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LATE EFFECTS OF CHILDHOOD CANCER
COGNITIVE AND PSYCHOSOCIAL DEVELOPMENT

by

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LATE EFFECTS OF CHILDHOOD CANCER ON COGNITIVE AND PSYCHOSOCIAL DEVELOPMENT

by

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The purpose of this research was twofold: to determine if CNS prophylaxis for acute lymphoblastic leukemia (ALL) has late effects on cognitive functioning; and to determine if childhood cancer and its treatment has late effects on psychosocial functioning. The study tested the vulnerable period hypothesis in relation to the delayed effects of CNS therapy on the developing brain and in relation to the long-term sequelae of cancer on selected aspects of psychosocial development.

Thirty-five subjects who were at least five years from the diagnosis of childhood cancer participated in this study of cognitive and psychosocial late effects. The subjects were divided into four groups to determine the effects of treatment (systemic therapy with and without CNS prophylaxis) and age at time of treatment (before or after 60 months) on cognitive functioning. Age at time of treatment was the major comparison variable in relation to psychosocial functioning.

The hypothesis that CNS prophylaxis has a significant adverse effect on subsequent cognitive functioning was supported consistently on the dependent measures of general intelligence, academic achievement, visuospatial skills, and visual memory. Subjects treated before the age of 60 months performed worse than those who received the same therapy after this age, supporting the hypothesis that the brain is particularly vulnerable to biologic insults during periods of rapid development.

Analysis of the Deasy-Spinetta Behavioral Questionnaire (DSBQ) for cancer subjects suggested that the type of malignancy did not have a significant effect on psychosocial functioning. The hypothesis that age at time of treatment would have a significant effect was not supported.

Comparisons between the cancer survivors and the controls on the DSBQ Total and Cognitive Subscale scores demonstrated that those treated previously for leukemia were functioning below their healthy peers on both measures. This was not the case with subjects who had survived a solid tumor.

The findings suggest that CNS prophylaxis results in deficits in cognitive functioning which are more severe during vulnerable periods of brain development, and that children treated for ALL may also experience long-term psychosocial problems. The results underscore the need for ongoing evaluation of the child receiving cancer therapy in order to detect and minimize late effects.

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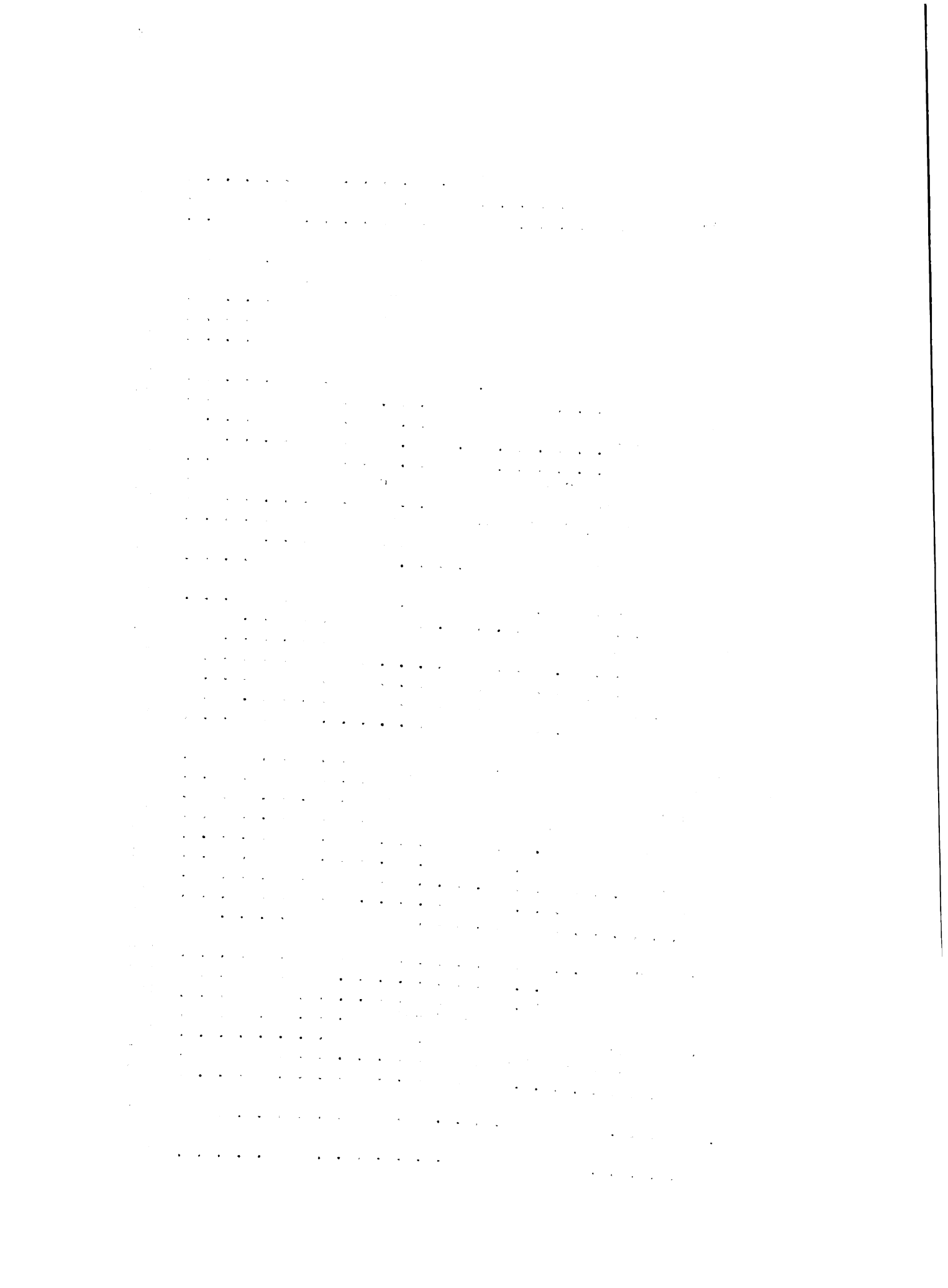

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CHAPTER ONE: STATEMENT OF THE PROBLEM

Introduction

Over 60 percent of children who are diagnosed with cancer will remain clinically free of disease for at least five years. For some malignancies, such as acute lymphoblastic leukemia (ALL), long-term survivals are as high as 70 percent. Such a dramatic improvement in the treatment of diseases which were rapidly fatal 20 years ago demonstrates the efficacy of sophisticated diagnostic methods and aggressive therapies. While the benefits of such successes are unquestioned, there is an increasing realization that radiation and chemotherapy can cause persistent adverse effects on normal tissues. There is also concern that the environmental and social changes which often accompany a life-threatening illness may have latent psychological and social consequences. A number of sequelae have been attributed to a previous cancer experience, and these collectively are referred to as late effects.

Late effects are defined as the chronic and adverse changes in tissues, organs, or behavioral systems which become manifest several months or years after the termination of cancer treatment (D'Angio, 1980; Koocher & O'Malley, 1981; Obetz, Smithson, Groover et al., 1979; Oliff & Levine, 1982; Verzosa, Aur, Simone et al., 1976). This definition implies that the acute and reversible responses to therapy have resolved, so that the alterations in structure and/or function are residual and persistent. To date, the late consequences of cancer treatment have been described as adverse complications. This is a valid definition for physiological sequelae. However, the nature of

psychosocial late effects is less well understood, and it may be that some outcomes are not deleterious.

The unique physiological, morphological, and behavioral changes that occur during development may put the child at greater risk for late effects. For example, the discovery of central nervous system (CNS) prophylactic therapy for acute lymphoblastic leukemia in the 1960s and 1970s significantly improved long-term survival from the disease. However the potential delayed effects of this treatment on the developing brain have only recently become apparent. There is also concern that the life-threatening nature of the cancer experience, the intensive therapy which is frequently accompanied by visible physical changes, and the fear of disease recurrence may interfere with social and emotional development.

Cognitive late effects often become apparent when the child begins experiencing problems with school. Academic difficulties make it difficult for the child to keep up with the class and he or she falls farther and farther behind. Psychosocial late effects may be manifested as difficulty with mastery of developmental tasks such as relinquishing dependency on parents, establishing peer relationships, and achieving a positive self-concept. The resulting lack of self-confidence can prevent the child from participating in age-appropriate activities.

Late Effects: Significance to the Domain of Nursing

Historically, nursing research in pediatric oncology has focused primarily on the problems of the fatally ill child. For example, Waechter's (1971; Moore, Gortner, & Waechter, 1983) studies of death anxiety in children with a life-threatening illness and Martinson's

(1978) research on home care for the dying child have had an important influence on the care of children with cancer.

Late effects is a relatively recent problem for nursing clinicians and scientists. However, with the realistic goal of cure for children with cancer, there will be an increasing demand for knowledge about the potential long-term consequences of the therapy and life-threatening illness experience on development. The need for intervention strategies aimed at minimizing sequelae and at maximizing the individual's potential for a healthy future are already becoming apparent, but will continue to grow. In keeping with this trend, nurse researchers are beginning to study systematically phenomena, such as late effects, which may influence the quality of living for the survivors.

Nurses are concerned with "the diagnosis and treatment of human responses to actual or potential health problems," and with the restoration of health (American Nurses' Association, Congress for Nursing Practice, 1980). In "Nursing, A Social Policy Statement," (American Nurses' Association, Congress for Nursing Practice, 1980), health is defined as "a dynamic state of being in which the developmental and behavioral potential of an individual is realized to the fullest extent possible".

Late effects represents a physiological and behavioral response to cancer or its therapy. The child may require assistance in achieving and maintaining a state of well being, or in adjusting to any long-term consequences of the disease or treatment. In light of nursing's emphasis on fostering development and restoring health, concern with this phenomenon is within the domain of nursing knowledge and nursing practice.

Current understanding of late effects is at a basic level; the majority of research has been descriptive or factor-isolating. More diagnostic information about the types of human responses which are characteristic of late effects is needed. The significance of the developmental stage of the child, the importance of interactions between the therapy and the host, and the contributions of environmental factors to the subsequent manifestation of sequelae have not been fully elucidated. Knowledge about these and other variables which may predict who is at risk for late effects is also needed. In this study, questions concerning the late effects of acute lymphoblastic leukemia and its treatment on neurocognitive and psychosocial functioning will be examined.

Purpose

The purpose of this research is twofold: 1) to determine the incidence and characteristics of selected late effects from central nervous system prophylaxis for acute lymphoblastic leukemia in a group of long-term survivors; and 2) to determine the incidence and characteristics of late effects from childhood cancer and its treatment on selected aspects of psychosocial functioning. In order to control for the potential contributions of systemic therapy and the life-threatening illness experience to cognitive late effects, a comparison group of children who are long-term survivors of a solid tumor malignancy will be included.

Study Aims

The specific aims of the study are:

1. To determine if treatment group (ALL or solid tumor) and age at time of treatment are significantly related to subsequent

cognitive functioning, treating time since diagnosis as a covariate;

2. To determine if treatment group (ALL or solid tumor) and age at time of treatment are significantly related to subsequent psychosocial functioning, treating time since diagnosis as a covariate;
3. To determine if there is an interaction effect between treatment group (ALL or solid tumor) and age at time of treatment;
4. To determine the degree of association between neuropsychological measures of cognitive functioning and the teacher and parent appraisal of academic functioning;
5. To determine the degree of association between the occurrence of cognitive and psychosocial late effects.

CHAPTER TWO: LITERATURE REVIEW

Introduction

The literature relevant to the cognitive and psychosocial late effects of acute lymphoblastic leukemia is summarized below. The process of development may put the child who is treated effectively for a malignancy at greater risk for these late effects. Therefore, knowledge about the major phases of brain growth and development, and about the major stages of psychosocial development during early childhood and adolescence is relevant to the questions addressed in this study. Literature on these aspects of development is also included.

Neurocognitive Late Effects of Acute Lymphoblastic Leukemia

Prior to the advent of prophylactic treatment, the central nervous system (CNS) was the most frequent site of initial relapse following bone marrow remission in children with acute lymphoblastic leukemia. During the 1960s and 1970s, clinical trials documented the efficacy of intrathecal (IT) methotrexate (MTX) and cranial or craniospinal radiation in preventing meningeal leukemia (Pinkel, 1972; Jenkins, 1979). Although such advances in treatment have made dramatic improvements in long-term survival, there is concern that radiation and chemotherapy can have persistent adverse effects on the developing central nervous system.

Growth and Development of the Brain

Growth and development of the brain begins during early fetal life and continues into childhood. Three stages of this process have been delineated from cross-sectional studies of brains taken from fetal abortions, and from children who died of an acute

non-neurological condition or who suffered an accidental death. In Table 1 the biochemical analyses and major findings of these studies are summarized.

Winick (1968), Howard, Granoff, and Bujnovszky (1969), Winick and Russo (1969), and Dobbing and Sands (1973) analyzed a total of 115 fetal brains, ranging in age from 10 to 40 weeks, for cell number, cell size, and the synthesis of cellular or myelin membranes. An increase in total DNA content per anatomical region was used as a reflection of growth due to an increase in cell number; growth in cell size was determined by an increase in either RNA or protein content relative to DNA. Cholesterol concentration or total cholesterol content served as an index of membrane synthesis. Although other lipids, such as cerebroside or spingomyelin (Himwich, 1970), are more specific to the process of myelination, cholesterol accumulation has a constant relation to these lipids (Dobbing, 1974), is easier to estimate, and is also more chemically stable in postmortem tissue (Dobbing & Sands, 1973).

At 10 weeks gestation, total DNA content was found to increase exponentially, and continued to rise at a rapid rate until 14 (Howard et al., 1969) or 18 weeks (Winick & Russo, 1969; Dobbing & Sands, 1973). The discrepancy in the data has been attributed to measurements taken in micromoles versus milligrams (Brasel & Gruen, 1978). This first phase of growth and development represents neuroblast proliferation and differentiation to non-dividing neurons, and occurs primarily during the second trimester of fetal life.

A differential growth pattern in the cerebellum was noted by Howard et al. (1969), in which DNA content increased exponentially

Table 1
Summary of Cross-Sectional Studies on Brain Development

Investigators/ Date	Sample	Analyses Measures	Major Findings
Winick (1968)	31 normal human brains 13-40 wks gestation (N=12) ½-12½ mo postnatal (N=19)	DNA content RNA content Protein content	DNA content increased linearly from 13 wks to birth, decelerating rate of increase from birth to 5 mo. RNA content increased linearly through period of life under study Protein content increased linearly through period of life under study
Howard, Granoff, & Bujnovszky (1969)	28 normal brains 10-30.9 wks gestation	DNA content RNA/DNA Cholesterol/DNA	Cerebral DNA content increased: 1) exponentially between 10 and 14 wks; 2) linearly from 14-30 wks Cerebellar DNA content increased exponentially through age period under study (as late as 30 wks) RNA/DNA: 1) no change in cerebrum between 10 and 14 wks, progressive increase thereafter; 2) no change in cerebellum until 12 wks, progressive increase thereafter Cholesterol/DNA: 1) exponential increase in cerebrum throughout age range; 2) increase in cerebellum from 11-15 wks, then plateaus
Winick & Russo (1969)	20 human brains 15 wks gestation to 11½ mo, well nourished (N=10)	DNA content RNA content Protein content	Well nourished sample: 1) DNA content increase rapidly from 15-18 wks gestation, reduced rate of increase until 8 mo postbirth;

(continued)

Table 1
Summary of Cross-Sectional Studies on Brain Development (cont'd)

Investigators/ Date	Sample	Analyses Measures	Major Findings
Winick & Russo (1969) (cont'd)	½ mo-11 mo, postnatal, malnourished (N=10)		Well nourished sample: 2) RNA content increased linearly throughout age period under study; 3) Protein content increase linearly throughout age period under study. Malnourished sample: 1) reduced DNA content; 2) reduction in RNA and protein roughly proportional to reduction in DNA; 3) retardation in brain growth due to decreased number of brain cells.
Winick (1970)	28 human brains 0-26 mo postbirth, well nourished (N=12) 1.3-24 mo, postnatal malnourished (N=16)	DNA content RNA content Protein content Dry weight	Well nourished sample: Progressive increase (approximately linear) in all measures in cerebrum, cerebellum, brain stem during first two years of life. Cerebrum increases in dry weight and DNA more slowly than in cerebellum. Malnourished sample: Reduced DNA content; Reduction in dry weight, protein, RNA, roughly proportional to reduction in DNA; The younger the child when malnourished, the more marked the effects.
Dobbing & Sands (1973)	139 normal human brains 10-36 wks gestation (N=65)	DNA content Cholesterol concentration	DNA content increased rapidly and exponentially from 10-18 weeks gestation; second phase of rapid increase from 20 wks gestation to 2 postnatal years.

(continued)

Table 1
Summary of Cross-Sectional Studies on Brain Development (cont'd)

Investigators/ Date	Sample	Analyses Measures	Major Findings
Dobbing & Sands (1973) (cont'd)	0-7 yrs postbirth (N=65) control adult brains (N=9)	Total cholesterol	DNA content in cerebellum increased later (mid-gestation) but ended sooner. Cholesterol concentration and total cholesterol increased rapidly from mid-gestation to 4 yrs, followed by gradual increase to adulthood.
Chase et al. (1974)	11 human brains 12-24 postnatal mo, malnourished (N=6) Control 11-22 mo, well nourished (N=5)	Water DNA Protein Total lipid Cholesterol Phospholipids Glycolipids Gangliolipids Gangliosides	Malnourished sample: Mean brain weight was significantly less than control; DNA content and concentration similar to control; Cell size significantly decreased in cerebellum and cerebrum-brain stem; When age differences were controlled for, cerebroside and sulfatide levels were lower per total brain; Significant reduction in total brain cholesterol and phospholipids.
Yusuf, Dickerson, Hey, & Waterlow (1981)	38 normal human brains 13 wks gestation to term (N=25) Newborn infants (N=3) 1-26 postnatal mo (N=10)	Cholesterol esters: concentration and total amount	Cholesterol concentration was the highest at 13 wks gestation and increased through the period of study. Transient rises occurred at birth for the forebrain, and from 1-6 mos in the cerebellum. Total amount of cholesterol esters slowly increased until 35 wks gestation, which was followed by another transient rise between birth and 10 mos.

from 10 to 30 weeks. These investigators suggested that there may be considerable postnatal division of neuronal precursors in the cerebellum. However, this substantive conclusion is misleading as the proportionally greater cellularity of the cerebellum and the overlapping increase in DNA content associated with the second stage of growth and development have not been taken into consideration. Dobbing and Sands (1973) also separately analyzed DNA content of the forebrain, cerebellum, and brain stem. They stressed that the cerebellum does not grow later than the rest of the brain; rather, proliferation starts later but, due to a more rapid rate of growth, ends sooner.

The second phase of growth and development of the brain is also reflected by an increase in DNA content, and predominantly involves glial cell proliferation. This stage, most clearly delineated by Dobbing and Sands (1973), commences at approximately 20 gestational weeks, and does not end much before two postnatal years. Winick (1968), and Winick and Russo (1969) also found increases in DNA content beyond 18 gestational weeks, but the increase was of a lesser magnitude and of much shorter duration (ending at five to eight postnatal months). These latter studies involved a limited number of specimens representing the total age span of glial cell proliferation, which probably accounts for these differences.

The brain growth spurt is defined as that transient period when the brain is growing most rapidly and begins after the adult complement of neurons has been largely achieved (Dobbing & Sands, 1973). The substantial phase of cell proliferation which occupies the early part of the growth spurt is predominantly glial--especially

oligodendroglial. The rapid increase in brain size during this time is also due to the growth of axons and dendrites, and to the establishment of neuroglial connections (Davison & Dobbing, 1968). The progressive increases in RNA and protein, especially after 20 weeks gestation, reported by Winick (1968), Howard et al. (1969), and Winick and Russo (1969) reflect this growth by the increase in cell size.

The onset of myelinogenesis corresponds to the final stage in brain development. Myelination of axons also constitutes the later phase of the brain growth spurt, following the proliferation of glial cells. This is a logical sequence of events as the oligodendroglial cells are responsible for the synthesis of myelin (Dobbing & Sands, 1973; Davison & Dobbing, 1968). The process involves a spiral wrapping of the phospholipid cellular membrane of the oligodendrocyte around nerve axons (Davison & Peters, 1970). Myelination serves two purposes: to insulate electrical impulses, and to provide a three fold increase in conduction velocity (Himwich, 1970).

Total cholesterol content is a more reliable biochemical measure of myelination than is cholesterol concentration because of the dilution effect resulting from concurrent growth in cell size. The early fetal increase (10 to 13 weeks) in cholesterol content reported by Howard et al. (1969) and Yusuf (1981) was attributed to an increase in cell membrane surface area. The period of active myelination occurs later, as reflected by the rise in total cholesterol that begins mid-to-late gestation, and continues beyond two postnatal years (Dobbing & Sands, 1973; Yusuf, 1981).

Because the sample was representative of a broader age range,

Dobbing and Sands (1973) were able to measure changes in brain cholesterol through seven years of age. According to this research, the spurt in cholesterol (and, therefore, in myelin) synthesis continues until almost four years of age. Research on the myelogentic cycles of regional maturation of the brain (Yakovlev & Lecours, 1967) supports the finding that myelination of many fiber systems within the central nervous system is completed by the age of five years. However, myelination of the reticular formation and of the long association and commissural fiber systems continues to at least the end of the first decade of life (Yakovlev & Lecours, 1967). Thus, the brain growth spurt, which primarily includes glial cell proliferation and myelination, begins during mid-gestation, but does not end until roughly four or five postnatal years. The major stages of brain growth and development, as well as the timing of the growth spurt, are summarized in Table 2.

Table 2

Stages of Brain Growth and Development Timing of the Brain Growth Spurt

Stage	I	II	III
Developmental process	neuroblast proliferation and differentiation to non-dividing neurons	glial cell proliferation	myelination
Peak age span in which event occurs	10 to 14 or 18 wks gestation (second trimester)	20 wks gestation to 2 postnatal yrs	mid-gestation to 4 postnatal yrs
Growth spurt	(-)*	(+)**	(+)**

(-)* Process not a component of the brain growth spurt

(+)** Process is involved in the brain growth spurt

The Brain Growth Spurt: A Vulnerable Period

Traditionally, the concept of a vulnerable period referred to the teratogenic sequelae that can occur during the early stages of organogenesis. However, Davison and Dobbing (1966) proposed that the events involved in the later phases of brain growth and development could also be susceptible to outside interference, and that such interference may produce effects which persist into adult life. In relation to the brain growth spurt, the vulnerable period hypothesis states that "processes of development in the brain are likely to be more vulnerable to restrictions and other stress at the time of their fastest rate," (Himwich, 1970). From this hypothesis, it follows that: 1) if a developmental process becomes affected by an insult at the time of its fastest rate, not only will the process be delayed, but the ultimate extent of growth will be restricted (Davison & Dobbing, 1966); and 2) the nearer the insult or stress is applied to the time of fastest growth, the severity of the insult required to produce a given effect will be less (Davison & Dobbing, 1966; Himwich, 1970).

Support for the validity of this hypothesis of vulnerability comes from knowledge about growth and development of the brain, and from investigations on the long-term effects of prenatal and early postnatal malnutrition. Multiplication and differentiation of neuroblasts occurs early in fetal life, a time relatively unaffected by maternal malnutrition. In contrast, glial cell proliferation and the subsequent myelination of axons are primarily events of the third trimester and of postnatal life. Therefore, these latter processes are much more sensitive to adverse external factors such as dietary

deficiencies, a metabolic disturbance of an enzyme system, or a restriction of cofactors. Myelination may be particularly vulnerable to such adversities, as this process continues at a reduced rate through the third or fourth decade of life (Rouser, Yamamoto, & Kritchevsky, 1971).

Winick and Russo (1969), Winick (1970), and Chase et al. (1974) studied the effects of early postnatal malnutrition on the pattern of brain growth and development (Table 1). Reductions in DNA, RNA, and protein content were documented in brains ranging from 0.5 to 11 (Winick & Russo, 1969), and from 1.3 to 24 (Winick, 1970) postnatal months. Because the reductions in RNA and protein content were roughly proportional to the decrease in total DNA, the retardation in growth was attributed to a decreased number of brain cells. Winick and Russo (1969) concluded that their study provided validity for the general principle that regions of rapid cell division are the most vulnerable to the adverse effects of malnutrition.

Chase et al. (1974) analyzed the brains of six children, 12 to 24 months of age, who died from malnutrition and compared them with five healthy control specimens. In comparison to the control group, the mean brain weight of the malnourished group was significantly less, but, in contrast to the earlier studies discussed above, DNA content did not differ. When developmental age was controlled for, total cholesterol and phospholipids, as well as cerebroside and sulfatide, were significantly reduced. These investigators concluded that undernutrition during the second year of postnatal life has a detrimental effect on myelination. The failure to detect changes in DNA content was explained by the fact that at 12 months of age, the

bulk of glial cell proliferation has ended (Chase et al., 1974). It is also noteworthy that a 12 month span of rapid brain development was represented by a small sample size.

These investigations do provide empirical evidence for the vulnerability of the later stages of brain development, which comprise the brain growth spurt, to adverse external conditions. However, the relationship of the findings to intelligence and to cognitive development is unknown. Dobbing (1974) proposed that normal intellectual functioning most likely depends on the degree of dendritic branching of neurons and on synaptic connectivity. Whether interference with glial cell proliferation or myelination will subsequently result in an impairment of cognitive functioning, or whether other concurrently developing systems within the brain are also vulnerable and of greater importance, is yet to be determined (Davison, 1966; Davison & Peters, 1970; Chase et al., 1974).

Pathogenesis of Delayed CNS Radiation Effects

As was mentioned earlier, central nervous system prophylaxis is regarded as a critical aspect of therapy for leukemia, and usually involves intrathecal methotrexate (MTX) and/or cranial radiation (18 to 2,400 rads). The pathogenesis of the late effects of radiation and methotrexate on the central nervous system, and the importance of these effects to brain development are discussed below.

In relation to normal tissue tolerance and damage from radiation, the brain is classified as a Type I organ: one which is vital to life, and whose damage is often fatal, or at least associated with severe and unacceptable morbidity (Committee for Radiation Oncology Studies, 1976). The acute effects of radiation on normal tissues

result from the mitotic death of stem cells and proliferating mature cells. This direct type of injury is most common in tissues with constant cell loss and relatively rapid renewal systems. There are also some nonspecific early postradiation changes such as edema, loss of taste, and the occurrence of nausea and vomiting. These changes probably are not related to cell killing, and can occur in tissues with or without rapid renewal systems (Committee for Radiation Oncology Studies, 1976).

The acute effects related to cell killing kinetics occur less frequently in critical organs, such as the brain, where cells are no longer proliferating. Of much greater significance and consequence are the late effects which become manifest months to years after irradiation. This delayed type of damage is thought to result from injury to the fine vasculature, and/or loss of parenchymal cells (Allen, 1978; Casarett, 1976; Committee for Radiation Oncology, 1976; Hopewell, 1979; Sheline, Wara, & Smith, 1980). Much of what is known about these physiological mechanisms of delayed injury has come from animal studies. When making generalizations to human systems the importance of factors such as dose equivalence, fractionation, time between radiation doses, the interaction of radiation with other chemical agents, and the developmental status of the system need to be kept in mind.

The initial vascular response to radiation involves an increase in endothelial permeability and transudation of plasma into vessel walls and parenchymal tissue. The transudate initiates an inflammatory response characterized by the infiltration of mononuclear cells (lymphocytes, plasma cells, and phagocytes), and the

transformation of these cells to fibroblasts. An increase in the amount and collagenous density of vascular, perivascular, and interstitial connective tissue occurs as a result of the increase in fibroblastic activity. These changes increase the diffusion barrier between the capillaries and the parenchyma, with a net decrease in perfusion. The end result is ischemic necrosis and a loss of parenchymal tissue function (Casarett, 1976). This cascade of vascular changes may occur after relatively modest doses of radiation (Casarett, 1976); and seem to become progressively more significant over time (Sheline et al., 1980).

Price and Jamieson (1975) described the morphological characteristics of the 13 cases of leukoencephalopathy--a generalized necrosis of CNS white matter--found from postmortem analyses of 231 brains taken from children who died of leukemia. Vascular changes were present in some specimens (statistics not reported), and included thickened capillary walls, as well as necrotizing and sclerotic microangiopathy. All 13 subjects had received at least 2000 rads of cranial radiation and methotrexate which was administered intrathecally and/or intravenously.

A slow reproductive loss of glial cells and the associated interference with myelination have also been postulated as a cause of delayed radiation injury. Glial cells proliferate during childhood, and are therefore radiosensitive (Hicks & D'Amato, 1980). Nevertheless, there is only meager evidence that therapeutic doses of irradiation disrupt this process. From a retrospective review of the neuropathology reports on 23 children who had died of ALL, glial cell changes (fibrillary gliosis) were documented in 22 subjects, with a

concurrent loss of myelin in only six cases. Cranial radiation had been used with only seven children, and the dose ranged from 600 to 3600 rads. The investigators suggested that the CNS alterations were due to several factors, including the leukemic process, disturbances in cerebral spinal fluid dynamics, and the combined effects of chemotherapy and radiation (Hendin, DeVivo, Torack et al., 1974).

The most predominant pathologic finding in the 13 cases of leukoencephalopathy described by Price and Jamieson (1975) was degenerative changes of the oligodendrocytes and disruption of myelin elements. These lesions were found only in subjects who had received 1) a cumulative radiation dose of 2000 rads, and 2) intravenous methotrexate. The incidence of delayed injury increased with higher doses of MTX. The 13 subjects were divided into those who had received cranial radiation before or after 8.3 years. Although the incidence of CNS changes was found to be similar in both groups, the age span of the younger group may have been too broad to detect any differences due to brain development. Other variables which also failed to influence the incidence of leukoencephalopathy included bacterial infections, protein malnutrition, presence of CNS leukemia, and MTX preservatives.

The authors proposed that the demyelinating lesions were a result of radiation induced alterations in the permeability of the blood-brain barrier, which allowed MTX to diffuse into CNS tissue and interfere with the metabolism of myelin-supporting elements (Price & Jamieson, 1975). A physiological interaction between cranial radiation and methotrexate has also been found in animal research (Griffen, Rasey, & Bleyer, 1977), and appears to be a dose dependent phenomenon.

Pathogenesis of Delayed CNS Effects from Methotrexate

Methotrexate belongs to the class of chemotherapeutic agents known as antimetabolites. This group of cytotoxic drugs produces their effect by competitive inhibition of an enzyme in a critical biosynthetic pathway. Methotrexate binds tightly to the enzyme dihydrofolate-reductase (DHFR) which prevents the reduction of the in vivo substrate, dihydrofolate, to tetrahydrofolate, and blocks the synthesis of folate. The cytotoxic effect of MTX is due to the competitive inhibition of folate synthesis as folate plays a central role in purine and pyrimidine metabolism (Creasey, 1976). Methotrexate binds very tightly to DHFR, thus the formation of tetrahydrofolate and folate can be blocked for prolonged periods (Creasey, 1976), and at very low doses (Chabner & Young, 1973).

Tetrahydrofolate is also necessary for the incorporation of carbon fragments into essential proteins and lipids (Martin, 1981). An interference with phospholipid synthesis by methotrexate has been hypothesized as the underlying mechanism of demyelination (Allen, 1978) and as a contributing factor to the pathogenesis of cognitive late effects (Meadows & Evans, 1976; Price & Jamieson, 1975). The significance of an interference with myelinogensis during the brain growth spurt has not been addressed, and warrants further attention.

Cognitive Late Effects of ALL: Related Research

Over the past 10 years, there has been an increasing amount of literature on the cognitive sequelae experienced by children who have received CNS prophylaxis for acute lymphoblastic leukemia. At present, the evidence for responsible agents, the quality and severity of insult, and important moderating variables is controversial. This

review of related studies is organized according to those that deal primarily with 1) the specific mode of therapy and the significance of age at time of treatment; 2) structural changes in the CNS following prophylactic treatment; and 3) the use of school performance as a measure of cognitive deficits.

Studies on Specific Modes of Therapy and Age at Time of Treatment

Soni et al. (1975) reported one of the first prospective and retrospective investigations of the effects of cranial radiation on neuropsychological functioning. In the prospective study, an experimental group of 14 leukemic children who had been randomized to receive either cranial radiation alone or in combination with intrathecal MTX, were compared with a control group of 19 children with various solid tumors. The retrospective study grouped leukemic children according to whether or not they had received prophylactic CNS irradiation. Because of a high attrition rate, the sample size in the retrospective study was small (five irradiated and nine nonirradiated subjects); in the prospective study, the controls were, on the average, five years older than the leukemic children. The investigators could not demonstrate any decline in functioning that was attributable to cranial radiation, and concluded that this form of prophylaxis had no adverse effects. This study and others pertaining to the late effects of CNS prophylaxis are summarized in Table 3.

Obetz et al. (1979) compared three groups of subjects treated with varying forms of CNS prophylaxis, and could find no differences in neuropsychological measures among the groups. Although the investigators concluded that there was no indication to modify current methods of therapy, 48 percent of subjects whose CNS prophylaxis

Table 3
Summary of Studies on the Late Effects of CNS Prophylaxis on Neurocognitive Functioning

Investigator(s)/ Date		Methods*	Sample Characteristics	Major Findings
Soni et al. (1975)	I	Prospective repeated measures, convenience sampling - standard IQ tests - neurologic exam	Exp gp ALL (N=14) X age at testing = 5 yrs Cranial RT/IT MTX Control gp solid tumor (N=9) X age at testing = 10 years No CNS prophylaxis	CNS prophylaxis (esp. radiation) had no adverse effects on neurocognitive functioning
	II	Retrospective, tested (2 yrs post-treatment) convenience sampling - standard IQ tests - neurologic exam	Exp gp ALL (N=5) X age at testing = 6 yrs Cranial RT Control gp ALL (N=9) X age at testing = 7 yrs No CNS prophylaxis	(same as above)
McIntosh et al. (1976)		Prospective, - neurologic exam (done every 6 mos) - psychometrics (done once, 8-25 mos post tx)	N=23 ALL Subjects X age at testing = 5.5 yrs Cranial RT and IV MTX	Neurological symptoms (N=12) characterized by incoordination (12), seizures (5), and learning disability (3)
Obetz et al. (1979)		Retrospective (tested at .5 to 12 yrs post CNS prophylaxis) Convenience sampling - neurologic exam - Neuropsychological Battery	N=23 ALL subjects divided into 3 groups Gp 1 IT MTX + cranial RT (N=19) Age at dx = 1.5 to 13.5 yrs Gp 2 IT MTX (N=8) Age at dx = 2 to 14.5 yrs Gp 3 IT and IV MTX (N=6) Age at dx = 1.5 to 12 yrs	1. Differences in neuropsychologic function could not be attributed to mode of CNS prophylaxis. 2. In subjects who had CNS therapy more than 2 yrs before testing, 48% had functional abnormalities.

(continued)

Table 3
Summary of Studies on the Late Effects of CNS Prophylaxis on Neurocognitive Functioning (cont'd)

Investigator(s)/ Date	Methods*	Sample Characteristics	Major Findings
Eiser & Lansdown (1977)	Retrospective, cognitive evaluation 2 to 3 yrs post diagnosis	Gp I ALL (N=15) cranial radiation Gp II (N=15) healthy children matched for age, sex, socioeconomic status and educational background	Younger children in Group I scored somewhat below average for their age. Comparison healthy group had higher overall scores ($p < 0.02$), and in quantitative, memory, and motor skills.
Eiser (1980)	Retrospective all cancer subjects in remission and off therapy from 3 mos to 5 yrs	Exp grp ALL (N=39) cranial radiation (2400 rads) and IT MTX Comp grp solid tumor (N=16) no CNS therapy Comp grp healthy controls	Cognitive skills of children treated for solid tumors were unaffected, children with leukemia significantly lower than healthy controls. Children with leukemia treated before the age of 5 yrs had the lowest scores.
Goff, Anderson, & Cooper (1980)	Retrospective convenience sampling measures of distractibility, academic achievement, and memory	37 long-term survivors of ALL who received cranial radiation; 21 of the subjects also received IT MTX. A comparison sample of 18 newly diagnosed ALL patients prior to or on the first day of cranial radiation (Age range: 7½ to 15-1/3 yrs). Subjects were grouped into younger (< 8 yrs) and older (> 8 yrs) at diagnosis.	A breakdown of the subscale scores revealed that the most consistent and extreme differences between the two groups occurred on scales measuring short-term memory and freedom from distractibility. Academic achievement appeared to be negatively affected among younger long-term survivors (treated before the age of eight years).

(continued)

Table 3
Summary of Studies on the Late Effects of CNS Prophylaxis on Neurocognitive Functioning (cont'd)

Investigator(s)/ Date	Methods*	Sample Characteristics	Major Findings
Meadows et al. (1981)	Prospective (time of testing variable) Convenience sampling - neuropsychological battery	Exp gp N=18 ALL Age at dx = 2.7 to 9.7 yrs Cranial RT and IT MTX tested 1 mo post dx and 3 yrs later Comp gp (1) N=6 ALL Age at dx = 1.5 to 7 yrs IT MTX, no cranial RT tested 7 to 13 yrs post dx Comp gp (2) N=5 Wilms tumor Age at dx = 1.8 to 13 yrs No CNS prophylaxis tested post dx and 1 yr later	1. Decline in IQ scores over time and learning disabilities in subjects treated with cranial RT and IT MTX. 2. Drop in IQ was greatest in subjects treated between 2 to 5 yrs, and in those with initial high scores. 3. Moderate to severe impairments were found in visual motor integration, psychomotor problem solving, and general memory.
Moss et al. (1981)	Retrospective (tested at 3 to 6 yrs post treatment and 1 yr later) Convenience Sampling - Wechsler Intelligence Test - Bender-Gestalt Test (perceptual motor function)	Exp gp N=24 ALL Median age at testing = 12.3 yrs Cranial RT and IT MTX or cytosine arabinoside Control gp (1) N=24 siblings Median age at testing = 12.2 yrs healthy, no treatment Control gp (2) N=13 ALL Median age at testing = 19 yrs No CNS prophylaxis N=10 siblings Median age at testing = 17 yrs healthy, no treatment	1. Subjects with CNS prophylaxis had significantly lower ($p < 0.001$) IQ scores than sibling controls 2. Greatest differences were found in measures of associative thinking, remote memory, abstract thinking, perceptual skills. 3. Greatest impairment occurred in subjects treated at young age (1.7 to 7.6 yrs).

(continued)

Table 3
Summary of Studies on the Late Effects of CNS Prophylaxis on Neurocognitive Functioning (cont'd)

Investigator(s)/ Date	Methods*	Sample Characteristics	Major Findings
Pavlovsky et al. (1983)	Retrospective Convenience sampling - Neuropsychological Battery - School performance	Group A N=19 ALL subjects 5.8 to 10.6 yrs post dx, cranial RT and IT MTX Group B N=23 ALL subjects 2.9 to 5.8 yrs post dx, IT MTX, no cranial RT	1. 8/19 (42%) of Group A subjects had abnormal test results; 7 were 5 yrs of age or younger when treated. No abnormal test findings in Group B ($p < 0.001$). 2. Deficits included short attention span, immaturity, visual perceptual impairment, failure to develop time and space structures, and clumsiness. 3. Learning problems were present in 65% (7/11) of the Group A and 28% (4/14) of the Group B children who were attending elementary school. 4. The higher incidence of abnormalities in Group A suggested more severe sequelae in children treated with cranial radiation and intrathecal methotrexate.
Moehle et al. (1983)	Retrospective Convenience sampling - five dependent measures of language-related skills: 1) Aphasia Screening Test; 2) Verbal IQ; 3) Wechsler vocabulary subtest; 4) WRAT reading; & 5) WRAT spelling	110 children treated for ALL who had received cranial radiation. Subjects were grouped along 2 dimensions: age at diagnosis (< or > 5 yrs), and age at evaluation (< or > 13 yrs). 34 subjects were still on therapy; 26 had been off therapy for less than 2 yrs; 61 were off therapy for more than 2 yrs.	The hypothesis that children diagnosed at an early age and evaluated in adolescence would demonstrate greater language-related deficits was not supported. Early diagnosed young children tended to perform worse on the Aphasia Screening Test. When subjects off therapy were compared to the remainder of the sample, there was a significant decline ($p < .005$) in the WRAT scores. No other contrasts approached significance.

(continued)

Table 3
Summary of Studies on the Late Effects of CNS Prophylaxis on Neurocognitive Functioning (cont'd)

Investigator(s)/ Date	Methods*	Sample Characteristics	Major Findings
Jannoun (1983)	Retrospective Convenience and random sampling - Psychosocial assessment using the British Abilities Scales (BAS) and a shortened version of the WISC-R	Three groups of long-term survivors of ALL: Gp I received CNS therapy, younger than 3 yrs (N=40); convenience sample Gp II received CNS therapy, between ages of 3 and 6 yrs (N=41); random sample Gp III received CNS therapy when 7 yrs of age or older (N=41); random sample CNS therapy included radiation and MTX Comparison group of 67 healthy siblings At the time of follow-up assessment, the child was in remission and had not received treatment for at least 6 mos, but time range was not stated.	Gps II and III scored significantly higher than Gp I ($p < 0.05$) on the WISC-R. A similar trend was found on the BAS ($p < 0.07$). Significant partial correlations were found between age at radiation and WISC-R full scale and performance IQ. Patients in Gps I and II had significantly ($p < 0.001$) lower IQs than the sibling controls.

(continued)

Table 3
Summary of Studies on the Late Effects of CNS Prophylaxis on Neurocognitive Functioning (cont'd)

Investigator(s)/ Date	Methods*	Sample Characteristics	Major Findings
Copeland et al. (1985)	Retrospective, comparative study of 3 groups on: - intellectual functioning - visual-motor skills - tactile spatial skills - fine motor skills - memory and learning - language - school achievement	Gp I ALL or undifferentiated lymphoma (N=24) IT medication; no CNS irradiation Gp II ALL (N=25) IT medication; CNS irradiation (2400 rads) Gp III solid tumor (N=25) No CNS therapy Subjects were evaluated at least 5 yrs post diagnosis. Subjects were also divided into those treated before and after 60 mos.	The Gp II (irradiated) children differed from Gps I and III primarily on non-language tests. There were relatively few differences on language measures. Significant age at diagnosis effects emerged for academic achievement ($p < .013$); visual-motor skills ($p < .023$); spatial memory ($p < .021$); and fine motor skills ($p < .052$). Regardless of treatment group, poorer performance was associated with earlier diagnosis, with the exception of reading skills. School achievement scores were lower in the older (school age) treatment groups except Gp III on Arithmetic and Reading Recognition.

*Methods: includes basic design, sampling, and dependent measures
IT MTX = intrathecal methotrexate
RT = radiation

occurred at least two years prior to testing had functional abnormalities. This lag period is not surprising and provides support for the hypothesized vascular changes which become more significant over time. As indicated in Table 3, there was a large age distribution within each treatment group. If the progression of delayed CNS injury is related to the underlying process of development, such a wide age span may have contributed to the nonsignificant findings.

In contrast to these two studies, there are other findings suggestive of a relationship between CNS prophylaxis and delayed neurocognitive sequelae (Table 3). In a prospective study of 23 leukemic subjects who had received cranial radiation and systemic methotrexate, McIntosh et al. (1976) described a spectrum of neurological symptoms including motor incoordination, seizures, and learning disabilities.

Thirty-seven children who were treated for leukemia and reported on previously by Verzosa et al. (1976), described here under "Studies Using School Performance as a Measure of Cognitive Deficits", and Soni et al. (1975), were administered a comprehensive neuropsychological test battery in order to identify manifestations of CNS damage (Goff et al., 1980, Table 3). Subjects, at the time of the evaluation, were four and one-half to 11 years past diagnosis. Sixteen subjects had received 2400 rads of cranial radiation and 21 had the same dose of radiation in addition to intrathecal MTX. The CNS treatment was confounded in eight cases by CNS leukemia, and in nine cases by single or multiple hemotologic relapses. The authors did not report whether or not any of the subjects with complications received additional CNS

therapy. The study also included a comparison group of 18 newly diagnosed leukemic patients.

The mean scores on general intelligence for the newly diagnosed group fell within the average range, and were significantly superior to the mean scores of the long-term survivors ($p < .05$). The most dramatic group differences were on the subscales designed to measure short-term memory skills and freedom from distractibility ($p < 0.02$); the most predominant memory deficits occurred in subjects diagnosed before the age of eight years.

Academic achievement, as measured by the Wide Range Achievement Test, was also adversely affected in the long-term survivor group. Mean standard scores fell approximately one standard deviation below the population mean, and were significantly poorer than the scores of the newly diagnosed comparison group ($p < .01$). The investigator acknowledged that missing school could influence overall levels of academic performance, however, this was not a prevalent finding in the study sample. Goff and colleagues concluded that neither school absences or emotional problems could account for the cognitive deficits, and attributed the findings to neurological (i.e. treatment) variables.

The newly diagnosed leukemia comparison group was unique to this investigation, and provides some estimate of pre-treatment functioning in children diagnosed between the ages of seven and 16 years. The authors provide no information on how well or sick the comparison subjects were at the time of testing. A second concern is the heterogeneity of the long-term survivors group. There was variability in the type of CNS treatment, as well as in the presence or absence of

CNS or hematological relapse.

Meadows et al. (1981) compared a group of 18 children treated with cranial radiation and intrathecal methotrexate with six leukemics who had received only methotrexate, and with five solid tumor patients (no CNS therapy). Declines in IQ scores over time and learning disabilities were found only in the irradiated group. The changes in performance were greatest in children who were treated at an early age (five years or younger), and in those with initial high scores. The use of repeated testing, especially in the irradiated group, strengthens these findings. However the comparison groups were small in light of the age span represented, and the time interval between testing was varied. These restrictions may have influenced the control group(s) results.

Moss et al. (1981) retrospectively investigated the effects of CNS prophylaxis on intellectual functioning in 24 subjects who had been treated three to six years earlier. These subjects were compared with their healthy siblings. A second control group consisted of 13 leukemia patients who received only systemic therapy. Ten of these subjects were also compared with healthy siblings (see Table 3 for additional information). Only the leukemic subjects with CNS therapy had significantly lower scores than their sibling controls. The greatest differences were found in measures of associative thinking, remote memory, abstract thinking, and perceptual skills. The deficits were the most significant in subjects treated at an early age (1.7 to 7.6 years). The use of sibling controls is unique to this study, and the investigators provide documentation for the validity of this approach. The major concern is the differences in age at time of

testing between the two leukemia groups (12.3 years and 19 years).

Pavlovsky et al. (1983) compared the long-term effects of two methods of CNS preventive therapy-cranial radiation in combination with IT methotrexate (Group A) and IT methotrexate alone (Group B) - on neurological and intellectual functions. The incidence of neuropsychological problems was significantly greater ($p < 0.001$) in subjects who received both radiation and chemotherapy, and occurred almost entirely in those who were five years of age or younger when treated. The deficits included short attention span, visual perceptual impairment, immaturity, failure in the development of time and space structures, and clumsiness. There was also a greater incidence of learning problems at school in Group A. The investigators concluded that there are long-term consequences of CNS treatment, particularly in children receiving both radiation and chemotherapy.

The length of time between treatment and testing was much greater in Group A, and highly variable within both groups (See Table 3). This discrepancy may have influenced the results, because children in group B could develop more observable problems. The age range under study was not specifically cited, but did include both school age children and adolescents. The potential confounding effect of age is difficult to assess without additional information. Despite these limitations, the finding that neurocognitive sequelae were the most prevalent in children who received CNS prophylaxis at an early age provides indirect evidence for the hypothesis that the later phases of brain growth and development may be vulnerable to adverse external conditions.

The importance of age at time of treatment and of length of time since completing treatment were demonstrated in the research by Jannoun (1983). This study included a large sample of children who were off leukemia therapy for at least six months. The sample was divided into three treatment groups: Treated before the age of three years (Gp I), treated between the ages of three and six years (Gp II), and treated when seven years of age or older (Gp III) (Table 3 provides additional design information). Each group was compared with a control group of healthy siblings (N = 67).

There were no significant differences between the two older treatment groups, while those subjects treated before the age of three years had significantly lower scores than the rest of the sample ($p < .05$). A second noteworthy finding was the significant negative correlation between IQ and since the time completion of therapy ($p < .004$) for Groups I and II. The comparisons with sibling controls demonstrated that Groups I and II had significantly lower scores than the healthy siblings ($p < .001$).

These findings support the vulnerability of the brain to biological stressors during periods of rapid development. The most significant cognitive deficits were found in children treated before three years of age--a time of glial cell proliferation and myelinogenesis. The three to six year old treatment group also had deficits in comparison to the siblings. This is an age of continued myelineation and dendritic branching. The delayed nature of the pathogenesis of late effects from radiation and methotrexate is supported by the negative correlations between time off therapy and IQ in the younger age at time of treatment groups.

Copeland et al. (1985) also documented significant long-term cognitive sequelae following central nervous system therapy. The study design included two CNS treatment groups--IT medication only and in combination with cranial radiation--as well as a non-CNS treatment comparison group. The IT therapy only group did not differ significantly from the comparison group. The significant ($p < .05$) differences occurred between the irradiated and the two non-irradiated groups, and were primarily in non-language skills (Table 3). Secondary analysis revealed significant age at time of diagnosis effects, but no age at time of treatment by treatment group interactions. Thus, regardless of treatment status, poorer performance was associated with earlier diagnosis (less than 60 months). The investigators concluded: 1) that CNS radiation exerts a detrimental effect, regardless of the age at time of treatment; and 2) that any child who receives cancer therapy before the age of five years is more likely to experience some cognitive difficulties.

The school achievement scores of all subjects diagnosed at an early (preschool) age were compared with those diagnosed during the school age years. In this analysis the older group had consistently lower scores which was attributed to the disruption in schooling caused by cancer treatment. The investigators proposed that the absence of significant interaction effect between age at time of treatment and treatment group, along with the lower academic achievement scores in the older age at treatment group questions the validity of the hypothesis that cognitive functions are significantly more affected by radiation in young children. This argument warrants further exploration. It is unfortunate that the authors did not

provide the descriptive and inferential statistics on the school achievement scores or on the amount of school that was missed. Thus it is impossible to determine the magnitude of the differences between the groups as well as how much the older group differed from the norms for healthy children. Combining subjects from the three groups to determine overall age effects may also be confounding the findings as age differences may vary depending on the treatment condition. The authors failed to specify if the IT medication was MTX or another chemotherapeutic agent. Therefore it is impossible to draw any conclusions about the comparative delayed toxicities of methotrexate and radiation.

The importance of age at the time of central nervous system prophylaxis was the major focus of two studies by Eiser and Lansdown (1977) and Eiser (1980). Eiser and Lansdown (1977) proposed that cognitive development in children treated for leukemia could be influenced by the emotional stresses accompanying a potentially fatal illness, as well as the adverse effects of cranial radiation long-term use of cytotoxic drugs. Fifteen children who had received cranial radiation and been off leukemic therapy for two to three years were compared with fifteen healthy children matched for age, sex, socioeconomic status and educational background. No significant differences were found between the groups of older subjects (8.3 to 9.5 years) on standardized tests of intellectual development. The younger children, who had been treated for leukemia between the ages of 2.6 and 4.5 years, scored somewhat below average for their age. When compared with the healthy controls, the latter group performed higher overall ($p < 0.02$); and on the component subscales for

quantitative ($p < 0.02$); memory ($p < 0.01$); and motor skills ($p < 0.01$).

Controlling for age at time of treatment and length of time between treatment and testing strengthens these findings. In other studies, the interval has been longer than two to three years; therefore it is possible that these leukemia subjects may manifest additional problems over time. The group of healthy subjects did not control for the "life-threatening" aspects of a serious illness such as cancer, or the potential effects of long-term administration of chemotherapeutic drugs. Because of this limitation, it is impossible to evaluate the significance of either variable as originally proposed by the investigators.

Eiser (1980) studied two groups of patients: 40 children who had been treated for ALL, and 16 who had received systemic therapy for various types of solid tumors to further evaluate the late effects of chronic illness and cranial radiation on intellectual development. Thirty-nine of the leukemia subjects had received cranial radiation (2400 rads) and intrathecal methotrexate. All cancer subjects were in remission and had been off therapy from three months to five years. Two groups of healthy children, who were matched on age, sex, and family socioeconomic status, served as controls. Using general measures of intellect and achievement, as well as more specific indicators of memory and learning, Eiser found that the cognitive abilities of children treated for solid tumors were unaffected, but that the leukemic child's scores were significantly lower ($p = 0.01$ to 0.001) than those of the healthy controls. The leukemia subjects were divided into those treated before or after five

years of age; the lower scores were obtained by the younger children.

The solid tumor subjects served as an appropriate control for the life-threatening and chronic nature of the cancer experience. Because of the nonsignificant finding in this group, Eiser concluded that this variable has no effect on intellectual development. The finding of decreased cognitive performance in younger children lends support to the hypothesis that CNS prophylaxis is more damaging during a period of rapid brain development. Almost all leukemia subjects received the same CNS therapy, making it impossible to determine the differential effects of radiation and methotrexate. Time between treatment and testing was variable for both cancer groups (three months to five years), and could confound the findings.

The study by Moehle et al. (1983) was based on previous findings (Eiser, 1980; Eiser & Lansdown, 1977) suggesting that language-related skills are spared during the early stages of leukemia therapy but are adversely affected in long-term survivors. The investigators used a model of neurolinguistic development to test the hypothesis that deficits in language-related skills would be present in children with ALL, particularly in adolescents diagnosed at or before the age of five years.

The study sample was large (110 children treated for ALL), but was comprised of subjects on therapy (N = 34) and off therapy for less than (N = 26) and more than (N = 61) two years. CNS prophylaxis involved only cranial radiation for all patients. Subjects completed five measures of language-related skills (Table 3). Educational level, time on therapy, and time off therapy were treated as covariates in the 2 x 2 factorial design. The grouping factors were

age at evaluation and age at diagnosis. The original hypothesis was not supported. The major finding was that (relative to the rest of the sample) patients off of therapy for more than two years demonstrated a significant decline on the WRAT spelling list ($p < .005$) with a similar, but nonsignificant trend, in all other measures.

This study, along with many others, failed to take account of the mechanisms of injury to the central nervous system particularly during stages of postnatal development. The finding that subjects off therapy for more than two years demonstrated declines in functioning is consistent with the delayed pattern of pathophysiological changes following cranial radiation. The study could be strengthened by a systemic therapy only comparison group to control for the competing hypothesis of time away from school which was raised by Goff et al (1980) and Copeland et al. (1985).

Studies on Structural Changes in the Central Nervous System Following Prophylactic Therapy

In the studies reviewed above, functional or behavioral measures were used to determine the incidence and characteristics of neurocognitive late effects. Structural changes, observed by computed tomography (CT) scans, have also been used to examine the relationship between CNS prophylaxis and delayed tissue injury. Investigations involving the latter measure are summarized in Table 4. Obetz et al. (1979) and Pavlovsky et al. (1983) included CT scans in their studies (described earlier) of the neuropsychological sequelae associated with various methods of CNS prophylaxis. Pavlovsky et al. (1983) observed abnormalities indicative of damage to neural and supportive tissue in

58 percent of subjects treated with both cranial radiation and IT methotrexate. The incidence of changes was much lower in the sample reported by Obetz et al. (1979), but was associated with the same combination therapy. In both investigations no correlations were found between structural abnormalities and functional problems.

Ochs et al. (1980) found a greater number (19%) of CT abnormalities in 43 asymptomatic children who had received IT methotrexate alone or in combination with 4 MTX, than in newly diagnosed leukemics (16%) or noncancer patients with recurrent headaches (4%). The interval between CNS therapy and testing ranged from .8 to 4.9 years. Although the lag time necessary for the manifestation of delayed structural neurological changes has not been determined, this degree of variability may have decreased the incidence of such pathology in the treatment group. Statistical analyses were not reported, therefore it is difficult to determine if the differences among the groups are significant. The investigators attributed the abnormal findings in cancer subjects to the disease or other chemotherapeutic agents. However, the importance of these variables was not formally tested.

In general, a major limitation to the use of structural changes as an outcome measure of delayed neurocognitive effects is the lack of correlation with functional deficits. Because some of the observable changes are of a nonspecific nature (Ochs, 1980), it may be difficult to conclude that the damage was due to cancer therapy rather than to some other type of insult.

Table 4
Summary of Studies on the CNS Structural Changes Following Prophylaxis

Investigator(s)/ Date	Methods*	Sample Characteristics	Major Findings
Obetz et al. (1979)	Retrospective (.5 to 12 yrs post CNS prophylaxis) Convenience sampling CT scan of head	N=33 ALL subjects divided into 3 groups: Gp 1 IT MTX + cranial RT (N=19) Age at dx = 1.5 to 13.5 yrs Gp 2 IT MTX (N=8) Age at dx = 2 to 14.5 yrs Gp 3 IT and 4 MTX (N=6) Age at dx = 1.5 to 12 yrs	1. CT scan appeared normal in 29 cases. Changes suggestive of parenchymal atrophy were found in Group 1 (N=3). 2. No correlations between abnormal CT scans and functional abnormalities were found.
Ochs et al. (1980)	Retrospective (.8 to 4.9 yrs post CNS prophylaxis) Convenience sampling CT scan of head	Exp gp N=43 ALL subjects IT MTX only (N=10) IT and 4 MTX (N=33) Control gp 1 N=13 subjects ALL 15 yrs or younger 24 hrs post dx Control gp 2 N=50 noncancer subjects recurrent headaches	1. Eight experimental subjects and 2 subjects in each control group had nonspecific abnormal findings. 2. Abnormal findings in cancer subjects were attributed to the disease or other chemotherapeutic agents.
Pavlovsky et al (1983)	Retrospective Convenience sampling CT scan of head	Group A N=19 ALL subjects 5.8 to 10.6 yrs post dx Cranial RT and IT MTX Group B N=23 ALL subjects 2.9 to 5.8 yrs post dx IT MTX, no cranial RT	1. CT abnormalities detected in 58% of Group A and 4% in Group B. 2. The CT abnormalities were indicative of damage to neural tissue and support structure. The potentiating effect of MTX and radiation was proposed as the underlying mechanism.

*Methods: include basic design, sampling, and dependent measures
CT = computed tomography
IT MTX = intrathecal methotrexate
RT = radiation

Studies Using School Performance as a Measure of Cognitive Deficits

Finally, two studies used school performance, which was evaluated by the child's teacher, as the criterion for delayed neurocognitive sequelae. Verzosa (1976) reported on a survey of the intellectual and physical features of 22 children who had received cranial radiation (2400 rads) and IT methotrexate (five doses) five years earlier. Age at time of diagnosis ranged from two to sixteen years. Nine categories were evaluated by the teacher--coordination, academic interest and achievement, approach to problems, imaginative abilities, energy level, motivation, attention span, and concrete/abstract thinking. One third of the subjects were evaluated as being below average on the latter four areas. The investigators concluded that the profiles of these children represented a normal distribution of intellectual and physical capabilities. However, they failed to explain how children who were fourteen years of age or older when treated for leukemia could be in secondary school five years later. The validity of teacher appraisal as a measure of cognitive deficits in students who have been treated for leukemia has not been established. The findings should be considered in light of this limitation, as well as the variability in age at time of diagnosis.

Inati, Sallen, Cassady et al. (1983) relied on teacher and/or parent evaluation of school performance (no specific criteria reported) to identify those children, previously treated for leukemia, who were experiencing learning disabilities. From a group of 66 children who had received CNS therapy (2400 rads of cranial radiation and concurrent IT methotrexate), 54 (82%) were reported to have normal school performance. The remaining 12 (18%) were considered to be at

risk for learning problems, and underwent a neuropsychologic evaluation; nine demonstrated one or more deficits in the areas of attention span, visual motor abilities, fine motor coordination, and quantitative skills, such as arithmetic. The sample was divided into those diagnosed before or after five years of age. Eleven of the subjects at high risk for, or with documented learning difficulties were in the younger age group; this was a highly significant finding ($p = 0.0008$).

Unfortunately, no additional neuropsychological testing was done on any of the remaining 54 subjects who were thought to have normal school performance. Therefore, the discriminate validity of teacher/parent appraisal of cognitive late effects cannot be determined. Parents and teachers, who have regular contact with the child, may prove to be a useful screening strategy. More specific information on the categories involved in the initial appraisal of school performance would be helpful.

Summary

These studies have been useful in describing the nature of neurocognitive late effects. There is evidence supporting the importance of age at time of treatment, mode of therapy, and length of time since CNS prophylaxis to the pathogenesis of neurocognitive sequelae. Further work needs to be done in refining these variables, in identifying other critical variables, and in establishing the relationships among variables. None of the studies reviewed here are theoretically based on postnatal development of the brain and the mechanisms of interference with this process. Finally, the nature and

severity of the deficits in cognitive function which have been attributed to CNS prophylaxis needs further explication. Additional research on the most valid and reliable indicators of this phenomenon is needed.

Psychosocial Late Effects of Acute Lymphoblastic Leukemia

The mastery of developmental tasks creates a challenge for any healthy child. A serious illness, such as cancer, adds an additional stress as the disease and treatment can influence resources for coping. Van Eyes (1977) writes that the child with cancer suffers from delayed development. There are only short periods for mastery of skills, and cancer interferes with the child's opportunities during these critical times (Van Eyes, 1977). There is evidence which suggests that during the maintenance phase of therapy, children and adolescents with chronic, life-threatening illness experience social and emotional problems. Development is a sequential process, and the child who survives a malignancy may have psychosocial late effects. However, very little is known about this phenomenon.

Studies which describe the nature of psychosocial problems experienced during the treatment phase are briefly summarized, and is followed by a more thorough review and critique of research on long-term effects. Erikson's theory of psychosocial development may be a useful framework for future investigations on late effects. Therefore, the major assumptions and stages of this theory are also discussed.

The Developmental Theory of Erik H. Erikson

From infancy through adolescence, the child encounters a variety of psychological and social events which provide the opportunity for successful mastery of new challenges. Erikson's theory of psychosocial development describes the qualitative nature of these events within the context of a sequence of phases. Central to this theory is the assumption that developmental stages or phases occur in the same predictable order; and that each has its own set of tasks which become

progressively more complex and differentiated (Maier, 1978).

Development, according to Erikson, is an evolutionary process: it takes place in the present, but is rooted in the past. That is, the skills acquired in previous stages provide the resources and confidence to face the challenges of current tasks. This characteristic of development underlies the assumption of polarity. Polarity refers to the pull of two opposing forces--a drive to reach out to more complex challenges, and a concurrent desire to return, or regress, to an earlier, more simplistic phase (Maier, 1978). Erikson conceptualizes development as a linear process. However, a constant state of imbalance, resulting from this pulling back and pushing forward, creates a zigzag course.

Finally, development involves interactions between the child and his/her significant others--care-giver or peers. This interactional aspect of development is the basis for Erikson's assumption of mutualities; with the quality of interpersonal relations being of particular importance to future growth (Erikson, 1963).

Five developmental phases of childhood were described by Erikson, and include acquiring a sense of trust, autonomy, initiative, industry, and identity. Phase II: Autonomy versus Shame and Doubt (toddler), Phase III: Initiative versus Guilt (preschool), and Phase IV: Industry versus Inferiority (school-age) are of particular interest as the children in the study were in these phases of psychosocial development and the time of the diagnosis and treatment of cancer. The major tasks of each phase are summarized below.

Phase I: Basic Trust versus Basic Mistrust

The first and most fundamental task of childhood is to establish a

sense of trust in oneself and in the environment. This phase occurs during infancy, a time characterized by total dependency upon the nurturant care of others. The newborn's initial contact with the outside world is through his/her mother or caregiver. A sense of trust is fostered when the infant's physical needs are cared for in a consistent and predictable manner (Erikson, 1963); and when he/she is provided with a variety of stimulating and socializing experiences (Lidz, 1968). Regularity of physiological functions, such as respiration, ingestion, and digestion are the early indicators of a trusting relationship between child and care-giver. Erikson (1963) writes that the infant's first social achievement is a willingness to let the mother figure out of sight without undue anxiety, because of an inner sense of certainty.

Infancy is also the time when boundaries between self and significant others are being established. Trust in oneself evolves through the integration of purposeful motor movements, and the ability to manipulate one's environment. Grasping and holding onto objects, visual perception and the recognition of sounds, and communicating with others are sources of self-satisfaction (Maier, 1978).

The infant is resilient and, over time, becomes capable of coping with occasional frustration, or with changes in the manner in which his/her physical needs are satisfied. However, an inadequate experience of receiving and nurturing can result in a sense of distrust, and may also have adverse consequences for future development.

Phase II: Autonomy versus Shame and Doubt

Around two years of age, the child begins to acquire a realization

of his will. As he begins to assert his will, his independence, or autonomy, grows. Play assumes special importance during this phase; the toddler can experiment with the boundaries of his own independence. The home and family provide a safe and sheltered environment within which the young child can acquire confidence in himself and his capabilities (Lidz, 1968). How much autonomy the child gains depends upon his parents' willingness to grant him freedom, within limits (Maier, 1978).

Freedom within limits is important. Sympathetic guidance and support from parents during this time is essential to preventing a feeling of helplessness and loss of control. According to Erikson (1963), "from a sense of loss of self-control and of foreign over-control comes a lasting propensity for doubt and shame."

Phase III: Initiative versus Guilt

The preschool years are filled with activity, curiosity, and fantasy. Having developed some degree of control over himself and the environment, the child uses language and mobility to master new skills and take on new responsibilities. Great effort is invested in refining muscular activities, in testing potential capabilities, and in communicating with others (Maier, 1978). The phase of initiative adds to autonomy the quality of undertaking, planning, and attacking a task (Erikson, 1963).

A sense of conscious emerges during this phase. The child begins to adopt the tastes, values, and traditions which he observes in significant adults. With the establishment of conscious comes the capacity to experience guilt. The danger in this stage is a sense of guilt over fantasies and behaviors involving aggression, or which

exceed the limits of self-control.

Phase IV: Industry versus Inferiority

The school age child is interested in finding out what he can do. Successful completion of a productive situation is the source of great pleasure, and is also an avenue for winning recognition from others. Socially, this is an important stage. The child is introduced to the concept of cooperation as he learns to work on an equal basis with others (Erikson, 1963).

The school serves a dual function in fostering a sense of industry: to strengthen many of the behaviors the child brings from home; and to increase his ability to respond to new, more complex stimuli (Travers, 1977). Intellectual experiences, recreational activities, and crafts provide numerous opportunities for industrious endeavors.

Meaningful experiences with significant others are essential to psychosocial development during middle childhood. Parents continue to be an important source of feedback; teachers serve as important role models as the child learns age-appropriate behaviors (Freiberg, 1979). Peers become increasingly important. As the child begins to gain independence from parents and to assume greater responsibility, peers provide emotional support and a necessary sense of belonging. Peers are also used to evaluate the success or failure of one's endeavors, and thereby influence self-esteem (Maier, 1978).

Experiencing success and achievement is central to developing a sense of industry. If the child repeatedly encounters failure, or if he fails to win recognition for his accomplishments, he is in danger of developing a sense of inferiority. Erikson writes:

> If he despairs of his tools and skills, or of his status among his tool partners, he may be discouraged from identification with them and with a section of the tool world (Erikson, 1963).

Phase V: Identity versus Role Confusion

Puberty is generally considered to mark the end of middle childhood and the beginning of adolescence. The adolescent is faced with the task of rediscovering who he is and planning for what he hopes to become. This requires an integration of earlier childhood identifications with biological drives, native endowments, and the opportunities offered by various social roles.

Establishing a positive ego identity is a difficult, and at times, painful process. The teenager is concerned with how he appears to others, and also with how he feels about himself (Erikson, 1963). This is a time of rapid physiological and anatomical changes. Previous trust in one's body and mastery of its functions are suddenly shaken. Peers, who are experiencing similar changes, can provide the support and assurance necessary for regaining self-confidence (Maier, 1978).

The adolescent is constantly striving to gain his independence, more so than in middle childhood. He often finds himself in the dilemma of seeking independence from parents while relying on them for emotional and physical support. Involvement in physical activities is a commonly used strategy for achieving a sense of competence and control (Ausubel, 1954).

Socially, the adolescent is very peer conscious. Acceptance and approval by peers, as well as conformity to the group's standards is of utmost importance (Anderson, 1976). During early adolescence, friends continue to be of the same sex, but soon, there is an increasing

awareness of the opposite sex which eventually leads to pairing of couples and dating.

Peers serve several functions for the adolescent, one of which is to provide emotional support. The teenager lacks the social experience of adults, but nevertheless, is often unwilling to accept their advice. In a time of numerous physical changes and emotional turmoil, the youth turns to his age-mates for strength and a sense of power. Peers serve another function by providing feedback necessary for the establishment of one's identity. Within this group, the teenager is able to learn, develop, and practice qualities and behaviors necessary for an adult life (Anderson, 1976).

The crisis of this developmental phase is planning for a future career that is both compatible with oneself and with the opportunities of society (Maier, 1978). The adolescent invests a great deal of effort in clarifying his role as a member of society. Erikson proposes the concept of a moratorium--a grace period--which allows youth the time to find themselves, and to integrate their thoughts, skills, and feelings (Erikson, 1963). The opportunity for extended education or training and experimentation with various roles will eventually result in either a positive identity or role confusion (Freiberg, 1979).

Impact of Childhood Cancer on Psychosocial Development: Treatment Phase

In a retrospective descriptive study, McCarthy (1975) interviewed the parents of 64 children who had leukemia about the social aspects of treatment. The children had been diagnosed two to three years earlier, and over half (38) had already died. The age range of the children was not reported. One of the side effects of therapy which was the most difficult to manage was the increased appetite due to steroids. Parents reported that this often resulted in the child feeling uncomfortable and embarrassed about his appearance. Alopecia was another commonly experienced side effect, however, according to the parents, this was not terribly distressing for the children. Twenty-three of the children were attending school at the time of the study. Seven parents indicated that their children were having school-related problems. Most notable were a lack of self-confidence, inability to relate to peers, and slower academic performance. This study of parent appraisal suggests that children with a serious illness, such as leukemia, do experience some psychosocial problems. Without additional demographic information, it is difficult to relate these problems to the age of the child or the stage of development.

Spinetta and Deasy-Spinetta (1981) developed and refined the Deasy-Spinetta Behavioral Questionnaire (DSBQ) in order to study teachers' evaluations of the school performance of children with cancer. The instrument was based on clinical interviews with pediatric oncologists, nurses, parents, and teachers regarding the types of attitudes and behavior patterns exhibited by children with cancer. The teacher was asked to complete the DSBQ on the student with cancer and

also on a student of the same sex who represented the general characteristics of the class population. Data was collected on a total of 122 cancer and healthy student pairs who ranged in age from five to 17 years, and were in kindergarten through 12th grade. The three-phase study demonstrated that pediatric cancer patients differ significantly from their classmates in certain school activities. The teachers indicated difficulties with attendance, completion of school work, and concentration. A higher rate of learning disabilities and lower energy level also created problems for the student with cancer. The cancer subjects were also different on an emotional level. They did not initiate activities, talk about their activities or try new things at the same level as the healthy controls.

Spinetta and Deasy-Spinetta's study (1981) involved children with leukemia and solid tumors at various stages of illness--newly diagnosed; in first remission but receiving maintenance therapy; in subsequent remission; being treated after relapse or recurrence; in relapse or recurrence; and off therapy. Of particular interest is the finding that children in remission but on medication and those in relapse or recurrence had a higher incidence of school problems than those in long-term remission (Spinetta & Deasy-Spinetta, 1981).

Alterations in body image, such as alopecia, were one of the most commonly documented concerns in a descriptive study of the psychological problems experienced by 76 adolescents with various malignancies (Moore, Holton, & Marten, 1969). To girls, the loss of hair meant a loss of attractiveness and femininity, to boys, it signified the loss of virility. The subjects also experienced difficulties in interpersonal relationships. Fear of rejection by

peers was of great concern to those who felt different and inferior to others. The findings also suggested that problems with adult relationships were intensified for adolescents with cancer. Feelings of enforced dependency and of powerlessness were the most common. Finally, thinking about the future was a source of distress. Many of the older adolescents asked questions such as "should I plan to go to college?" which were interpreted by the investigators as conveying a sense of uncertainty (Moore et al., 1969).

Zelter, Kellerman, Ellenberg et al. (1980) asked a sample of 168 adolescents with a variety of chronic diseases, including cancer, and a comparison group of 345 essentially healthy adolescents about their perceptions of illness - induced disruptions in a variety of areas. The investigators developed the Illness-Impact Questionnaire for this study, and included developmental issues such as relationships with significant others, school and peer activities, achieving independence, and future orientation. Unfortunately, the validity and reliability of the instrument have not been established (personal communication with first author). Adolescents with cancer were the most likely to view treatment as disruptive. They felt the therapy caused general problems ($p < 0.0005$), and also affected body image relative to healthy ($p < 0.0001$) and to other chronically ill adolescents ($p < 0.01$). In comparison to the other chronically ill subjects, those with cancer expressed more illness-induced family problems ($p < 0.05$). Finally, and not surprisingly, this group also reported more disruptions related to school work and school-related activities ($p < 0.001$) than did their healthy counterpart.

Late Effects on Psychosocial Development

To date little is known about the psychosocial sequelae of the cancer experience on long-term survivors. Koocher and O'Malley (1981) suggest that with long treatment-free, disease-free periods comes the threat of uncertainty--will cancer recur? The length and intensity of treatment (Eiser, 1979), numerous painful procedures, and alterations in activity level (Fergusson, 1976) often result in some degree of emotional maladjustment. Among the most difficult emotional consequences of treatment are the child's discomfort or embarrassment about appearance following visible physical changes such as alopecia (McCarthy, 1975). Teenagers with chronic illness frequently demonstrate an increased dependence on parents, social immaturity, poor self-image, decreased confidence, and a fear of failure. These problems interfere with peer acceptance and are difficult obstacles to the accomplishment of the psychosocial tasks of adolescence (Leichtman & Friedman, 1975). D'Angio (1978) acknowledges that there is an aura of incurability associated with the diagnosis of cancer. However, he stresses the resilience of the child who may, in fact, emerge from the experience as a stronger individual, with a better sense of values and a heightened awareness of the meaning of life.

There is a paucity of research designed to determine the importance of variables, such as those just mentioned, to psychosocial adjustment. This is understandable in light of the fact that the possibility of long-term survival is a relatively recent accomplishment. The few investigations on the phenomenon of psychosocial late effects are reviewed and critiqued below. Table 5 provides a more detailed summary of the characteristics of each study.

Table 5
Summary of Studies on Psychosocial Late Effects

Investigator(s)/ Date	Methods*	Characteristics	Findings
Fergusson (1976)	Case studies of children previously treated for cancer Convenience Sampling - Telephone interview with parent - Draw a Person Test - House Tree Technique - Lowenfeld Mosaic Test - Sentence completion and making 3 wishes	N=18 children previously treated for various malignancies between 2 & 5 yrs of age (N=17) and less than 1 yr of age (N=1); Length of time between hospitalization for initiation of treatment and testing varied greatly from 4 to 13 yrs	Moderately severe adjustments problems found in only 2 children. In most cases, when the diagnosis of cancer was freely and fully discussed with the child, later functioning appeared to be normal. Factors identified (from parental interview) as contributing to the child's well-being included: relationship with parents; changes in family structure; interaction with health team (no specific criteria given).
Verzosa	Retrospective, review of social-emotional features 5 yrs following CNS therapy - teacher appraisal of social acceptance, adjustment in/out of class, acceptance of authority, emotional stability, self concept, adaptability, passive/ aggressive, general adjustment (validity and reliability not discussed)	N=21 children treated for leukemia 5 yrs earlier; age at time of diagnosis ranged from 2 to 16 yrs; Comparison group = school peers (no specific variables controlled for)	Majority of subjects were evaluated as average to above average on all criteria, and judged to be comparable to that of school peers.

(continued)

Table 5
Summary of Studies on Psychosocial Late Effects (cont'd)

Investigator(s)/ Date	Methods*	Characteristics	Findings
Eiser & Lansdown (1977)	Retrospective, 2-3 yrs post-leukemic therapy - teacher interviews to identify social or be-behavioral problems (validity & reliability not discussed)	N=13 of 15 ALL subjects studied No control group used for this component of the study	Teachers described 9 subjects (71%) as shy, quiet, withdrawn, and having few friends. Most (86%) were viewed as pleasant and polite.
Koocher & O'Malley (1982)	Retrospective (5.3 to 32.7 years since diagnosis) - psychiatric interview - mental status evaluation - content interview - psychometrics - Vineland Social Maturity Scale - measures of depression, anxiety, and death anxiety - index of adjustment and values	A) N=117 former cancer patients: - treated for childhood malignancy before 18 yrs of age (range = 3 mos to 18 yrs) - diagnosis and initiation of therapy at least 60 months earlier (range = 5.3 to 32.7 yrs), - off therapy at least 12 months - disease-free at time of testing - age at time of testing (5.6 to 37 yrs) B) Subsample: N=22 matched pairs of children treated for cancer and for other chronic illness (not life-threatening). Subjects matched on: sex, age at diagnosis, age at interview, socioeconomic status, years of education, estimated verbal IQ, time since diagnosis, current level of social functioning.	Of the total sample (117), 62 (53%) were rated as well adjusted; no evidence of symptomatology. The remaining 55 subjects had adjustment problems ranging from mild (30) to moderate (12) to impaired (13). The highest incidence of adjustment problems were found in survivors of Hodgkins disease or leukemia. Factors related to optimal long-term adjustment included: 1) a relatively short course of treatment; 2) having a relapse or recurrence-free period; and 3) having the disease during infancy or early childhood. In the subsample (N=22 matched pairs), the cancer survivors demonstrated significantly greater psychopathology, lower levels of self-satisfaction, and more manifest anxiety than did the control group.

* Methods include basic design, sampling, and dependent measures

Eiser and Lansdown's retrospective study (1977) of intellectual development in long-term survivors of leukemia included an interview with the school teachers of 13 children (5.5 to 9.5 years of age) for the purpose of identifying behavioral or social problems. The interview format was not described, and no control group was used for this aspect of the research. Most children (86%) were described by their teachers as being pleasant and polite, however, nine (71%) were characterized as shy, quiet, withdrawn, and as having few friends.

Verzosa and Associates (1976) also used teacher appraisal of various characteristics of social-emotional adjustment (Table 5) as the measure of long-term effects of leukemia on survivors. The 21 subjects, who ranged in age at time of diagnosis from 2 to 16 years, were evaluated five years following central nervous system prophylactic therapy. When compared to others in the class, the majority of subjects were rated as average to above average, and the investigators concluded that the overall distribution of responses was representative of relatively normal development.

In both of these studies, age at time of treatment and subsequent evaluation were quite variable, especially considering the developmental span being represented. The validity of the dependent measures and the reliability of teacher appraisal of psychosocial development in long-term survivors of leukemia were not addressed. Finally, the absence of a well defined control group limits the usefulness of the findings of either investigation.

Fergusson (1976) reported a study on the late psychologic effects of a serious illness during childhood. The study included 18 children who were hospitalized and treated for various malignancies before the

age of five years. The type and length of therapy were not consistent among subjects. The interval between treatment and time of testing varied greatly, from 4 to 13 years. Data were collected on measures of intellectual function, illness concerns, behavioral adjustment, and also from a telephone interview with the child's parent. Only two of the children studied were found to have moderately severe adjustment problems, and these were thought to be due primarily to continuing family stress. Fergusson concluded that young children who experience a life-threatening illness do not necessarily have psychosocial problems at a later age.

All the subjects in this study were treated for cancer before the age of five years, and one was younger than two years. The high degree of variability in the length of time since diagnosis and in the subjects' ages at the time of follow-up are of concern. This limitation precludes any analysis which might address the importance of the child's developmental level. The appropriateness of several of the projective tests for older subjects, and the validity of some of the less standardized measures of illness concerns were not addressed.

Koocher and O'Malley (1981) studied the impact of the cancer experience on psychosocial adjustment in later life. Survivorship was defined as living five years past diagnosis, and varied in the sample of 117 subjects from 5.3 to 32.7 years. Age at time of diagnosis ranged from zero to 18 years; age when tested from 5.6 to 37 years. A variety of measures of psychosocial adjustment were used (see Table 5). Forty-seven percent of the subjects were evaluated as experiencing some degree of adjustment problems (mild to severe). The highest incidence of problems were among survivors of Hodgkins disease and leukemia.

Length of time on therapy (four to five years), number of treatment related side effects, and degree of uncertainty about survival were suggested as variables which might contribute to this finding. Using multiple regression analysis, five variables were identified as significant predictors of adjustment problems. An interesting variable is age at time of diagnosis--being diagnosed with cancer in infancy or early childhood is predictive of fewer long-term problems. Verbal IQ, current level of depression, self-esteem problems, and time elapsed since diagnosis were also significant predictors of later psychosocial adjustment.

From the sample of 117 survivors, 22 were matched on a number of potentially confounding variables (Table 5) with a control group of survivors of a chronic illness with a good prognosis. The two groups differed on three variables related to the uncertainty and life-threatening nature of cancer: the cancer survivors scored higher on the overall adjustment rating, reflecting greater psychopathology; the former cancer group reported significantly lower levels of self-satisfaction; and they also reported more manifest anxiety.

Koocher and O'Malley's study (1981) on psychosocial late effects addresses concepts relevant to long-term emotional functioning, and is the most rigorous of those reviewed here. Although age at time of diagnosis and number of years since cessation of therapy were highly variable in the sample, both factors were controlled statistically. Some of the instruments used to measure psychosocial adjustment have been developed for and standardized on adult populations with entirely different characteristics than this sample. Although these measures could be appropriate for the older subjects, their validity as

indicators of the types psychosocial problems experienced by the younger subjects is questionable. Waechter's projective test was used as a measure of death anxiety. Previous research has used this instrument with school age children and may not be appropriate for adults. A major contribution of the study is the identification of variables which could significantly influence the impact of cancer on subsequent psychosocial development.

Summary

The studies on the emotional and social problems experienced by children and adolescents during the treatment phase of cancer provide some clues about the nature of long-term psychosocial sequelae. As might be inferred from this review of related literature, research on psychosocial late effects is in its early stages. The methods, particularly with regards to design and measurement, are in need of refinement. Theoretically, the underlying process of development has not always been represented. Therefore, further delineation and testing of variables which influence long-term psychosocial development in children with leukemia is warranted. In light of the importance of development as the theoretical framework, areas which may be of particular importance to future studies include: 1) age and developmental stage at the time of diagnosis and treatment; 2) length of time since diagnosis and since completion of therapy; 3) frequency and severity or impact of disease- and treatment-related complications; 4) problems with school attendance and performance; 5) difficulties with peer and family relationships; and 6) presence and severity of other sequelae, such as cognitive late effects.

Theoretical Framework

The Developmental Model

The study proposed to test the vulnerable period hypothesis as it relates to selected phases of psychosocial and brain development. This hypothesis states that developmental processes are more vulnerable to insults and stressors at the time of most rapid physiological and morphological change.

A developmental model was used to delineate variables of importance to the investigation of cognitive and psychosocial late effects. The emphasis of the model is on changes in human growth and behavior that occur as an individual progresses toward more complex levels of functioning. The focus is on describing the processes which are involved in development, and on identifying variables that facilitate or interfere with this process (Kimmel, 1974; Waechter, 1978). The basic assumptions and major concepts of the model are discussed below.

Basic Assumptions

One of the most fundamental assumptions underlying the developmental model is the view that life is a continuous, unidirectional process of sequential and orderly change (Chin, 1980). This assumption of sequential and orderly change implies that development is predictable, that is, each stage or phase can be characterized by various challenges and tasks (Waechter, 1978; Kimmel, 1974). Another, assumption, related to the concept of sequential and predictable change, is that each successive stage of the life cycle builds on the preceding one, and becomes more complex and differentiated. Thus, mastery of the tasks in one developmental stage

contributes substantially to success in future stages (Maier, 1978; Waechter, 1978).

In spite of the emphasis on orderliness and predictability, the developmental model underscores the reality of individual differences. The assumption of individuality states that although all individuals follow a definite pattern of growth and development, each does so in his/her own style (Kaluger & Kaluger, 1974). Individual differences may be due to innate biological characteristics or to variations in cultural and environmental influences.

Finally, the physical, emotional, social, and cognitive processes of development are assumed to be complex and interrelated. However, they are often arbitrarily divided into categories such as neurological, physical, and gross and fine motor. While these dimensions are often examined independently, it is important to recognize that each area impinges on and influences the other (Maier, 1978; Waechter, 1978).

Development

Development is most commonly defined as alterations in the composition, position, structure, or activity of physical, cognitive, and social processes. This involves the evolution from a prior and lower stage to a more complex and advanced one. Another referent for development is differentiation, which implies a qualitative change in function, or an increase in skills and complexity (Lowrey, 1978; Kaluger & Kaluger, 1974).

Growth

Growth involves an increase in physical size of the whole or of any of its parts (Lowrey, 1978). The concept of growth refers to an

increase in volume and surface area, and to an acceleration of cellular proliferation. Growth is characterized by biochemical phenomena including an increase in protein synthesis and in the incorporation of nucleic acid precursors into RNA and DNA (Winter, 1978). According to Falkner and Tanner (1978), differential growth creates form: externally, through variable growth rates, and internally, through cellular events which create specialized functions.

Growth Spurt

The concept of growth spurt refers to a transient period characterized by rapid growth of an organ or individual (Dobbing & Sands, 1973). The timing of the growth spurt varies from organ to organ, and is frequently delineated by a specific age span.

Vulnerable Period

The concept of a vulnerable period is used to describe the span of time most favorable for successful completion of a new process (Maier, 1978); or the time of greatest sensitivity of an organ or system to a specific action (Lowrey, 1978) or insult (Himwich, 1970).

An insult which occurs during a vulnerable period has the greatest potential for causing damage. The nature, severity, duration, and timing of the insult are factors which will influence the degree of recovery from damage.

Stressors

Stressors, or insults, are intrinsic--arising within the individual at some time during the life cycle--or extrinsic--arising from the environment--stimuli which impact on the individual and alter development. The manifestation of an insult or stressor on development is modulated by internal and/or environmental variables.

Three hypotheses concerning the relationship among the concepts of stressor, growth spurt and vulnerable period have been proposed: 1) if a developmental process becomes affected by an insult at the time of its fastest rate of change, not only will the process be delayed, but also the ultimate extent of development will be restricted (Davison & Dobbing, 1966); 2) the nearer the insult or stress is applied to the time of fastest growth, the severity of the insult required to produce a given effect will be less (Davison & Dobbing, 1966; Himwich, 1970); and 3) the nearer an insult is applied to a vulnerable period, the greater the potential for causing damage (Himwich, 1970).

Conceptual Model for the Study

The relationships among cancer and cancer treatment, selected intrinsic variables, and the late effects on cognitive and psychosocial functioning were the focus of this study. Cancer treatment (CNS prophylaxis and systemic therapy) and the life-threatening nature of the illness were conceptualized as biological and environmental stressors which may interfere with the selected aspects of development. Age at time of treatment served as the criterion for the stage of development of the central nervous system and of psychosocial development. Time since diagnosis was used as the measure of the temporal delay which is characteristic of late effects. Figures 1 and 2 provide diagrams of the developmental models for cognitive and psychosocial late effects.

Figure 1

Late Effects of Childhood Cancer on Cognitive Development

Conceptual Model of Study Variables

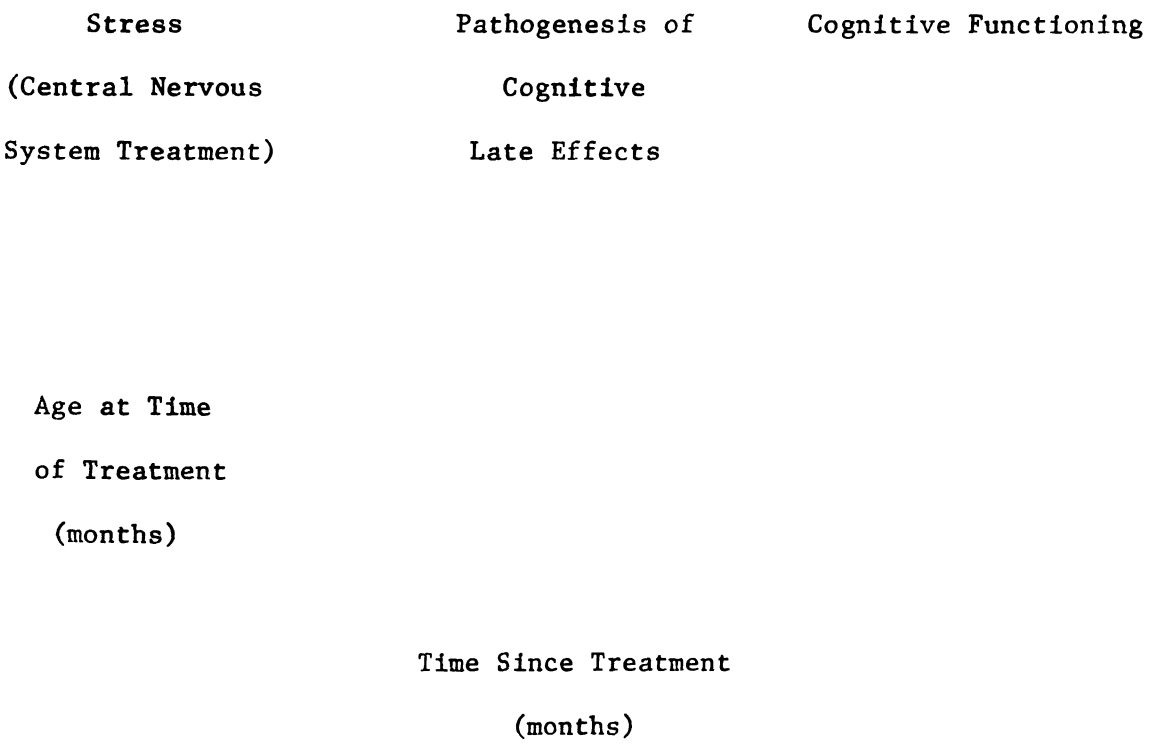
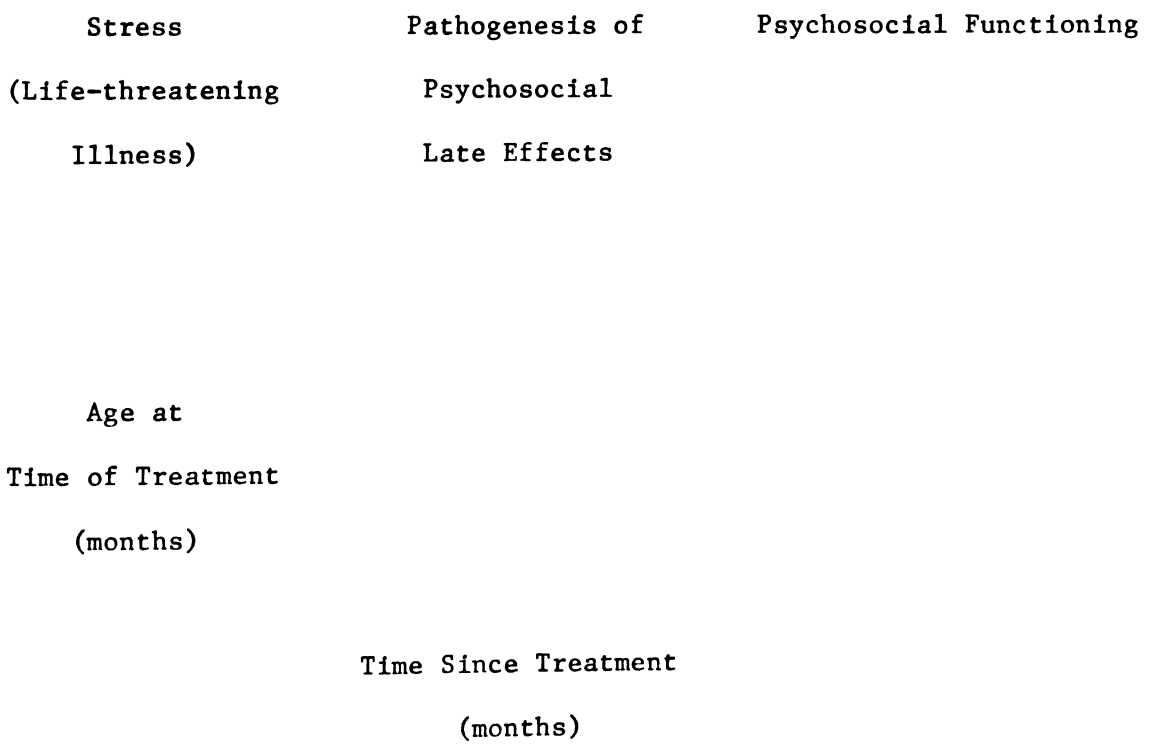


Figure 2

Late Effects of Childhood Cancer on Psychosocial Development

Conceptual Model of Study Variables



Assumptions of the Study

This study assumed the following statements to be valid.

1. Children who receive treatment for cancer continue to grow and develop although;
2. The cancer treatment and life-threatening illness experience may alter the processes of growth and development.
3. The cognitive and psychosocial aspects of development can be measured independently, although they are thought to be interrelated.
4. Cognitive functioning is a valid measure of the late effects of central nervous system prophylactic treatment on development of the central nervous system.
5. Psychosocial functioning is a valid measure of the late effects of the cancer experience on social and emotional development.

Research Questions

The following research questions and subquestions were answered in this study.

Cognitive Late Effects

Major Questions

1. Does the CNS prophylactic treatment for acute lymphoblastic leukemia have late effects on cognitive functioning?
2. Is there a significant relationship between age at time of treatment and cognitive functioning?

Subquestions

1. Is there a significant interaction between treatment group (ALL or solid tumor) and age at time of treatment in relation to cognitive functioning?

2. Is time since diagnosis a significant covariate when determining the effects of treatment group and age at time of treatment on cognitive functioning?
3. What is the degree of correlation between parent and teacher appraisal of cognitive functioning and the neuropsychological test battery?

Hypotheses

1. Central nervous system prophylactic treatment has a significant effect on general intellectual potential.
2. Central nervous system prophylactic treatment has a significant effect on academic achievement.
3. Central nervous system prophylactic treatment has a significant effect on visuospatial skills.
4. Central nervous system prophylactic treatment has a significant effect on language development.
5. Central nervous system prophylactic treatment has a significant effect on conceptual skills.
6. Central nervous system prophylactic treatment has a significant effect on auditory memory.
7. Central nervous system prophylactic treatment has a significant effect on visual memory.
8. Age at time of CNS prophylactic treatment will be significantly related to cognitive functioning.
9. There will be a significant interaction between treatment group (ALL or solid tumor) and age at time of treatment in relation to cognitive functioning.

Psychosocial Late Effects

Major Question

1. Does acute lymphoblastic leukemia and its treatment or a solid tumor malignancy and its treatment have late effects on psychosocial functioning?

Subquestions

1. Is age at time of diagnosis significantly related to psychosocial functioning?
2. Is there a significant interaction between treatment group (ALL or solid tumor) and age at time of treatment in relation to psychosocial functioning?
3. Is there a significant correlation between cognitive and psychosocial functioning?

Hypotheses

1. Age at time of treatment for acute lymphoblastic leukemia or a solid tumor malignancy will be significantly related to psychosocial functioning.
2. There will be a significant correlation between cognitive and psychosocial functioning.

Operational Definitions

Acute Lymphoblastic Leukemia (ALL): A common pediatric hematologic neoplasm of the lymphoid cell line; diagnosis is confirmed by the presence of lymphoblasts in the bone marrow. In this study, the previous diagnosis of ALL will be obtained from the subject's medical record.

Solid Tumor: A non-hematologic neoplasm characterized by a primary tumor site, with or without metastasis. The two solid tumors which will be included in the study sample are neuroblastoma and Wilms tumor. The tumor and its treatment does not involve the central nervous system.

Neuroblastoma: A tumor of sympathetic nervous system tissue which originates from embryonic neural crest cells. The most common locations for the tumor are abdominal (near the adrenal) and paraspinal.

Wilms Tumor: A malignant embryonal neoplasm of mixed histology that involves the kidney. In this study, the previous diagnosis of Wilms tumor will be confirmed from the subject's medical record.

Central Nervous System Prophylaxis: The component of total therapy directed toward the destruction of subclinical foci of leukemia cells sequestered in the leptomeningeal tissues covering the brain. CNS prophylactic therapy involves ionizing radiation (2400 rads in 15 fractions) and intrathecal methotrexate (12 mgs., one administration per week for 6 weeks).

Ionizing radiation: A modality of cancer therapy which destroys cells by producing structural damage to the chromosome during interphase. Previous treatment with CNS radiation will be determined from the

subject's medical record.

Methotrexate: An antifolate chemotherapeutic agent used in the treatment of ALL. Previous treatment with intrathecal methotrexate will be determined from the patient's medical record.

Intrathecal: Introduced into the cerebral spinal fluid in the subarachnoid space by means of a lumbar puncture.

Late Effects: The chronic changes in normal tissues, organs, or behavioral systems which become manifest several months or years after the termination of cancer treatment. Cognitive and psychosocial late effects will be examined in this study.

Cognitive Late Effects: Long-term effects on the brain and neurological processes which are necessary for the development of the following intellectual functions: general intellectual potential, academic achievement, visuospatial skills, language development, concept skills, verbal learning, and memory. Cognitive late effects will be measured by a battery of standardized neuropsychological instruments, and by a Cognitive Subscale derived from the Deasy-Spinetta Behavioral Questionnaire.

Psychosocial Late Effects: Long-term effects on the accomplishment of age-appropriate social and emotional tasks including interpersonal skills, self-concept, school performance, and emotional stability, as measured by the Deasy-Spinetta Behavioral Questionnaire and subjects' open-ended questions regarding the previous cancer experience.

Age at Time of Treatment: Chronological age rounded to the nearest month at the time of initiation of treatment for ALL or for a solid tumor malignancy as measured by the medical record.

CHAPTER THREE: METHODS

Design

The study used a factorial design to compare cognitive and psychosocial functioning in two groups of long-term survivors of childhood cancer. The two grouping factors were treatment (ALL or ST) and age at time of treatment (before or after 60 months). For research questions regarding the late effects of central nervous system prophylactic therapy on cognitive functioning, the children with acute lymphoblastic leukemia were the experimental group as they received the treatment of interest, and the children who were long-term survivors of a solid tumor malignancy were the comparison group as they received only systemic therapy.

Children who were long-term survivors of acute lymphoblastic leukemia or of a solid tumor were the major comparison groups for answering the research questions regarding psychosocial late effects. Both groups had experienced a life-threatening illness and had received systemic chemotherapy. Thus, they were assumed to be comparable on emotional problems, such as body image changes or interference with interpersonal relationships.

Setting and Sample

The population of children who were diagnosed with and received treatment for acute lymphoblastic leukemia or a solid tumor malignancy at the University of California, San Francisco, Department of Pediatric Oncology, five to ten years ago were contacted via telephone by the principle investigator to schedule an appointment for the Long-term Survivors Oncology Clinic. Within each major diagnostic category, subjects were grouped according to whether they were treated

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Setting and Sample

The population of children who were diagnosed with and received treatment for acute lymphoblastic leukemia or a solid tumor malignancy at the University of California, San Francisco, Department of Pediatric Oncology, five to ten years ago were contacted via telephone by the principle investigator to schedule an appointment for the Long-term Survivors Oncology Clinic. Within each major diagnostic category, subjects were grouped according to whether they were treated

before or after the age of 60 months. At this time, any child who satisfied the sample selection criteria (listed below), and his or her family were asked to participate in this study. The purpose of the study, what participation would involve, and the potential risks and benefits of the research was explained. For those families who agreed to be a part of the study, arrangements were made for scheduling the neuropsychological testing (described under procedure and instruments). The only financial cost to the subject's family was travel to the medical center; there was no financial compensation for participation.

Sample Selection Criteria

All participants satisfied the following sample selection criteria.

1. Being diagnosed with and treated for acute lymphoblastic leukemia or a solid tumor malignancy at least five, but no longer than ten, years ago.
2. Having been between the ages of six months and ten years at the time of diagnosis.
3. If diagnosed with a solid tumor, the malignancy and its therapy did not involve the head or neck.
4. Having remained clinically tumor-free since completion of therapy (any child who received additional therapy for relapse or recurrence was excluded from the study).
5. Not having experienced any other serious illness (documentation from chart and parents).
6. Not having any pre-existing central nervous system abnormality (documentation from chart and parents).

7. Parents and child spoke and read English.

Data Collection Procedure

1. Review of medical records: The medical records of all subjects were reviewed the day before the scheduled clinic visit in the Medical Records reading room. The following data were collected from the medical record and recorded on the Data Collection Form (Appendix B): gender; diagnosis; age at time of diagnosis; treatment protocol [chemotherapeutic drugs and doses, radiation dose and fractionation, length of time, in months, on treatment]; date and subject age when therapy was completed; other pre-existing or interim health problems; and ethnicity. Background data on standing height during and following therapy were also collected.

2. All consenting subjects were assigned a code number for the purpose of insuring confidentiality. Subjects were then provided with a copy of the consent form and the Subjects' Bill of Rights (Appendix A). Prior to any further data collection, the investigator responded to questions the subjects or parents had and assured them that the information they provided would be kept confidential.

3. Additional demographic data: After the consent forms were signed, the following demographic information was obtained from the subject and parent: current grade in school; school absences while on cancer therapy within the past year; name and address of school teacher the subject agreed could complete the Deasy-Spinetta Behavioral Questionnaire; family constellation; and current medications.

4. Neuropsychological Battery: For all subjects, the test battery was administered and evaluated by a trained neuropsychologist (Dr.

Joel Kramer), who was blind to the subject's treatment group and age at time of treatment. Dr. Kramer has done post-doctoral work in neuropsychology, and is experienced in the use of neuropsychological measures of cognitive functioning. All testing took place in a quiet room, free of interruptions, located at the Langley Porter Psychiatric Institute. The cost of the neuropsychological testing was assumed by the principal investigator.

This aspect of the data collection procedure was lengthy, requiring approximately three and one-half hours. The testing was divided into two sessions by an hour lunch break. This was designed to prevent subject fatigue. Some participants required addition time to complete the cognitive battery. In these cases a second testing day was scheduled whenever possible. Neuropsychological instruments purport to measure stable aspects of cognitive functioning, therefore, this variability in the timing of data collection should not pose any threats to the reliability of the results. For subjects who traveled a considerable distance to UCSF Medical Center, testing began the morning of the scheduled afternoon appointment at the Long-term Survivors Clinic, and was completed after the appointment or the following morning. Lodging for these families was provided at a guest house near UCSF. The cost of lodging was assumed by the principal investigator. For subjects who resided within the San Francisco area, testing was arranged to coincide with the Long-term Survivors Clinic appointment and to minimize any inconvenience to the subject or his/her family. The order of instrument administration and time required per instrument are provided in Table 6.

Table 6

Neuropsychological Test Battery

Cognitive Function	Instrument*	Time Required for Administration
1. General Intelligence	WISC-R	90 minutes
2. Academic Achievement	WRAT	30 minutes
3. Visuospatial Skills	Berry Test of Visual Motor Integration	20 minutes
	Rey-Osterrieth Block Design Scale from WISC-R	10 minutes
4. Language Development	Clinical Evaluation of Language Function	30 minutes
	FAS	5 minutes
5. Concept Development	Woodcock-Johnson Concept Formation Test	20 minutes
6. Auditory Memory	Digit-Span Subscale from WISC-R	
	Bushke Selective Reminding Procedure	30 minutes
7. Visual Memory	Benton Visual Retention Test	15 minutes
	Rey-Osterrieth Recall	10 minutes

*Instruments listed in the order of presentation to all subjects.

5. Current Standing Height: During the subject's scheduled Long-term Survivors Clinic visit, standing height (in centimeters) was measured and recorded. All subjects were measured, with shoes removed, by the investigator.

6. Deasy-Spinetta Behavioral Questionnaire: The parent accompanying the subject was asked to complete the Deasy-Spinetta Behavioral Questionnaire (Appendix D). The following instructions were given to every parent: "The purpose of this questionnaire is to assess how your child is functioning emotionally and physically, in school, with friends and with family. Read each item on the Questionnaire, think of your child's behavior on a typical day, and in comparison to other children of the same age and sex, and circle 'yes' if the statement is characteristic of your child, or 'no' if the statement is not characteristic of your child." After the parent completed the questionnaire, the principle investigator provided time to discuss any behaviors which were of concern.

The following day, the cover letter to the subject's teacher (Appendix F), a copy of the subject's and parents' consent allowing the teacher to be contacted, and a self-addressed stamped return envelope were mailed to the teacher. The teacher was instructed to complete one questionnaire on the student-subject, and a second questionnaire on another (unidentified) student who was of the same sex, in the same classroom, and represented the general characteristics of the classroom population.

7. The subject completed the open-ended questions (Appendix E) while waiting to see the oncologist for his/her long-term evaluation. At this time the investigator reviewed the questions with the subject.

8. At the completion of the data collection procedure and the clinic appointment, the principle investigator thanked the subjects and their families for participating in the study, and provided time to answer any questions they had.

Instruments

I. Neurocognitive functioning.

The major dependent measure of neurocognitive functioning was the neuropsychological test battery (Table 9). The instruments were selected on the basis of their ability to measure those aspects of cognitive functioning which appear to be the most vulnerable to the adverse effects of CNS prophylactic therapy (Kirs & Herman, 1980), and on their ability to discriminate between brain damaged and non-brain damaged individuals (Lezak, 1983). The tests yield interval data, and age-adjusted norms on healthy children are available.

The following description of the test battery is organized by the functional area the instrument purports to measure.

A. General Measure of Cognitive Functioning

The Wechsler Intelligence Scale for Children - Revised (WISC-R) is a standardized test, for children 6 years to 16 years, 11 months. This test yields a full scale IQ score as well as 11 subscale scores. Reliability of the WISC-R is well established: split half, R = .90 to .96; test-retest, R = .90 to .95 (Anastasi, 1976). In addition to discriminate validity, concurrent predictive validity with other achievement measures, such as school performance, has been established (Anastasi, 1976). The subscales are: similarity, arithmetic, vocabulary, comprehension, digit span picture completion, picture arrangement, object assembly, block design, and coding.

B. Academic Achievement

General Academic Skills were measured by the Wide Range Achievement Test (WRAT). This standardized test (test-retest reliability = .90 to .95) measures skills in reading, spelling, and arithmetic. Each of these areas are divided into two levels.

a) reading: Level I is based on letter reading.

b) spelling: Level I is based on copying short sets of nonsense figures and to write the subject's name.
Level II tests spelling words of increasing difficulty.

c) arithmetic: Both Level I and Level II involve oral performance and written arithmetic, but of increasing difficulty (Lezak, 1983).

C. Visuospatial Skills

1. Rey-Osterrieth Complex Figure

The Complex figure (Figure 3) purports to measure perceptual organization and visual memory. The test consists of the figure, blank type-writer size paper, and five or six colored pens or pencils. The subject was instructed to copy the figure. He or she was given different colored pencils for completing sections of the drawing in order to track his/her performance. Overall evaluation of the success of drawing the figure is based on a unit scoring system (Lezak, 1983).

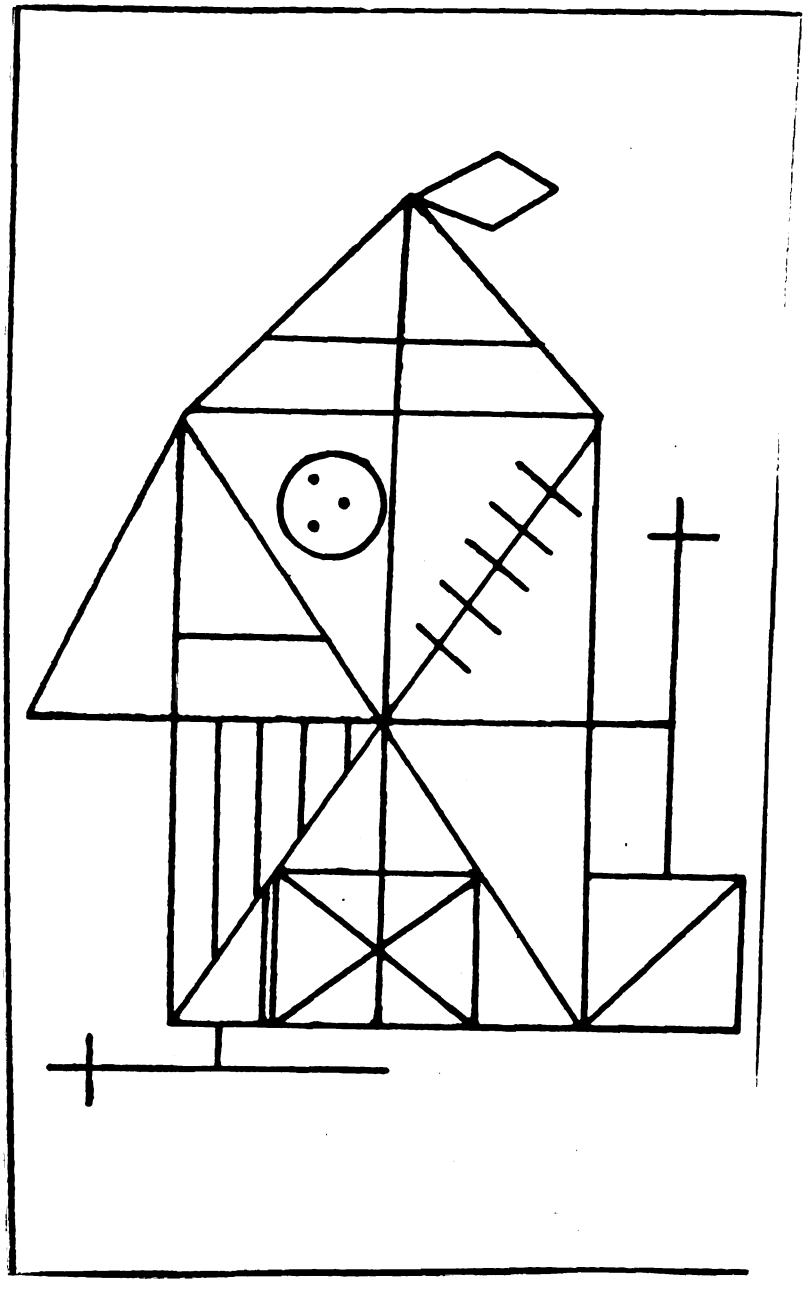


Figure 3

The Rey-Oseterrieth Complex Figure

2. Beery Test of Visual Motor Integration

The Beery Test assesses visual motor integration by determining the degree to which the subject can view a geometric design and reproduce it. The subject was given the task of copying 24 geometric figures of increasing complexity. Scoring is on a pass/fail basis; the Total Score equals the number of correct copies until three consecutive errors occurred. Median split-half reliability = .79; test-retest reliability = .81 (Lezak, 1983).

D. Language Development

1. The Clinical Evaluation of Language Function (CELF) was used as the measure of language development. The CELF briefly assesses the child's expressive and receptive language skills. He or she was asked to respond to commands of varying syntactical complexity, and to perform a variety of language tasks. The instrument has been evaluated for reliability. Internal consistency estimates yield a coefficient > .78 (Lezak, 1983).

2. FAS (Controlled Oral Word Association Test)

The FAS test consists of three word-naming trials. These letters (FAS) were selected on the basis of the frequency of English words beginning with these letters. The examiner asked the subject to say as many words that begin with the given letter, excluding proper nouns, numbers, and the same word with a different suffix. The score, which is the sum of all acceptable words produced in the three one-minute

trials is adjusted for age, sex, and education.

Word fluency as measured by FAS has proven to be a sensitive indicator of brain dysfunction. Frontal lesions, regardless of side, tend to depress fluency scores, with left frontal lesions resulting in lower word production than right frontal lesions (Lezak, 1983).

E. Concept Development

1. The Woodcock-Johnson Concept Formation Test

In this measure of concept development, the subject was requested to identify concepts when visually presented with examples and non-examples of the target concept. Internal consistency of the instrument has been assessed using a form of split half (r = .90) (Lezak, 1983).

2. Similarity Subscale from the WISC-R

This subscale is a test of verbal concept formation. The subject had to explain what each of a pair of words has in common. The word pairs range in difficulty from the simplest to the most difficult. The test begins with the first item for all subjects and is discontinued after four failures. Similarities is described as an excellent test of general intellectual ability as it does not depend on academic skills and is relatively independent of background experiences, and social or educational background (Lezak, 1983).

F. Auditory Memory

1. Bushke Selective Reminding Procedure

The selective reminding procedure is comprised of 10

unrelated nouns of high frequency in the English language. Items were presented aurally at the rate of one per second. The Bushke allows for the analysis of the following aspects of verbal memory functioning: 1) total free recall; 2) storage into long-term memory (LTS) the number of words encoded into long-term storage; 3) the proportion of items recalled that were retrieved from long-term memory (LTR/Total); and 4) the extent to which subjects consistently recalled items presumed to be stored in long-term memory (Con LTR/LTS).

3. Digit Span Subtest of the WISC-R. This test is one of the subscales of the Wechsler Intelligence Scale for Children - Revised (WISC-R) which was administered to all subjects. The examiner read aloud seven pairs of random number sequences at the rate of one per second. The subject was instructed to recall the digits forwards and backwards. The total score is computed from the average of the correct responses from the forward and reverse recall (Lezak, 1983). Test-retest reliability is reported to be R = .78 (Anastasi, 1976).

G. Visual Memory

1. Benton Visual Retention Test. In this memory test, the subject was provided with a 10 second exposure to a ten card series. Each card has a three figure design format. Recall is measured by having the subject draw the figure. The test yields two scores--number correct and number of errors. The instrument is reported to be highly reliable on repeated

administrations. The coefficients of concordance are .74 for number correct; and .77 for errors (Lezak, 1983).

2. Rey-Osterrieth Complex Figure-Recall

The Rey-Osterrieth Complex Figure Test is described under "C. Visuospatial Skills". At the completion of the evaluation session, the subject was instructed to draw the figure from recall, without viewing the target stimulus. The same scoring system is used for the recall copy.

II. Cognitive Appraisal by Parent and Teacher

At present, there is a paucity of instruments which can be used to identify those children who are long-term cancer survivors and may be experiencing neurocognitive problems. While the neuropsychological evaluation is a sensitive method for identifying functional deficits, it is lengthy, costly, and requires a trained neuropsychologist for administration and evaluation. Therefore, a subscale score from the Deasy-Spinetta Behavioral Questionnaire (DSBQ) which is described under the instrumentation for Psychosocial Late Effects was included as a second dependent measure of neurocognitive functioning. This measure requires a minimal amount of time, can be completed by the subject's parent and/or teacher, and is easy to score. The items from the DSBQ which comprised the neurocognitive subscale are listed in Table 7. This is the first time the DSBQ has been used in this manner. Therefore, reliability data are not available, but were generated.

Table 7

Cognitive Subscale: Deasy-Spinetta Behavioral Questionnaire

Item	Behavior		
4.	Keeps up with school work	Yes	No
5.	Completes assigned school work	Yes	No
6.	Is able to concentrate	Yes	No
7.	Indicates signs of learning disabilities	Yes	No
11.	Can't sit still, is restless or hyperactive	Yes	No
41.	Has difficulty remembering, sequencing	Yes	No
42.	Indicates specific reading difficulties	Yes	No
43.	Indicates specific difficulties with mathematics .	Yes	No
44.	Has difficulty with tasks requiring reasoning . . .	Yes	No

II. Psychosocial Functioning

The Deasy-Spinetta Behavioral Questionnaire (DSBQ, Appendix D) was used to measure late effects on selected aspects of psychosocial functioning. The DSBQ is a forced choice questionnaire consisting of 53 items which purport to measure differences in attitude and behavior between normal children who have been diagnosed with cancer and normal healthy children.

The instrument was developed on the basis of clinical interviews with pediatric oncologists, nurses, parents, and teachers regarding the types of attitudes and behavior patterns exhibited by children with cancer (Spinetta and Deasy-Spinetta, 1981). The instrument was revised on the basis of three pilot studies over a three year period. Content validity was established from the panel of professionals and parents who have worked with children with cancer. Instrument reliability (reliability estimates for each item not published) was established by comparing the data which were available for the same subjects over the three year pilot study phase. The subjects with cancer demonstrated behaviors that were significantly at variance from those of controls ($p = .001$ to $.05$); this finding was not influenced by age or sex, and was stable over the three year period (Spinetta & Deasy-Spinetta, 1981).

The DSBQ can be completed by either the subject's parent or teacher. The parent is instructed to respond (yes or no) to each item on the basis of whether or not the behavior is characteristic of the child. The comparison norm is other healthy children of the same age and sex (i.e. peers). The teacher is instructed to complete one questionnaire on the student-subject, and a second questionnaire

on another healthy student of the same sex, in the same classroom, and who represents the general characteristics of the class population.

This instrument yields a Total Score for the child with cancer and the control. A Total Discrepancy Score is determined on the basis of response agreement with the selected control (Teacher completed instruments only). The data collected from parental appraisal of psychosocial functioning were analyzed by the following variables: diagnosis, age at time of diagnosis, and length of time since treatment.

Statistical Analysis

1. Cognitive Functioning

A two-way analysis of covariance (ANCOVA) was used to analyze the interval data from the neuropsychological battery with the exception of the Bushke Selective Reminding Procedure. The grouping factors of interest were treatment status (ALL or solid tumor) and age at time of treatment (younger or older than 60 months). The analysis also tested for an interaction effect between age at treatment and treatment status. A repeated measures ANCOVA was used to determine if there were differences across the ten trials on the Bushke data by treatment group and by age at time of treatment. Time since diagnosis (measured in months) was treated as the covariate on all measures which had age-adjusted scores. Current age was the covariate for the following instruments which did not yield age-adjusted scores: Rey-Osterrieth Complex Figure, FAS, Woodcock-Johnson Concept Formation, Bushke Selective Reminding procedure, and the Benton-Visual Retention Test.

An ANCOVA was also used to analyze the data from the Cognitive Subscale of the DSBQ. A Pearson-Product Moment Correlation was used

to determine the significance of correlation between the scores on the standardized neuropsychological instruments and the DSBQ subscale.

2. Psychosocial Functioning

Deasy-Spinetta Behavioral Questionnaire: Teachers

From this data, a total discrepancy score was calculated for each subject. An analysis of covariance (ANCOVA) was used to test for the effects of treatment (ALL or solid tumor) and age at time of treatment (younger or older than 60 months) on psychosocial functioning. The total and cognitive subscale scores for the two treatment groups were compared with those for the comparison groups of healthy children by the Student's t-test. A t-test was also used to determine if there were differences between parent and teacher appraisal of the child's functioning as measured by the Deasy-Spinetta Behavioral Questionnaire.

CHAPTER FOUR: RESULTS

Clinical Characteristics of the Sample

A total of 36 long-term cancer survivors who met the selection criteria were identified and invited to participate in the study. One family refused. This family was Hispanic; no additional data is available. The study sample was comprised of 35 long-term survivors of childhood cancer. Nineteen subjects had received therapy for acute lymphoblastic leukemia and 16 for a solid tumor (ST). Diagnoses in the ST group included Wilm's tumor (N = 12, 75%), neuroblastoma (N = 3, 19%), and hepatoblastoma (N = 1, 6%). The clinical characteristics of the sample are summarized by diagnostic category in Table 8.

Age at the time of the cancer diagnosis ranged from 4 to 116 months. Subjects with a solid tumor tended to be diagnosed at an earlier age ($\bar{X}$ = 47.44 months, SD = 32.72) than those with ALL ($\bar{X}$ = 62.00 months, SD = 25.66). Twelve of the ST participants were diagnosed before and four after the age of 60 months. Within the leukemia group, 10 subjects were diagnosed before and 9 after 60 months of age. Leukemia therapy was of longer duration. Thus, subjects in the ALL group had received more months of therapy ($\bar{X}$ = 37.05, SD = 11.85) than the ST subjects ($\bar{X}$ = 22.4, SD = 9.11). The potential influence of months since diagnosis (months on therapy plus months off therapy) was adjusted for by treating this variable as a covariate on all measures with age-adjusted scores.

The two groups were comparable on age at time of evaluation, which ranged from 104 to 209 months. The mean age of the ALL group was 160.1

Table 8

Clinical Characteristics of the Sample by Treatment Group

Clinical Characteristics	ALL (N = 19)	ST (N = 16)
Current age (months)		
Range	104 - 199	107 - 209
Mean (SD)	160.05 (31.72)	161.5 (33.15)
Age at diagnosis (months)		
Range	27 - 110	4 - 116
Mean (SD)	62.00 (25.66)	47.44 (32.72)
Months of therapy		
Range	24 - 66	11 - 36
Mean (SD)	37.05 (11.85)	22.4 (9.11)
Months off therapy		
Range	25 - 90	48 - 130
Mean (SD)	60.74 (31.2)	88.03 (34.03)
Time since diagnosis (months)		
Range	69 - 136	68 - 148
Mean (SD)	97.74 (23.49)	104.00 (25.72)
Concurrent health problem		
Yes	1 (5%)	3 (19%)
No	18 (95%)	13 (81%)
Current use of medications		
Yes	___	2 (13%)[1]
No	19 (100%)	14 (87%)

[1]medications in both cases were antihistamines for allergies

months (SD = 31.72) and 161.5 months (SD = 33.15) for the solid tumor group. The mean current age was 142.3 months (SD = 34.5) for the 10 ALL participants treated prior to and 179.8 months (SD = 9.4) for those (N = 9) treated after the age of 60 months. Within the solid tumor group, the 12 subjects treated early (less than 60 months) had a mean age of 152.4 months (SD = 32.2), while the mean age of the 4 subjects treated after 60 months was 188.89 (SD = 19.5).

Treatment for ALL included an initial induction period, CNS prophylaxis, and a maintenance phase. The induction regimen for 18 patients consisted of prednisone, L-Asparaginase, and vincristine. One subject also received cytoxan. All patients had both cranial radiation and IT methotrexate (10 - 12 mg weekly x 6) for CNS prophylactic therapy. Eighteen subjects had 2400 rads in 14 or 15 fractions, one child received only 1800 rads in 10 fractions. Duration of maintenance ALL chemotherapy ranged from 22 to 63 months, and always included 6-MP and oral methotrexate. Most subjects (N = 16) also received prednisone and vincristine, and one subject had ARA-C.

All of the long-term survivors of a solid tumor had undergone surgery. Fourteen subjects had radiation to the tumor site. The two exceptions were one case of a Stage I Wilm's tumor, and the child diagnosed with hepatoblastoma. Chemotherapy protocols were more variable for the ST group. Eight of the Wilm's tumor patients had two drug therapy (vincristine and actinomycin) and four had three drugs (vincristine, actinomycin, and adriamycin). Two of the neuroblastoma patients were treated with cytoxan and one with cytoxan, DTIC, and vincristine. The chemotherapy regimen for the patient with hepatoblastoma included cytoxan, vincristine, and 5-fluoruracil.

Very few subjects were experiencing any health problems at the time of data collection. One subject in the ALL group and two in the ST group had allergies which, in two cases, were treated with antihistamines. Scoliosis secondary to unilateral radiation of the tumor bed was noted in five of the long-term survivors of Wilms tumor. However, only one subject had spinal curvature severe enough to necessitate a brace.

Demographic Characteristics of the Sample

The study groups did not differ significantly on the demographic variables of sex, race, and family constellation (Table 9). The sample included 19 females and 16 males with a slightly higher percentage of females in both groups. Eighty-six percent (N = 30) of the sample was White. Three subjects (ALL group) were Black and two (ST group) were Hispanic.

Approximately half the subjects in each group were living with both parents and 40 percent with a single parent. One subject in the ST group was adopted and two in the ALL group were living with grandparents. The number of siblings ranged from zero to eight; most participants had one or two siblings.

Academic Characteristics of the Study

The sample included school age subjects who ranged from the third to the twelfth grade, with a mean grade of seven for both treatment groups. School absences during the current academic year were minimal for both treatment groups (Table 10, Academic Characteristics). However, the ALL and ST groups differed dramatically on the variables of school absences during treatment and history of being held back.

Fifteen of the 19 long-term leukemia survivors (79%) frequently

Table 9

Demographic Characteristics of the Sample by Treatment Group

Demographic Characteristic	ALL (N = 19)	ST (N = 16)
Sex		
Female	10 (53%)	9 (56%)
Male	9 (47%)	7 (44%)
Race		
White	16 (84%)	14 (88%)
Black	3 (16%)	
Hispanic	---	1 (6%)
White/American-Indian	---	1 (6%)
Family/Parents		
Two-parent family	9 (47%)	8 (50%)
Single-parent family	8 (42%)	7 (44%)
Adopted parents	---	1 (6%)
Grandparents	2 (11%)	---

Table 10

Academic Characteristics of the Sample by Treatment Group

Academic Characteristic	ALL (N = 19)	ST (N = 16)
Current grade in school		
Range	3 - 11	3 - 12
Mean	7.05 (2.78)	7.33 (2.72)
School absences during treatment[1]		
Yes	15 (79%)	4 (25%)
No	4 (21%)	12 (75%)
School absences during current year		
Yes	1 (05%)	2 (13%)
No	18 (95%)	14 (87%)
History of being held back		
Yes	9 (47%)	1 (6%)
No	10 (53%)	15 (94%)

[1]School absences during treatment: Subjects diagnosed before the age of five years could have missed school, if time on therapy continued into the school age years.

missed school during treatment. Forty-seven percent of this treatment group had repeated at least one grade. Seven of the 10 subjects treated with CNS prophylaxis prior to the age of 60 months had repeated one or more grades. In contrast, only 25 percent (N = 4) of the ST group missed school while on therapy, and one subject (6%) had been held back a grade.

Findings Related to the Research Questions on Cognitive Late Effects

An extensive neuropsychological test battery was administered to all subjects for the purpose of investigating the relationship between central nervous system prophylactic therapy for ALL and subsequent cognitive functioning. Time constraints prevented some subjects from completing the entire battery. With one exception, this was due to the time required for travel and a concurrent clinic appointment or to the additional testing time required for subjects with obvious learning problems. In one case, the subject became too emotionally distressed to complete the study and was supported in her decision to withdraw. Whenever the analysis on a dependent measure does not include the complete sample of 35 subjects this is indicated in the narrative and the appropriate tables.

The narrative report on the research findings refers to the following comparison groups:

Group I: ALL treated before the age of 60 months (N = 10);

Group II: ALL treated after the age of 60 months (N = 9);

Group III: ST treated before the age of 60 months (N = 12);

Group IV: ST treated after the age of 60 months (N = 4).

General Intelligence

All subjects were administered the WISC-R. Full Scale scores ranged from 65 to 132; Verbal Scale scores ranged from 67 to 141; and Performance Scale scores ranged from 54 to 131. The mean Full Scale, Performance Scale, and Verbal Scale IQ scores with standard deviations are reported in Table 11. For all three Scales, the ST group had significantly higher scores ($p \leq .001$), supporting the hypothesis that CNS prophylaxis has a significant effect on general intelligence.

The mean Full Scale, Performance, and Verbal IQ scores by age at time of treatment (ALL and ST combined) were 98.59, 96.95, 98.68 for the younger group (treated before the age of 60 months) and 99.44, 103.62, and 97.42 for the group of subjects treated after the age of 60 months. Figure 4 graphs the effects of age at time of treatment. This age effect was significant for the Full Scale and Performance scores ($p = .044$ and $p = .038$) but not for Verbal IQ ($p = .725$). Thus, the hypothesis that age at time of treatment effects general intelligence was partially supported. A t-test was done to compare the mean IQ scores of Groups I and II. The findings were consistent with the original analysis of covariance.

Group I subjects had consistently lower mean IQ scores than Group II subjects as demonstrated in Figure 4. The effect of age at time of treatment was more pronounced for the leukemia group than for the solid tumor group. However, this differential age effect was not statistically significant, and the hypothesis of an interaction effect was not supported ($p > .05$). Months since diagnosis, the covariate, was not significantly related to the WISC-R scores.

Table 11

Cognitive Functioning: Group Differences* on Measures of General Intelligence

	ALL		ST					
	$\bar{X}$ (SD)	$\bar{X}$ (SD)	$\bar{X}$ (SD)	$\bar{X}$ (SD)	Tx[1]	Age at Tx[2]	Interaction[3]	Covariate[4]
WISC-R	(< 60 mo.)	(> 60 mo.)	(< 60 mo.)	(> 60 mo.)	F (p)	F (p)	F (p)	F (p)
	(N = 10)	(N = 9)	(N = 12)	(N = 4)				
Full scale IQ	84.50 (15.2)	99.44 (12.0)	110.33 (14.0)	114.00 (9.9)	25.51 (<.001)	4.42 (.044)	1.81 (.189)	1.04 (.317)
Verbal IQ	85.30 (14.0)	89.90 (32.7)	109.83 (13.6)	112.50 (9.7)	13.83 (.001)	.13 (.725)	.05 (.831)	.34 (.567)
Performance IQ	85.40 (16.1)	99.44 (13.4)	106.58 (11.4)	113.0 (14.6)	14.92 (.001)	4.77 (.038)	.63 (.434)	.00 (.984)

*2 x 2 ANCOVA with months since diagnosis as the covariate

[1]Tx: Significance of the effect of treatment group (ALL vs. ST) on the measures of general intelligence

[2]Age at Tx: Significance of the effect of age at time of treatment group (< 60 or > 60 mo.) on the measures of general intelligence

[3]Interaction: Significance of the interaction between treatment group and age at time of treatment on the measures of general intelligence

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis) and the measures of general intelligence.

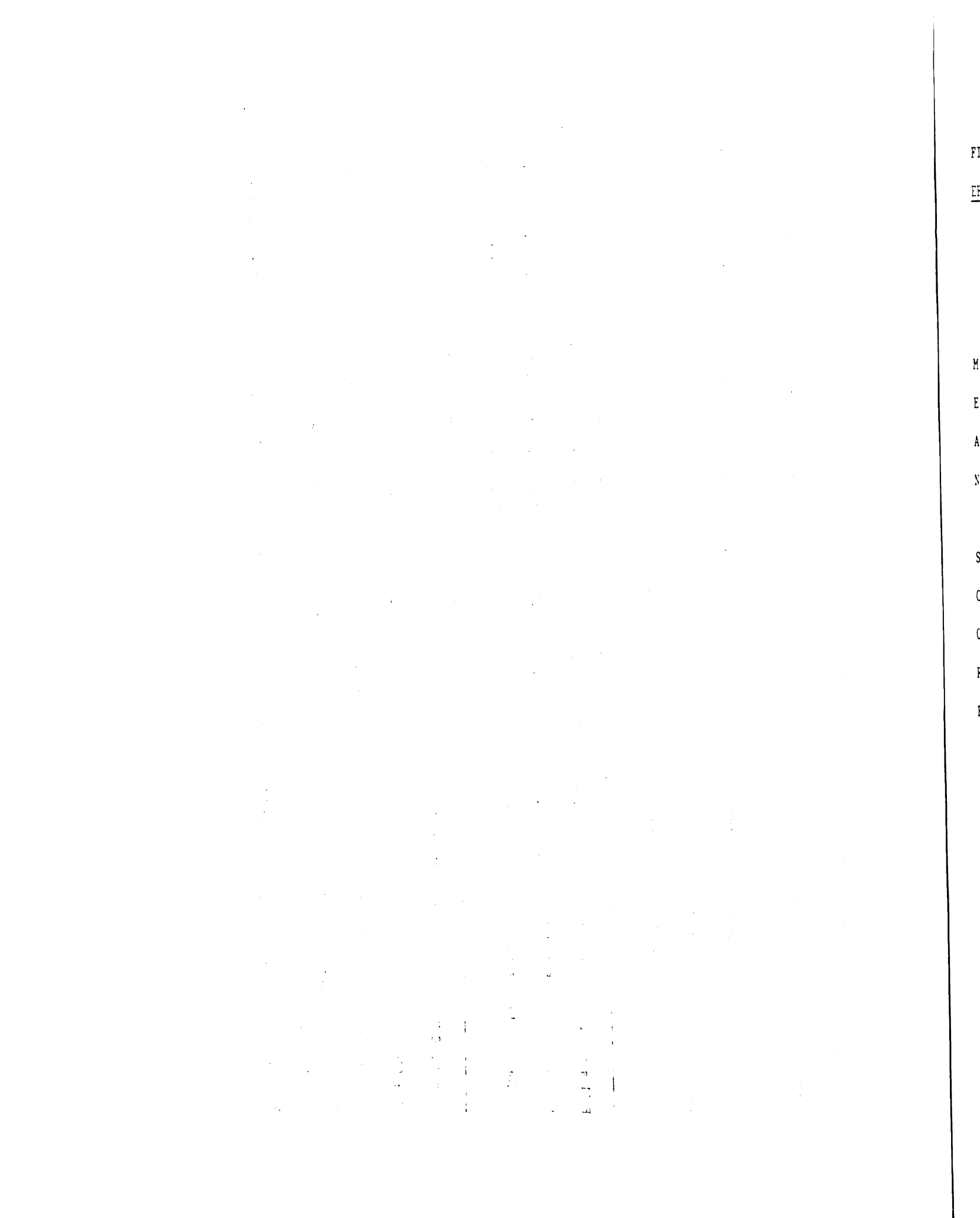
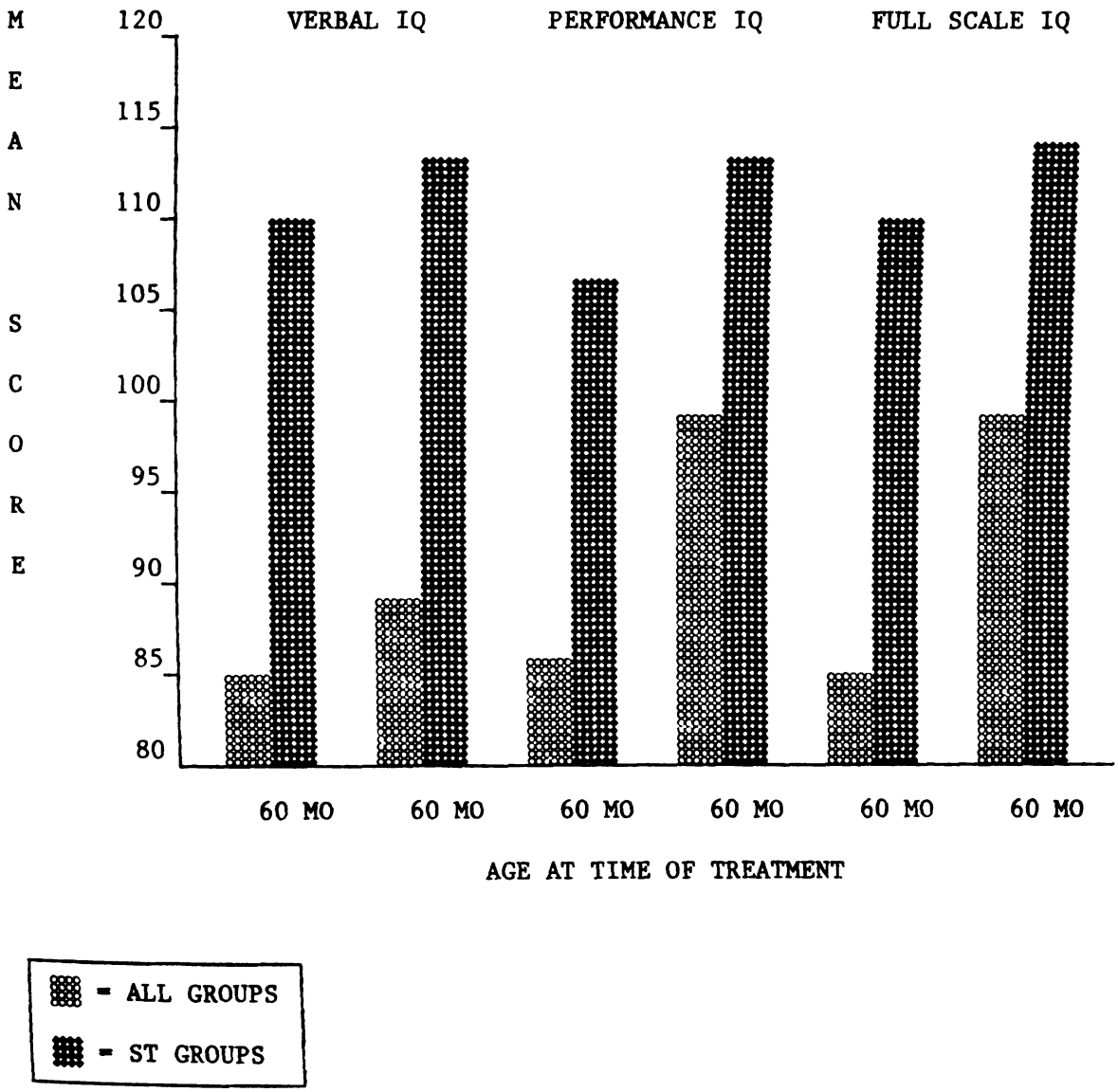
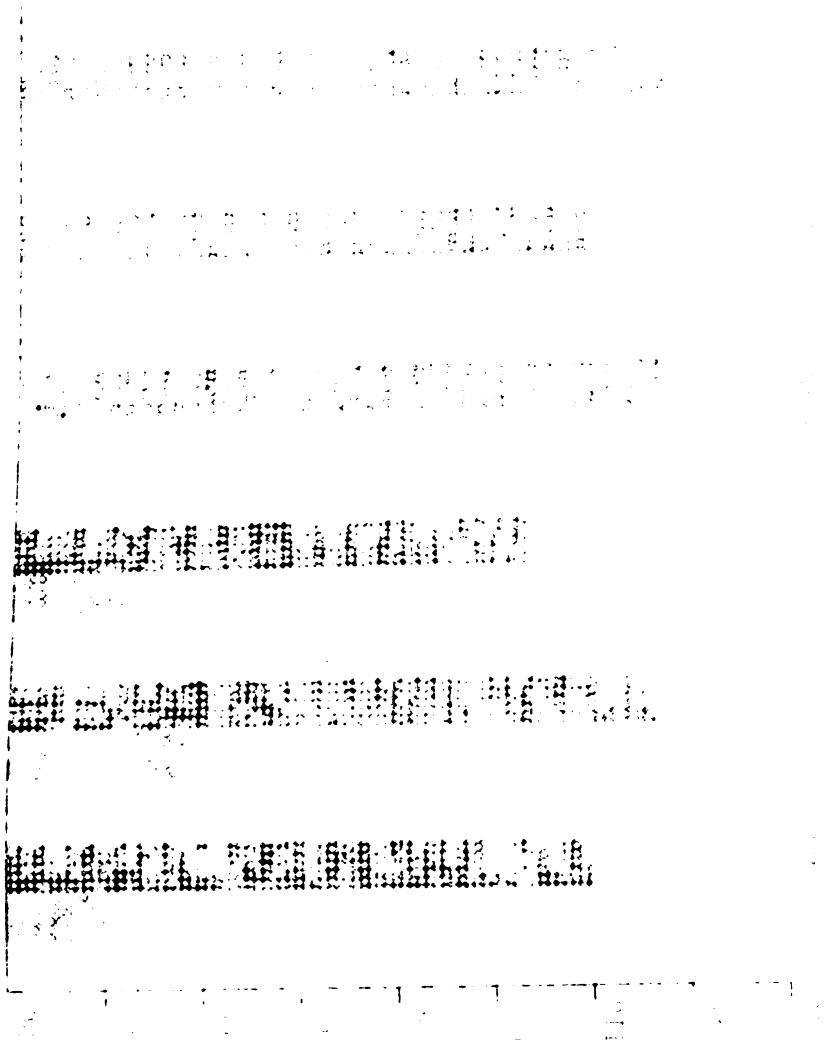


FIGURE 4

EFFECTS OF AGE AT TIME OF TREATMENT ON GENERAL INTELLIGENCE





Academic Achievement

Academic achievement included reading comprehension from the Piat test and the Wide Range Achievement Test (WRAT) of Reading, Spelling, and Arithmetic. Standard scores ranged from 8 to 126 on the Piat Reading Comprehension, 7 to 129 on the WRAT Reading, 9 to 127 on the WRAT Spelling, and from 18 to 114 on the WRAT Arithmetic.

The ALL treatment groups had consistently lower mean scores than the ST treatment comparison groups (Table 12). The magnitude of the difference was significant for the three WRAT scores ($p < .001$) and approached significance on the Piat Reading Comprehension test ($p = .060$). The difference in the mean scores between ALL subjects treated before and after 60 months was greater than that of the solid tumor age at treatment groups for all the WRAT scores. The effect of age at time of treatment did not reach significance ($p = .1$ to $.815$), and the treatment by age at treatment interaction was non-significant ($p = .4$ to $.8$). The follow-up t-test comparing the mean academic achievement scores of the two ALL treatment groups confirmed the non-significance of age at time of treatment for the Piat Reading, WRAT Spelling, and WRAT Arithmetic. There was a trend toward significance for a WRAT Reading ($p = .07$). Figure 5 demonstrates the differences in mean scores by treatment and age at time of treatment groups for the WRAT Reading and Arithmetic tests.

Visuospatial Skills

The neuropsychological battery yielded three independent measures of visuospatial skills (Beery Test of Visuomotor Integration, Block Design Scale from WISC-R, and Rey-Osterrieth Complex Figure Copy). Table 13 presents the mean group scores, standard deviations, and the

Table 12

Group Differences* on Measures of Academic Achievement

Measures of Academic Achievement	ALL $\bar{X}$ (SD) (< 60 mo.) (N = 10)	ALL $\bar{X}$ (SD) (> 60 mo.) (N = 9)	ST $\bar{X}$ (SD) (< 60 mo.) (N = 12)	ST $\bar{X}$ (SD) (> 60 mo.) (N = 4)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Piat Reading Comprehension	93.62 (12.4)	97.00 (12.3)	102.22 (13.4)	106.67 (8.9)	3.97 (.060)	.095 (.761)	.038 (.847)	2.217 (.151)
WRAT Reading	90.20 (14.2)	102.25 (12.4)	112.00 (13.1)	116.50 (12.8)	18.85 (< .001)	2.90 (.100)	.771 (.406)	.237 (.630)
WRAT Spelling	89.90 (12.8)	93.13 (11.6)	108.50 (12.2)	107.25 (13.4)	15.47 (< .001)	.06 (.815)	.26 (.611)	.10 (.748)
WRAT Arithmetic	81.00 (12.7)	89.38 (8.3)	100.08 (9.3)	98.50 (9.0)	20.39 (< .001)	1.06 (.313)	1.87 (.182)	.01 (.906)

*2 x 2 ANCOVA with months since diagnosis as the covariate

[1]Tx: Significance of the effect of treatment groups (ALL vs. ST) on the measures of academic achievement

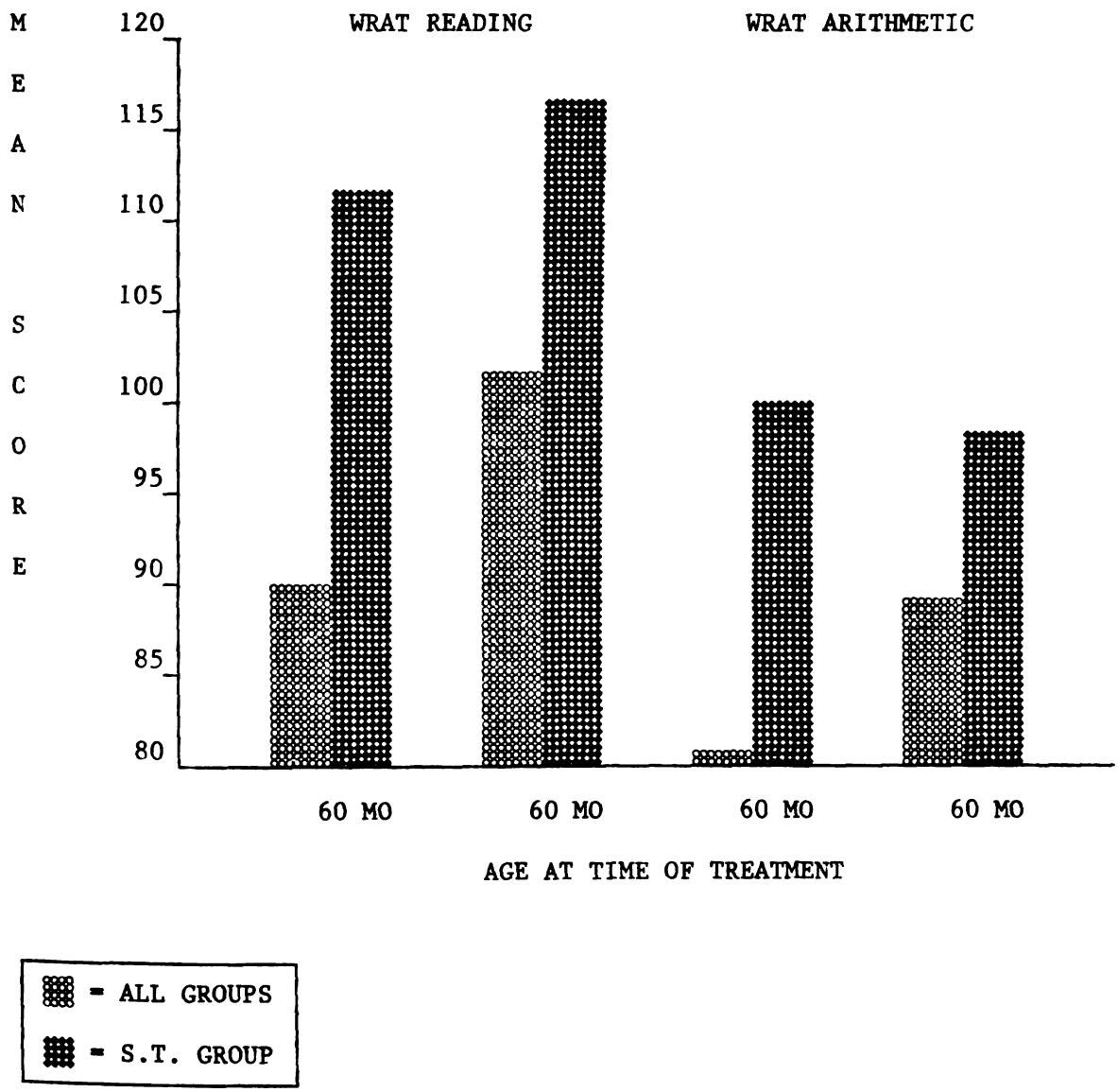
[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the measures of academic achievement

[3]Interaction: Significance of the interaction between treatment groups and age at time of treatment on the measures of academic achievement

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis) and the dependent measures of academic achievement.

FIGURE 5

ACADEMIC ACHIEVEMENT: EFFECT OF AGE AT TIME OF TREATMENT ON MEAN SCORES



associated level of significance for the variables of interest. Six participants from the ALL group and two from the ST group did not complete the Rey-Osterrieth Copy.

Percentile scores on the Beery Test of Visuomotor Integration (VMI) ranged from 1 to 99. The Block Design Scale scores ranged from 1 to 17, and from 12 to 36 on the Rey-Osterrieth Copy. Groups I and II (CNS prophylaxis) had significantly lower mean scores than Groups III and IV (systemic therapy only) on the Beery Test of Visuomotor Integration (30.17 versus 55.06; $p = .002$) and the Block Design Scale score (8.16 versus 11.38, $p = .001$). The Rey-Osterrieth scoring system does not adjust for current age. Therefore, age was treated as the covariate for this dependent measure, and was found to be significantly related to the observed scores ($p = .014$). The combined mean Rey-Osterrieth score for Groups I and II was 31.42 and 34.64 for Groups III and IV. After adjusting for the covariate, the treatment effect was not significant for this measure ($p = .122$).

Age at time of treatment had a significant effect on the Beery Test of Visuomotor Integration and the Block Design Scale scores. The mean Beery score was 31.79 for subjects treated before and 35.30 for those treated after the age of 60 months ($p = .039$). A graph of the effects of age at time of treatment on the Beery scores is presented in Figure 6.

Age at time of treatment was also significant for the Block Design Scale (Table 13). Here the mean scores for those treated before and after 60 months were 8.73 and 11.15, respectively, ($P = .005$). The direction and magnitude of the age at treatment differences on the Beery and Block Design Scale scores were comparable for both treatment

Table 13

Group Differences on Measures of Visuospatial Skills*

Table 13

Group Differences* on Measures of Visuospatial Skills

Measures of Visuospatial Skills	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Beery Test of Visuomotor Integration %	19.70 (22.8) (N = 10)	43.25 (33.7) (N = 8)	48.08 (23.3) (N = 12)	76.00 (26.9) (N = 4)	11.092 (.002)	4.67 (.039)	.007 (.932)	2.162 (.117)
Block Design Subscale from WISC-R	6.4 (3.7) (N = 10)	10.11 (3.1) (N = 9)	10.67 (2.1) (N = 12)	13.50 (2.8) (N = 4)	14.292 (.001)	9.317 (.005)	.191 (.665)	.005 (.945)
Rey-Oseterrieth Copy	27.93 (11.5) (N = 7)	35.50 (.55) (N = 6)	34.50 (1.8) (N = 10)	35.00 (2.0) (N = 4)	2.590 (.122)	.478 (.497)	2.996 (.097)	7.135 (.014)

*2 x 2 ANCOVA Covariates: Months since diagnosis for the Beery Test and the Block Design Subscale current age for the Rey-Oseterrieth Copy

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the measures of visuospatial skills

[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the measures of visuospatial skills

[3]Interaction: Significance of the interaction between treatment and age at time of treatment groups on the measures of visuospatial skills

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis or current age) and the measures of visuospatial skills

FIGURE 6

EFFECTS OF AGE

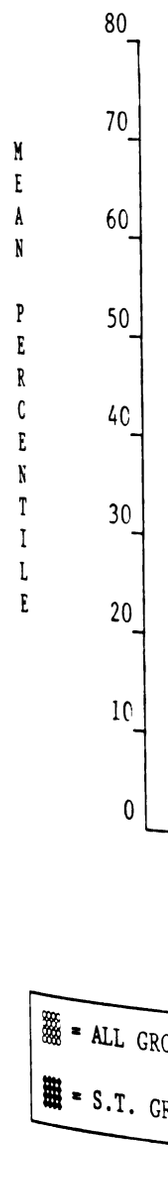
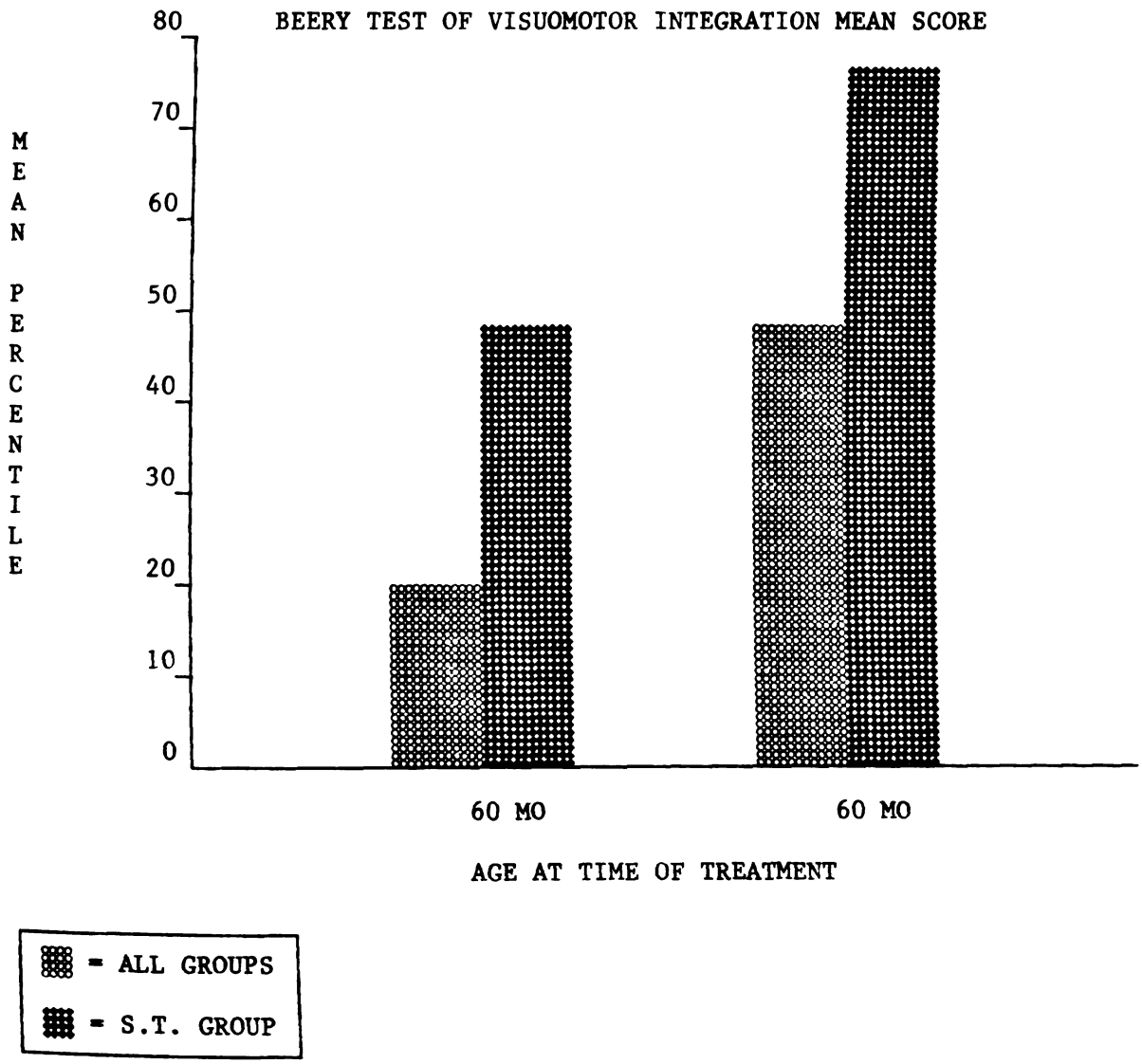
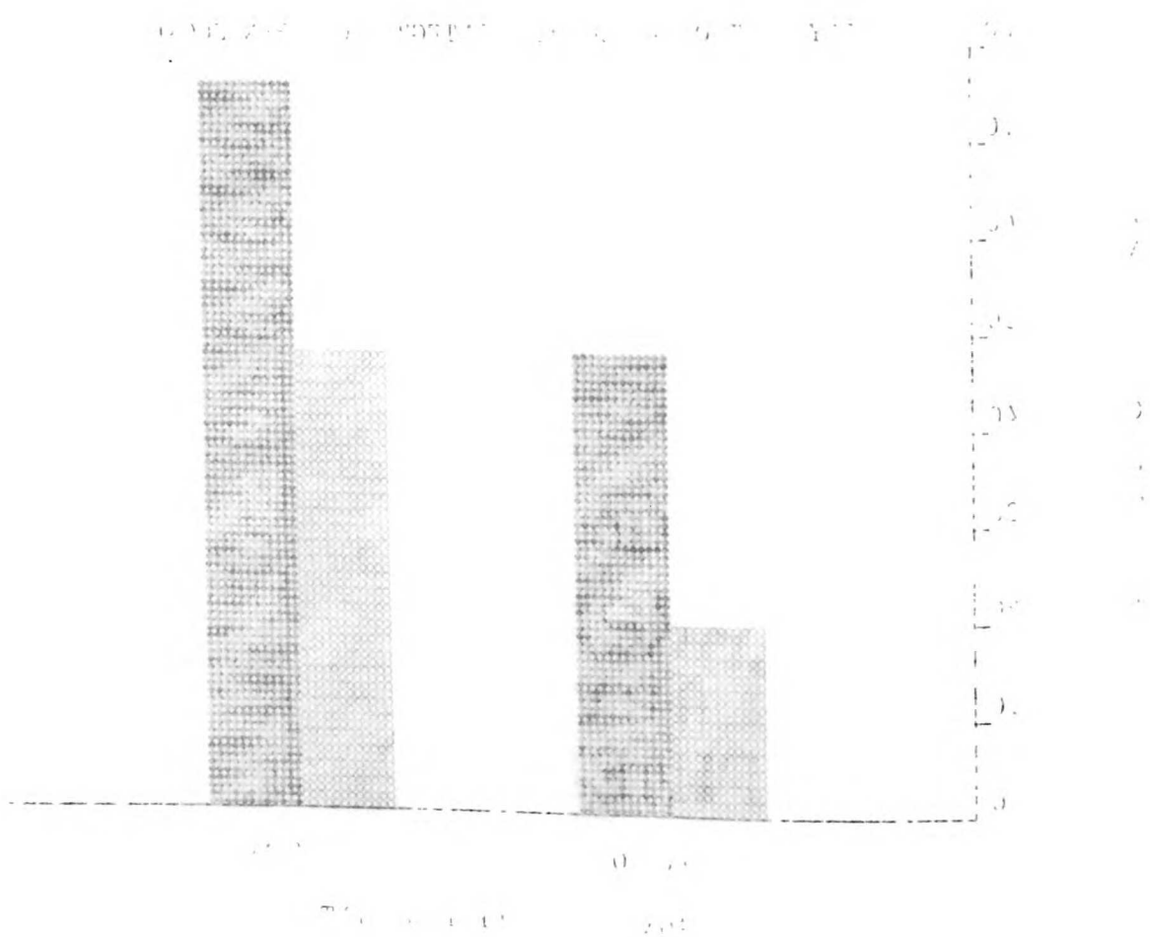


FIGURE 6

EFFECTS OF AGE AT TIME OF TREATMENT ON VISUOSPATIAL SKILLS





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Group I subjects had the lowest mean score (27.93) on the Rey-Osterrieth Copy, while the mean scores for Groups II, III and IV ranged from 34.50 to 35.50 (Figure 7). Mean scores were adjusted for current age, and then, the effect of age at time of treatment was not significant ($p = .497$). A follow-up comparison of the mean Rey-Osterrieth Copy scores for the two groups of ALL subjects also demonstrates that the effect of age at time of treatment did not reach statistical significance ($p = .123$). The interaction effect approached significance ($p = .097$), and, as demonstrated in Figure 7, is related to the much lower mean score obtained by Group I.

In conclusion, the hypotheses that CNS prophylaxis and age at time of treatment are significantly related to visuospatial skills were partially supported. There was less support for the hypothesized effect due to age at time or treatment and the treatment by age at time of treatment interaction. The latter was significant only on the Rey-Osterrieth Copy which failed to demonstrate the significance of treatment or age at time of treatment.

Language Skills

Language skills were measured by the FAS and the CELF (Table 14). Data from the FAS are available on 29 subjects (N = 14 ALL and N = 15 ST). Fewer participants were able to complete the CELF, and complete data are available on only 19 participants (N = 11 ALL and N = 8 ST).

The FAS yields a raw score which ranged from 2 to 48. The score is not age-adjusted. Therefore, current age was treated as the covariate and found to be significantly related to the observed mean scores

FIGURE 7

EFFECTS OF AGE

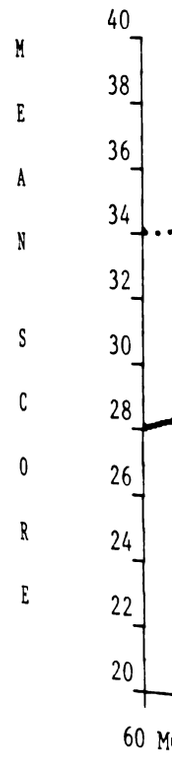
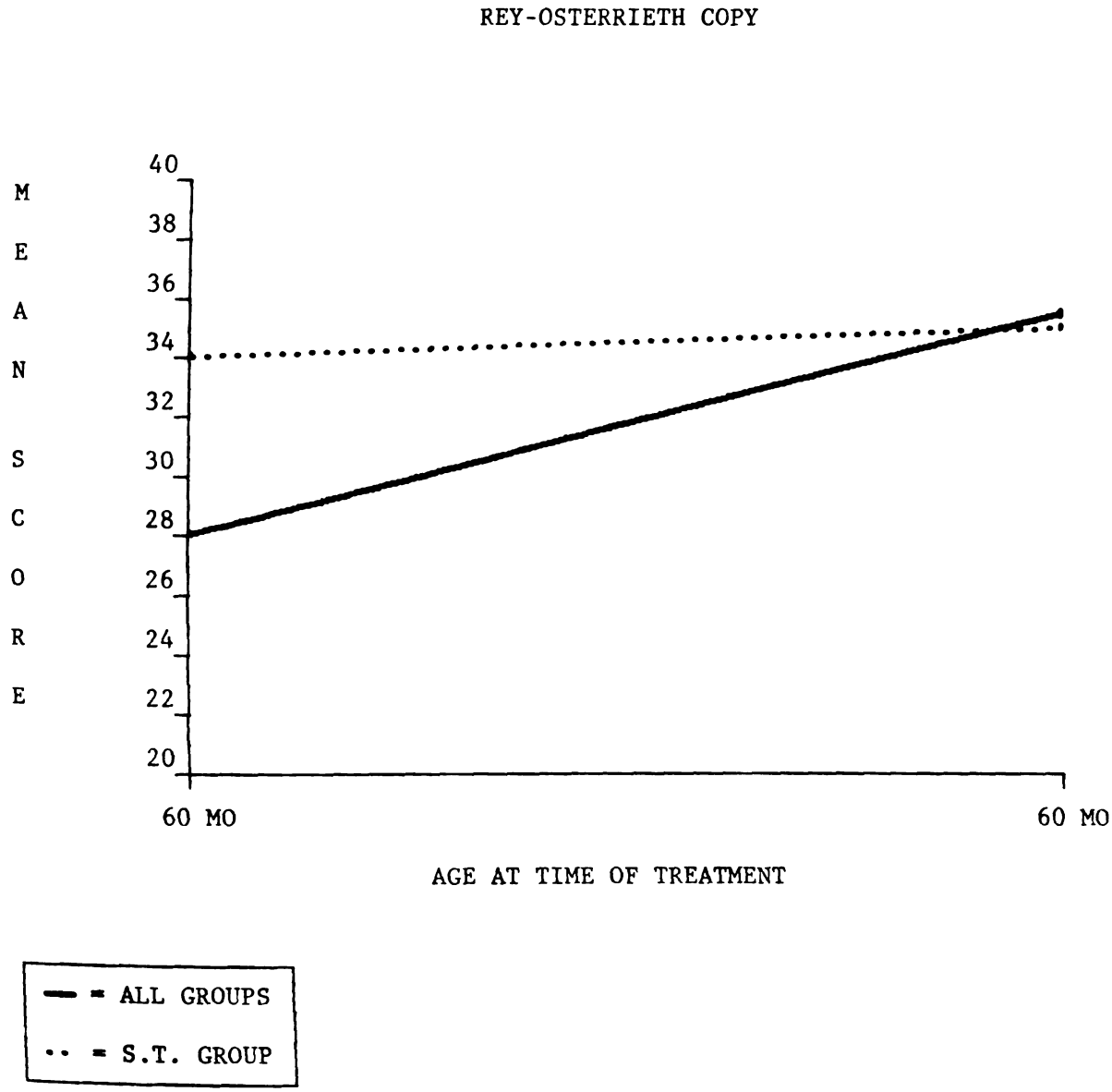


FIGURE 7

EFFECTS OF AGE AT TIME OF TREATMENT ON VISUOSPATIAL SKILLS



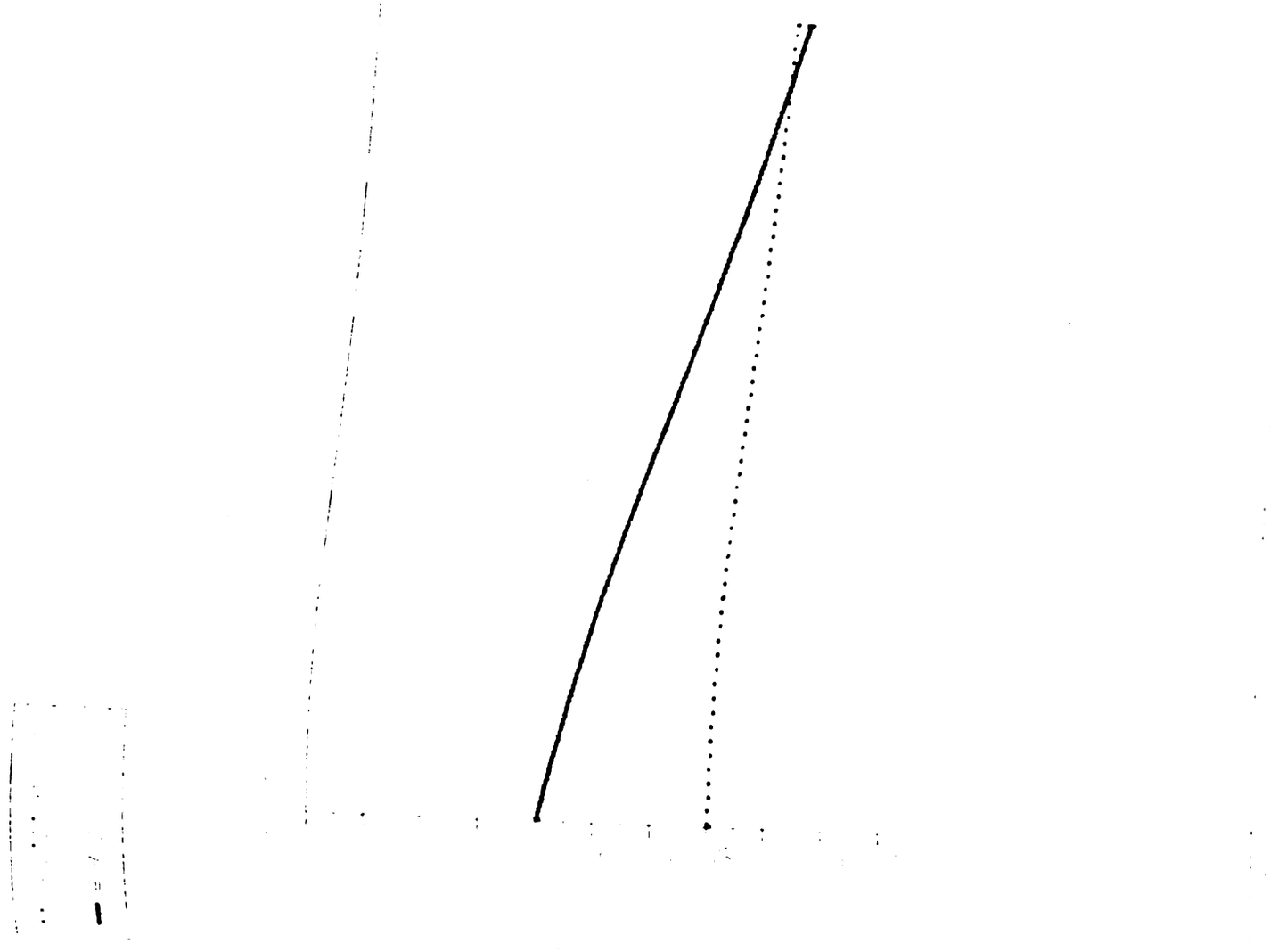


Table 14

Group Differences* on Language Skills

Table 14

Group Differences* on Language Skills

Measures of Language Skills	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
FAS	17.50 (10.6) (N = 8)	30.67 (10.9) (N = 6)	28.27 (10.0) (N = 11)	36.75 (3.8) (N = 4)	5.498 (.028)	1.622 (.215)	.773 (.388)	22.997 (< .001)
CELF** Processing %	20.57 (17.0) (N = 7)	53.25 (36.0) (N = 4)	58.50 (19.1) (N = 5)	69.00 (18.7) (N = 3)	5.268 (.038)	5.706 (.032)	.649 (.434)	.546 (.472)
Production %	28.43 (26.6) (N = 7)	57.00 (30.0) (N = 4)	55.20 (34.4) (N = 5)	71.67 (7.8) (N = 3)	2.023 (.177)	2.931 (.109)	.121 (.733)	.004 (.950)
Total %	23.14 (21.4) (N = 7)	57.75 (32.0) (N = 4)	59.20 (21.7) (N = 5)	74.67 (9.6) (N = 3)	4.981 (.042)	6.463 (.023)	.456 (.510)	.187 (.672)

*2 x 2 ANCOVA Covariate is months since diagnosis for the CELF and current age for the FAS

**CELF: Clinical Evaluation of Language Function

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the measures of language skills

[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the measures of language skills

[3]Interaction: Significance of the interaction between treatment and age at time of treatment groups on the measures of language skills

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis or current age) and the measures of language skills

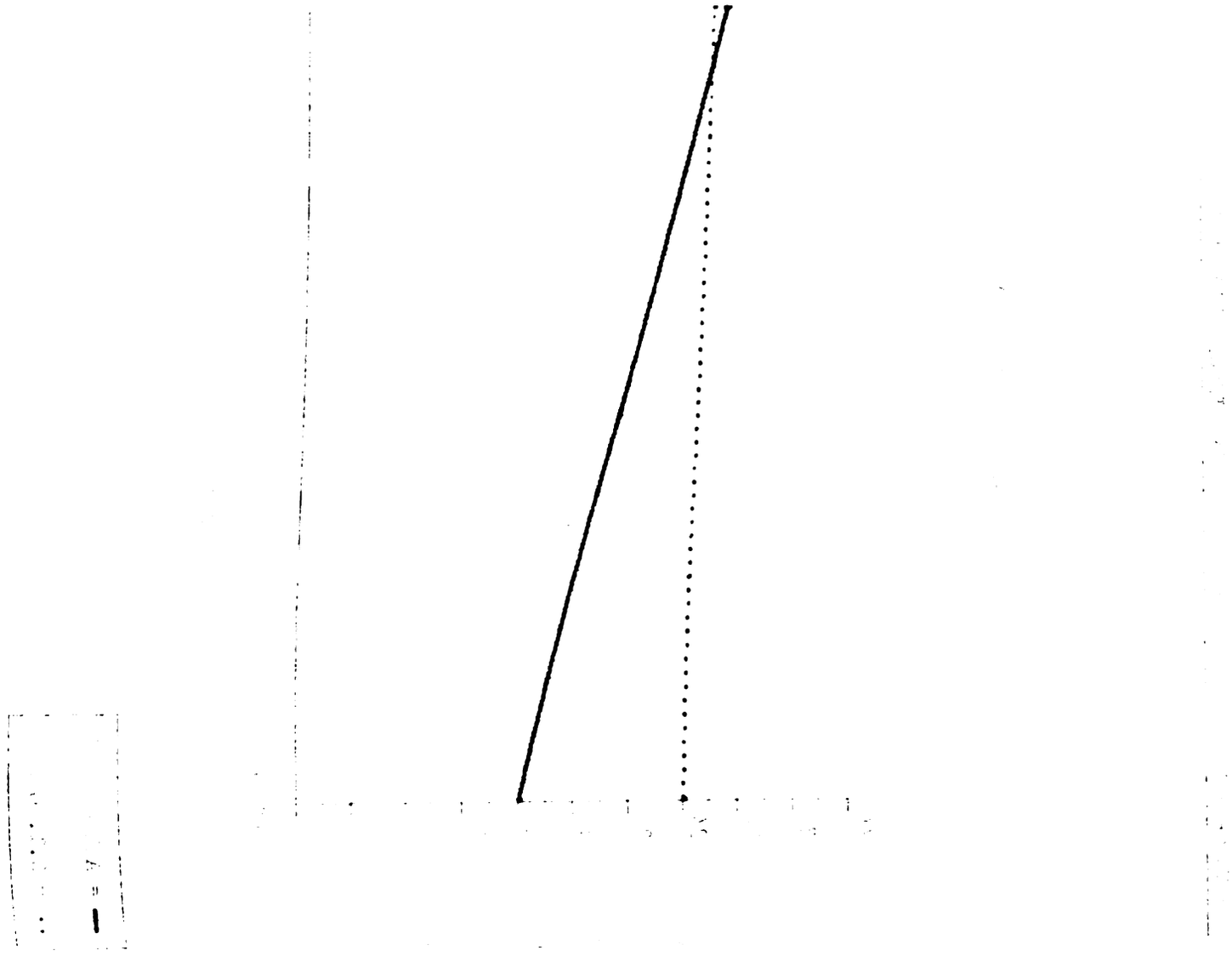


Table 14

Group Differences* on Language Skills

Table 14

Group Differences* on Language Skills

Measures of Language Skills	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
FAS	17.50 (10.6) (N = 8)	30.67 (10.9) (N = 6)	28.27 (10.0) (N = 11)	36.75 (3.8) (N = 4)	5.498 (.028)	1.622 (.215)	.773 (.388)	22.997 (< .001)
CELF** Processing %	20.57 (17.0) (N = 7)	53.25 (36.0) (N = 4)	58.50 (19.1) (N = 5)	69.00 (18.7) (N = 3)	5.268 (.038)	5.706 (.032)	.649 (.434)	.546 (.472)
Production %	28.43 (26.6) (N = 7)	57.00 (30.0) (N = 4)	55.20 (34.4) (N = 5)	71.67 (7.8) (N = 3)	2.023 (.177)	2.931 (.109)	.121 (.733)	.004 (.950)
Total %	23.14 (21.4) (N = 7)	57.75 (32.0) (N = 4)	59.20 (21.7) (N = 5)	74.67 (9.6) (N = 3)	4.981 (.042)	6.463 (.023)	.456 (.510)	.187 (.672)

*2 x 2 ANCOVA Covariate is months since diagnosis for the CELF and current age for the FAS

**CELF: Clinical Evaluation of Language Function

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the measures of language skills

[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the measures of language skills

[3]Interaction: Significance of the interaction between treatment and age at time of treatment groups on the measures of language skills

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis or current age) and the measures of language skills

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($p < .001$). The age-adjusted mean score for the CNS treatment groups (I and II) was 23.16 and 30.53 for the ST treatment groups (III and IV). The treatment effect was statistically significant ($p = .028$).

Subjects treated before 60 months, Groups I and III, had lower mean scores than their counterparts in Groups II and IV who were treated at an older age (Figure 8). This effect of age at time of treatment was not statistically significant with the sample size of 29 subjects. The interaction effect was also non-significant. In a secondary analysis, a t-test was done to compare the mean scores of the Group I and Group II ALL subjects. This analysis demonstrated a significant age at treatment effect ($p = .046$), however, the scores were not adjusted for current age, which in the major analysis was a significant covariate.

The Clinical Evaluation of Language Function (CELF) yields three percentile scores: Language Processing, Language Production, and the Total or composite score (refer to Table 14 for a summary of the ANCOVA results). The mean percentiles for the 11 CNS treatment group subjects (Processing: 32.45; Production: 38.82; and Total: 35.73) were consistently lower than those of the 8 ST participants (62.63, 61.38, and 65.00, respectively). The treatment effect was significant for Processing ($p = .038$) and Total ($p = .042$), but only approached significance for Production ($p = .177$).

The 12 subjects treated before 60 months of age had lower mean percentiles than those ($N = 7$) treated after this age. The effect due to age at time of treatment was significant for Processing ($p = .032$) and Total ($p = .023$), but again, only approached significance for Language Production ($p = .109$). The age differences were more dramatic

FIGURE 8

EFFECTS OF AGE

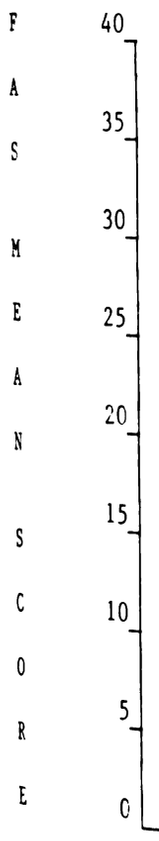

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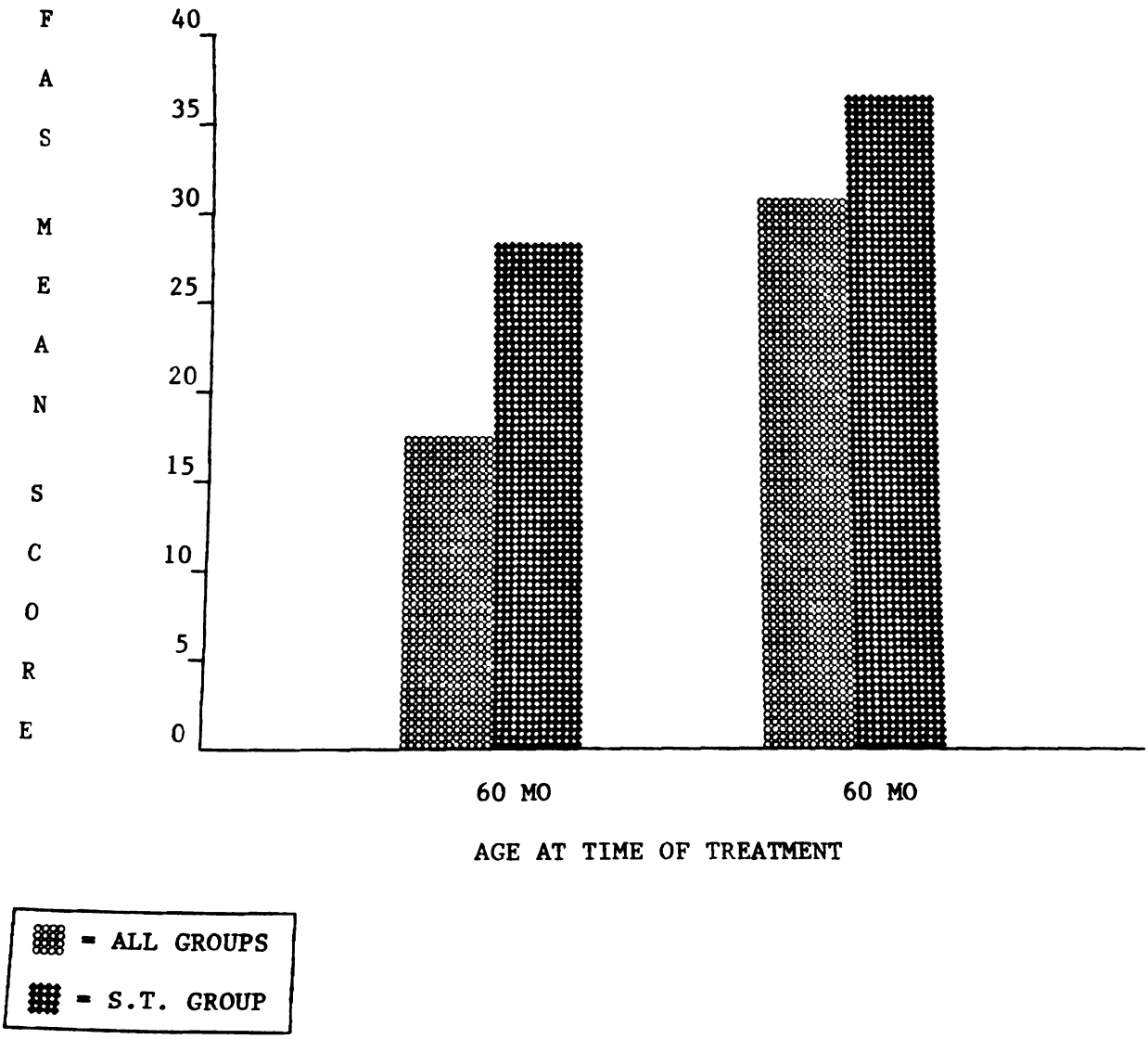
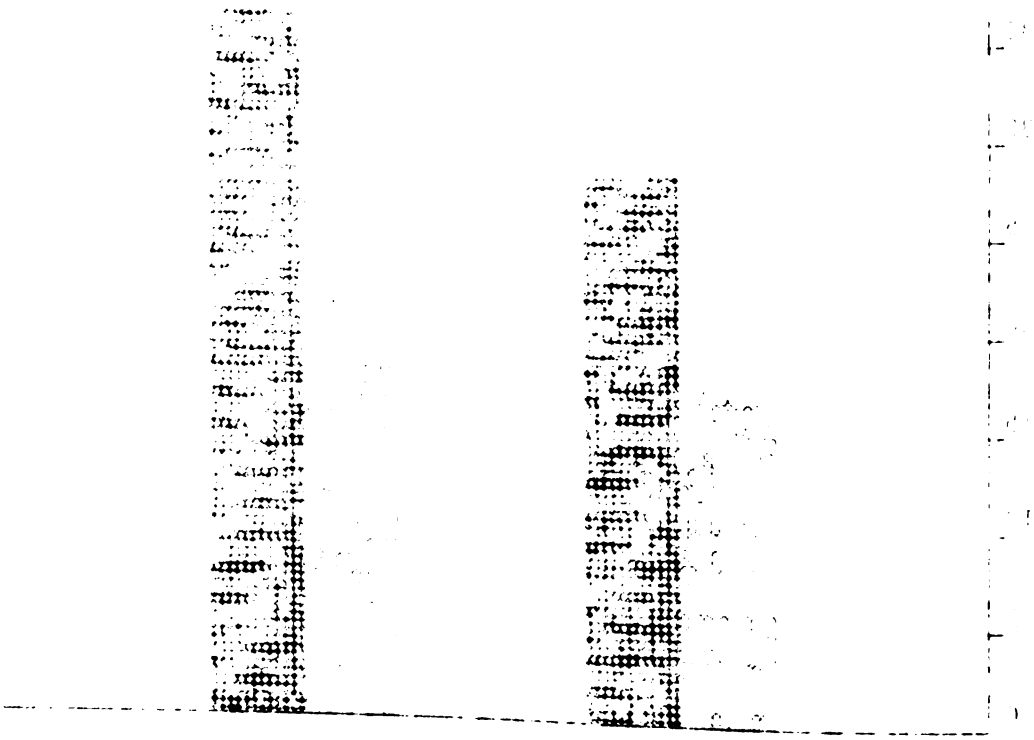
FIGURE 8

EFFECTS OF AGE AT TIME OF TREATMENT ON THE FAS





in the ALL groups (Figure 9), but the discrepancies by treatment condition were not statistically significant (interaction effect $p > .05$).

Conceptual Skills

Two measures of concept development were included in the cognitive profile. The Similarity Subscale from the WISC-R was completed by the entire sample; thirteen from the leukemia group and 15 from the ST group completed the Woodcock-Johnson Concept Formation Test. Current age was treated as the covariate for the Woodcock-Johnson, as the scoring system does not adjust for age. Table 15 summarizes the major findings from this area of cognitive functioning.

Scores on the Similarity Subscale ranged from 5 to 19. The ALL Groups I and II had a significantly lower mean score than the ST subjects in Groups III and IV ($p < .001$), supporting the hypothesis that central nervous system therapy has late effects on conceptual skills. The age at time of treatment differences were not as dramatic and failed to reach significance ($p = .484$). An interesting finding was the significant treatment by age at time of treatment interaction ($p = .017$). This interaction, graphed in Figure 10, is due to a lower mean score in Group I as compared to Group II, but a higher mean score in Group III as compared to Group IV. Groups I and III represent those subjects who were treated before 60 months of age. Months since diagnosis was significantly related to the Similarity Subscale ($p = .051$), therefore the observed scores were adjusted for the covariate.

Subject scores on the Woodcock-Johnson ranged from 1 to 54, but did not demonstrate significant treatment or age at time of treatment

FIGURE

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FIGURE 9

EFFECTS OF AGE AT TIME OF TREATMENT ON THE CLINICAL EVALUATION OF LANGUAGE FUNCTION

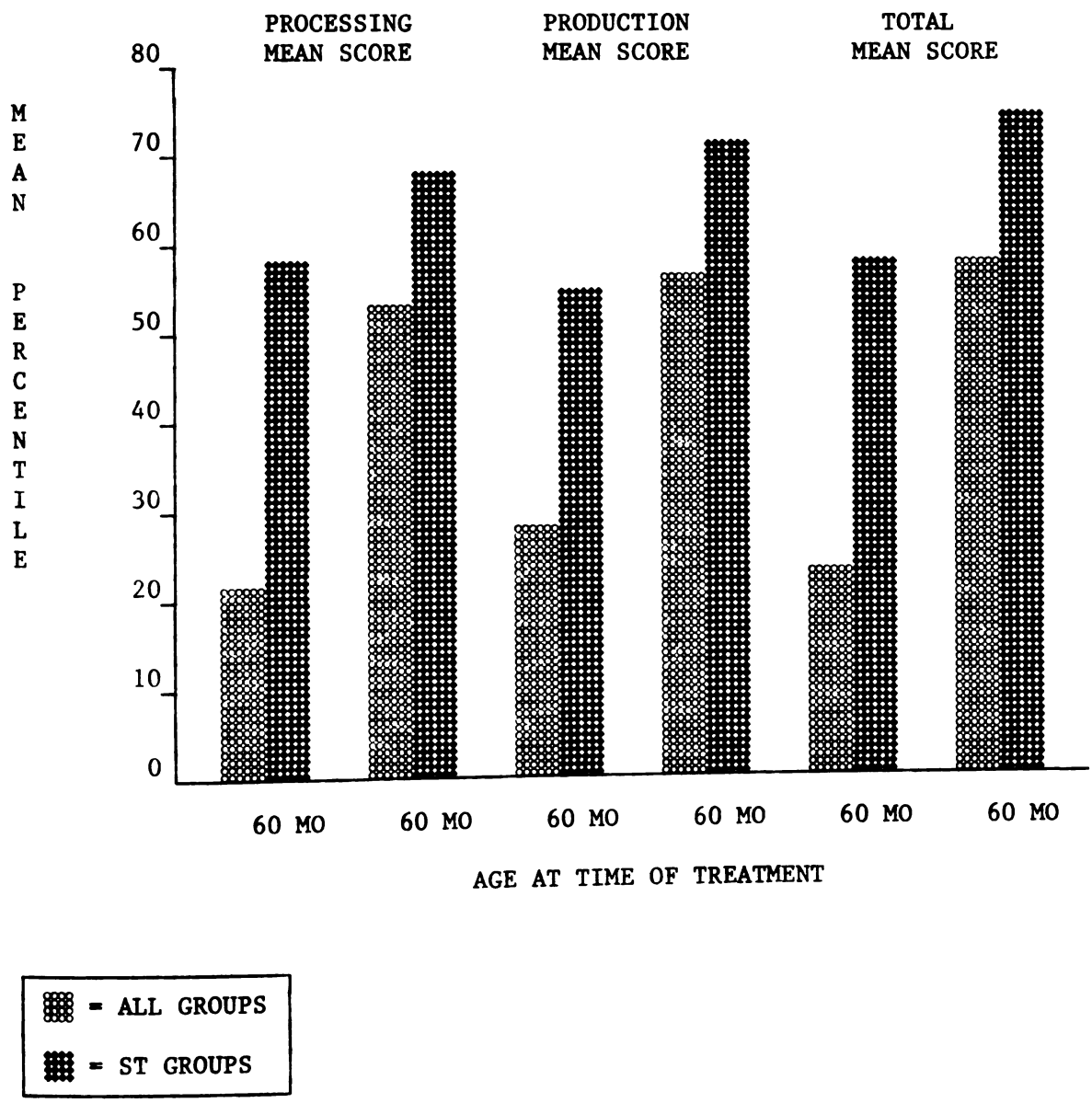

Table 15

Table 15

Group Differences* on Conceptual Skills

Measures of Conceptual Skills	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Woodcock-Johnson Concept Formation	15.86 (18.0) (N = 7)	25.50 (8.7) (N = 6)	24.25 (5.9) (N = 12)	25.67 (2.9) (N = 3)	1.353 (.257)	1.013 (.912)	1.845 (.188)	8.382 (.008)
Similarity Subscale from WISC-R	8.00 (2.7) (N = 10)	10.22 (2.0) (N = 9)	13.25 (3.0) (N = 12)	11.75 (2.1) (N = 4)	29.815 (< .001)	.503 (.484)	6.348 (.017)	4.143 (.051)

*2 x 2 ANCOVA with current age as the covariate for the Woodcock-Johnson Concept Formation and months since diagnosis as the covariate for the Similarity Subscale

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the measures of conceptual skills

[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the measures of conceptual skills

[3]Interaction: Significance of the interaction between treatment and age at time of treatment groups on the measures of conceptual skills

[4]Covariate: Significance of the relationship between the covariate (current age or months since diagnosis) and the measures of conceptual skills

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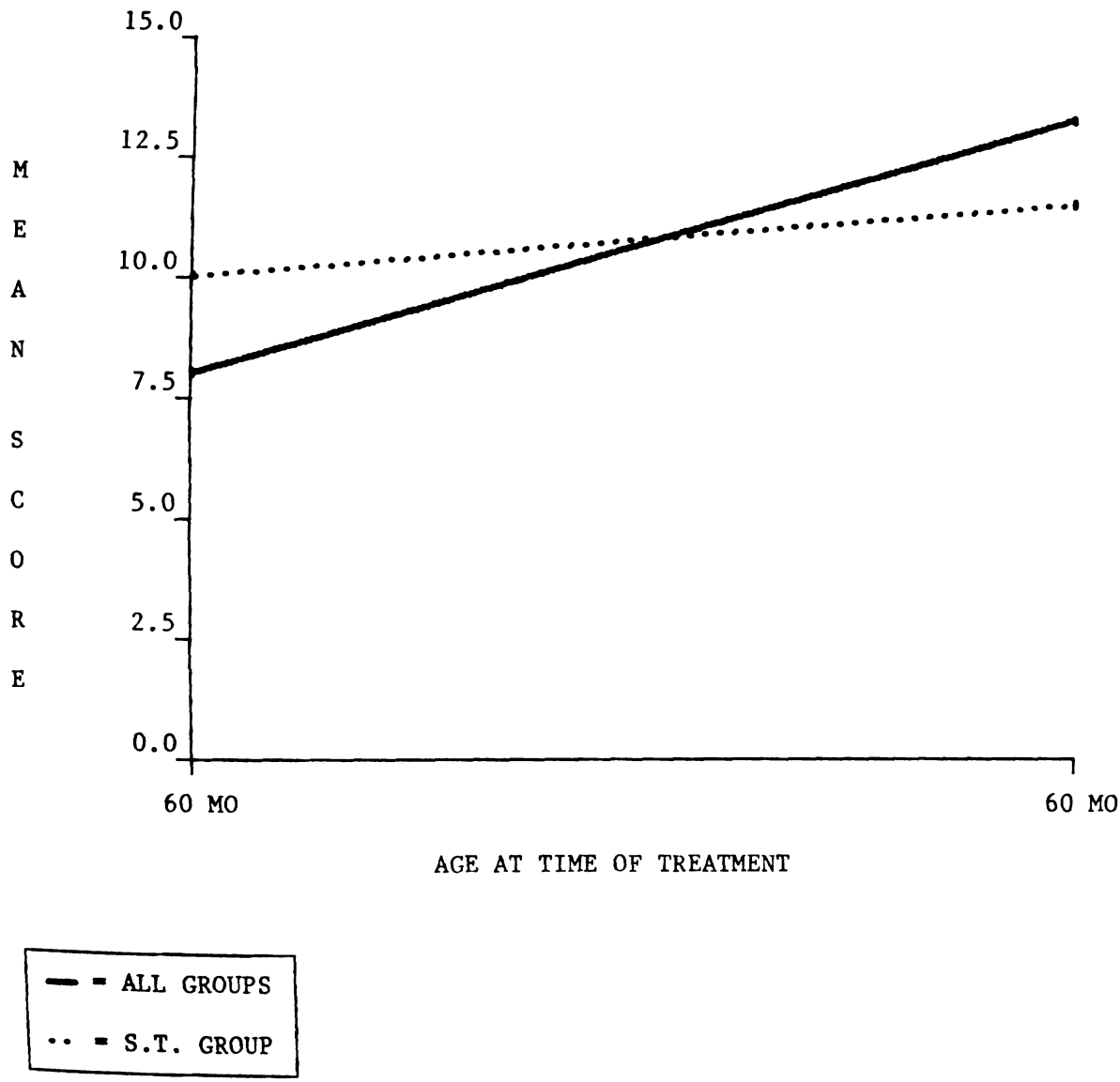
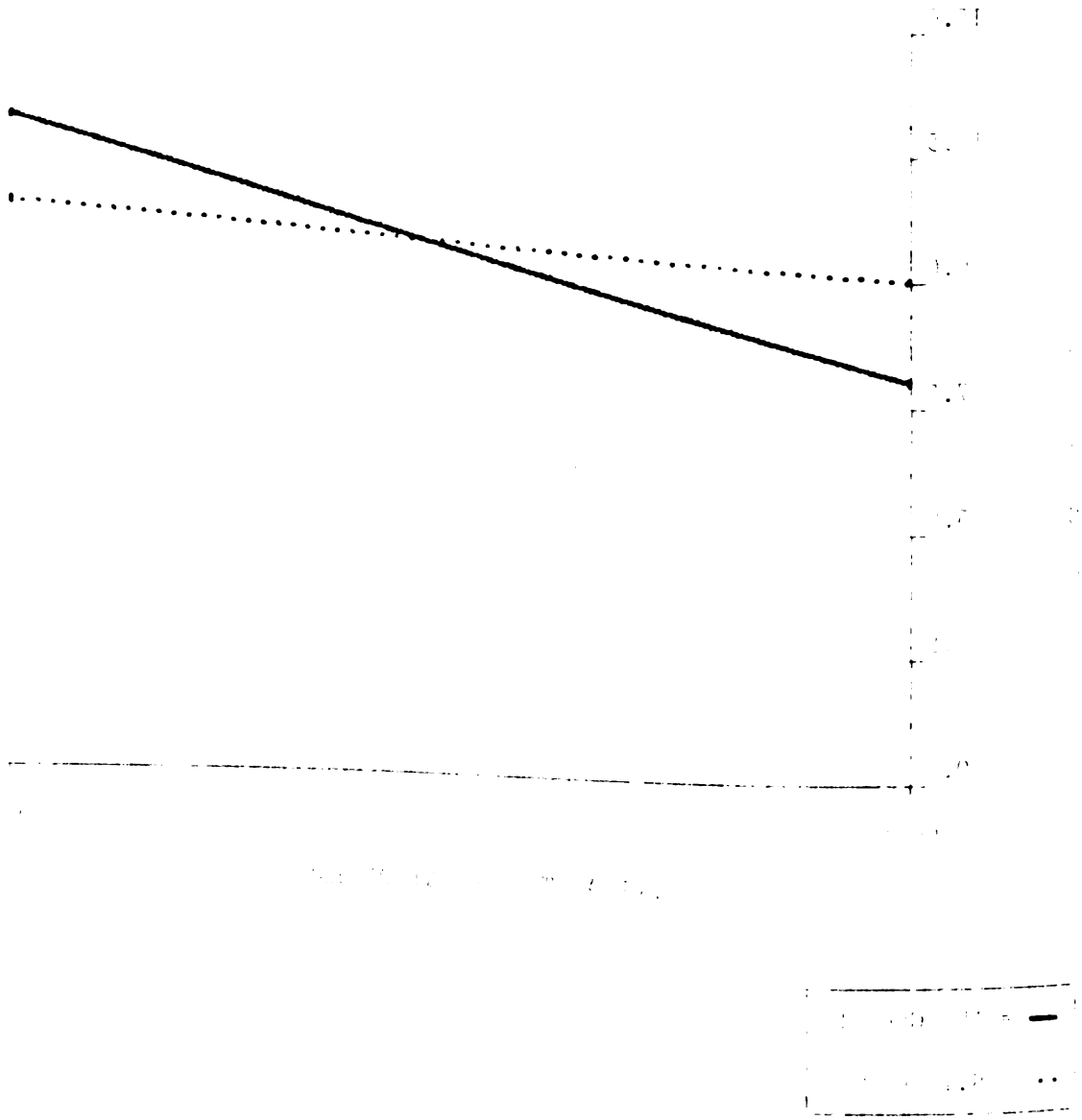
FIGURE 10

TREATMENT BY AGE AT TIME OF TREATMENT INTERACTION ON SIMILARITY SUBSCALE FROM WISC-R





effects (Table 15). The mean score for Group I (15.86) was lower than those of Groups II, III, and IV. However, Group I scores had much more variability (larger standard deviation) which influences the magnitude of the significance of the differences among the groups.

Age at time of treatment and the treatment by age at time of treatment interaction were not significant ($p = .912$ and $p = .188$). Current age was significantly related to the dependent measure ($p = .008$), and the observed scores were adjusted for this covariate.

In conclusion, the hypothesis that conceptual skills are affected by CNS prophylaxis was partially supported. The treatment groups had statistically significant differences on the Similarity Subscale. The effects of age at time of treatment were nonsignificant; this hypothesis was not supported. There was some evidence for an interaction between treatment condition and age at time of treatment.

Auditory Memory

The Digit Span Scale from the WISC-R and the Bushke Selective Reminding Procedure served as the measures of auditory memory. Digit span data are available on all 35 subject; however, only 28 subjects (Group I = 8; Group II = 6; Group III = 10; Group IV = 4) completed the Bushke. Refer to pages 82 and 83 (Methods) for a description of the four memory measures within the Bushke paradigm.

A two by two analysis of covariance, with current age as the covariate, was originally planned for the Bushke data. This analysis was completed. Significant ($p < .05$) treatment by age at time of treatment interactions occurred, necessitating a one-way four group (Group I = ALL treated before 60 months; Group II = ALL treated after 60 months; Group III = ST treated before 60 months; and Group IV = ST

treated after 60 months) analysis of covariance with the same covariate. This analysis demonstrated a significant trial effect ($p = .01$ to $.05$) but no group effect for the four scores. Further inspection of the data revealed that Group IV had much more within group variability (larger standard deviations) than did the remaining three groups. For example, the standard deviations for Groups I, II and III on long-term storage ranged from .8 to 2.0 while in Group IV the standard deviation ranged from 1.7 to 2.8.

Unequal variance violates one of the assumptions of ANCOVA. Therefore, Group IV was dropped, and a one-way three group analysis was done with current age as the covariate. Table 16 summarizes the findings. The trial by group interaction as well as the covariate were not significant for any of the four scores.

Total free call represents the number of words the subject correctly recalled for the 10 trials. The mean for the 10 trials was lowest (6.61) for the Group I and highest (8.01) for the Group III subjects. The group effect was significant ($p = .014$). All groups improved their scores over the 10 trials, resulting in a significant trial effect ($p < .01$).

Long-term storage (LTS) reflects how many of the 10 stimulus words the subjects encodes into long-term memory. Again, the Group I subjects had the lowest mean scores across the trials and the difference among the groups approached significance ($p = .058$). Group II subjects had a slightly higher score than their counterpart in Group III (7.57 versus 7.50). The effect of the trials was significant as all three groups improved their performance over the trials ($p < .01$). LTR/Total represents the proportion of items (words) recalled that were retrieved

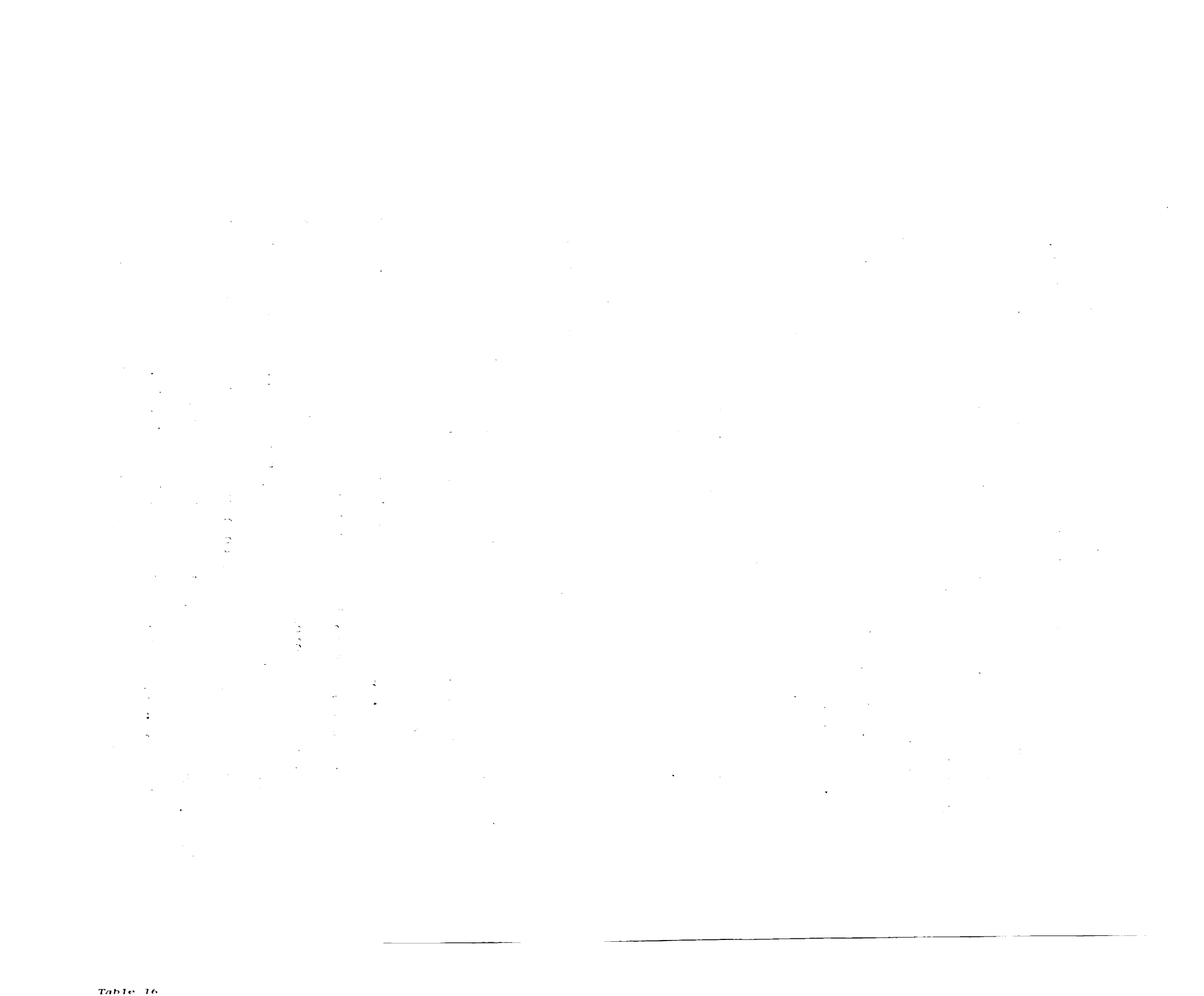


Table 16

Group Differences* on Auditory Memory: The Bushke Selective Reminding Procedure

Bushke Score	Group I ALL (< 60 mo.) trial $\bar{X}$ (N = 8)	Group II ALL (< 60 mo.) trial $\bar{X}$ (N = 6)	Group III ST (< 60 mo.) trial $\bar{X}$ (N = 10)	Group[1] F (p)	Trial[2] F (p)	Trial/Group Interaction[3] F (p)	Covariate[4] F (p)
Total[5]	6.61	7.92	8.01	5.32 (.014)	37.72 (< .01)	.92 (.556)	2.67 (.117)
LTS[6]	5.86	7.57	7.50	3.25 (.058)	128.88 (< .01)	1.32 (.176)	1.80 (.194)
LTR/Total[7]	0.74	0.85	0.86	2.33 (.121)	20.86 (< .01)	1.30 (.189)	0.74 (.40)
Con LTR/Total[8]	0.47	0.59	0.71	3.54 (.047)	18.16 (< .01)	1.24 (.23)	0.46 (.506)

*One way 3-group analysis of covariate with current age as the covariate

[1]Group: Significance of the effect of group on the dependent measures

[2]Trial: Significance of the effect of the 10 trials on the dependent measures

[3]Trial/Grp Interaction: Significance of the effect of interaction between trial factor and the group factor on the dependent measure

[4]Covariate: Significance of the relationship between the covariate (current age) and dependent measure

[5]Total: Total free recall

[6]LTS: Storage into long-term memory

[7]LTR/Total: Proportion of items recalled that were retrieved from long-term memory

[8]Con LTR/LTS: How consistently subjects recalled items presumed to be in long-term storage

from long-term memory. The groups did not differ on this component of memory ($p = .121$), and all groups improved their scores significantly over time ($p < .01$).

Finally, the Bushke yields a measure of the extent to which the subject consistently recalled items presumed to be stored in long-term memory. The Group I subjects (ALL, treated before 60 months) had the lowest mean ratio (0.47) followed by Group II (ALL treated after 60 months), and Group III subjects had the highest score ($\bar{X} = .71$). The differences due to group were significant ($p = .047$) and the trial effect was also significant.

Results from the Digit Span Scale also demonstrated a significant effect due to treatment group (Table 17). The combined mean score of the ALL groups was 7.79 and 11.06 for the ST groups ($p = .001$). Long-term leukemia survivors treated before 60 months of age had a lower mean score than those treated later; within the ST treatment condition, the subjects treated early had a higher mean score than those treated after five years (Figure 11). The effect of age at time of treatment and the treatment by age at treatment interaction were not dramatic enough for the sample size to reach statistical significance ($p = .194$ and $p = .110$).

Visual Memory

The Benton Visual Retention Test (BVRT) and the Rey-Osterrieth Recall required the subject to recall visually presented stimuli. These measures of visual memory concluded the cognitive battery. Time constraints prevented all subjects from completing these instruments. The sample size for each dependent measure of visual memory and the results are provided in Table 18.

Table 17

Table 17

Group Differences* on Auditory Memory: Digit Span Subscale from the WISC-R

	ALL		ST					
	$\bar{X}$ (SD) (< 60 mo.) (N = 10)	$\bar{X}$ (SD) (> 60 mo.) (N = 9)	$\bar{X}$ (SD) (< 60 mo.) (N = 12)	$\bar{X}$ (SD) (> 60 mo.) (N = 4)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Digit Span Scale Score	6.60 (3.0)	9.11 (2.5)	11.25 (2.6)	10.50 (1.0)	14.011 (.001)	1.764 (.194)	2.718 (.110)	.755 (.392)

*2 x 2 ANCOVA with months since diagnosis as the covariate

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the Digit Span Score

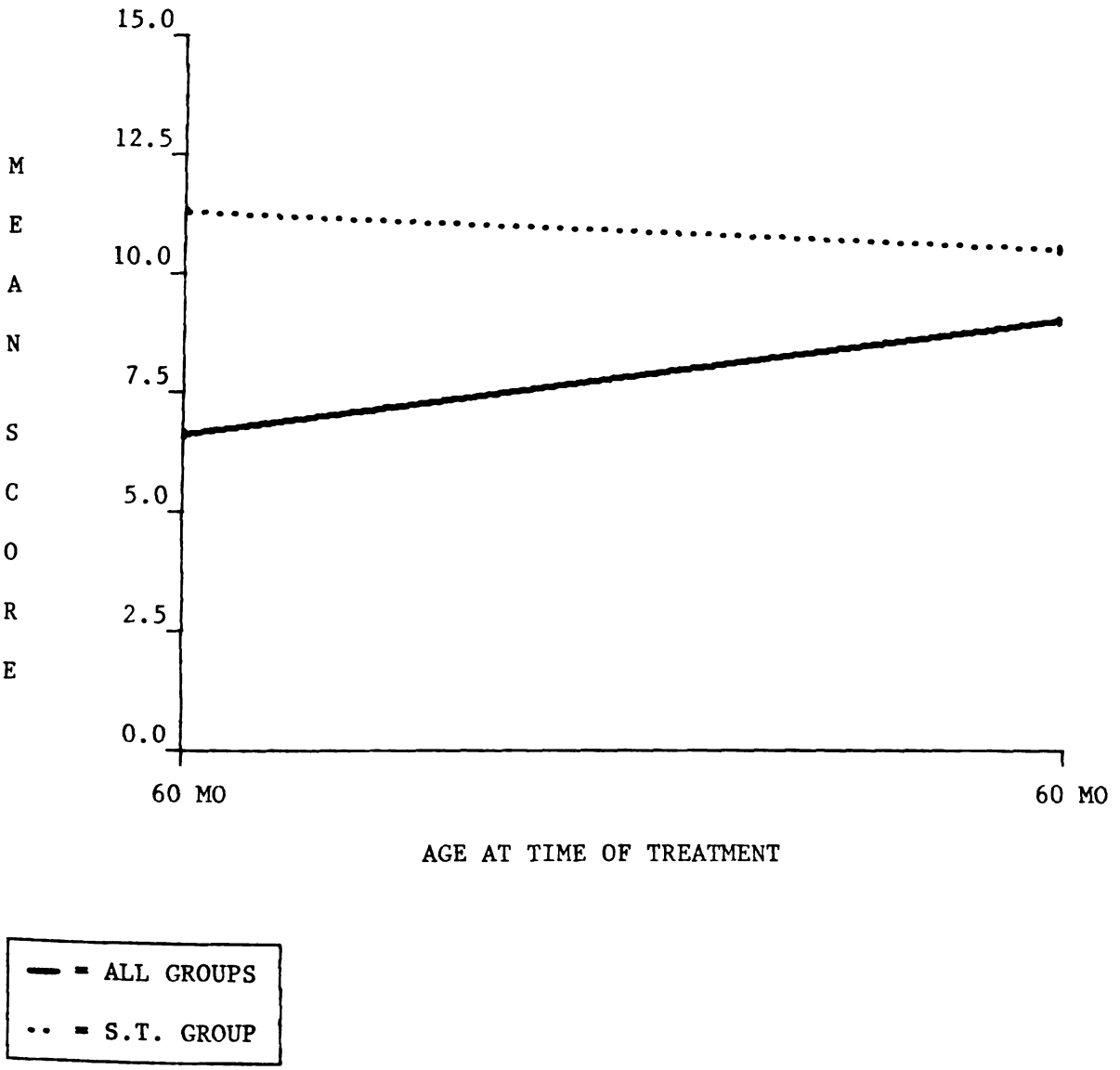
[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the Digit Span Scale Score

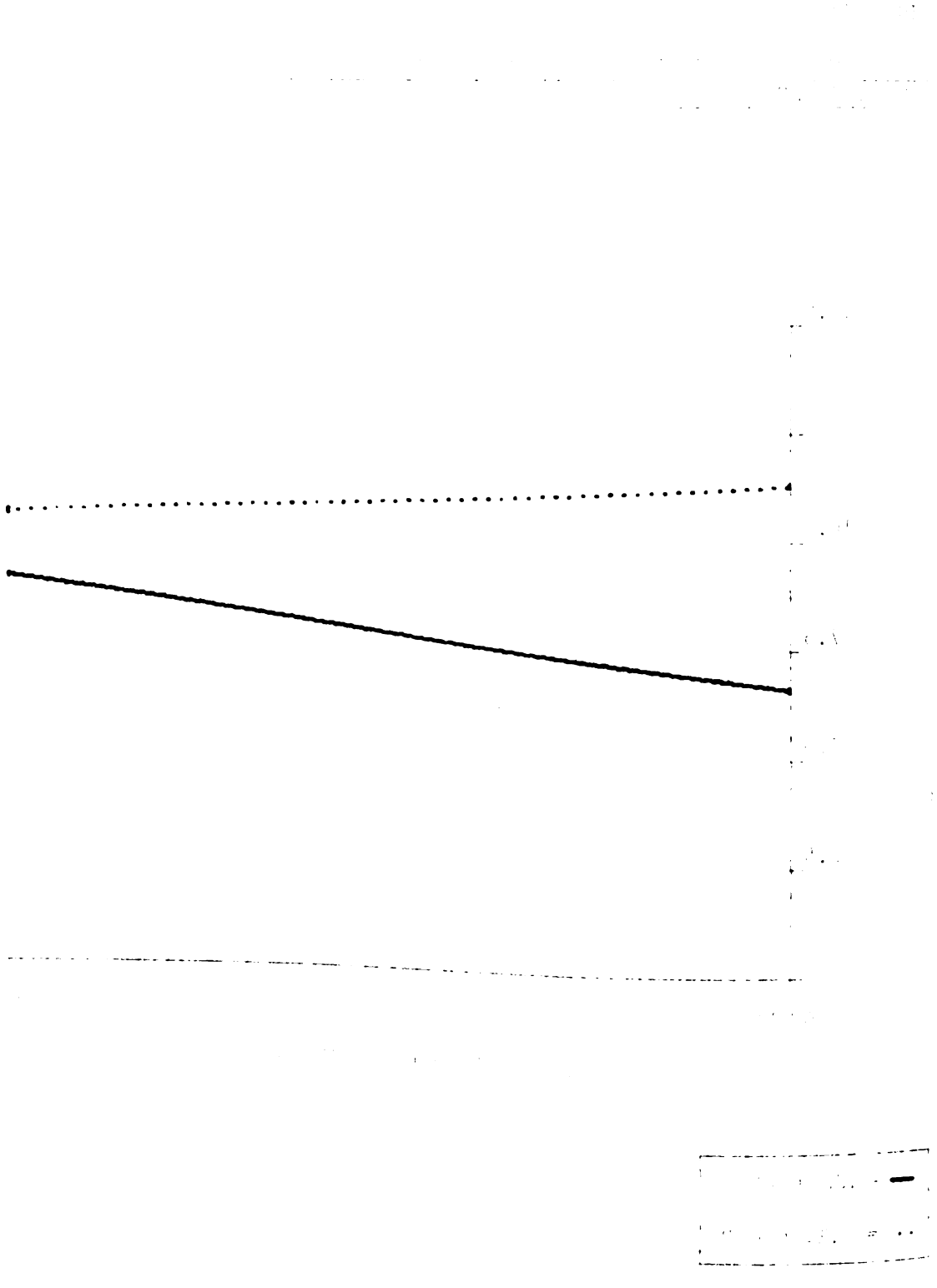
[3]Interaction: Significance of the interaction between treatment and age at time of treatment groups on the Digit Span Scale Score

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis) and the Digit Span Scale Score

FIGURE 11

TREATMENT BY AGE AT TIME OF TREATMENT INTERACTION ON DIGIT SPAN SCALE FROM WISC-R





The BVRT is scored for the number correct as well as the number of errors. The Number Correct scores ranged from 0 to 10. The mean score of the ALL groups was 6.25 and 7.67 for the ST groups, which was statistically significant ($p = .002$). The mean scores by ages at time of treatment were 4.61 and 7.43 for Groups I and II and 7.38 and 8.23 for Groups III and IV. The difference due to the age at time of treatment was significant ($p = .028$). Figure 12 demonstrates the influence of the mean Group I Number Correct score on the significant treatment by age at time of treatment interaction ($p = .027$). The covariate, current age, was significantly related to the dependent measure ($p = .004$). Observed scores were, therefore, adjusted for the influence of age.

The number of errors on the BVRT ranged from 0 to 10. The group of five long-term leukemia survivors treated before 60 months of age made, on the average, twice as many errors as the other three groups (Table 18). The difference due to treatment condition was significant ($p = .014$). Figure 13 demonstrates the differential effect of treatment according to the age at which the treatment occurred. As noted in Figure 13 the difference between the mean number of errors made by Group I (7.2) and Group III (3.0) is much more dramatic than that between Group II (3.6) and IV (2.8). The effect due to age at time of treatment was significant ($p = .031$) as was the treatment by age at treatment interaction ($p = .013$). The number of observed errors were adjusted for current age as the covariate was significant ($p = .005$).

The second measure of visual memory was the recall drawing of the Rey-Osterrieth Complex Figure. This was completed by 24 subjects. Scores on the recall drawing ranged from seven to 36; the highest

Table 18

Group Differences* on Visual Memory

Measures of Visual Memory	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Benton Visual Retention Test								
No Correct	4.6 (1.9)	7.43 (1.3)	7.38 (1.1)	8.25 (1.5)	12.734 (.002)	5.654 (.028)	5.757 (.027)	10.811 (.004)
No Errors	7.20 (3.0) (N = 5)	3.00 (1.6) (N = 7)	3.63 (1.4) (N = 8)	2.75 (2.2) (N = 4)	7.391 (.014)	5.413 (.031)	7.425 (.013)	9.889 (.005)
Rey-Osterrieth Recall	15.86 (8.2) (N = 7)	24.42 (6.8) (N = 6)	21.06 (5.2) (N = 8)	29.00 (6.2) (N = 3)	3.740 (.068)	2.296 (.146)	0.277 (.605)	12.032 (.003)

*2 x 2 ANCOVA with current age as the covariate

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the measures of visual memory

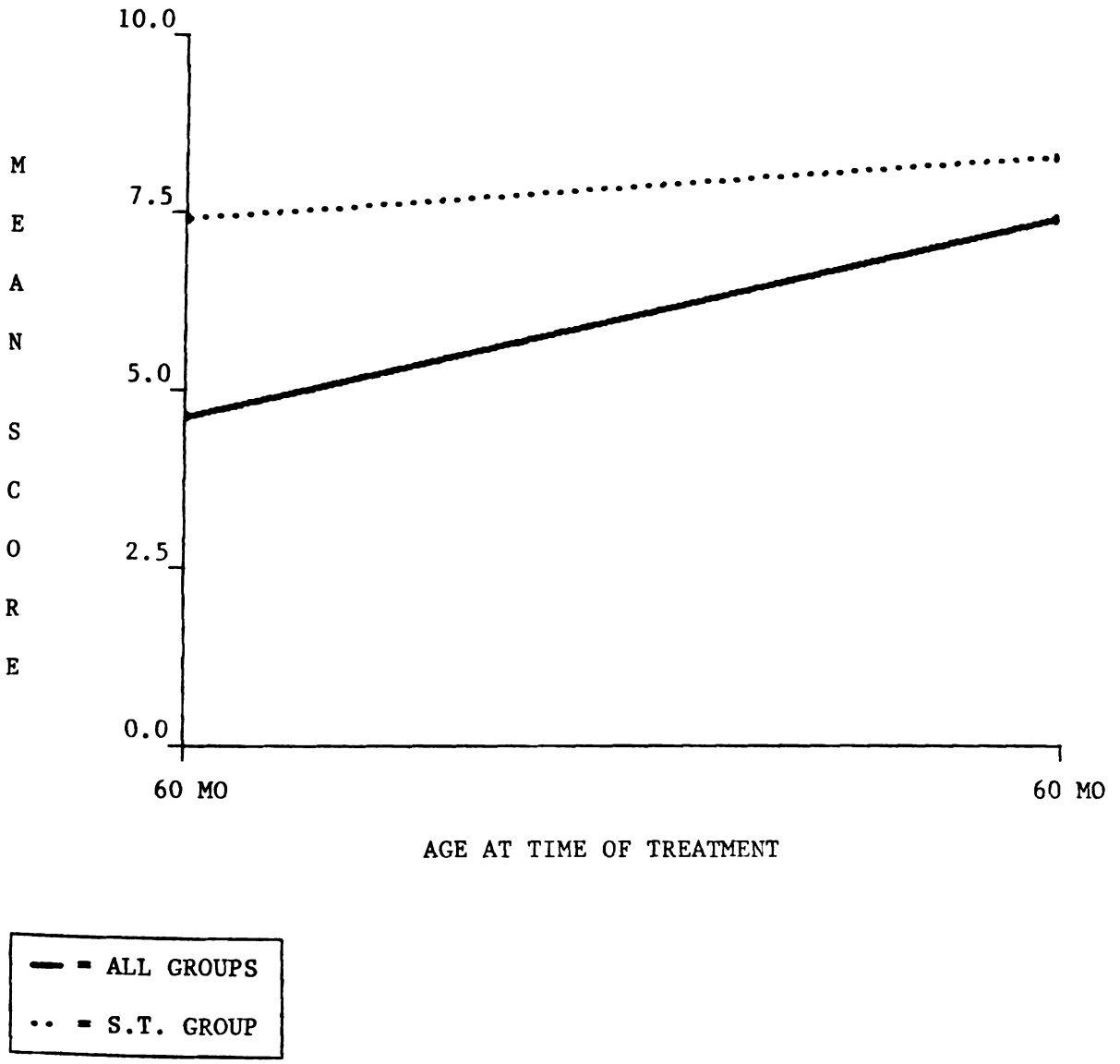
[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the measures of visual memory

[3]Interaction: Significance of the interaction between treatment and age at time of treatment groups on the measures of visual memory

[4]Covariate: Significance of the relationship between the covariate (current age) and the measures of visual memory

FIGURE 12

TREATMENT BY AGE AT TIME OF TREATMENT INTERACTION ON BENTON VISUAL RETENTION TEST: NUMBER CORRECT



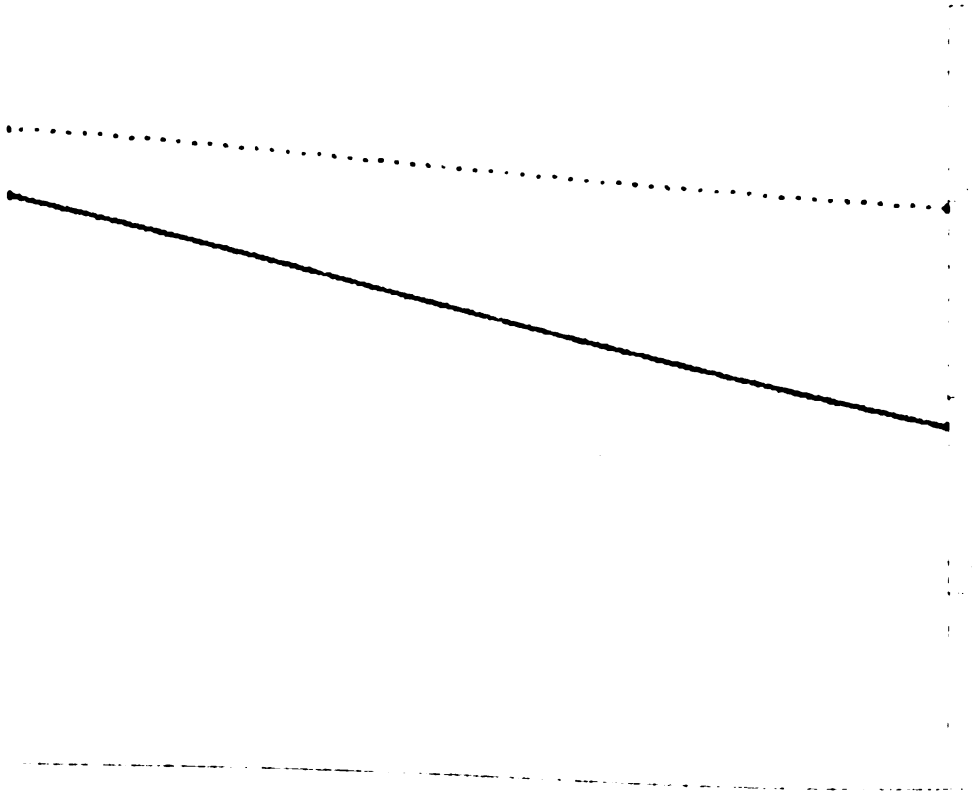
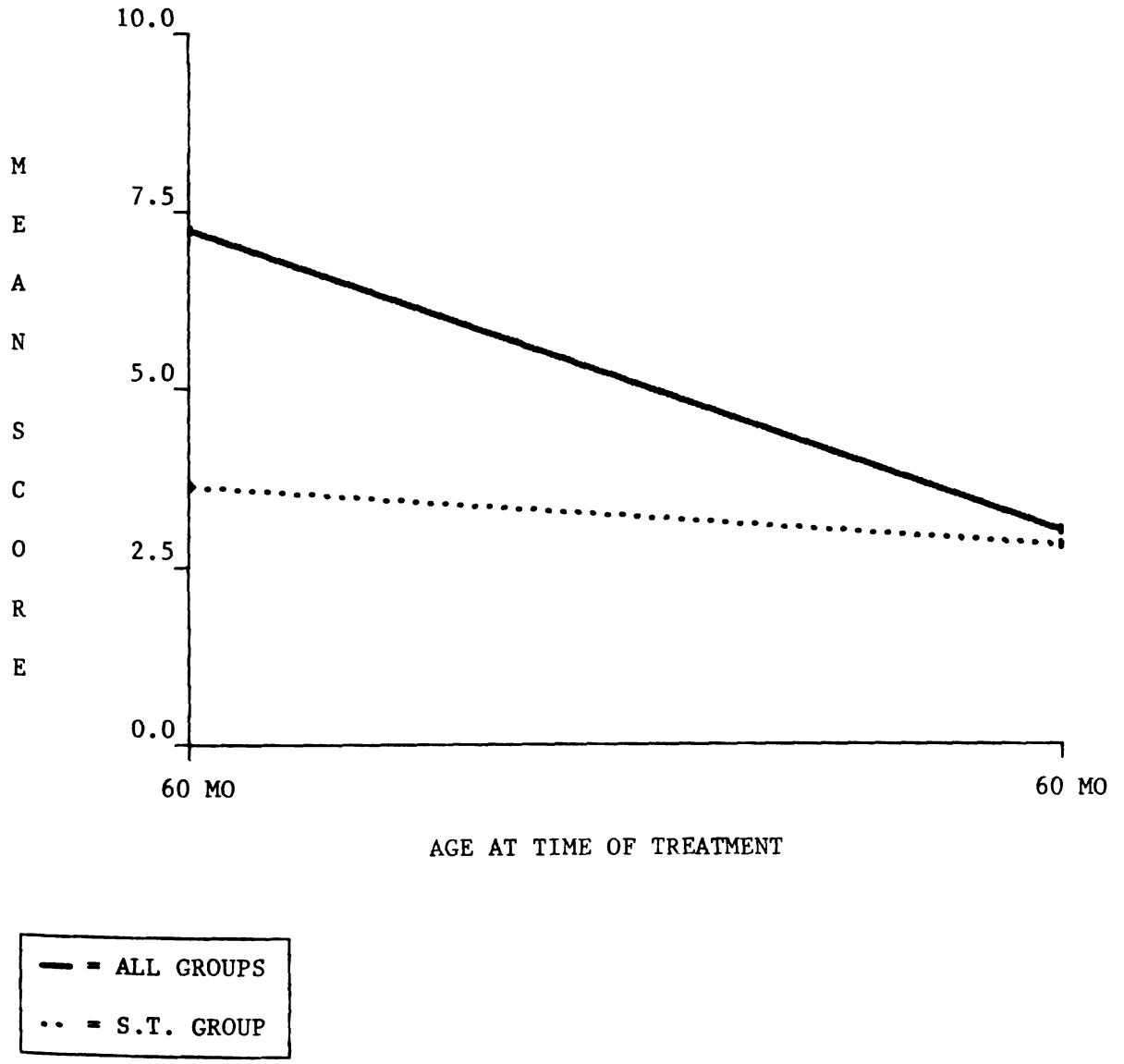
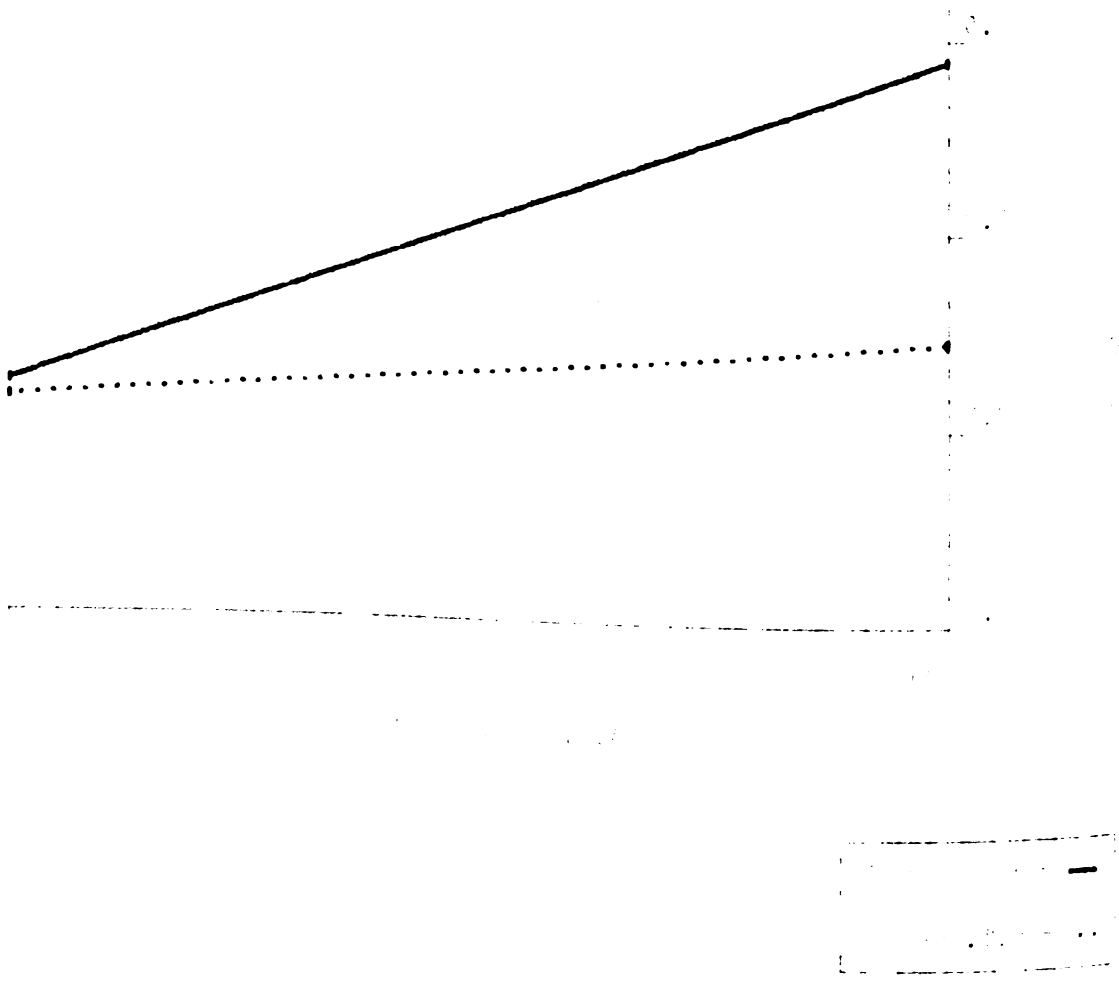


FIGURE 13

TREATMENT BY AGE AT TIME OF TREATMENT INTERACTION ON BENTON VISUAL RETENTION TEST: NUMBER OF ERRORS





possible score is 36. The combined mean scores for the two major groups were 19.81 for the ALLs and 23.23 for the solid tumors. There was a trend toward a statistically significant effect ($p = .068$). Regardless of treatment condition (ALL or ST) subjects treated at a young age had lower mean scores than those treated after 60 months. The observed scores were age-adjusted as current age was a significant covariate. The effect due to age at time of treatment was not significant for this sample size ($p = .146$). The effects of treatment and age at time of treatment were not interactive ($p = .605$).

Deasy-Spinetta Behavioral Questionnaire: Cognitive Subscale

Parent and teacher appraisal of the subject's cognitive functioning were measured by the Cognitive Subscale from the DSBQ. The questionnaire items contained in the Cognitive Subscale are listed in Table 17. All 35 parents completed the questionnaire; two teachers of subjects from the ST group did not return the questionnaire (94.3% return rate). The Cognitive Subscale score is determined by items to which the respondent agrees that the target child is experiencing problems. Thus, a higher score denotes lower functioning.

The DSBQ data were analyzed in two ways. First, a two by two ANCOVA (treatment condition by age at time of treatment, with months since diagnosis as the covariate) was done to analyze three data sets: 1) parental appraisal of the long-term survivors; 2) teacher appraisal of the long-term survivor; and 3) teacher appraisal of the comparison child. Second, the Cognitive Subscale from the parents and teachers were independently correlated with the instruments from the neuropsychological battery with the most complete data set.

Parent Appraisal

The Cognitive Subscale scores from parents ranged from 0 to 9. The combined mean subscale score for the ALL subjects (Groups I and II) was 4.42 and 1.13 for the two ST groups; the treatment effect was highly significant ($p = .001$). Table 19 summarizes the data from parent's appraisal of the long-term survivors cognitive functioning. The difference between the mean scores of subjects treated for leukemia before and after 60 months was 4.77; this difference was only 1.11 for the solid tumor groups. The interaction between treatment condition and age is graphed in Figure 14. The effect of age at time of treatment was not significant ($p = .267$) but the treatment by age at time of treatment interaction approached significance ($p = .065$). Months since diagnosis was not a significant covariate.

A t-test was done comparing the mean scores between Groups I and II. The difference did not reach statistical significance although the trend was in the predicted direction ($p = .106$).

Teacher Appraisal

The findings from the teacher's appraisal of the long-term survivors cognitive functioning differed from that of the parents. The subscale scores ranged from 0 to 8. The higher combined mean score by treatment group occurred in those subjects who had received CNS prophylaxis (2.42 as compared to 1.31 for the systemic therapy only group). This difference failed to reach statistical significance ($p = .177$). The difference between Group I and Group II mean scores was 2.73; and .97 between Group III and Group IV. Group I had the highest (worst) score and Group III had the lowest (best) score. Age at time of treatment was significant ($p = .053$); and the treatment by age at time

Table 19

Deasy-Spinetta Behavioral Questionnaire Mean Cognitive Scores* by Treatment and Age of Treatment Groups**

Respondent/ Subject	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Parent/long-term survivor	5.60 (3.2)	3.11 (3.1)	0.83 (1.5)	2.00 (1.8)	14.765 (.001)	1.280 (.267)	3.668 (.065)	.288 (.595)
Teacher/long-term survivor	3.90 (3.2)	0.78 (1.0)	1.17 (2.4)	1.75 (3.5)	1.914 (.177)	4.050 (.053)	3.403 (.075)	3.346 (.077)
Teacher/control	2.30 (2.9)	0.0 (0.0)	0.83 (1.3)	1.00 (2.0)	.641 (.430)	4.133 (.051)	2.836 (.103)	.641 (.430)

*Higher score denotes lower cognitive function

**2 x 2 ANCOVA with months since diagnosis as the covariate

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the DSBQ Cognitive Score

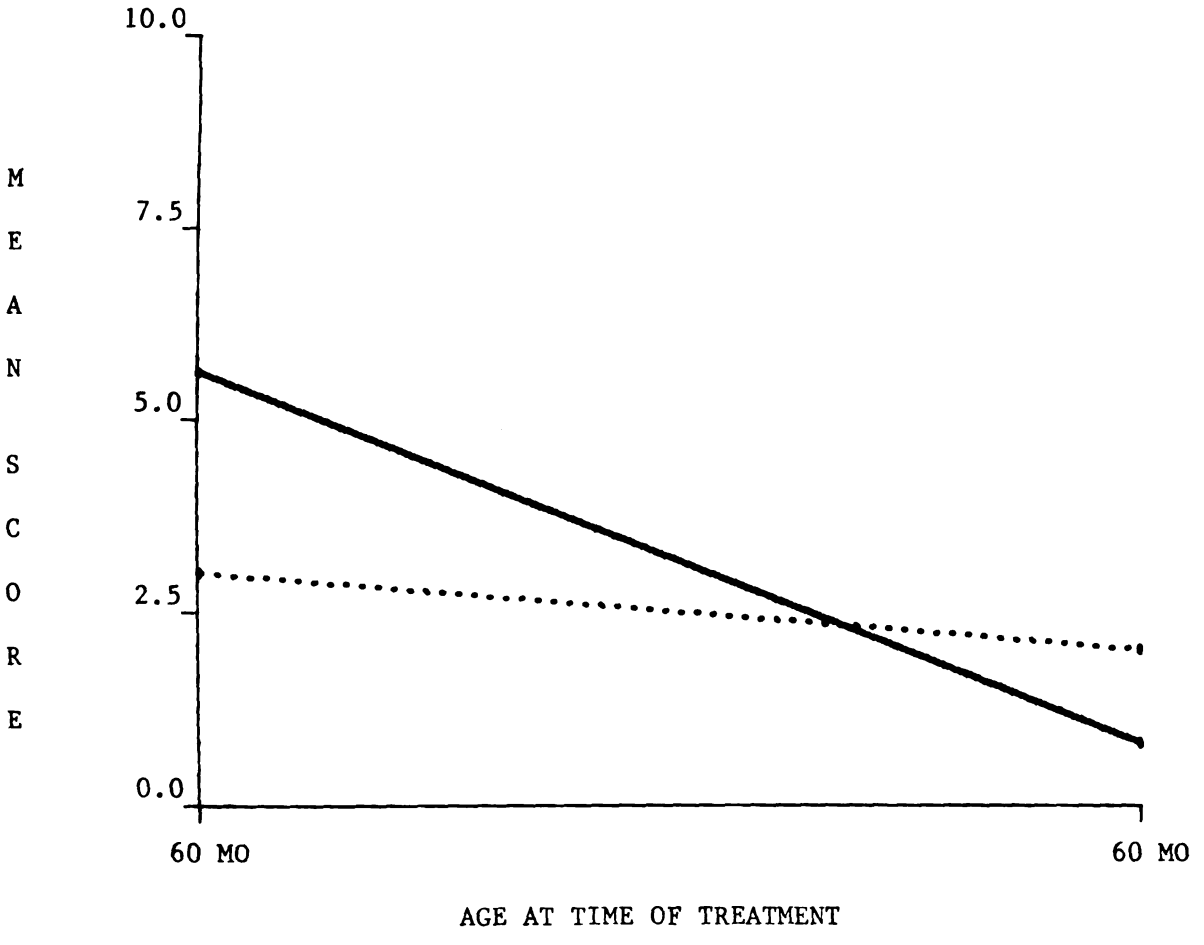
[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the DSBQ Cognitive Score

[3]Interaction: Significance of the interaction between treatment and age at time of treatment on the DSBQ Cognitive Score

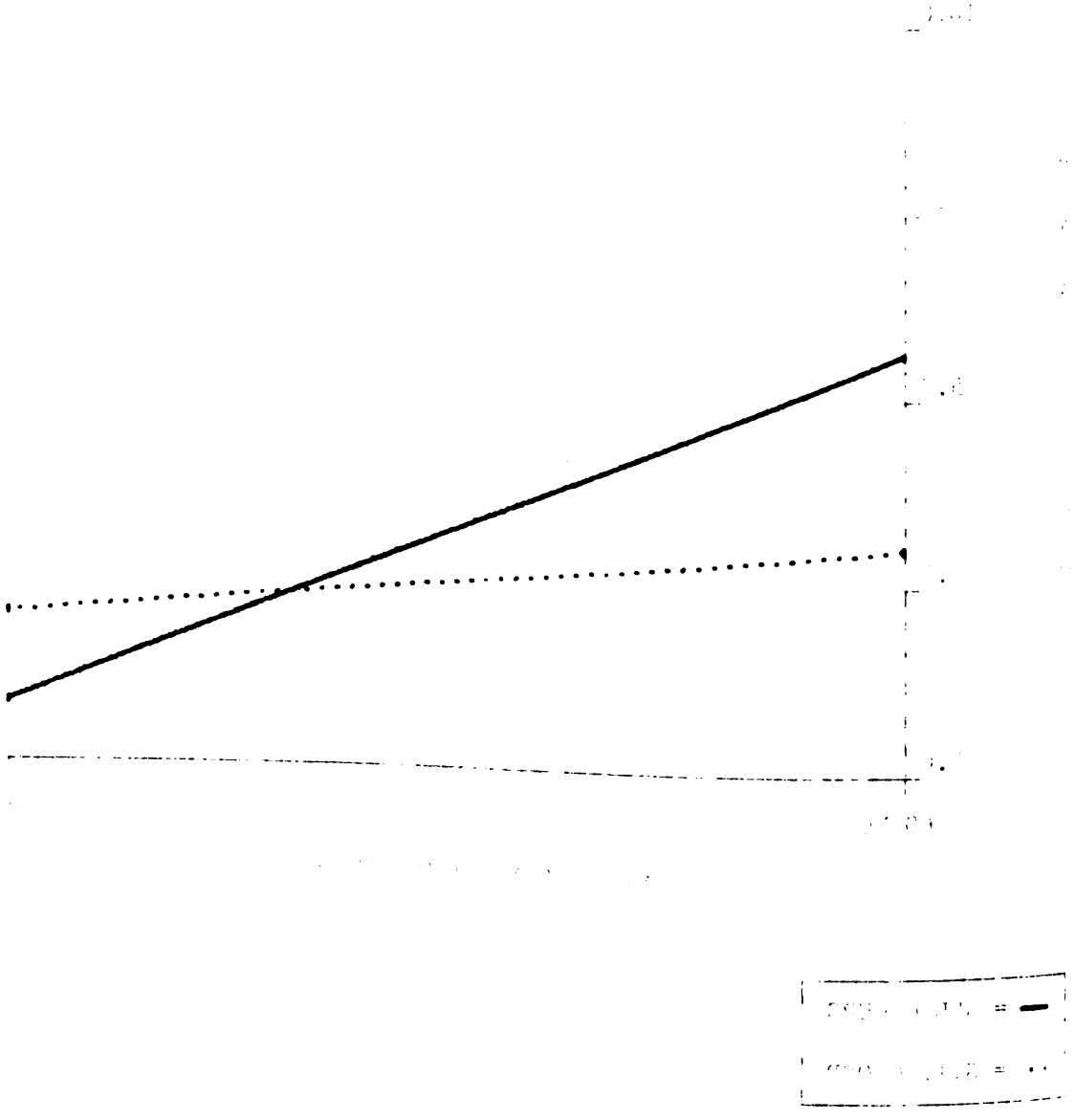
[4]Covariate: Significance of the relationship between the covariate (months since diagnosis) and the DSBQ Cognitive Score

FIGURE 14

TREATMENT BY AGE AT TIME OF TREATMENT INTERACTION ON DSBQ COGNITIVE SUBSCALE:* PARENT APPRAISAL



* HIGHER SCORE DENOTES LOWER FUNCTIONING



of treatment interaction approached significance (p = .075). It is interesting to note that months since diagnosis was an almost significant covariate (p = .077), and, therefore, tended to be related to the teacher's appraisal of the child's functioning. The t-test comparing the mean cognitive scores of Groups I and II ALL subjects was highly significant (p = .014).

Teacher Appraisal of the Control

The teacher of the cancer survivor also completed the DSBQ on a child of the same sex and age, and who represented the norm of the class. The comparison subjects were grouped by the treatment and age at time of treatment factors of their cancer-survivor counterpart. Treatment assignment (ALL or ST) did not have a significant effect on the Cognitive Subscale scores (p = .43). Thus, there was no difference between the healthy children assigned to the ALL treatment group and those assigned to the ST group. The age at time of treatment effect was significant for the teacher/control (p = .051). The magnitude of the effect was comparable to that of the teacher/long-term survivor. The significance of age at time of treatment for the group of healthy school peers raises a concern about the potential relationship between current age and the cognitive subscale scores. There was no significant interaction (p = .103) and months since diagnosis was not significantly related to the subscale scores (p = .430). In a secondary analysis on the Cognitive Subscale, current age was treated as the covariate.

DSBQ Cognitive Subscale: Secondary Analysis

The secondary analysis on the DSBQ Cognitive Subscale scores was done to adjust for the apparent influence of current age. This covariate was not significantly related to the scores from parents

($p = .294$). The age-adjustment, therefore, did not alter the earlier finding of a significant treatment effect ($p = .001$), a non-significant age at treatment effect ($p = .477$), and a trend toward a significant treatment by age at time of treatment interaction.

The new covariate, was significantly related to the teachers' cognitive scores on the cancer survivors ($p = .004$). The scores were adjusted for current age. The effects of treatment remained non-significant ($p = .192$), and age at time of treatment was no longer significant ($p = .754$). Current age was not significantly related to the teachers' cognitive scores on the healthy children ($p = .162$). Treatment effects remained non-significant ($p = .392$), and age at time of treatment was no longer significant ($p = .170$).

DSBQ Cognitive Subscale: Correlations with the Neuropsychological Battery

Parent and teacher responses on the DSBQ Cognitive Subscale were correlated with selected measures from the neuropsychological battery. The purpose was to determine the degree of association between cognitive functioning as measured by an extensive battery of standardized tests and behavioral appraisals of the child by the parent or teacher. Table 20 presents the findings from correlating the Cognitive Subscale (parent and teacher) with measures of general intelligence, academic achievement, and visuomotor integration.

There was an inverse association between parental appraisal and the selected tests which was highly significant ($p = .026$ to $< .001$). Thus, as the Cognitive Subscale score increased, the score from the cognitive test battery decreased. This is due to the fact that on the DSBQ Cognitive Subscale, a higher score denotes lower functioning while on the tests from the battery, a higher score denotes higher functioning.

Table 20

Deasy-Spinetta Behavioral Questionnaire Cognitive Subscale and Neuropsychological Measures of Cognitive Function: Pearson Product Correlations

Neuropsychological Measures of Cognitive Function	Cognitive Subscale* Parent r	p	Cognitive Subscale* Teacher r	p
Full Scale IQ	-.6257**	< .001	-.4318**	.010
Verbal IQ	-.6274**	< .001	-.3697**	.031
Performance IQ	-.6202**	< .001	-.3515**	.038
PIAT Reading Comprehension	-.4998**	.009	-.4315**	.028
WRAT Reading	-.6457**	< .001	-.6353**	< .001
WRAT Spelling	-.6382**	< .001	-.5326**	.001
WRAT Arithmetic	-.6870**	< .001	-.5336**	.001
Beery Test of Visuomotor Integration	-.3803**	.026	-.2448**	.163

*High score denotes lower cognitive functioning

**(-) denotes a negative correlation (lower score on Cognitive Subscale with higher score on neuropsychological measures

The teacher's appraisal of the cancer survivor's cognitive functioning did not correlate as strongly with the IQ scores or the Piat Reading Comprehension score, but were significant ($p = .01$ to $.03$). The teacher's rating on the Cognitive Subscale did not correlate with the Beery VMI ($p = .163$). All other correlations were significant ($p \leq .01$ to $.028$). In conclusion, there was a high degree of significant correlation between how the parent and teacher evaluated the cognitive functioning of the cancer survivor and cognitive functioning as determined by the neuropsychological battery.

Findings Related to the Research Questions on Psychosocial Late Effects

One parent of each study participant was requested to complete the Deasy-Spinetta Behavioral Questionnaire. The return rate was 100%. Thirty-three of the 35 teachers completed questionnaires on the subject and on a healthy comparison child in the same classroom (the two teachers who did not return the DSBQ were teachers of subjects from the solid tumor group treated before 60 months of age). Data from parents and teachers were analyzed with a two by two analysis of covariance (with months since diagnosis as the covariate) to detect differences due to either treatment (ALL or ST), age at time of treatment (prior to or after 60 months), and a treatment by age at treatment interaction. Correlations were done between the DSBQ scores and selected tests from the neuropsychological battery to determine the degree of association between psychosocial and cognitive late effects.

Each child was asked to complete the open-ended questions regarding his or her previous cancer experience. Some of the questions (Appendix E) were difficult for subjects who were treated at a very young age as they stated remembering very little of the previous cancer experience.

The Deasy-Spinetta Behavioral Questionnaire

The analysis of covariance results are presented in Table 21 for the parent appraisal of the long-term survivor, teacher appraisal of the long-term survivor, and teacher appraisal of the comparison or control child. The grouping factors were treatment (ALL or ST) and age at diagnosis (less than or greater than 60 months), with months since diagnosis as the covariate.

Total DSBQ scores on the cancer subjects ranged from 24 to 36 if the parent was the respondent and from 26 to 46 if the teacher completed the questionnaire. The mean total scores from parents of the two leukemia groups were 37.16, and 42.19 from parents of the combined solid tumor groups. The teacher ratings were 32.89 and 33.19, respectively. The type of treatment (ALL or ST) did not significantly affect how the child treated for cancer was functioning as viewed by the parent ($p = .120$) or by the teacher ($p = .792$). Age at time of treatment also did not have a significant effect on the Total scores ($p = .644$ for parent; $p = .486$ for teacher). There was no significant interaction effect ($p = .705$), and the covariate was not related to the scores of either parents or teachers.

The same analysis was done on the teacher's appraisal of the control child to identify any biasing factors. Neither of the grouping factors (treatment and age by treatment) nor the interaction of these factors were significant ($p = .5$ to $.84$). Months since diagnosis was not a significant covariate ($p = .475$).

Total Score: Secondary Analysis

Current age was treated as the covariate in a secondary analysis on the DSBQ Cognitive Subscale. This Subscale was taken from questionnaire

Table 21

Deasy-Spinetta Behavioral Questionnaire Mean Total Scores by Treatment and Age of Treatment Groups*

Respondent/ Subject	ALL $\bar{X}$ (SD) (< 60 mo.)	ALL $\bar{X}$ (SD) (> 60 mo.)	ST $\bar{X}$ (SD) (< 60 mo.)	ST $\bar{X}$ (SD) (> 60 mo.)	Tx[1] F (p)	Age at Tx[2] F (p)	Interaction[3] F (p)	Covariate[4] F (p)
Parent/long-term survivor	35.20 (22.0)	39.33 (10.1)	42.42 (14.0)	41.50 (5.8)	2.562 (.120)	.218 (.644)	.536 (.470)	.656 (.424)
Teacher/long-term survivor	31.20 (17.2)	34.78 (16.6)	31.50 (19.4)	38.25 (15.7)	.071 (.792)	.498 (.486)	.042 (.839)	.134 (.717)
Teacher/control	35.40 (19.4)	37.78 (17.0)	31.25 (19.7)	40.00 (11.1)	.043 (.836)	.463 (.501)	.170 (.683)	.524 (.475)

*2 x 2 ANCOVA with months since diagnosis as the covariate

[1]Treatment: Significance of the effect of treatment groups (ALL vs. ST) on the DSBQ Total Score

[2]Age at Tx: Significance of the effect of age at time of treatment groups (< 60 or > 60 mo.) on the DSBQ Total Score

[3]Interaction: Significance of the interaction between treatment and age at time of treatment on the DSBQ Total Score

[4]Covariate: Significance of the relationship between the covariate (months since diagnosis) and the DSBQ Total Score

items which are part of the Total Score. Therefore, a second ANCOVA was done to determine if current age was significantly related to the Total Score on the DSBQ.

The secondary analysis did not alter the findings from the teacher and parent appraisals of the child treated for cancer. Here the covariate was not significant ($p = .8$ for parent; $p = .3$ for teacher). However, on the teacher appraisal of the control child, current age approached significance as a covariate ($p = .09$) and the effect of age at time of treatment was now significant ($p = .044$).

Long-term Cancer Survivor: Parent versus Teacher Appraisal

Comparisons were made between the parent's and teacher's appraisal of the cancer survivor and between the teacher's appraisal of the cancer survivor and of the comparison child. The two group comparisons were done with the student's t-test on the Cognitive Subscale scores as well as the Total score.

Parent Total scores on the DSBQ tended to be higher, reflecting better functioning, than those from teacher (Table 22). The difference in the mean scores of parents and teachers was significant for the total sample (Parent $\bar{X} = 39.46$; Teacher $\bar{X} = 33.03$, $p = .044$). The larger difference occurred in the solid tumor group (Parent $\bar{X} = 42.19$; Teacher $\bar{X} = 33.19$, $p = .077$). The difference between how parents and teachers rated the child treated for ALL on the Total score was non-significant ($p = .306$).

Children treated for leukemia and who received CNS prophylaxis had a mean Cognitive Subscale score of 4.42 from parents and 2.42 from teacher. Thus, parents felt the ALL subjects had more cognitive problems than did the teachers ($p = .013$). The differences between

Table 22

Deasy-Spinetta Behavioral Questionnaire Mean Scores of the Parent and Teacher Appraisal of the Long-term Survivor

DSBQ Scores by Treatment Group	Parent/Long-term Survivor $\bar{X}$	SD	Teacher/Long-term Survivor $\bar{X}$	SD	t*	p
DSBQ Total Score[1]						
Total sample (N = 33)	39.46	10.91	33.03	17.31	2.10	.044
ALL group (N = 19)	37.16	9.32	32.89	16.56	1.05	.306
ST group (N = 14)	42.19	12.28	33.19	18.71	1.90	.077
DSBQ Cogitive Subscale[2]						
Total sample (N = 33)	2.91	3.13	1.91	2.77	1.91	.065
ALL group (N = 19)	4.42	3.34	2.42	2.85	2.77	.013
ST group (N = 14)	1.13	1.59	1.31	2.63	-0.28	.782

*t-test

[1]DSBQ Total Score: Higher score denotes more age-appropriate psychosocial functioning

[2]DSBQ Cognitive Subscale: Higher score denotes more problems in cognitive functioning

parent and teacher appraisal of the subjects treated for a solid tumor was non-significant (p = .782).

Teacher Appraisal: Long-term Cancer Survivor versus Control

The second comparison was between the teacher's appraisal of the child treated for cancer and the control child, and is summarized in Table 23. The mean total score for the cancer sample (N = 33) was 33.03 (SD = 17.31) and 35.11 (SD = 17.72) for the healthy sample (p = .030). As noted in Table 26, there were no differences between subjects treated for a solid tumor and their comparison group (p = .857). The differences in psychosocial functioning were accounted for by the discrepancy between teacher appraisal of cancer survivors treated for leukemia and their control group of healthy classmates (p = .006).

Comparing the cognitive functioning of the cancer survivors with that of the control group demonstrated a similar pattern (Table 23). The mean Cognitive Subscale score for the total cancer sample was 2.91 (SD = 3.13) and 1.91 (SD = 2.77) for the total control group. The scores reflect lower functioning in the cancer group and approached significance (p = .065). The difference between the cancer and non-cancer samples existed in the group of subjects treated for leukemia, and who, therefore, received CNS prophylaxis. The leukemia group had a significantly higher score than that of the controls (p = .043), while the solid tumor did not differ from their comparison group (p = .410).

DSBQ Total Score: Correlations with the Neuropsychological Battery

The parent and teacher DSBQ Total scores on the long-term cancer survivors were independently correlated with selected dependent measures of cognitive functioning (general intelligence, academic achievement,

Table 23

Deasy-Spinetta Behavioral Questionnaire Mean Scores of Long-term Survivors and Controls by Treatment Group

DSBQ Scores by Treatment Group	Teacher/Long-term Survivor $\bar{X}$	SD	Teacher/Control $\bar{X}$	SD	t*	p
DSBQ Total Score[1]						
Total sample (N = 33)	33.03	17.31	35.11	17.72	-2.26	.030
ALL group (N = 19)	32.89	16.56	36.53	17.82	-3.09	.006
ST group (N = 14)	33.19	18.71	33.43	18.03	-0.18	.857
DSBQ Cogitive Subscale[2]						
Total sample (N = 33)	1.92	2.77	1.06	2.00	2.24	.032
ALL group (N = 19)	2.42	2.85	1.21	2.39	2.18	.043
ST group (N = 14)	1.31	2.63	0.88	1.46	0.85	.410

*t-test

[1]DSBQ Total Score: Higher score denotes more age-appropriate psychosocial functioning

[2]DSBQ Cognitive Subscale: Higher score denotes more problems in cognitive functioning

and visuospatial skills). The purpose was to answer the research question: Is there an association between the occurrence of cognitive and psychosocial late effects? Results from the Pearson Product Correlations are found in Table 24.

With two exceptions, there was a significant positive correlation between the parent DSBQ Total score and the cognitive scores ($p < .001$ to $p = .049$). The two exceptions were WRAT Spelling ($p = .102$) and WRAT Arithmetic ($p = .078$). When the teacher DSBQ Total scores were correlated with the measures of cognitive functioning, the results were much different. Piat Reading Comprehension was the only measure that was significantly associated with the teacher appraisal of psychosocial functioning ($p = .042$). The remainder of the correlations were either very weak or negative ($p = .626$ to $.993$).

In conclusion, the degree of correlation between cognitive and psychosocial late effects depended on the source of the appraisal on the DSBQ. There was a fairly consistent positive association between the parent DSBQ Total score and the neuropsychological battery. However, when the teacher was the respondent, the correlations were almost always non-significant, and, in three cases, negative.

Other Findings Related to Cognitive Late Effects

The descriptive analysis of the academic characteristics of the study sample revealed that 79 percent of subjects who were treated for leukemia had missed school during therapy, as compared to only 25 percent of those treated for a solid tumor. Thus, time away from school could have a confounding effect on cognitive functioning, particularly in relation to academic achievement. A second two by two analysis of

Table 24

Deasy-Spinetta Behavioral Questionnaire Total Score and Neuropsychological Measures of Cognitive Function: Pearson Product Correlations

Neuropsychological Measures of Cognitive Function	Total Score* Parent r	p	Total Score* Teacher r	p
Full Scale IQ	.5699	< .001	.0016	.993
Verbal IQ	.5109	.002	.0093	.958
Performance IQ	.5578	< .001	-.0315**	.857
PIAT Reading Comprehension	.4967	.010	.4009	.042
WRAT Reading	.4642	.015	.0868	.626
WRAT Spelling	.2849	.102	.0137	.946
WRAT Arithmetic	.3058	.078	-.0212**	.905
Beery Test of Visuomotor Integration	.3396	.049	-.0606**	.733

*High total score denotes more age-appropriate psychosocial functioning

**Negative correlation

variance--with treatment (ALL or ST) and absences during treatment (yes or no) as the grouping factors--was done on the academic achievement scores. Months since diagnosis was not entered into the equation as this covariate was not significant in the first analysis.

The following discussion of the findings on the secondary analysis of academic achievement refers to four groups:

Group I (N = 15): ALL treatment and missed school during therapy;

Group II (N = 4): ALL treatment and did not miss school during therapy;

Group III (N = 4): ST treatment and missed school during therapy;

Group IV (N = 12): ST treatment and did not miss school during therapy.

The summary statistics are presented in Table 25.

Groups I and II had consistently lower mean academic achievement scores than the Group III and IV subjects. The effect due to treatment was the most dramatic on the WRAT Arithmetic scores. The combined mean score of the 19 leukemic subjects was 84.72 and 99.69 for the 16 solid tumor participants ($p = .002$). The treatment effect was also significant for the WRAT Reading ($p = .003$) and Spelling ($p = .004$); there was a trend toward significance for Piat Reading Comprehension ($p = .071$).

The effect of school absences on the mean Group scores was not significant ($p = .393$ to $.827$). The treatment by absence interaction was also not significant ($p = .879$ to $.921$). In conclusion, whether or not the subject missed school while on cancer therapy did not have a statistically significant effect on subsequent academic achievement scores.

Table 25

Late Effects of Treatment and School Absences on Academic Achievement*

Academic Achievement Scores	ALL Grp I $\bar{X}$	ALL Grp II $\bar{X}$	ST Grp III $\bar{X}$	ST Grp IV $\bar{X}$	Treatment[1] F (p)	Absent[2] F (p)	Interaction[3] F (p)
Piat Reading Comprehension	96.27	90.67	106.67	102.22	3.59 (.071)	.759 (.393)	.010 (.921)
WRAT Reading	95.36	96.25	116.50	112.00	10.624 (.003)	.096 (.759)	.226 (.638)
WRAT Spelling	90.71	93.50	107.25	108.50	9.902 (.004)	.164 (.688)	.023 (.879)
WRAT Arithmetic	84.64	85.00	98.50	100.08	11.093 (.002)	.049 (.827)	.020 (.889)

*2 x 2 analysis by variance

[1]Treatment: Significance of the effect of treatment on the academic achievement scores

[2]Absent: Significance of the effect of absences from school on the academic achievement scores

[3]Interaction: Significance of the effect of interaction between treatment and school absence on the academic achievement scores

Impact of the Previous Cancer Experience: Subject's Responses

Each study participant was asked to respond to questions regarding the impact the previous cancer experience has had on school, friends, and family, and whether or not he or she felt different from others of the same age. Subjects who were diagnosed and treated before the age of five years often found the questions difficult to answer. "I don't know--can't remember" was a frequent response to many of the questions.

Two subjects treated at a very young age for Wilm's Tumor, reported "not remembering" anything. Little data could be gathered even after probing by the investigator, and these participants were excluded from the qualitative analysis. One subject from the leukemia group withdrew from the study and the other did not complete the questionnaire because of time constraints. Qualitative data are available on 31 subjects. Table 26 summarizes the responses to each question by treatment and age at time of treatment groups.

In response to "Do you think that cancer and/or its treatment has had any long-term effects on your schoolwork?" eight (47.1%) of the 17 leukemia survivors said yes as compared to 3 (21.4%) of the 14 solid tumor subjects. Comments from those who felt their schoolwork had been affected included: "I just don't understand, the work is very hard, I always get D's", "I can never catch up", or "some things that came easily before, became more difficult, like math". Almost all those who experienced difficulty with schoolwork also felt that the illness or treatment had adversely influenced their ability to learn.

The majority, 97 percent, reported getting along well with school mates and with family. One child treated for leukemia at the age of 27 months said, "No, they (school mates) all make fun of me." The same

child and her single parent were seeking counselling for emotional problems within the family."

Thirteen, or 42 percent, of the subjects said they did wonder about certain patients they had known while on therapy. This was fairly evenly divided between the two treatment groups. Those who responded "no" frequently commented that they did not know any other patients.

Seventy-one percent of the subjects who had undergone leukemia therapy and 43 percent of those treated from a solid tumor felt that their parents and other family members continued to have concerns about the subject's previous cancer experience. One girl, a long-term leukemia survivor remarked, "They worry that if I take a certain medicine or get a cold then I might get a relapse"; and one boy said "Whenever I get sick, I know they are always thinking it is happening again."

Finally, in response to "how do you feel differently from others your age due to your experience with cancer and its treatment?", almost half of the sample (N = 15, 48.4%) stated emphatically that they felt no different. One boy said "I don't feel different because I try not to think about it."

Fifty-two percent of the respondents did feel different from their peers. The feelings ranged from having missed out on a part of childhood and having to grow-up too fast to feeling unlucky or "weird" (Table 26). Five participants felt the cancer experience had changed their lives in a maturing way. These subjects stressed how they had learned to appreciate life, have a positive attitude, and not fear death. One girl wrote "I feel that I am definitely more mature...I was faced with a situation that not many people may age experience. It taught me to not fear death, but

Table 26

Subject Responses to the Open-ended Questions

Question	ALL				ST				Total	
	(< 60 mo.)		(> 60 mo.)		(< 60 mo.)		(> 60 mo.)			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Do you think cancer and/or its treatment has had any long-term effects on:										
1. Your schoolwork?										
yes	5	(56)	3	(37)	2	(20)	1	(25)	11	(35)
no	4	(44)	5	(63)	8	(80)	3	(75)	20	(65)
2. Your ability to learn?										
yes	4	(44)	3	(37)	1	(10)	--		8	(26)
no	5	(56)	5	(63)	9	(90)	4	(100)	23	(74)
How do you get along with:										
3. Friends and schoolmates										
well	8	(89)	8	(100)	10	(100)	4	(100)	30	(97)
not well	1	(11)	--		--		--		1	(03)
4. Your family										
well	8	(89)	8	(100)	10	(100)	4	(100)	30	(97)
not well	1	(11)	--		--		--		1	(03)

(continued)

Table 26

Subject Responses to the Open-ended Questions (cont'd)

Question	ALL (< 60 mo.) N (%)	ALL (> 60 mo.) N (%)	ST (< 60 mo.) N (%)	ST (> 60 mo.) N (%)	Total N (%)
5. Have you wondered about any of the other cancer patients you knew?					
yes	4 (44)	3 (38)	6 (60)	---	13 (42)
no	5 (66)	5 (62)	4 (40)	4 (100)	18 (58)
6. Do you think your parents or other family members have any worries about your past cancer experience?					
yes	6 (67)	6 (75)	4 (40)	2 (50)	18 (42)
no	3 (33)	2 (25)	6 (60)	2 (50)	13 (58)
7. How do you feel different from others your age due to cancer?					
don't feel different	5 (56)	3 (38)	6 (60)	1 (25)	15 (48)
a lot more mature	1 (11)	2 (25)	1 (10)	1 (25)	5 (16)
unlucky		1 (12)	1 (10)	1 (25)	3 (10)
missed out on childhood/sick more	3 (33)	2 (25)	1 (10)	1 (25)	7 (23)
wierd			1 (10)		1 (3)

to live my life one day at a time."

Summary of the Major Findings

Thirty-five subjects who were at least five years from the diagnosis of childhood cancer participated in this study of cognitive and psychosocial late effects. The subjects were divided into four groups to determine the effects of treatment (systemic therapy with and without CNS prophylaxis) and age at time of treatment (before or after 60 months) on cognitive functioning. Age at time of treatment was the major comparison variable in relation to psychosocial functioning.

Table 27 summarizes the findings relevant to the proposed hypotheses regarding cognitive late effects. The hypothesis that central nervous system prophylaxis has a significant effect on subsequent cognitive functioning was supported consistently by the neuropsychological measures, with the one exception of the Woodcock-Johnson Concept Formation Test. Results from the Parent Cognitive Subscale score from the DSBQ also supported the treatment hypothesis, while the same score from the teacher did not.

It was also hypothesized that age at time of treatment has a significant effect on subsequent cognitive functioning. This hypothesis was at least partially supported by the measures of general intelligence (Full Scale and Performance IQ), visuospatial skills (except the Rey-Osterrieth Copy), language skills, and visual memory. Age at time of treatment did not have a statistically significant effect on academic achievement scores, or on measures of concept development.

The data from the Bushke Selective Reminding Procedure was analyzed with a one way-three group repeated measures ANOVA. There was a significant group effect with subjects receiving CNS therapy before 60

months functioning at a lower level than the other two groups (ALL and ST treated after 60 months). These results also provide evidence for the influence of treatment and the age at which treatment is administered on subsequent cognitive functioning.

There was minimal support for interactive effect between treatment and age at time of treatment on subsequent cognitive functioning. Visual memory, as measured by the Benton Visual Retention Test (BVRT), was the only area which supported the hypothesized interaction.

The analysis of the DSBQ Total Scores for cancer subjects suggested that the type of malignancy--ALL or ST--did not have a significant effect on psychosocial functioning. The hypothesis that age at time of treatment would have a significant effect was not supported.

Comparisons between the cancer survivors and the controls on the DSBQ Total and Cognitive Subscale scores demonstrated that those treated previously for leukemia were functioning below their healthy peers on both measures. This was not the case with subjects who had survived a solid tumor.

The hypothesis of a significant correlation between the occurrence of cognitive and psychosocial late effects was partially supported. There was a strong positive association between the neuropsychological measures and the DSBQ Total scores from the parents. Scores from the teachers had either a weak positive or, sometimes negative, correlation with the neuropsychological measures.

Table 27

Study Hypotheses: Summary of the Research Findings on Cognitive Late Effects

Dependent Measures of Cognitive Function	Treatment Effect	Age at Treatment Effect	Treatment by Age at Treatment Interaction
General Intelligence			
Full Scale IQ	+	+	*
Verbal IQ	+	-	-
Performance IQ	+	+	-
Academic Achievement			
Piat Reading			
Comprehension	*	-	-
WRAT Reading	+	*	-
WRAT Spelling	+	-	-
WRAT Arithmetic	+	-	-
Visuospatial Skills			
Beery VMI	+	+	-
Block Design (WISC-R)	+	+	-
Rey-Osterrieth Copy	*	-	*
Language Skills			
FAS	+	-	-
CELF[1]	+	+	-

(continued)

Table 27

Study Hypotheses: Summary of the Research Findings on Cognitive Late Effects (cont'd)

Dependent Measures of Cognitive Function	Treatment Effect	Age at Treatment Effect	Treatment by Age at Treatment Interaction
Conceptual Skills			
Woodcock-Johnson	-	-	-
Similarity Subscale (WISC-R)	+	-	+
Auditory Memory[2]			
Digit Span (WISC-R)	+	-	-
Visual Memory			
BVRT correct	+	+	+
BVRT errors	+	+	+
Rey-Osterrieth Recall	*	*	-
DSBQ Cognitive Subscale			
Parent	+	-	*
Teacher	-	+	*

+ = hypothesis supported

* = hypothesis not supported at $p \geq .05$, but trend toward significance

- = hypothesis not supported

[1]CELF: hypothesis supported for Processing and Total but not for Production

[2]Auditory Memory: The Bushke Selective Reminding Procedure demonstrated a significant group effect.

CHAPTER FIVE: DISCUSSION OF THE FINDINGS

The purpose of this study was twofold: to determine if central nervous system prophylactic therapy for acute lymphoblastic leukemia has late effects on cognitive functioning; and to determine if childhood cancer and its treatment has late effects on psychosocial functioning. The vulnerable period hypothesis and theories on the mechanisms of delayed injury to the CNS following prophylactic leukemia therapy provided the basis for formulating the research questions and hypotheses related to cognitive late effects. The questions and hypotheses pertaining to psychosocial late effects were derived from a framework which was based on the developmental theory of Erikson. The sample was divided into four groups to investigate the significance of the effects of treatment and age at time of treatment on cognitive and psychosocial functioning.

Cognitive Late Effects

The findings from the neuropsychological measures support the hypothesis that CNS prophylactic treatment--IT MTX and 2400 rads of cranial radiation--has delayed adverse effects on cognitive functioning. These effects were manifested as lower levels of general intelligence, academic achievement, visuospatial and language skills, and deficits in auditory and visual memory processes.

Age at time of treatment served as the criterion for the stage of brain development at the time the therapy was administered. It was hypothesized that age at time of treatment has a significant effect on cognitive functioning. Furthermore, it was hypothesized that an interactive effect between treatment and age at treatment would occur;

that is, children treated with CNS prophylaxis prior to 60 months of age were in a vulnerable period of brain development. The delayed effects on cognitive functioning in this group should be greater than those who received the same therapy after 60 months of age. This age effect was not predicted in the comparison group of solid tumor survivors.

Age at time of treatment had a significant effect on Full Scale and Performance IQ, visuospatial skills, visual memory, one measure of language skills, and on the parent Cognitive Subscale score from the DSBQ. Subjects treated prior to 60 months did have lower scores on the neuropsychological battery than those treated after this age. The younger age at treatment group had the higher parent Cognitive Subscale score denoting a lower level of function. However, the hypothesized treatment by age at time of treatment interaction was not supported except in the measures of visual memory. Thus, the magnitude of the effect due to age at time of CNS prophylaxis was not dramatic enough to reach statistical significance.

There are several factors which may explain why there was such a significant treatment effect, less evidence for the significance of the effect of age at treatment, and even less support for the proposed treatment by age at time of treatment interaction. These factors are discussed below.

Three mechanisms of delayed injury from CNS prophylactic therapy were proposed: 1) an interference with glial cell mitosis by radiation; 2) an interference with myelinogenesis by methotrexate; and 3) a decrease in cerebral perfusion as a result of radiation-induced damage to the intimal layer of the cerebral microvasculature. An interference with glial cell proliferation could occur up to the age of 24 to 30

months. The bulk of myelination occurs during early childhood (birth to 60 months), however, major cortical pathways are not completely myelinated until later, through 120 months of age (Yakovleo & Lecours, 1967). The degree of disruption in myelin synthesis could be greater in subjects treated during the time of the brain growth spurt, but the pathways myelinated in later childhood could be more important for the types of cognitive processes that were measured in this study. Radiation induced changes in the cerebral microvasculature are age-independent. Thus the effects of this type of delayed injury on cognitive functioning would be predicted to occur in both groups of irradiated subjects.

Other studies on cognitive late effects have investigated the effects of: 1) IT methotrexate without cranial radiation (Obetz et al., 1979; Meadows et al., 1981; Pavlovsky et al., 1983); 2) a combination of IT MTX and cranial radiation (Obetz et al., 1979; Eiser, 1980; Meadows et al., 1981; Moss et al., 1981; Pavlovsky et al., 1983; Jannoun, 1983; Copeland et al., 1985); and 3) cranial radiation without IT MTX (Eiser & Lansdown, 1977; Moehle et al., 1983).

Neither of the two studies which isolated the effects of IT MTX on cognitive functioning found delayed sequelae. The findings from investigations on cranial radiation without MTX suggested trends toward lower levels of functioning. All except one study (Obetz et al., 1979) involving combination CNS prophylaxis documented cognitive deficits which were more pronounced in younger subjects. The effect due to age at time of treatment was always analyzed by comparing the scores of only the ALL subjects.

In the present study, the significance of age at time of treatment

was determined within two treatment groups, ALL and ST. Examination of the cell means for each treatment and age at time of treatment group demonstrated that the effects of age at treatment was not consistent for all measures of cognitive function. This has implications for determining the potential adverse effects of CNS prophylaxis on specific cognitive functions at different developmental levels.

The dramatic treatment effect found in this study occurred regardless of age at time of treatment. This may be due in part to the delayed injury to the cerebral microvasculature. Other studies suggest that radiation in combination with methotrexate is more damaging than radiation alone. Thus, a disruption in myelinogensis during later childhood could also contribute to this research finding. Price and Jamieson (1975) reported vascular changes in their postmortem analysis of 13 subjects with leukoencephalopathy. In all cases, the CNS therapy included cranial radiation with at least 2000 rads. These investigators also found degenerative changes in the oligodendrocytes and a disruption in myelin elements. An age at time of treatment effect was not found, however, the sample was small.

Price and Jamieson (1975) proposed that cranial radiation alters the permeability of the blood-brain barrier, allowing systemic methotrexate to cross. The maintenance leukemia protocol for subjects in this study included oral methotrexate. This study did not determine whether or not systemic MTX was present in the CSF of the leukemia subject. It was impossible to determine statistically the effects of this variable because all 19 subjects treated with CNS prophylaxis had taken oral MTX. Nevertheless, it is important to recognize that following alterations in the blood-brain barrier, systemic MTX may

contribute to delayed cognitive sequelae.

Sample size is another factor contributing to the failure to detect the hypothesized age at time of treatment effect in this study. The power analysis was computed to detect a large difference (no less than one standard deviation) in functioning among the four groups 80 percent of the time. This degree of power required a sample of 40 subjects divided evenly among the four groups. The group of solid tumor subjects treated after the age of 60 months was small (N = 4). It was difficult to find subjects who met the study criteria and who fell into this group. These four subjects probably do not represent the total distribution of solid tumor subjects treated after the age of 60 months, which would influence the findings.

Finally, examination of the observed mean scores from the four groups demonstrates that both of the ST groups were functioning at or above the norm for healthy children and that the four who were treated for a solid tumor after 60 months of age often had higher mean scores than those who received comparable treatment at an earlier age. Conversely, the group of ALL subjects treated before 60 months of age had the lowest mean scores on all the cognitive measures and these scores were below those of healthy children. Clinically, the child treated at an early age with the CNS prophylactic regimen described in this study was functioning below normal. Five of the 10 subjects in this group were in special classes for at least a part of the school day and 70 percent had repeated at least one grade. Thus, clinically, the hypothesis that age at time of CNS treatment would be significant was validated.

Time since the diagnosis of cancer was treated as a covariate in

this study. The statistical analysis tested for the significance of the relationship between the covariate and the dependent measure of cognitive functioning. The relationship was nonsignificant. This finding was not surprising as all subjects were at least five years from diagnosis. The study by Meadows et al. (1981) suggests that cognitive sequelae become apparent approximately two years following CNS therapy. The most logical conclusion is that time does have a significant relationship to the manifestations of delayed damage, but by five years the changes have already taken place.

Current age can bias the findings from instruments which do not yield age-adjusted scores. Whenever the dependent measure of cognitive function was not adjusted for current age, it was treated as the covariate. Other investigations on cognitive late effects have not addressed the potential influence of age on the observed scores, and therefore, on the findings and conclusions.

The results from the parent DSBQ Cognitive Subscale score supported the hypothesized treatment effect and the treatment by age at time of treatment interaction. The difference in mean scores due to age at treatment alone was not sufficiently dramatic to reach statistical significance, although the differences were in the predicted direction. The findings were comparable to those from the neuropsychological battery. This similarity was validated by the strong degree of correlation between the parent Cognitive Subscale and the standardized measures selected from the battery.

Inati et al. (1983) also included parent evaluation of school performance to identify children who were having learning problems following CNS therapy. The investigators did not include any additional

dependent measures of functioning. Therefore, the concurrent validity of their tool was not determined. The findings from this research suggest that if the measure has established reliability and validity, parent appraisal can be a very sensitive indicator of cognitive functioning.

The results from the analysis of covariance on the teacher responses to the Cognitive Subscale failed to support any of the study hypotheses. The degree of association between teacher scores and the neuropsychological measures was not as great as that of parents. Nevertheless, almost all of the correlations were significant.

A significant effect of age at time of treatment in the teacher-selected comparison group of healthy children was unexpected as these subjects were not treated for cancer. This prompted a second analysis in which current age was the covariate. When the covariate was adjusted for, treatment age became nonsignificant. This can be explained by the fact that the two groups of subjects treated before 60 months of age were younger at the time of evaluation than subjects treated after 60 months. In this study, age at time of treatment and current age were related. The finding also underscores the influence age can have on developmental scales. If the scores are not adjusted for age, then they should be adjusted for age statistically.

Comparisons on the Cognitive Subscale scores between parents and teachers on the cancer survivors, and between the cancer and teacher-selected healthy comparison groups revealed several discrepancies for the leukemia subjects only. Parents felt the subjects were experiencing more cognitive problems than the teachers did, but teachers felt the child treated with CNS prophylaxis was functioning below the healthy

comparison child. Teachers may have been less sensitive to the severity of the cognitive deficits in this group. A potentially confounding factor may be the selection of the comparison child. Nine of the 19 ALL subjects had been held back and five of the 10 participants treated at an early age were receiving remedial assistance. In spite of the directions for selecting the comparison child the teacher may have chosen a child who was also functioning below average. This could deflate the magnitude of difference. Secondly, if the teacher was unaware of the child's history of being held back, the comparison healthy child may have been at least one year younger. Therefore, the child treated for leukemia would have been compared with a more developmentally immature peer.

The assumption that cognitive functioning is a valid measure of cognitive late effects was supported by the consistency of the findings across the dependent measures. The significant correlations between the DSBQ Cognitive Subscale and the Cognitive Battery provides further support for this assumption.

Finally, whether or not teacher and parent appraisal of cognitive effects is valid appears to depend on the sensitivity of the behavioral instrument. The findings from the correlational analyses provide evidence that the DSBQ Cognitive Subscale is strongly associated with more expensive and previously standardized neuropsychological measures.

Several studies (Copeland, 1985; Goff et al., 1980) proposed that absences from school while the child was on cancer therapy could adversely influence subsequent academic achievement. The two treatment groups in this study were found to differ on school absences during therapy. A secondary analysis was done to determine the potential

effect this had on the dependent measures of academic achievement. The lower scores in the ALL group were found to be due to treatment and not school absence.

Findings Related to the Conceptual Model

The findings from this study partially supported the conceptual model. The biological stressor of CNS prophylactic therapy did effect cognitive functioning. It is assumed that this occurred through pathological changes in the cerebral microvasculature, alterations in myelinogenesis, and perhaps diminished glial cell proliferation. The influence of age at time of treatment was partially supported but the magnitude of the effect was not dramatic enough to support the hypothesized treatment by age at time of treatment interaction.

Psychosocial Late Effects

The Deasy-Spinetta Behavioral Questionnaire Total score was the major dependent measure of psychosocial functioning in long-term survivors of childhood cancer. Data were collected from parents and teachers. Findings from the two by two analysis of covariance, with months since diagnosis as the covariable, suggest that neither the treatment group (ALL or ST) nor the age at time of treatment had a significant effect on current functioning. There was no interaction and months since diagnosis was not significantly related to the dependent measure.

The hypothesis of a significant age at time of treatment effect was not supported. Spinetta and Deasy-Spinetta (1981) also found that age at time of treatment did not have a significant effect on functioning as measured by the DSBQ. Thus, the failure to detect an age difference may be related to the generalizability of the items in the DSBQ across

developmentally different age groups.

Koocher and O'Malley (1982) found that having the disease during infancy or early childhood was predictive of better long-term adjustment. Theoretically, this can be explained by the fact that the mastery of developmental tasks of schoolage children and adolescents are more likely to be disrupted by cancer and its therapy than would occur at a younger age. The discrepancy between the findings of this study and that of Koocher and O'Malley (1982) may be explained by two factors. Their sample included 13 subjects treated during the schoolage years. A larger sample would increase the power to detect differences due to age at time of treatment. Methodology is a second consideration. Koocher and O'Malley (1982) utilized structured indepth psychological interviews to determine the impact of childhood cancer on psychological functioning. This study used a 53 item questionnaire with a yes/no format. The items were intended to be an index of overall functioning, and probably more global in focus than the interview used by Koocher and O'Malley.

Sixty percent of subjects who were treated after the age of 60 months (both ALL and ST groups) acknowledged in response to the open-ended questions that as a result of cancer they felt different from peers. Approximately 40 percent of subjects treated at an earlier age had similar feelings. Those who felt they had missed out on part of their childhood explained this as not always getting to participate in activities with their friends, feeling "left out", or having to grow up too fast.

Months since diagnosis was not significantly related to the DSBQ Total scores. There have been no prospective investigations of

psychosocial late effects. Little is known, therefore, about the temporal characteristics of this phenomenon. All participants in this study were at least five years from the diagnosis of cancer. It may be that after five years, time does not influence the manifestations of long-term sequelae.

The comparison between the teacher's appraisal of the cancer survivor and the healthy comparison child demonstrated that there were no differences between the group of solid tumor subjects and the control group. However, the ALL survivors were functioning significantly below their healthy counterpart. Spinetta and Deasy-Spinetta (1981) did not analyze their data by diagnosis. Koocher and O'Malley (1982) reported that the highest incidence of adjustment problems occurred in survivors of Hodgkins disease and leukemia. These investigators proposed that this could be due to factors such as duration of therapy and the number of related side effects. In this study, those treated for ALL did have more months of therapy than those treated for a ST. The importance of this variable to the pathogenesis of psychosocial sequelae warrants further attention.

The study findings suggest that psychosocial functioning is a valid criterion for measuring psychosocial late effects. A more cogent concern has to do with the psychometric properties of the selected instrument. The goal is to maximize the measurement of variance that is due to the effects of the life-threatening illness on development and to minimize error variance. As the instrumentation for measuring psychosocial late effects improves, the importance of variables such as the type of malignancy or the age at time of treatment should become more apparent.

The question of the significant association between the occurrence of psychosocial and cognitive late effects was based on the assumption that the emotional, social, and cognitive aspects of development are interrelated. The parent Total score was significantly correlated with neuropsychological measures of cognitive functioning while the teacher Total score was not. This finding creates the problem of determining which respondent--parent or teacher--provides the most valid appraisal of the child's psychosocial functioning.

The purpose of the study was explained to each potential participant. Therefore, parents knew that the study was designed to determine if there were any long-term cognitive and psychosocial effects from the previous cancer experience. This may have resulted in a heightened awareness of problems or a response bias toward more psychosocial problems. In contrast, teachers often commented that they either did not know or knew very little about the child's past experience with cancer. Their responses may reflect a lack of awareness of any subtle problems the child was experiencing. There are no reports of studies which independently compared parent and teacher evaluation of psychosocial functioning with standardized measures of cognitive functioning. The findings from this investigation suggest that if parents have the more accurate view of the child, there is a positive association.

The Perspective of the Long-term Survivor

The study participants were querried about the impact of the previous cancer experience on their lives. Obtaining this data was the most challenging aspect of the study. Many of the subjects who were treated at an early age would respond with "I don't know" or "can't

remember". During the scheduled clinic visit with the oncologist, it became clear that many actually knew very little. For example, the majority did not know the name of the malignancy, why they returned for follow-up examination, or whether or not the disease would return.

Subjects who were treated at an older age were more aware and candid. They asked questions, particularly about long-term physical effects and about the risk of recurrence. They were more likely to express how they felt different from others their age. This finding is consistent with that of Moore et al. (1969) which documented problems with body image, self-concept, and peer relationships which were experienced by adolescents receiving cancer therapy.

Five subjects felt the cancer experience had a "maturing" influence. In one case this was followed by the qualifying statement, "I missed out on part of my childhood." The underlying theme that emerged when talking with the four subjects who had positive feelings about this maturing aspect was one of strong family support and open communication. They also commented about the importance of a positive attitude about themselves and felt this was critical to surviving the disease. There are no other reports on the positive outcomes of the cancer experience. This finding underscores the importance of exploring this aspect of the cancer illness experience.

Findings Related to the Conceptual Model

The conceptual model was not fully supported in this study. The stress of the life-threatening illness experience did influence the psychosocial functioning of those treated for leukemia. This was true only in comparison to the healthy controls. The analysis of covariance did not support the hypothesized effect of age at time of treatment, and

months since diagnosis was not a significant covariable.

Limitations of the Study

Subject accrual required considerable effort. Participation in the study entailed coordinating the family's travel to the university and the child's annual clinic visit. Only one family refused to participate. Nevertheless, the sample size of 35 limited the statistical power to test adequately all the research hypotheses, particularly regarding the significance of age at time of treatment.

A second limitation of the study is the instrumentation for measuring the psychosocial late effects of childhood cancer. The parent and teacher were the major sources of information. The DSBQ was developed by experts in the field of pediatric oncology. Nevertheless, it serves only as a global index of overall functioning and does not measure the long-term impact of cancer on specific areas such as self-concept, body image, or independence. Currently, Deasy-Spinetta is collecting sufficient data for factor analysis (personal communication). The explication of factor scales should help to identify the unique problems of cancer survivors.

It was difficult to glean indepth information about the impact of the cancer experience from the open-ended questions. This may be due to the fact that the questions were quite general and to the limited amount of time for conducting the interview. Comments from participants such as, "I don't feel different because I try not to think about it", raise concerns about the degree to which the questions actually measured how the subjects felt about their past experience with cancer.

Another limitation has to do with methods. Post-treatment data were collected from a convenience sampling. The comparative study

design used convenience sampling. There are no data on cognitive and psychosocial functioning prior to the initiation of cancer therapy. It is possible that the leukemia treated group started at a lower level of functioning than those treated for a solid tumor. It is also possible that the subjects differed on an intervening variable(s) which could influence the findings. There are no data on psychosocial functioning at various stages during the cancer experience. Therefore it is impossible to make any conclusive statements about the trajectory of psychosocial late effects.

Finally, the ALL and ST groups differed on the variable of months of therapy. Those treated for leukemia all had more months of chemotherapy. In essence, time on therapy defined the two treatment groups. This prevented any follow-up analysis to determine if the duration of therapy had a significant effect on subsequent functioning.

Implications for Nursing Practice

The study findings underscore the importance of ongoing evaluation of the child treated for cancer and his or her family. Early detection of problems is important for planning interventions designed to facilitate optimal functioning. Careful attention should be given to the parent's appraisal of how the child is developing. The results support the often held belief that parents are sensitive to changes in the child's behavior and are, therefore, reliable informants.

Another implication is the usefulness of the DSBQ Cognitive Subscale in screening children who are experiencing learning problems and need referral for further evaluations. The DSBQ is inexpensive to use and requires a minimal amount of time. This type of screening evaluation would be both time and cost effective.

The finding that subjects who were treated at an early age reported knowing very little about their previous cancer experience has implications for the type of information these long-term survivors need. It is important to elicit the child's perception of his or her previous illness experience. This interpretation provides the basis for reinforcing and clarifying in order to provide an accurate age-appropriate explanation of the cancer diagnosis, the purpose of follow-up evaluation, and the risk of disease recurrence. Parents require additional information on monitoring for disease recurrence, late effects, and second malignancies. For example many parents needed information on the signs and symptoms of recurrence, as well as how frequently the child should have a physical examination and a complete blood count. Parents also needed information on how to monitor for secondary sequelae such as scoliosis, a decreased height velocity, or interference with secondary sexual development.

The teachers who were working with the subjects with cognitive deficits knew very little about the nature of this problem. In some cases, once participation in the study was complete, the investigator contacted the school. The purpose was to provide information about the types of damage to the CNS that might have occurred, the results of the child's cognitive evaluation, and to explore ways of helping the child. Some parents recalled that one of the greatest obstacles they had to overcome in reintegrating their child was teachers.

Communication with the schools is an important area for nursing and others caring for the child with cancer. Contact with the teacher is vital and should occur as soon as possible, paying particular attention to educating school staff about the needs of the child with cancer and

identifying additional learning resources within the school system.

This research required the efforts of several disciplines: nursing, medicine, psychiatry, and neuropsychology. The implications for practice generalize beyond nursing. For example, current CNS prophylactic protocols have become less intensive: methotrexate and CNS radiation are not always used in combination and the radiation dose has been reduced. The one child in this study who received only 1800 rads of cranial radiation was as impaired as those subjects who were treated with 2400 rads. It is impossible to make conclusions from one case. However, two questions are raised: will 1800 rads of cranial radiation be associated with cognitive late effects?, and will age at time of treatment make a difference?

The expertise of neuropsychology can be utilized in developing intervention strategies for assisting children who are experiencing learning problems. Career counseling will be important for helping adolescents plan a future which is compatible with their abilities.

Some of the subjects and their parents continued to feel the pain they had experienced at the time of cancer diagnosis and treatment. For example, the teenager who withdrew from the study could not say "leukemia" without crying. Individuals such as this need special help in dealing with the long-term psychological sequelae of the cancer experience.

The findings from the parent data support the assumption that the physical, emotional, and cognitive aspects of development are interrelated. This underscores the importance of a comprehensive assessment. Clinicians need to be mindful of the fact that if a problem is identified, it is important to evaluate other areas of functioning

which also could be affected.

It was gratifying to learn that many subjects, according to parents and teachers, were functioning in an age-appropriate manner. These participants felt that their experience with cancer was difficult and painful. Yet, they felt they had gained something important: a belief in oneself; a different view of life; an acceptance of death; and maturity. In almost every instance, the subject attributed this to the vigilence and strong support they received from their families. Perhaps we can translate the insights these subjects have offered to those who are currently undergoing cancer therapy. As clinicians and scientists, we need to learn more about the specific factors which contribute to positive psychosocial outcomes. This can also be used to generate a more specific conceptual framework for understanding the late effects of childhood cancer on psychosocial development.

Implications for Future Research

This research may have raised more questions than it answered. The major areas for future inquiry are summarized below.

Current protocols for CNS prophylactic leukemia therapy are less intensive. A prospective study will enable questions such as the following to be answered:

1. Does current CNS prophylaxis have delayed effects on cognitive functioning?
2. Which biological stressor has the most deleterious delayed effects on cognitive functioning? and at what age? This information can then be used to infer which processes of brain development are more adversely affected.
3. What is the magnitude of the change in cognitive functioning

over time?

4. At what time following CNS prophylaxis will intervention programs be most effective in facilitating optimal academic functioning?

5. Does the duration of therapy significantly influence subsequent cognitive functioning?

In light of the limitation of small sample size that results from single site investigations, multi-site studies should be explored. This would increase the number of subjects per variable of interest and, therefore, increase the statistical power to detect real differences.

Biological measures of delayed injury to the central nervous system is another area for future study. This research did not include any direct measures of interference with myelinogenesis, glial cell proliferation, or damage to the microvasculature. Findings from previous studies (Obetz et al., 1979; Oches et al., 1980; Pavlovsky et al., 1983) are contradictory about the correlation between CT scans and measures of cognitive functioning. Technological advances such as magnetic resonance imaging (MRI) offers new approaches to this problem.

There are no studies investigating the efficacy of intervention strategies designed to facilitate cognitive functioning following CNS therapy. This is an important area for future research as many children diagnosed with leukemia will continue to receive some type of CNS prophylactic therapy.

There are many unanswered questions about the phenomenon of psychosocial late effects. Prospective studies are needed in order to answer questions such as:

1. What is the influence of duration of therapy to subsequent

functioning?

2. What is the influence of time off therapy to subsequent functioning?
3. What variables are predictive of future psychosocial adjustment? (i.e. family characteristics; age at time of treatment; disease- or therapy-related complications)
4. What are the specific late effects on psychosocial functioning? (i.e. body image, self-concept; self-esteem; interpersonal relationships; and achieving independence)

A final area for investigation is the measurement of psychosocial functioning. A review of existing instruments suggested that the DSBQ was the most valid measure of the differences in psychosocial functioning which result from cancer or its therapy. However, it serves only as a global index of functioning and forces yes/no responses. Validation of the DSBQ factor scales will be needed as well as other measures of specific developmental issues such as those listed above.

Conclusion

This investigation of the late effects of childhood cancer on cognitive and psychosocial development supports the hypothesis that CNS prophylaxis involving 2400 rads of cranial radiation in combination with IT MTX has delayed toxicity on the brain. This was manifested as deficits in cognitive functioning which are of broad spectra. Further work is needed to understand more clearly the vulnerability of the brain during specific developmental stages to specific treatment agents, and the relationship this has to functioning. Implications for prospective studies on current CNS prophylaxis protocols were addressed.

The delayed effects on psychosocial functioning were more prevalent

in the long-term survivors of ALL. The findings suggest a relationship between psychosocial and cognitive late effects, at least from the perspective of the parent. Further work is needed in defining more precisely the manifestations of psychosocial late effects, as well as, how they evolve over time.

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APPENDIX A
University of California, San Francisco

Consent to be a Research Subject

Ki Moore, a graduate nursing student, has asked me/my child/ ward to be part of a research project to study the long-term effects of cancer and its treatment on growth and development. If I/my child/ward agree to be in this study, the following will occur:

1. Complete a series of tests which will evaluate learning and motor skills. The tests will assess attention, memory, motor skills, language development, reading, writing, and arithmetic. These tests will be given by a specially trained neuropsychologist, will require 3½ to 4 hours, and will be conducted in two sessions if necessary.

2. A questionnaire asking about school attendance, school work, and behavior with others during school will be mailed to the child's teacher for the present school year, and will also be completed by the parent or guardian.

3. Respond in writing to several open-ended questions about how the previous cancer experience has affected me.

4. Information from the physical examination and from laboratory tests which are part of the routine clinic visit will also be recorded.

The advantage of being part of this project is that I/my child/ward will have an opportunity to discuss questions or concerns about the previous cancer experience. Being in this study should not cause any additional risks.

If I/my child/ward participate(s) in this project, I/my child/ward will be assigned a code number so that others will not identify the information. The information will be stored in a safe place, and be kept as confidential as possible. If it seems important for some of the information obtained to be shared with the physician, permission to share this information will first be obtained from me/my child/ward.

I have talked with Ki Moore about this project, and she has answered my questions. If I have other questions I can call her at 666-5964. I have been offered a copy of the Experimental Subject's Bill of Rights and a copy of this consent form to keep.

Being part of this project is voluntary, I can refuse to participate or may withdraw at any time. My treatment during the clinic will not be affected by my decision.

_____ date _____ signature

APPENDIX A
University of California, San Francisco

Consent to be a Research Subject
(continued)

I agree that my/my child's/ward's teacher for the present school year can be contacted, and asked to complete a school questionnaire for me/my child/ward and for one classmate. My/my child's/ward's name will not be used after the information is collected, and the information will be stored in a safe, locked cabinet.

_____ date _____ signature

_____parent/guardian

APPENDIX B
Data Collection Flow Sheet

Late Effects of Cancer and Cancer Therapy on Neurocognitive and Psychosocial Functioning

Subject ID _____

A. Demographic Data

1. Birthdate _____

2. Age: yrs. _____ months _____

3. Sex: female = 1 _____; male = 2 _____

4. Ethnicity: White = 1 _____; Black = 2 _____; Asian = 3 _____
   Hispanic = 4 _____; other = 9 _____

5. Family constellation, parents:
   Living with both parents = 1 _____
   Living with one parent = 2 _____
   Not living with parents = 3 _____
   Other = 9 _____

6. Family constellation, siblings:
   Number of siblings _____

7. Birth order: oldest = 1 _____; middle = 2 _____;
   youngest = 3 _____; not appropriate = 9 _____

8. Grade in school _____

9. School absences during treatment
   yes = 1 _____ explain:

   no = 2 _____

10. School absences during past school year
    yes = 1 _____ explain:

    no = 2 _____

B. Treatment Data

1. Diagnosis: ALL = 1 _____; ST = 2 _____ (specify)

2. Date of diagnosis: _____

3. Age at diagnosis: _____ yrs. _____ months

4. Number of years of therapy: _____ yrs. _____ months

5. Number of years off therapy: _____ yrs. _____ months

APPENDIX B
Data Collection Flow Sheet

Late Effects of Cancer and Cancer Therapy on Neurocognitive and Psychosocial Functioning

B. Treatment Data (cont'd)

6. CNS prophylaxis:
   IT MTX: dose _____
   CNS radiation: dose _____; factions _____
   none _____

7. Maintenance Therapy: list drugs

8. Concurrent medical condition and therapy

9. Current use of nutritional supplements

C. Neurocognitive Data

1. Neuropsychological Test Battery (see Appendix C)
   Complete _____
   Schedule second visit _____

APPENDIX B
Data Collection Flow Sheet

Late Effects of Cancer and Cancer Therapy on Neurocognitive and Psychosocial Functioning

B. Treatment Data (cont'd)

6. CNS prophylaxis:
   IT MTX: dose _____
   CNS radiation: dose _____; factions _____
   none _____

7. Maintenance Therapy: list drugs

8. Concurrent medical condition and therapy

9. Current use of nutritional supplements

C. Neurocognitive Data

1. Neuropsychological Test Battery (see Appendix C)
   Complete _____
   Schedule second visit _____

APPENDIX B
Data Collection Flow Sheet

Late Effects of Cancer and Cancer Therapy on Neurocognitive and Psychosocial Functioning

C. Neurocognitive Data (cont'd)

2. Deasy-Spinetta Behavioral Questionnaire Neuorcognitive Functioning Subscale: (sum of items: 4, 5, 6, 7, 11, 41, 42, 43, 44, 51, 53)

Source	Subject Score	Control Score
Parent	_____	
Teacher	_____	_____

D. Psychosocial Data

1. Deasy-Spinetta Behavioral Questionnaire (DSBQ)

A. Parent — Subject Total Score _____

B. Teacher — Subject Total Score _____

Control Total Score _____

Discrepancy Score _____

2. Open-ended questions (see attached)

3. Additional comments:

APPENDIX B
Data Collection Flow Sheet

Late Effects of Cancer and Cancer Therapy on
Neurocognitive and Psychosocial Functioning (cont'd)

E. Background Data

1. Diagnosis _____
2. 6 months _____
3. 12 months _____
4. 18 months _____
5. 24 months _____
6. 30 months _____
7. 36 months _____
8. 4 years _____
9. 5 years _____
10. 6 years _____
11. 7 years _____
12. 8 years _____
13. Current _____

APPENDIX C
Neuropsychological Evaluation Summary Sheet

Name:

Age:

DOB:

Testing dates:

WISC-R/WAIS-R

VIQ: PIQ: FSIQ:

Info:
Sim:
Arith:
Vocab:
Comp:
DigSp:

Pix Comp:
Pix Arr:
Blk Des:
Obj Ass:
Cod/DSym:

Comments:

ACADEMIC ACHIEVEMENT

	Grade	SS	%ile
PIAT Reading Comp			
WRAT Reading			
WRAT Spelling			
WRAT Arith			

Error types:

VISUOSPATIAL

Beery VMI age: Scale score:

Block Design scale score:

Rey-Osterrieth copy:

Descriptive comments:

APPENDIX C
Neuropsychological Evaluation Summary Sheet (cont'd)

LANGUAGE

CELF
Processing: percentile
Production:
Total:

FAS

CONCEPTUAL SKILLS

Category Test:

Similarity SS:

CVLT cluster:

AUDITORY MEMORY

Digit Span scale score: DF: DB:

CVLT

Imm Rec: _____ _____ _____ _____ _____ _____ total

Cluster: Persev: Instru: Rate:

Short Del: Free rec: Cl:
Cued rec:

Long Del: Free rec: Cl:
Cued rec:
Recognition:

Cl enhancement: SD dec: LD dec:

Bushke

WMS LM: A: B:

APPENDIX C
Neuropsychological Evaluation Summary Sheet (cont'd)

VISUAL MEMORY

BVRT
Correct:
Errors:
Error types:

Rey-Osterrieth:

APPENDIX D

Deasy-Spinetta Behavioral Questionniare

Name of child: _____ Completed by: (circle one)

Date: _____ Mother

Grade: _____ Father

Age: _____ Teacher

Answer each of the following questions either YES or NO (circle the correct response).

1.	Attends school willingly	Yes	No
2.	Attends school regularly	Yes	No
3.	Expresses apprenhension regarding school	Yes	No
4.	Keeps up with school work.	Yes	No
5.	Completes assigned school work	Yes	No
6.	Is able to concentrate	Yes	No
7.	Indicates signs of learning disabilities	Yes	No
8.	Outgoing, interacts with friends	Yes	No
9.	Participates in FORMAL sports or other organized physical activities	Yes	No
10.	Participates in UNSTRUCTURED school activities	Yes	No
11.	Can't sit still, is restless or hyperactive.	Yes	No
12.	Talks about his/her activities	Yes	No
13.	Initiates activities with peers.	Yes	No
14.	Talks easily with adults	Yes	No
15.	Spends time along playing.	Yes	No
16.	Spends time along brooding	Yes	No
17.	Underactive, slow moving or lacks energy	Yes	No
18.	Gets teased a lot.	Yes	No
19.	Tries new things	Yes	No
20.	Tries adventurous/possibly dangerous activities.	Yes	No
21.	Gets hurt a lot, accident prone.	Yes	No
22.	Keeps up personal appearance (clothes, hair, etc.)	Yes	No
23.	Cries, whines or complains	Yes	No
24.	Worries a lot.	Yes	No
25.	Argues a lot	Yes	No
26.	Expresses concern for others	Yes	No
27.	Seeks verbal and/or physical expression of affection or approval	Yes	No
28.	Clings to adults or too dependent.	Yes	No
29.	Self-conscious or easily embarrassed	Yes	No

EXPRESSES THE FOLLOWING POSITIVE FEELINGS OPENLY

30.	Joy	Yes	No
31.	Happiness.	Yes	No
32.	Love	Yes	No

APPENDIX D
Behavioral Questionnaire (cont'd)

EXPRESSES THE FOLLOWING NEGATIVE FEELING OPENLY

33.	Anger	Yes	No
34.	Sadness	Yes	No
35.	Frustration	Yes	No
36.	Confusion	Yes	No
37.	Aloneness	Yes	No
38.	Feels worthless or inferior	Yes	No
39.	Acts up in class	Yes	No
40.	Indicates signs of emotional problems	Yes	No
41.	Has difficulty remembering, sequencing	Yes	No
42.	Indicates specific reading difficulties	Yes	No
43.	Indicates specific difficulties with mathematics	Yes	No
44.	Has difficulty with tasks requiring reasoning	Yes	No
45.	Has two or three close friends	Yes	No
46.	Acts too young for his/her age	Yes	No
47.	Acts too old for his/her age	Yes	No
48.	Tries to manipulate to his/her advantage	Yes	No
49.	Daydreams	Yes	No

---

50. Attends school with some visible sign of illness . . . . Yes No
(e.g., hair loss, prosthesis, weight gain, weight loss) Underline

Other: _____

51. Attends a special class . . . . . Yes No
If yes, indicate type of class (e.g., Learning Disability, Educationally Handicapped, Gifted Program, Special Tutoring, Ph/DIS - PH/RC) Underline
Other: _____

52. Participates in age appropriate extracurricular activities . . . . . Yes No
If yes, indicates activities (e.g., athletics, student government, drama, music, soccer, gymnastics) Underline

Other: _____

53. Has received home tutoring during academic year. . . . . Yes No
If yes, how long? _____

Spinetta and Deasy-Spinetta (1981). Living with Childhood Cancer. St.Louis: C.V. Mosby.

APPENDIX E
Long-Term Cancer Survivors: Open-Ended Questions

Below are several questions about your past cancer illness and treatment. Please answer each question.

1. Do you think that cancer and/or its treatment has had any long-term effects on:
   A. Your school work, thinking, or learning?
      Yes _____
      No _____
      If yes, please explain

   B. How you get along with friends and school mates?
      Yes _____
      No _____
      If yes, please explain

   C. How you get along with your family?
      Yes _____
      No _____
      If yes, please explain

2. Have you kept in contact with or wondered about any of the other cancer patients you knew?
   Yes _____
   No _____
   If yes, please explain

3. Do you think that your parents or other family members have any concerns or worries about your past cancer experience?
   Yes _____
   No _____
   If yes, please explain

APPENDIX F
Cover Letter to Subject's Teacher

Dear Teacher:

I am a graduate student in nursing and associated with the Department of Pediatric Oncology at the University of California, San Francisco Medical Center. I am conducting a study on the long-term effects of cancer therapy and the illness experience on the child's growth and development. Psychosocial development and school performance are important parts of this research. The enclosed instrument--The Deasy-Spinetta Behavioral Questionnaire--has been used to evaluate how the child with cancer manages at school.

As you know, _____ received treatment for cancer at the University of California, San Francisco Medical Center. I have spoken with _____ and his/her parents about the questionnaire, and obtained their permission to contact you. (Copies of their consents are attached.) Would you be willing to help me evaluate this questionnaire?

Your participation in this informal project will involve:

I. Completing one questionnaire on _____. For each item, circle your impression of _____'s behavior/performance.

II. Complete the second questionnaire in the same manner for a child who represents a "typical" student in _____'s class. This student should be of the same sex, in the same classroom, and represent the general characteristics of the class population. Do <u>not</u> include any identifying information on the second questionnaire.

APPENDIX F

Cover Letter to Subject's Teacher (cont'd)

III. Finally, on the back of the questionnaire, or a separate sheet of paper, please indicate any comments you have, for example, additional areas that you think are important but that were not addressed. Return the materials to me in the envelope provided within the next two weeks.

Please keep in mind that the information will be kept confidential. Completion of the questionnaire will represent your consent to participate. I have enclosed a copy of the consent form to assure you that proper consent has been obtained. If you have any questions or concerns, please contact me.

Thank you for considering my request.

Sincerely,

Ki Moore, R.N., M.A.
(415) 359-3043 Home
(415) 666-5964 Work