75.

RECEPTORS FOR PEANUT AGGLUTININ IN THE IMMUNOLOGICAL SUB-GROUPING OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).
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Childhood ALL is composed of subgroups defined by immunologic markers and certain markers are known to have prognostic significance. Null cell ALL is the largest subgroup and additional markers are needed to identify patients at increased risk of early relapse within this non-T, non-B category. We have used a direct immunofluorescence assay to identify the presence of receptors for the lectin peanut agglutin (PNA) on blasts from 26/46 (63%) of our null cell ALL patients and have subsequently noted a high rate of relapse (17/26) in this PNA+ group. Relapse has occurred in only 5/20 patients whose blasts lacked the PNA receptor. The PNA+ and PNA- groups were comparable in clinical features (i.e., age, leukocyte count, follow-up times) and the striking difference in relapse rate was correlated only with the presence of receptors for the lectin ($p<0.01$). PNA receptors are commonly found on fetal thymocytes but not on mature peripheral lymphocytes except after neuraminidase treatment. SDS-PAGE analysis of NaB^3H_4-galactose oxidase labelled solubilized cell membrane extracts revealed a 68,000 dalton glycoprotein found only on PNA+ ALL lymphoblasts. Neither PNA- blasts nor PNA+ normal thymocytes expressed this component. The lectin PNA seems to define a high risk group of null cell ALL patients and to be associated with a specific cell membrane component.
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76.

NEWER MODES OF TREATMENT IN CHILDHOOD ALL.
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All children, suffering from leukaemia are treated in Hungary by one of the 10 centres participating in the Working Party. In the early 70-ies, treatment results improved as a result of CNS prophylaxis. No further improvement was seen however, despite efforts to establish new approaches. As from 1980 VCR-DR-Pred and daily Asp have been used in remission induction while CP and Ara-C in the consolidation phase. Remission rate rose and preliminary analysis of CCR is encouraging.

In 1981, 54 new patients with ALL were started on a new protocol, which in addition to the above cytostatics employs medium-dose MTX and for high-risk cases a 2 week combination of Ara-C and VM-26. Remission rate and early treatment results are promising, and so far the ratio of complications and side effects remains very low according to a close neurological survey of all patients.

77.

OUTCOME OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN INITIAL RELAPSE: RELATIONSHIP TO TYPE OF RELAPSE, PROGNOSTIC FACTORS, AND TREATMENT.
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From 1975-1981, the CCSG entered 3514 children with ALL into five treatment protocols. We recently reviewed the subsequent treatment and outcome of those children who had an initial relapse in the marrow (499), central nervous system (150) or testes (66) while still on therapy. The treatment for patients with relapse in the CNS or testes was local treatment to that site plus reinduction followed by reconsolidation and remaintenance chemotherapy. Patients who had an initial relapse in the marrow were treated on specific relapsing ALL protocols. Recently some patients with an initial marrow relapse and with a suitable sibling donor have received a bone marrow transplant (BMT). Comparing the outcome of those children with initial relapse in the marrow, testes and CNS, there is a highly significant difference ($p<.0001$). The life table survival at 3 years from time of initial relapse is: marrow-7%, testes-36%, CNS-39%. Within each of these groups there is heterogeneity of outcome that can be partially explained by prognostic factors. For marrow relapse, the duration of initial remission and age at diagnosis are the most important factors. For extramedullary sites, the important factors are duration of initial remission and these characteristics at the time of original diagnosis: age, white blood count, presence of mediastinal mass, and hemoglobin level. Outcome for the 21 children who received BMT shows that at one year from transplant the life table survival is 32% and at two years is 29%. Of the 5 children with current follow-up of one year or more from BMT, one has died. Longer follow-up will be necessary to assess whether a "cure rate" in the range of 20-25% is achieved with BMT. If so, this would be an improvement over conventional treatment of initial marrow relapse.

78.

FATE AFTER OCCULT TESTICULAR RELAPSE (OTR) IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): THE ROLE OF TESTICULAR BIOPSY.
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Cessation of therapy after 3 years of continuous complete remission (CCR) is associated with a bone marrow (BM) relapse rate of 10-20%, higher in males than females, and a testicular relapse (TR) rate of 10-40%. In CCG 101/143, 15% of boys developed OTR off therapy, of whom 55% remained in BM remission with a median follow-up of 50 mos. The purpose of this study was to 1) determine the incidence of OTR after 3 yrs. of CCR; 2) identify males at risk of OTR off therapy; and 3) prolong subsequent disease-free survival of boys with OTR. Of 465 boys entered on CCG 141 between 1975 and 1977 and achieving CR, 261 (56.1%) were in CCR at 3 yrs. Two hundred thirty-five underwent open wedge testicular biopsy; 26 refused biopsy.

Isolated OTR was detected in 26 boys (11.1%). Two had concomitant BM relapse. None were in the poor prognostic group (initial WBC>$50x10^9/\ell$), and no other distinguishing clinical features (age, FAB morphology, lymphoma syndrome, massive splenomegaly, hemoglobin and immunoglobulin levels, day 14 BM) were associated with OTR. Treatment consisted of testicular radiation, systemic reinduction, CNS prophylaxis with intrathecal methotrexate, and maintenance therapy for 3 yrs. Of the 26, 20 (77%) are in CCR 12 to 34 mos. after OTR, 4 are alive after BM relapse, and 2 died 22 and 24 mos. after TR. Overt TR occurred 8-26 mos. off therapy in 6 boys (2.6%) with presumed negative biopsies at 3 yrs. of CCR; 3 were isolated, 3 had concomitant BM relapse. All were given local and systemic therapy and are alive 8-35 mos. after TR. In conclusion, open wedge testicular biopsy after 3 yrs. of CCR identified males with OTR which can be effectively controlled with local radiation, systemic reinduction and maintenance therapy, and CNS prophylaxis.

79.

MORPHOLOGIC FINDINGS IN OCCULT TESTICULAR RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.
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Cessation of therapy after 3 years continuous complete remission (CCR) is associated with a testicular relapse (TR) rate of 10-40%. To determine the incidence of occult TR at the 3 year endpoint in CCG-141 all eligible boys were subjected to open wedge testicular biopsy. Occult TR was detected in 26 boys (11.1%) who subsequertly were effectively treated with testicular irradiation, further chemotherapy and CNS prophylaxis therapy.

The morphologic criteria for leukemic involvement applied in the CCG pathology review were derived from a systematic light and electron microscopic study of CCG-141 patients treated at Columbus Children's Hospital. No satisfactory accounts of the developmental changes in the prepubertal human testes were available. In particular, the origins of several immature-appearing cell populations within the interstitium were obscure and led in several early instances to an erroneous diagnosis of leukemic involvement. Ultrastructurally we have shown these cells to be components in the maturation sequence of the Leydig cell. Each has distinctive ultrastructural features and is distinguishable from a lymphoblastic cell.

Occult testicular leukemic (OTL) involvement in CCG-141 was present usually as a variably dense, diffuse interstitial

infiltrate. Occasionally OTL was limited to a single lobule. Rarely only small numbers of lymphoblasts were identified, typically grouped around capillary vessels. The latter findings support extension of the biopsy-taking to several sites rather than the single testicular biopsy(bilateral) now taken. Overt TR occurred 8-26 mos. in 6 boys after negative testicular biopsies at 3 yrs. of CCR. More extensive biopsying may have permitted earlier recognition of OTR. Very little evidence of therapy-induced changes in either the interstitial or tubular components was found in this study.

80.

HANDMIRROR CELLS AND CENTRAL NERVOUS SYSTEM RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

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Handmirror cell (HMC) percentages of washed lymphoblasts were counted in cytocentrifuge-preparations of thirty-three children with acute lymphoblastic leukemia (ALL). Nine children developed a central nervous system (CNS) relapse; all nine had a HMC-percentage less than 10 %. From the other twenty-four children without such a relapse only nine had a HMC-percentage less than 10 %. This difference is statistically significant (Wilcoxon: p 0,001). CNS-relapse was also correlated with a high initial white bloodcell count (p 0,01) and T-ALL (p 0,05). It appears that HMC-percentage in cytocentrifuge-preparations is more reliable than in bone-marrow smears.
Our conclusion is that a HMC-percentage less than 10 % in ALL might be a prognostic factor for the development of a CNS-relapse.

81.

CHANGES IN THE MONAMINE METABOLITES IN THE CEREBRAL SPINAL FLUID OF CHILDREN WITH ALL

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A pilot study was carried out to investigate Monoamin metabolites in CSF of children with ALL. The main objectives of this study were:

1) To examine intrapatient and interpatient's variations in the Monamine metabolites (5-HIAA and HVA).
2) To study the correlation between the behavior status of these patients and the metabolites levels in the CSF.
3) To examine the relationship between the clinical status of the patient and the CSF level of metabolites.

Methods and Results

The CSF samples were collected under identical conditions by LP. The samples were analyzed by High Performance Liquid Chromatography using electro-chemical detector. A reverse phase C_{18} (5_u) column was used for the analysis. The CSF samples were run directly on the column using 50 ul or 100 ul depending on the concentration.

Over 50 cerebral spinal fluids have been analyzed so far and wide variations between subjects are seen as also variations between samples from the same patient collected at different intervals. In view of the postulated role for catecholamine in learning, memory, affect and emotional behavior in man and animal, it appears from the preliminary data that the study may be of potential value in understanding the biochemical changes in these patients. It may also help to correlate with the behavior and intellectual functions. A prospective study is being undertaken at the present time.

82.

SERUM COPPER AND ZINC VALUES AND COPPER/ZINC RATIO IN ACUTE LEUKEMIA AND RELATION TO PROGNOSIS

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Serum Cu and Zn levels and Cu/Zn ratio were measured in 69 cases with acute leukemia.The mean serum Cu level of the controls was 178.2±55.0 ug %; it was 275.8±76.0 ug % in acute lymphoblastic leukemia (ALL) and it was 220.8±39.3 ug %in acute myelomonoblastic leukemia (AMML).The mean serum level of Cu in untreated leukemic children was significantly higher than the controls ($P < 0.01$ and $P<0.001$).Serum Cu levels decreased to normal values in ALL and in AMML in remission . This concentrations were significantly lower than values in untreated stage ($P<0.001$).The mean serum Zn level of the controls was 112.7±26.5 ug %, it was 81.5±28.0 ug % in ALL and it was 79.5±30.7 ug % in AMML.The mean serum level of Zn was significantly lower in untreated leukemic children than the control group ($P<0.001$).Serum Zn levels reached to normal values in remission.The mean Cu/Zn ratio in controls was 1.7±0.8. The mean Cu/Zn ratio in ALL and in AMML were 3.80±1.50 and 3.12±1.31 respectively.The mean Cu/Zn ratio decreased in remission 1.4±0.4 in ALL and 1.86±0.5 in AMML ($P<0.001$).The relationship between serum Cu and Zn levels and prognosis was also investigated.The patients who have normal serum Cu levels in pretreatment stage have good prognosis.Patients with serum Zn levels lower than 70 ug % seem to have shorter survival rate in ALL.

83.

SIGNIFIANCE OF CYTOGENETIC STUDIES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).

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Cytogenetic studies were performed in 22 children with ALL (October 1979 to April 1982). 20 cases were classified by immunological markers. 3 high risk ALL patients over 22 had striking chromosomal abnormalities, 2 at diagnosis and relapse, the third one only at relapse.
Case 1 : non B non T ALL - 47,XY,-9,+8,inv(5),+mar.
Case 2 : pre-B ALL - 47,XY,-8,-11,+X,+i(8q),+mar.
Case 3 : non B non T ALL - 46,XX,ring 17 - 18
These 3 patients had early hematological relapses.
2 ALL children showed a congenital chromosome abnormality. In the first case, a pericentric inversion of chromosome 11 : inv(11)(p15q13) was seen and discovered to be present in 5 other members of the family over two generations. In the second case, the presence of a congenital ring chromosome 21 : 46,XX,r(21) was considered to result from a "de novo" mutation. The possible relation between congenital chromosome anomalies and a predisposition to neoplasia raises the question as to whether the association is fortuitous or has causal implications. No chromosome abnormalities were seen in the karyotypes of the 17 remaining patients.
These data seem to corroborate recent works showing that the karyotype alone, may have prognostic value.

84.

TREATMENT OF ACUTE NON LYMPHOCYTIC LEUKEMIA (ANLL) WITH HIGH DOSE CYTOSINE ARABINOSIDE (AC) AT MAXIMUM RECRUITMENT INTERVALS.

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5 patients with acute non lymphocytic leukemia were treated with AC 1000 mg/m^2 i.v. push at 12 consecutive days at maximum S-phase following recruitments. Recruitment time was estimated by flow cytometry and varied between 24-36 hours in individual pats. Bone marrow aspirates were done at expected time intervals after one AC dose estimated on initial % S-phase cells. A straight line could be drawn correlating the initial S-phase cells with the maximum of recruitments induced by the first injection. AC was followed by 1 or 2 Adriamycin (AC) doses 40 mg/m^2 i.v. to turn off recruitment as expected to be initiated after each AC dose and to kill residual cells unresponsive to AC treatment.
Total expected tumour burden: 10^{12} would be eliminated in 12 doses (1 log each dose). All primary patients went into haematological remission: 1 patient with myelofibrosis who did not respond to AC but to AD died; 1 patient had a first relapse (relapse 5$^+$ months) when entering this protocol.
Bone marrow aplasia persisted for 2-3 weeks with full recovery and maintained remission for 6-7 months, with repeated half treatment courses (6 x AC, 1 x AD) every 6 weeks. Duration of bone marrow aplasia after each treatment course was 1-2 weeks.
We conclude: complete remission can be obtained with one treatment course and maintained with full haematology recovery and good physical performances.
