mean 99.9 ± 30.5) and 5'-NT (mean 22.6 ± 13.4) were relatively 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 ± 0.25 U/10^9 cells), but PNP (mean 86.9 ± 21.3 U/10^9 cells) and 5'-NT (mean 13.4 ± 9.7 U/10^9 cells) activities were moderately high. Circulating cells of PLL were shown to have low levels of ADA (mean 1.59 ± 1.99 U/10^9 cells), PNP (35.9 ± 36.0 U/10^9 cells), and 5'-NT (mean 1.61 ± 1.36 U/10^9 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.
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48 TRANSFERRIN RECEPTOR EXPRESSION IN NON-HODGKIN LYMPHOMAS (NHL). AN IMMUNOHISTOCHEMICAL STUDY.
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The monoclonal antibody OT9 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 OT9 positive cells in lymphomatosus nodal tissue 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 OT9 on lymphoid tissue of NHL diagnosed according to Kiel. Our results confirm a well defined OT9 reactivity pattern, which corresponds to the grade of malignancy. Moreover, within the low grade lymphomas, a group of cases displayed 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 transformation, it must be outlined that the recognition of areas with a higher content of OT9 positive cells might have prognostic relevance, especially in low grade cases with an initial evolution into a more aggressive form.

49 BANDED CHROMOSOME ABNORMALITIES IN NON-BURKITT’S NON-HODGKIN’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 of lymphomas in 94 patients with malignant lymphoma (Cancer Research 43:2595, 1983). Clonal chromosome abnormalities were found 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 (12% 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 1q (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;10)(q24;q32) and t(1;14)(q21;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)(q21;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(6;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 T lymphomas, and the heavy chain was more common and less frequently 6u than among the total B-lymphoma population. Interestingly, both cases with t(3;14)(p21;q32) expressed u heavy chain and both cases with t(14;19)(q21;q32) expressed cu. Finally, preliminary analysis in our lymphomas indicates that recurring chromosome abnormalities are frequently in areas to which oncogenes have been localized.