LATE EFFECTS OF TREATMENT

IN SURVIVORS OF

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

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ABSTRACT

Long-term survival and probable cure have become norms in acute lymphoblastic leukaemia of childhood. The adverse effects of treatment for leukaemia are diverse and complex. In many cases, treatment effects come to light long after the end of therapy. These so-called late effects (which are as yet obscure and incompletely understood) have become increasingly important as the number of children surviving leukaemia increases.

This thesis describes a comprehensive study of leukaemia survivors attending the Oncology Clinic of the Red Cross War Memorial Children's Hospital. The study sample consisted of all leukaemia survivors in long-term remission, disease free and off treatment up to January 1st, 1984.

The study is introduced by a chapter which describes acute lymphoblastic leukaemia and pays particular attention to the effects of the primary disease on organs which may subsequently exhibit late effects of treatment. Treatment of acute lymphoblastic leukaemia is described in some detail and the reasons for current treatment strategies are outlined. Individual modalities of treatment are then discussed with reference to their mechanisms of action and potential for damage to non-neoplastic tissue.

The study then examines all systems likely to have been damaged during therapy, in order to achieve a comprehensive impression of the late effects of leukaemia treatment. In each chapter, pertinent literature was reviewed up to January 1987.

Growth is a major task of childhood. Many chronic diseases are potential causes of growth failure. A longitudinal retrospective study showed that statural growth in leukaemia survivors was stunted during treatment. Catch-up growth did not occur at the end of treatment, although normal growth velocity was resumed. Adult height was expected to be reduced as a result. In addition to temporary stunting of statural growth, leukaemia survivors showed a progressive increase in weight-for-height during treatment. This trend continued after treatment had ended. These changes in weight and height were peculiar to leukaemia survivors. Control groups of children with solid tumours in longterm remission showed less stunting during treatment and had catch-up growth after treatment, except when they had undergone spinal irradiation.

Normal endocrine function is a prerequisite for normal growth and development. Although growth hormone responses to insulin-induced hypoglcaemia were frequently and significantly abnormal in survivors of childhood leukaemia, these children grew normally once treatment had stopped. Impaired growth hormone secretion appeared to be a marker of hypothalamic damage caused by leukaemia therapy. Testicular and ovarian function was normal in the absence of irradiation of these organs. Thyroid function was normal in leukaemia survivors although a minority showed evidence of hypothalamic damage in their response to thyrotropin releasing hormone. Normal prolactin levels in children showing other hormonal evidence of hypothalamic damage were thought to indicate the selectivity of damage caused by leukaemia treatment. Adrenal control and function was normal in leukaemia survivors. In the absence of a growth disorder, only thyroid status may need longterm assessment in leukaemia survivors.

Intellectual development is a further major task of childhood. A sibling controlled study of intellectual function indicated an intelligence deficit in children surviving leukaemia and its treatment. This deficit was thought to be the consequence of therapy, since children surviving solid tumours showed no such deficit in comparison with their sibling controls. Survivors of childhood leukaemia also had an increased incidence of visual perceptual difficulty and more school problems than survivors of solid tumours, particularly in early primary grades. Intellectual outcome and school performance in leukaemia survivors may be improved by early visual perceptual training.

Children surviving acute lymphoblastic leukaemia had significantly more minor motor abnormalities than children surviving solid tumours. Minor motor abnormalities were frequently and significantly associated with abnormalities of the brain visualized by computerized tomography. Neurophysiologic measurement (EEG, VER, BAER) did not contribute to the assessment of neurological outcome and correlated poorly with clinical and CT scan findings. A functional assessment of neurological outcome in leukaemia survivors should include a clinical examination for minor motor dysfunction.

Some children manifested other organ-specific damage due to chemotherapy or radiotherapy. These isolated cases are discussed in the form of case reports and literature reviews. Patients who receive treatment with cytotoxic drugs in addition to standard leukaemia therapy need to be followed for treatment-specific late effects.

The psychological outcome of leukaemia survivors was assessed by means of parent interviews and teacher questionnaires. In terms of a low

frequency of behaviour problems reported by these observers, psychosocial adaptation in leukaemia survivors was surprisingly good. Children surviving solid tumours and healthy school children from the same community (the latter from a literature report) had similar frequencies of behavioural problems. In both leukaemic children and solid tumour control patients, certain patterns of family behaviour were predictive of a poor psychological outcome. It appears that an early family assessment may identify families 'at risk'. It needs to be shown whether such families would benefit from professional psychological support.

In the final chapter a 'functional deficit score' is offered as a measure of overall outcome in terms of late effects of therapy. Patients were rated in five categories (growth, intellectual outcome, neurological status, miscellaneous organ damage and psychosocial adaptation) according to the severity of persistent late effects. Children surviving acute lymphoblastic leukaemia were shown to have been more seriously damaged by their treatment than children surviving solid tumours. The difference in overall damage was the consequence of central nervous system injury. Available evidence indicates that this central nervous system injury is caused by radiotherapy (with or without a synergistic effect with intrathecal methotrexate) given as central nervous system 'prophylaxis'.

With few exceptions, leukaemia survivors in this study had received 2400 rads of deep x-ray therapy as cranial irradiation. This dosage has since been reduced world-wide. Current cranial irradiation 'prophylaxis' consists of 1800 rad of megavoltage radiotherapy.

Follow-up studies of survivor cohorts given such radiotherapy should include the measures embodied in the 'functional deficit score' described above.

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ABBREVIATIONS USED IN THIS THESIS

abn	abnormal
ACTH	adrenocorticotrophic hormone
Adria	Adriamycin
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
BAER	brainstem audio evoked response
BAS	British Ability Scales
CDC	Centres for Disease Control
CI	cranial irradiation
CNS	central nervous system
Co^{60}	cobalt 60
CSF	cerebro-spinal fluid
CT	computerized tomography
cycle	cyclophosphamide
d	delta (change)
Dauno	Daunorubicin
DNA	Desoxyribonucleic acid
DOPA	3,4-dihydroxyphenylalamine
EEG	electro-encephalogram
FSH	follicle stimulating hormone
GOS	Great Ormond Street
GhF	Growth hormone releasing factor
HCG	Human chorionic gonadotrophin
hGH	Human growth hormone
Ht	height
Hydrox	Hydroxyurea
IQ	Intelligence quotient

IT cytosar	intrathecal cytosine arabinoside
IT MTX	intrathecal methotrexate
IU	international unit
IV	intravenous
l-	levo
laspar	L-asparagine
LET	linear energy transfer
LH	luteinizing hormone
LH/FSH RH	luteinizing hormone/follicle stimulating hormone releasing hormone
M	molar
Mev	megavoltage
ml	millilitre
MRC	Medical Research Council
MTX	methotrexate
MSH	melanocyte stimulating hormone
μ	micro
μg	microgram
n	number
ng	nanogram
NCHS	National Centre for Health Statistics
NCI	National Cancer Institute
NHL	Non-Hodgkins Lymphoma
pg	picogram
PIF	Prolactin inhibiting factor
PGM	Pia-glial membrane
Pred	prednisone
r	rad
RIA	Radio-immuno assay

RNA	ribonucleic acid
RT	radiotherapy
Rx	treatment
S Binet	Standford Binet
SD	standard deviation
SDS	standard deviation score
SIADH	syndrome of inappropriate anti-diuretic hormone secretion
SSAIS	Senior South African Intelligence Scale
ST	solid tumour
T_3	Triiodothyronine
T_4	thyroxin
THIO	thioguanine
TRH	Thryotropin releasing hormone
TSH	Thyroid stimulating hormone
UCT	University of Cape Town
VER	visual evoked response
VINC	Vincristine
VMI	visuo-motor integration
VMN	ventro-medial nucleus
V-p, V/P	verbal - performance
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organisation
WISC(-R)	Wechsler Intelligence Scale for Children (- revised)
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAT	Wide Range Achievement Test
wt	weight

χ^2	chi-squared
$\bar{x}$	mean
6-MP	6-mercapto-purine

CHAPTER 1

INTRODUCTION

1.1 ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

ALL is a rapid, uncontrolled proliferation of abnormal leukocytes which is fatal if untreated. It is a primary disorder of bone marrow in which normal marrow elements are replaced by immature or undifferentiated lymphoblastic cells. Secondary leukaemic infiltration of the reticulo-endothelial system, the central nervous system, gonads, kidneys, and the gastrointestinal tract may occur.

ALL may occur at any time during childhood, but its peak incidence is between the ages of 2 and 6 years. In the United States of America, the risk of developing acute leukaemia in the first 10 years of life is 1 per 2880 population (Miller).

Ninety per cent of acute leukaemia in childhood is ALL. Careful morphologic and immunologic evaluation has demonstrated that ALL is not a homogeneous entity, but a group of several diseases, with different prognoses. Although these separate diseases have not been characterised fully, certain quantifiable factors have been shown to differentiate between high and low risk groups. These factors include age at diagnosis (Robinson), initial white cell count (Simone 1976) (Poplack), bone marrow morphology (Bennett), initial haemoglobin concentration (Bleyer 1985), karyotype of abnormal lymphoblasts (Third) (Secker-Walker) and degree of CNS and reticulo-endothelial involvement at diagnosis (Bleyer 1985).

The recognition that clinical and laboratory characteristics have prognostic value and allow classification of patients into

prognostic groups has revolutionised the therapeutic approach to ALL Patients with 'standard risk' ALL may now be treated with less intensive and hopefully less toxic regimens, whereas it is justified to treat patients who present with poor risk features with more aggressive therapeutic protocols.

1.2 ACUTE LYMPHOBLASTIC LEUKAEMIA AND THE CENTRAL NERVOUS SYSTEM

1.2.1 Incidence of CNS leukaemia

Before the introduction of chemotherapy, central nervous system (CNS) involvement by leukaemia was thought to be rare (Bass). In acute lymphoblastic leukaemia, CNS involvement was more frequently diagnosed at autopsy than during the course of the disease (Diamond) (Schwab) (Leidler). The reverse, with earlier clinical presentation of neurological symptoms, was true for other forms of leukaemia (Pole).

Following the introduction of systemic therapy in 1948 (Farber) the incidence of CNS leukaemia rose sharply. At one centre, it increased from 0% in 1947 to 40% in 1960 (Evans 1964) and 57% in 1965 (Evans 1970). Central nervous system disease developed both during haematological remission (Haghbin) (Hardisty) and during relapse. The success of systemic therapy was the direct cause of this increased incidence because it prolonged survival (Evans 1970) (Shaw). It was evident that systemic treatment was not reaching CNS leukaemic infiltrates.

1.2.2 Pathology of the CNS in leukaemia

All children with acute lymphoblastic leukaemia are at risk of CNS disease. CNS pathology may be due to malignant infiltration, haemorrhage or infection. These three processes may also interact.

i. Infiltration

Neural infiltration by leukaemia was first described in 1823 (in Dock). This infiltrate occurred in the eye, was first called 'chloroma' in 1870 (in Dock) and identified as a manifestation of acute myeloid leukaemia (AML) in 1893 (Dock). Meningeal leukaemia, also in AML, was first described in 1920 (Munro). It subsequently became apparent that meningeal leukaemia occurred more commonly in ALL than in AML (Nieri).

Invasion of CNS parenchyma was frequently observed in autopsy studies. This was first thought to follow intracerebral haemorrhage (Diamond) (West), or malignant transformation of pluripotent connective tissue cells in vessel walls (Jaffe in Diamond). Leukaemic invasion of the CNS was only properly understood once Price and Johnson (1973) demonstrated in their autopsy study of 126 children with ALL, how leukaemic cells follow a predictable anatomical course as they infiltrate the CNS.

Leukaemic cells in the walls of veins in the leptomeninges (arachnoid and pia mater) are the first sign of meningeal disease. As postulated by Fried in 1926 and Diamond this

suggests that leukaemic cells diapedese through vessel walls to invade tissue. The arachnoid, which consists of connective tissue trabeculae containing blood vessels, and is interlaced by cerebro-spinal-fluid (CSF) channels, is the first layer to be invaded. The connective tissue trabeculae are densely infiltrated by leukaemic cells and distended. This restricts CSF flow. The leukaemic infiltrate then begins to destroy the arachnoid trabeculae and, as first suggested by Schwab (1935), leukaemic cells are released into the CSF. At this point a cytological diagnosis of meningeal leukaemia can be made by examination of the CSF.

With more advanced infiltration, leukaemic cells extend into the deep arachnoid. The pia-glial membrane (PGM) (which extends from the surface of the brain to the level of the pre-capilliary arteriole and post capillary venule) protects CNS parenchyma from direct leukaemic infiltration while it remains intact. Extra-pial arachnoid leukaemia may nevertheless damage brain parenchyma by obstructing CSF flow through the distended arachnoid and thus elevating intracranial pressure (Moore) (Price and Johnson). The foramina of Luschka and Magendie and the arachnoid granules remain intact. Vessels traversing the densely infiltrated arachnoid are also compressed by an expanding leukaemic cell mass and perfusion of adjacent cerebral cortex is compromised. Multiple foci of cortical necrosis occur (Price and Johnson) showing the histological pattern which follows diminished cerebral perfusion (Denny-Brown).

The final stage of meningeal leukaemia follows breach of the pia-glial membrane. This stage is seen in less than 15% of children dying in relapse (Price and Johnson). Infiltration of any part of the brain may follow. Nerve root (Shaw) spinal cord (Stefannson) (Pierce) hypothalamic (Shaw) and pituitary lesions (Sullivan) have been described.

ii. Haemorrhage

Intracranial haemorrhage in leukaemia was previously thought to be due to thrombocytopaenia alone (Pierce) or a very high peripheral blast count. A 'blastic crisis' was thought to cause 'leukostasis' (Moore) (Groch) (Fritz) (Freireich) (Phair) (Pierce) which led to vessel wall injury (Fritz) and rupture. Another theory suggested that proliferation of leukaemia cells within the vessel wall caused destruction and haemorrhage (Freireich).

The present view is that cerebral haemorrhage follows ischaemic changes due to compression of vessels traversing a severely infiltrated deep arachnoid (Price and Johnson) or disseminated intravascular coagulation (Packer). Thrombocytopaenia may aggravate haemorrhage. Degenerative vasculopathy caused by bacterial invasion may also occur. High peripheral blast counts and thrombocytopaenia may occur at the same time as severe deep arachnoid leukaemia, and would have been frequent in terminal patients before the use of present chemotherapeutic agents. Intracerebral haemorrhage in ALL patients with hyperleukocytosis

(peripheral count 100,000) is now rare as are cerebrovascular accidents (Packer). So called 'leukostasis' and leukaemic nodules in cerebral tissue are deep extensions of arachnoid leukaemia and not intravascular phenomena.

Intracranial extracerebral bleeds occur rarely, and are due to arachnoid leukaemia or thrombocytopaenia (Belmisto) or due to disseminated intravascular coagulation (Packer).

iii. Infection

The leukaemic process (Bodey) and chemotherapy (Hersh) both reduce the number of healthy granulocytes and the efficiency of other immune mechanisms, predisposing the child with leukaemia to infection. Severe CNS infection occurs in 1% (Hora) to 5% (Campbell) of cases. The incidence is higher in autopsy studies (Crossley). Approximately 40% of CNS infections are bacterial and 60% viral. Fungal infections are more common in autopsy studies (Crossley).

Bacterial infection may be due to common or unusual CNS pathogens (Campbell) (Eortc). Gram negative infections are prominent (Chernick 1973) (Crossley). Meningitis due to Listeria monocytogenes is unusually frequent (Chernick 1977) (Hora).

Bacterial infections present as brain abscess or meningitis. Gram negative septicaemia is implicated in the pathogenesis of some cases of intracerebral haemorrhage (Campbell), because of associated disseminated intravascular coagulation (Packer).

Fungal infections with Monilia (Crossley), Aspergillus (Crossley) (Chernick), Cryptococcus (Chernick 1973) and Mucor species (Chernick 1977) are described, as is cerebral toxoplasmosis (Crossley). These infections also present as meningitis or brain abscess.

Viral infections are particularly virulent in the acute leukaemic patient on immunosuppressive therapy. Measles and varicella encephalitis may be lethal, or may leave serious neurological sequelae (Campbell). Mumps meningoencephalitis and varicella encephalitis are usually mild diseases.

1.2.3 Clinical Features

Meningeal disease is rarely the presenting feature of leukaemia (Levine) (Munro) (Pole) (Bass) but silent infiltration of the central nervous system is frequent. In patients dying of systemic leukaemia before the introduction of chemotherapy 25% (Schwab) to 35% (Leidler) had leukaemic CNS infiltration at autopsy.

Today central nervous system infiltration presents most frequently as a meningeal illness, with headache, vomiting and

meningismus. Raised intracranial pressure may cause papilloedema, cranial nerve palsy and blurred vision (Hyman) (Phair) (Sullivan) (Pierce). Hydrocephalus may have an early onset (Moore) (Borgstedt). Convulsions may be caused by pressure, infiltration or haemorrhage (Haghbin) (Hardisty 1967).

Deeper infiltration is more rare and causes symptoms such as the hypothalamic syndrome (Hardisty 1967) (Shaw), acute paraplegia (Steffanson) (Pierce) (Wolcott), diffuse myelitis (Pierce) and cranial nerve palsies (Schwab).

1.2.4 Diagnosis

The diagnosis of CNS leukaemia is made by the observation of leukaemic cells in a Wright-stained centrifugate of cerebrospinal fluid. CSF pressure may be increased, protein increased and sugar decreased (Pierce) (Sullivan). The differentiation of CNS relapse from methotrexate arachnoiditis or intercurrent viral, bacterial or fungal infection may be difficult (Komp) (Aaronson). A CNS meningeal infiltrate may be present without cells in the CSF (Aaronson).

1.2.5 Central Nervous System Leukaemia and Late Sequelae

It is now known that central nervous system leukaemia is a meningeal disease. When the meninges are minimally infiltrated, the cerebrospinal fluid void of blast cells and the patient without neurological symptoms or signs, central nervous system parenchymal damage has in all probability not yet occurred. This is the neurological status in the majority of newly diagnosed cases of childhood acute lymphoblastic leukaemia.

Patients who have meningeal leukaemia (i.e. malignant cells in the CSF) at diagnosis, may have extensive meningeal infiltration which, when it occurs over 'silent' areas of the cortex, may be associated with profound local damage without causing neurological symptoms or signs. It is not known how much such silent infiltrates contribute to late central nervous system damage, but patients presenting with meningeal leukaemia are more likely to sustain severe damage on standard regimens of central nervous system prophylaxis (Gribbin).

Intracerebral haemorrhage in leukaemia is usually catastrophic and a late or terminal event. Small bleeds may occur, related to thrombocytopaenia at diagnosis or to local meningeal infiltration, but are reportedly rare (Price and Johnson).

Central nervous system infection is a serious cause of late morbidity. Survivors may suffer late sequelae of viral, bacterial, fungal or protozoal infections, but these infections will clearly manifest clinically.

In the absence of meningeal leukaemia at diagnosis, or of intracranial haemorrhage or infection during treatment, late neurological sequelae of acute lymphoblastic leukaemia are thought to be due to therapy.

1.3 TREATMENT OF ALL

1.3.1 Introduction

Before 1948 the prognosis of ALL in childhood was hopeless.

Starting with the introduction of the antifolate compounds (Farber) the outlook has improved year by year. Today, a child with ALL has an 85 to 95 per cent chance of achieving complete remission (Mauer).

This remarkable improvement is the result of vast cooperative study programmes involving the development of new agents, study of cell kinetics and drug mechanisms, systematic investigation of the usefulness of a large number of single and combination drug therapies and improved supportive care.

A variety of useful drugs were discovered in the search for compounds capable of regulating growth of leukaemic cells. These include the periwinkle alkaloids, antibiotics, hormones, enzymes, mustard compounds and antimetabolites (Henderson 1969). Agents were initially used empirically and progress in treatment was slow, largely because the pathogenesis and pathophysiology of leukaemia remained poorly understood.

In recent years treatment for children with ALL has become progressively more sophisticated. Whereas earlier treatment protocols managed all patients alike, the heterogeneity of leukaemia and recognition that children can be stratified according to risk factors now indicate that treatment of all patients with a standard ALL regimen is not appropriate.

Combination chemotherapy with or without radiotherapy to sanctuary sites is the principal modality used to treat ALL. Most regimens are divided into four phases: induction of

remission, central nervous system preventive therapy, consolidation and maintenance.

1.3.2 Induction Therapy

The first aim in ALL treatment is to induce remission. The basic two drug combination of vincristine and prednisone will achieve this in approximately 85 per cent of children with ALL (Henderson). Addition of L-asparaginase and/or an anthracycline improves the induction rate to approximately 95 per cent (Nesbit 1983). Adding a third agent to prednisone and vincristine has also prolonged remission (Mauer 1978). Using a fourth drug during remission induction may add to toxicity and is usually reserved for patients in higher risk groups, who might benefit from accelerated rates of cytoreduction (Frei 1978).

1.3.3 Central Nervous System Preventive Therapy

Before central nervous system 'prophylaxis' was introduced, improvements in systemic chemotherapy were associated with progressively increasing risk of central nervous system relapse. In one series the incidence of meningeal relapse was as high as 75 per cent (Hardisty). Central nervous system relapse was almost inevitably followed by marrow relapse and treatment failure (Gribbin 1977). The value of preventive therapy to the central nervous system was first shown by investigators at St Judes Children's Research Hospital. They reduced the incidence of central nervous system relapse to 10 per cent by administration of 2400 rads of cranial or craniospinal radiation and 5 doses of intrathecal methotrexate (Aur 1971). Craniospinal radiation was discarded because of excessive

myelosuppression and 2400 rads of cranial irradiation and intrathecal methotrexate became 'standard' central nervous system preventive therapy.

Because of concern about adverse effects of cranial irradiation, manifest as CT brain scan abnormalities (Peylan-Ramu), altered intellectual and psychomotor function (Eiser 1977) and neuroendocrine dysfunction (Shalet 1981(b)), alternative less toxic forms of preventive central nervous system therapy have been sought. Lower doses of cranial irradiation (1800 rads) with intrathecal methotrexate (Nesbit (1981(b)), intrathecal methotrexate, cytosine arabinoside and hydrocortisone (Poplack 1981) intrathecal methotrexate alone (Sullivan 1982) and high dose systemic methotrexate (Poplack 1983) are some of the strategies in use at present.

Risk factors for central nervous system leukaemia have been identified. These are a high initial leukocyte count, T-cell disease, a young age at diagnosis, thrombocytopaenia, massive lymphadenopathy, hepatomegaly or splenomegaly and black race (Bleyer 1985). Whereas intrathecal methotrexate alone may be adequate to prevent central nervous system relapse in patients at low risk, optimal management of higher risk patients has yet to be established (Poplack 1985).

1.3.4 Consolidation and Maintenance Therapy

Once complete remission has been achieved, additional chemotherapy is needed to maintain it. Without maintenance therapy, remission was brief (Frei 1965). Biopsy of

extramedullary tissue shortly after obtaining remission will reveal histologic evidence of leukaemia in one third to half of patients (Mauer). Such infiltrates represent clones of resistant cells which would lead to relapse on treatment (Simone, 1976).

Methotrexate (MTX) and 6-mercapto-purine (6-MP) respectively administered weekly or biweekly and daily, are the two agents most commonly used as maintenance chemotherapy. Intermittent pulses of vincristine and prednisone added to this standard maintenance therapy may extend remission, but are probably not necessary for all patients (Simone 1976).

High risk groups may require more intensive maintenance therapy. 'Consolidation' therapy consisting of intensified therapy immediately after remission (with drugs chosen to minimize theoretical cross resistance) has improved the duration of remission for these patients. The BFM West German Study Group has reported prolonged disease free survival in more than 75 per cent of children with ALL (including those with high risk features) through the use of intensive induction, consolidation, reinduction and reconsolidation in the early maintenance phase (Lampert).

The optimal duration of maintenance therapy may depend on the patient's risk of relapse. Most centres continue treatment for 2½ to 3 years. There is no benefit in continuing to 5 years (Nesbit 1981). For some patient groups, such as girls in the 'standard risk' category, 1½ years of treatment is adequate (MRC).

Prognosis for patients completing 3 years of treatment relapse free is good. Approximately 80 per cent will remain disease free. Of those who relapse, most do so in the first year of treatment. In the next 3 years, relapse risk is 2 to 3 per cent per year. After 4 years, the risk of relapse is very low (George).

1.4. INDIVIDUAL AGENTS USED IN TREATMENT. ACTIONS AND TOXICITY

1.4.1 The Adrenocortical Steroids

The glucocorticoids were demonstrated to be lympholytic by White and Dougherty (1948) and were first used in leukaemia therapy in 1949 (Pearson). Prednisone and prednisolone are most often used because of a favourable therapeutic ratio between lympholysis and toxicity. Glucocorticoids act directly against mature and immature lymphocytes, sparing myeloid precursors and mature granulocytes (Cline).

Glucocorticoids are distributed into total body water, including cerebrospinal fluid. Biologically significant blood levels are maintained for more than 24 hours after a standard oral or parenteral dose (Chard). These compounds are most important in chemotherapy because of a relative lack of marrow toxicity and their ability to cross the blood-brain barrier.

Psychosis may be a toxic side-effect of glucocorticoids (Rome) but there is no evidence in the literature of lasting neurologic or intellectual damage. Young people on prolonged steroid therapy show marked cerebral atrophy on CT scan (Bentson). The

reason for this apparent atrophy is unknown. Steroid induced catabolism producing similar atrophy to that seen in skin, muscle and vessels, or loss of brain water have been postulated to explain this phenomenon. These 'atrophic' changes are reversible (Bentson).

1.4.2 Vincristine

The plant Vinca rosea (Periwinkle) of the family Apocynaecae is an ornamental everblooming shrub. Because it is a tropical species, it is more correctly named Cantharanthus rosea. Members of the genus Cantharanthus have played an important role in folk medicine. In Brasil, an infusion of the leaves was used to control haemorrhage and scurvy and to heal chronic wounds. In the British West Indies, it was used to treat diabetic ulcers, and in the Phillipines and in South Africa it was claimed to have hypoglycaemic properties.

Its potential for use in diabetes led to laboratory investigation by two independent groups. Although neither could confirm any hypoglycaemic action, both found that certain alkaloids derived from the plant have leukopaenic and anti-leukaemic action (Johnson). Vincristine, one of the biologically active alkaloids derived from Cantharanthus rosea, was found capable of inducing remission from childhood acute lymphoblastic leukaemia (Karon). It has been used as an agent for induction of remission ever since. It is also used in the treatment of lymphoma and other solid tumours.

Neurotoxicity is dose limiting in vincristine therapy. Almost all patients present with some features of neurotoxicity. Reported incidence depends on the clinical index of suspicion (Hanefeld) (Bradley). Factors influencing toxicity are dose, duration of therapy, nutritional state, mobility, liver function and prior disorder of the peripheral nervous system. Neurotoxicity is enhanced when vincristine is used in combination with L-asparaginase, actinomycin, methotrexate and prednisone (Woods). These drugs reduce vincristine catabolism and excretion by the liver. Radiotherapy may enhance vincristine neurotoxicity (Byfield).

Vincristine causes a peripheral neuropathy. Bilateral symmetrical foot and/or wrist drop with symmetrical depression of tendon jerks is the most common presentation of the motor component (Holland) (Ryan). When treatment stops, nerve function improves immediately and returns to normal although without due care muscular contractures may occur (Ryan). Cranial nerve palsies may also occur. The facial, abducens and laryngeal nerves are most frequently affected (Weiss). Sensory neuropathy presents as neuralgia, paraesthesiae and rarely, with objective sensory loss. Autonomic neuropathy leads to constipation, ileus, colic and orthostatic hypotension (Weiss).

Myopathy occurs both as a consequence of denervation and as a direct effect of vincristine toxicity (Bradley) (Weiss).

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been described in both children (Suskind) (Slater)

and adults during vincristine therapy. This syndrome occurs infrequently (Haggard). Pathophysiology of the increased blood hormone levels remains unclear (Suskind). Coma (Whittaker) and seizures (Johnson) (Rosenthal) have occurred during vincristine therapy, which are clearly related to hyponatraemia resulting from SIADH. However, in some patients no metabolic or structural abnormalities have been present to explain the occurrence of convulsions after therapy (Johnson) (Hardisty 1969).

Vincristine has its cytotoxic effect by damaging the nuclear mitotic spindle to cause a colchicine-like metaphase arrest during cell division (Weiss). Peripheral neuropathy is thought to be due to damage to microtubules and neurofilaments in axons, which are replaced by paracrystalline structures (Green) (Weiss). This direct effect on the axonal membrane is believed to impede axoplasmic flow. Muscle damage is thought to occur in the muscle spindles (Bradley). Demyelination of peripheral nerves is secondary to axonal damage (Weiss). Neuromyopathy is present in all patients treated with vincristine for more than 2 months (Bradley).

Autopsy study indicates normal brain histology in the presence of neuromyopathy. Vincristine does not appear to cross the blood brain barrier (Karon), but intrathecal administration of vincristine has been uniformly fatal. The drug is rapidly distributed and bound to neurons, causing acute neuronal death (Gaidys).

Neurotoxicity due to vincristine occurs outside the central nervous system, in the absence of intrathecal administration. Late CNS effects in survivors are therefore unlikely to be related to treatment with vincristine.

1.4.3 L-Asparaginase

Acute lymphoblastic leukaemia cells lack asparagine synthetase activity and therefore require external sources of asparagine (Dolowy). Most normal tissue cells possess the enzyme asparagine synthetase which catalyses the hydrolysis of L-asparagine in blood and tissue fluid, to the products L-aspartate, L-glutamate and ammonia (Broome). The enzyme L-asparaginase exploits this difference in nutritional requirement between normal and leukaemic cells. Anti-leukaemia effects of L-asparaginase were discovered after the observation that guinea-pig serum inhibits the growth of leukaemia in mice (Boyse) (Dolowy).

L-asparaginase has exhibited toxic effects on liver, pancreas, kidney, central nervous system and the immune system (Haskell). Hypersensitivity reactions to L-asparaginase are the most common toxic effect. It's incidence is variable and partly related to dose and route of administration. Symptoms and signs range from urticaria to anaphylaxis.

Liver toxicity may be secondary to inhibition of protein synthesis. Laboratory changes consist of hypoalbuminaemia, elevated transaminases and liver alkaline phosphatase, hypocholesterolaemia, hypolipoproteinaemia and an elevation in

bilirubin. All liver-produced clotting factors are decreased because of a decrease in synthesis.

Central nervous system toxicity occurs in acute, delayed (Ohnuma) and late (Royds) forms. Acute CNS toxicity presents as an encephalopathy, with lethargy, somnolence, disorientation and confusion (Oettgen) (Ohnuma) (Royds). Convulsions occur infrequently (Campbell). These symptoms occur in 25-50% of patients treated with L-asparaginase. The encephalopathy clears rapidly in the acute form, but may last for weeks when the onset is delayed. Acute encephalopathy is not caused by L-asparaginase directly, because the compound does not cross the blood-brain barrier (Weiss). It is thought rather, that large amounts of L-aspartate, L-glutamate and ammonia are produced by action of the enzyme. Since liver function is also impaired, the body's ability to handle large amounts of ammonia is reduced (Weiss) (Ohnuma) (Moure). Symptoms are reversed by stopping treatment (Moure) and have been observed to improve after infusion of L-asparagine. Severe toxicity is rarely a reason to withhold treatment.

Acute neurological symptoms may also be due to L-asparaginase-associated arterial or venous thrombosis. These complications may occur at the end of induction and are heralded by generalized seizures and coma (in venous sinus thrombosis) or focal seizures and neurological deficits in focal arterial thrombosis.

Electroencephalographic changes of diffuse slowing, reduced alpha, increased theta and delta waves have been observed during clinical toxicity (Moure). Alpha and gamma enolase levels in CSF are elevated (Royds), indicating glial and neuronal damage respectively.

Late L-asparagine CNS toxicity may be due to haemorrhage (Royds) (Urban) which occurs as a result of coagulopathy. Haemorrhages have been noted on CT scan (Urban) and may later present as intracerebral calcification (Royds). Late mild intellectual impairment and seizures are reported (Royds).

1.4.4 Cytosine Arabinoside (Ara-C)

Cytosine arabinoside is a pyrimidine antagonist effective against acute lymphoblastic leukaemia (Howard). It acts by inhibition of DNA synthesis. Ara-C may be the cause of acute encephalopathy and later seizures, paresis, perceptual motor handicap and learning disorder (Grossman) (McIntosh 1976). Intracerebral calcification has been noted as a late effect and may be aggravated by concurrent treatment with large, cumulative doses of methotrexate (McIntosh 1977). Severe damage to cells, myelin and dendrites has been described in the developing nervous systems of mice (Ashwal) and hamsters (Fischer). These changes are consistent with inhibition of DNA synthesis during periods of rapid cellular proliferation.

Cytosine arabinoside is currently part of regimens using triple intrathecal chemotherapy (with hydrocortisone and methotrexate) as CNS 'prophylaxis'. It is also used during induction,

consolidation and in maintenance to prevent meningeal relapse (Sullivan 1982).

1.4.5 Methotrexate

The first remissions from childhood acute lymphoblastic leukaemia were induced by amethopterin (Farber) an antifolate analogue of methotrexate (aminopterin). Folate antagonists are no longer used as induction agents, but methotrexate is given orally during maintenance chemotherapy (Bleyer 1978) and intrathecally via lumbar puncture as treatment for silent meningeal leukaemia (CNS 'prophylaxis') (Simone).

Although intravenous (IV) administration of MTX is more efficient in the maintenance of remission than the oral route (Selawry), rates of late neurological complications are unacceptibly high, parlicularly when IV administration is preceded by cranial irradiation (Bleyer 1981) (Price 1975) (Kay 1971) (Bjorgen) (Abelsohn). Intravenous methotrexate is now only used in treatment protocols which exclude cranial irradiation. Injection of MTX into the cerebral ventricles via an Ommaya valve has been used for treatment of overt meningeal leukaemia (Shapiro) (Pizzo) as well as for CNS prophylaxis (Haghbin).

Methotrexate and its antifolate analogues are competitive inhibitors of the enzyme dihydrofolate reductase (Bertino). Inhibition occurs because of the similarity in structure between these drugs and natural dihydrofolate. MTX is 4-amino-4-deoxy-N^{10}-methyl pteroylglutamic acid and differs from folic acid in

that folate has a hydroxyl group in the place of the 4 amino on the pteridine ring and that there is no methyl group at the N^{10} position. Aminopterin is also without this methyl group.

Dihydrofolate reductase is required for maintenance of an intracellular pool of reduced folate cofactors (tetrahydrofolates). These are necessary for the synthesis of the purine nucleotides and thymidylate (Hoffbrand) which occurs during RNA and DNA replication (Bleyer 1973). Tetrahydrofolates are also essential for incorporation of single carbon fractions into lipids such as lethecin, a major component in myelin (Meadows 1976). Tetrahydrofolate is a cofactor in hydroxylation reactions during the formation of L-DOPA from tyrosine and formation of 5-hydroxy-tryptamine from phenylalanine and tryptophan (Spero). Folate antagonists may therefore inhibit the formation of neurogenic amines (Banerjee). Furthermore, antifolates interfere with protein synthesis, since reduced folates are also required for formation of glycine to serine and homocysteine to methionine.

After intravenous administration, methotrexate is distributed rapidly through the extracellular space, and then into total body water (Bleyer 1978). Transport into cells is by the same energy coupled transport mechanism for all folate analogues (Poplack 1977). Cytotoxic effects only occur above a threshold plasma concentration. Effects are proportional to the length of time levels remain above the threshold (Bleyer 1978). Threshold for cytotoxicity is organ specific (Chabner).

Following intravenous administration, disappearance of MTX is triphasic. The first half-life probably represents distribution, the second renal clearance and the third an enterohepatic circulation (Bleyer 1978). Renal disease and hepatic dysfunction may therefore prolong half-lives and increase methotrexate cytotoxicity. The enterotoxic effect of MTX does not affect the drug's absorption when it is given orally (Pinkerton 1981).

Methotrexate is a highly ionized lipid-insoluble molecule at physiological pH (Bleyer 1981) (Weiss) (Rall), and therefore does not readily cross the blood brain barrier. The bbb slows entry of MTX into the CNS, so that under steady state conditions the CSF: plasma ratio is between 0,02 and 0,05 (Poplack 1977). In order to achieve CSF methotrexate above 10^{-5} Molar, plasma drug levels must be maintained above 5×10^{-4}M for at least 12 hours. Cranial irradiation in doses above 2000 rad alters the bbb of experimental animals to allow MTX across (Yadin) (Griffin) (Griffin). There is evidence that similar damage is caused in man (Siemes) (Stephani) (Schettler). Patients are therefore at risk of MTX neurotoxicity if systemic MTX is administered after cranial irradiation. The risk is negligible with oral therapy, but increases stepwise with intrathecal therapy, intravenous therapy and a combination of these (Bleyer 1981).

Once across the bbb, methotrexate is thought to cause neurotoxicity by interference with pyrimidine and purine formation in neuroglial cells (Bleyer 1981), myelin formation by

oligodendrocytes (Meadows 1977) and neurotransmitter production in neurons (Spero). Dihydrofolate reductase is found in all regions of the brain, so that its inhibition would have widespread effects (Abelson). Interference with purine and pyrimidine formation is most significant in young patients where the neuroglia are actively replicating.

Intrathecal MTX produces three clinical patterns of neurotoxicity. The earliest, acute form is an arachnoiditis, which presents with meningism, fever, headache and a CSF pleocytosis. The first reported cases were due to a preservative in the fluid vehicle (Norrel) which has since been removed.

The second form of intrathecal toxicity presents subacutely. Patients develop para- or quadriplegia, cerebellar dysfunction, cranial nerve palsy and seizures (Weiss) (Gagliano). This complication occurs more frequently in patients being treated for overt meningeal leukaemia (Bleyer 1973), those receiving twice weekly administration and those treated via an Ommaya valve (Pizzo) (Shapiro). It is possible that overt meningeal leukaemia interferes with bbb function (Bleyer 1973) or obstructs CSF drainage, leading to higher than desired concentrations of MTX in some areas.

A late form of neurotoxicity presenting months or years after treatment is necrotizing demyelinating encephalopathy (Kay) (Hendin). This is similar to the necrotizing leukoencephalopathy described by Price (1975) following intravenous methotrexate and cranial irradiation.

1.4.6 Radiotherapy

The tissue effect of radiotherapy occurs through the absorption of radiation energy, which causes the ionization of atoms. An external electron is expelled from the atom absorbing energy. This produces a positively charged ion and an electron, which may attach to another ion. With some forms of radiation (X or gamma rays) the expelled electron has the energy to produce more than one set of ion pairs.

The various types of ionizing radiations have different levels of linear energy transfer (LET). This means that they lose different amounts of energy over a given distance. Highly penetrating radiations have a low LET and therefore produce fewer ion pairs. The relative biological effectiveness (RBE) of different types of radiation depends on their LET and the ion concentration (relative ionization) they produce (Rubin and Casaret).

The lower biological effectiveness of high energy radiations (megavoltage or Mev) is primarily due to a lower specific ionization. They yield approximately 8,5 ion pairs per micron pathway. In contrast, low energy radiations (kilovoltage or kv) yield 80 ion pairs per micron. As a result, kv X-rays have a RBE 40% greater than Mev radiation (Arnold).

Ionization of atoms produces chemical changes in molecules. The alteration causes them to react with other chemical entities or to dissociate into reactive breakdown products. An example of these molecular changes is dissociation of water molecules to

produce hydroxyl (CH^-), perhydroxyl (HO_2) and peroxide (H_2O_2) radicals. These radiation induced oxidative reactions are increased in the presence of oxygen, and may produce secondary chains of molecular, organelle, cellular and tissue damage.

Fundamental mechanisms by which alterations in molecular structure result in damage to cells are not fully understood. When the primary changes induce damage to duplicated organelles (e.g. mitochondria) radiation may have a less profound effect than when damage is to highly specific structures (e.g. chromosomes) of great importance to cell function.

Cellular injury may be due to a direct, one-step mechanism, or may be indirect and dependent upon intermediate chemical reactions (e.g. water ionization). It may also depend on earlier damage to other cellular components of the organ parenchyma. In brain neuronal damage may occur late, secondary to vascular, astrocytic or oligodendroglial damage. Various damage mechanisms take different lengths of time to work. The same dose of the same type of ionizing radiation produces variable damage. This is because of variability in radiation sensitivity and random absorption of ionizing energy.

Visible effects of radiation are not unique to radiation. They are qualitatively similar for different types of radiotherapy, but differ quantitatively, depending upon LET and specific ionization.

1.4.6 CNS Response to Radiation

The outcome of a damaging event anywhere in the body is a result of the magnitude of the insult and the organ's capacity for repair. Because cellular function is highly specific in neural tissue and the capacity for repair is low, the brain has a low functional tolerance to damage of any kind.

The brain's tolerance of ionizing radiation is unknown. Assessment on the basis of animal experiments is difficult because investigators have not used standard dosage, radiation sources or fractionation, or the same animal models. Autopsy studies are difficult to analyse because the effects of primary brain pathology and concommitant chemotherapy are not separable from those of radiation. In addition, radiation sets several trains of damaging effects in motion. These develop at different rates, which makes a cross-sectional analysis (such as from an autopsy series) misleading.

Increased cerebral susceptibility to any diffuse insult is commonly observed in infants (Dobbing). Younger animals are also more sensitive to radiation (Zeman) (Price 1975) (Rubin and Casaret). Between the ages of 4 months and 12 years, the brain mass increases by about 46% (Minkowski). This gain is due to myelination and production of neuroglia in the sub-ependymal plate. Lower tolerance to radiation in young animals is thought to be due to interference with these processes (Cavanagh) (Price 1975).

Neurons are highly specialized long-lived cells which have lost their ability to divide mitotically and cannot be replaced (fixed post mitotic cells). They are therefore highly resistant to the direct cytocidal effects of radiation. Some acute response to ionizing radiation occurs in an immediate arousal pattern seen encephalographically (Garcia) following small fractions of radiation. Direct interphase damage and death may occur after very high doses (10,000 rad fractions) (Quinlan).

Clinical features suggesting cerebral oedema have been recorded (Kramer) but not histologically confirmed. Direct effects on dendritic arborization and synapses have been postulated but remain unconfirmed (Bleyer 1981). According to present knowledge, cranial irradiation in 200 rad fractions to maximal dose of 2400 rad has no immediate or direct effect on neuronal structure or function.

The neuroglial support system is made up of highly specialized, long-lived cells which rarely divide under normal circumstances in the adult human, but can proliferate during regeneration after damage (reverting postmitotic cells). These cells are still actively multiplying in the sub-ependymal plate during childhood (Cavenagh). Proliferation during brain growth and regeneration may be affected by radiation.

Radiation causes immediate damage to myelin sheaths (Gangji) which is manifest as an elevation of myelin basic protein in CSF. No clinical signs accompany this early damage. Delayed damage to white matter may be widespread (Robani) (Haymaker)

(Lampert 1984) (Pennybacker) (Hopewell). The latent period before demyelinating lesions appear suggests that the primary radiation injury is to oligodendrocytes, which then fail to maintain myelin turnover (Jones) (Boldrey) (Schjeide). Failure of oligodendrocytes to respond to damage also suggests damage to the sub-ependymal plate (Cavanagh) (Hopewell). Subacute demyelination is thought to be the pathological basis of the 'somnolence syndrome' (see below).

Astrocyte damage is thought to contribute to breakdown of the blood brain barrier (bbb) (Kramer) along with damage to microvascular endothelium and basement membrane (Schettler). Radiation damage to the bbb was first demonstrated by Larson (1960) using 10,000 - 40,000 rad exposure on experimental animals. More recently CSF elevation of alanine aminotransferase (Similä) and albumen (Siemes) (Stephani) have been interpreted as evidence of bbb leak following cranial irradiation. It has been demonstrated that tryptan blue (Larson) technetium^{99} (T'Chieng) and methotrexate (Griffin) can pass through a bbb damaged by varying doses of ionizing radiation.

Vasculopathy after high dose radiation is well described (Haymaker) (Hopewell) (Lampert) (Rubin and Casarette) (Zeman). In several of these early studies both frequency and extent of degenerative changes in bloodvessels were dose related (Hopewell) (Lampert). Characteristically radiogenic lesions take months or years to develop. In an autopsy study of 163 patients treated with a combination of cranial irradiation and

systemic chemotherapy, Price and Birdwell (1978) found no degenerative lesions where patients had survived less than 10 months after radiation. Morphologically, lesions resemble classically described radiogenic changes in the cerebral microvasculature. The principal feature is accumulation of either acidophilic-, basophilic or amphophilic staining material around small bloodvessels. These deposits consistently contain calcium and mucopolysaccharides and occasionally small amounts of iron. The vessels primarily affected are small arteries, precapilliary arterioles, capillaries and venules. In arteries, deposits are frequently limited to the intima which at times shows signs of fibrosis. Lumens of the smaller vessels are usually occluded by this mineralizing microangiopathy. Most brains contain varying amounts of mineralizing necrotic tissue surrounding the diseased vessels. This histological picture represents a late stage of progressive fibrosis and degeneration of the vessel wall and the consequences of altered vascular permeability. These changes are consistent with the process of dystrophic calcification, which takes place primarily in tissues which degenerate over a long period. Such vascular changes are slowly progressive and may lead to circulatory impairment and regional tissue hypoxia.

1.4.7 The Anthracyclines

Daunorubicin, an antibiotic of the anthracycline group, isolated from cultures of Streptomyces peucetius was first noted to have anti-tumour activity in rats and human tumour cell (Hela) culture (Di Marco 1984). Doxorubicin (Adriamycin) is a biosynthetic analogue of Daunorubicin with greater anti-tumour activity and less immunosuppressive toxicity (Di Marco 1975).

The anthracyclines have multiple modes of action including intercalation with DNA (Di Marco 1975), inhibition of mitochondrial respiratory enzymes (Domae), inhibition of sodium-potassium ATP-ase (Gosálves), chelation of divalent metal ions (Lenaz) and lipid peroxidation (Caulfield).

Severe cardiotoxicity limits the total cumulative dose of anthracyclines (Tan) (Lefrak) (Ragab). Damage is to myocardial cell nuclei (Ferrans), cytoplasmic organelles (Billingham) and cell walls (Caulfield).

Anthracyclines are effective against acute lymphoblastic leukaemia, but not in treatment or prevention of meningeal leukaemia (Henderson). Central nervous system toxicity has not been described.

1.4.8 6-Mercapto-purine

6-Mercapto-purine is a competitive inhibitor of purine synthesis. It must be incorporated into the intracellular nucleotide pool to be effective and is only active during the RNA and DNA synthetic phases of the cell cycle (Henderson 1969a). 6-Mercapto-purine maintenance therapy substantially increases the duration of remission in ALL when given in a daily oral dose (Freireich 1963). No central nervous toxicity has been attributed to this drug.

1.4.9 Cyclophosphamide

Cyclophosphamide is the alkylating agent of choice in acute leukaemia (Fernback). It is not effective against meningeal

leukaemia because it does not cross the blood-brain barrier. No neurotoxicity has been described (Henderson 1969b). It has been reported to cause ovarian dysfunction in prepubertal girls treated for acute leukaemia (Lentz).

1.5 SUMMARY

Acute lymphoblastic leukaemia may damage the central nervous system by infiltration, haemorrhage or by predisposing it to infection. Central nervous system leukaemia occurs in the acute stage of the disease and damage caused at this time is clinically overt. In the absence of neurological signs or symptoms or leukaemic cells in the cerebrospinal fluid, the central nervous system of a child with acute lymphoblastic leukaemia is presumed to be intact.

An acute leukaemic infiltrate may be present in other organs at the time of diagnosis. In the absence of clinical signs these infiltrates are unlikely to be the cause of organ damage.

The treatment of acute lymphoblastic leukaemia has evolved in response to successful experimentation and clinical trials. Additional treatment modalities such as 'CNS prophylaxis' have been introduced by necessity. Present treatment exists because of its success but at the price of treatment side effects.

Individual modalities of treatment cause specific damage which may be immediate or delayed and leads to persistent or 'late effects' of cancer therapy.

As part of the care of children with cancer these late effects must be sought in all body systems known to be at risk.

CHAPTER 2

GROWTH FOLLOWING THE TREATMENT OF CHILDHOOD LEUKAEMIA

2.1 INTRODUCTION

Most chronic illness are potential causes of sub-optimal growth. In the case of acute lymphoblastic leukaemia the treatment which produces remission of the disease, may itself pose a threat to healthy growth.

Both normal (Shalet 1979) (Berglund) and abnormal growth (Hakimi) (Robinson) have been reported during and after conventional therapy for acute leukaemia. It has commonly been observed that induction chemotherapy, with high doses of steroid, vincristine, daunorubicin and cytosine arabinoside, produces a transient decrease in growth velocity (Berry) (Shalet 1981) (Berglund).

How these agents produce their effects on growth is not quite clear, although endocrine function has been shown to be altered: Steroids may inhibit somatomedin secretion (Elders 1975) and antagonize peripheral effects of growth hormone (Morris 1968). Cartilage response to somatomedin is greatly suppressed by steroid and daunorubicin, and less severely by vincristine and cytosine arabinoside (Price 1981). Somatomedin production is profoundly suppressed by vincristine, lowered by cytosine arabinoside, but unaffected by steroid and daunorubicin (Price 1981).

More general factors, such as drug induced anorexia (Theologides), intercurrent infections due to suppression of immunity, taste aversion (De Wys) (Bernstein) and the emotional deprivation of hospitalization (Powell), probably

contribute to undernutrition and a failure to attain optimal growth.

Maintenance chemotherapy with methotrexate and 6-mercapto-purine may also have an adverse effect on growth. Methotrexate induced enteropathy is well described (Pinkerton) (Lewis) and leads to variable degrees of malabsorption. A normal growth pattern may be resumed at the end of chemotherapy and some children may demonstrate a 'catch-up' growth spurt (Pinkel) (Sunderman).

Cranial irradiation, which is given at the end of induction chemotherapy once bone marrow remission has been achieved, is potentially the most serious threat to growth in children with leukaemia (Wells) (Robinson). The first indication that radiation might affect the growth of children came from the study of survivors of the atomic bombing of Hiroshima and Nagasaki (Gruelich 1953). Children were found to be retarded in height, weight and skeletal development, up to five years after the event. Sutow and co-workers found retardation in statural growth and skeletal maturation in boys exposed to fall-out radiation in the Marshall Islands (Sutow 1965). Boys under 5 at the time of exposure were most severely affected.

Whereas there may be many reasons for growth retardation following whole-body irradiation, the growth effects of cranial irradiation are thought to be mediated by damage to the hypothalamo-pituitary axis. Such damage was first demonstrated in growth retarded patients who had received cranial irradiation as treatment for brain tumours (Shalet 1977). This study

used an oral stimulus (Bovril) and insulin hypoglycaemia to stimulate growth hormone secretion. Insulin induced hypoglycaemia acts via the hypothalamus to induce growth hormone secretion by the pituitary gland. The same stimuli were used in a group of leukaemia survivors who had received cranial irradiation. Abnormally low responses were also recorded in these patients (Shalet 1976) following a lower dose of cranial irradiation than was used in the treatment of brain tumours. These results were confirmed by the same (Shalet 1979) and other workers (Wells) and it became clear that abnormalities of neuroendocrine function occurred commonly in survivors of leukaemia and that the incidence of dysfunction was dependent on the age of the child at radiation, the dose of radiation given and the techniques of radiotherapy used (see section 1.4.6). Younger children who received more than 3000 rads of radiotherapy were found to be at greatest risk of growth failure (Shalet 1976) (Shalet 1982) (Arnold 1956).

The relationship between abnormal hypothalamo-pituitary control of growth hormone release after cranial irradiation and subsequent growth is not at all clear. Shalet et al (1979) have described normal growth despite abnormalities of growth hormone secretion (Shalet 1979) and dispute the theories of others, that cranial irradiation results in transient growth hormone deficiency (Wells) (Dacou-Voutetakis 1975, 1977) (Griffin) during treatment, thereby causing transient growth impairment. A possible reason for differences in opinion is that Shalet used insulin induced hypoglycaemia to assess growth hormone release whereas Daou-Voutetakis used the physiological stimulus of sleep. This will be discussed further in Chapter 3.

Whereas most authors report a return to normal growth velocity at the end of treatment (Swift) (Griffin) (Wells) (Shalet 1979) (Robinson), the observation has been made that in some patients a post-treatment 'catch-up' growth spurt, such as would be expected after recovery from prolonged ill-health (Prader 1963) does not occur (Griffin) (Robinson). Without such a growth spurt, there would be an eventual deficit in adult height (Robinson).

Inter-study differences might be explained by the observation that, to date, cross sectional growth data from all patients have been studied collectively, comparing mean height, and mean height velocity of patient groups at different times during longitudinal study (Shalet 1979) (Griffin) (Wells) (Robinson). At first glance, such an approach would appear valid, but consideration of the normal growth curve raises serious objections. Most importantly, the wide variation in the age of onset of the pubertal growth spurt (Tanner 1962) invalidates the comparison of height velocity of children who are prepubertal at the time of diagnosis with any other age group. Nor, in boys or girls, does weight-for-height in prepubertal patient change at the same rate as in children under the age of five. It is therefore not appropriate to group all survivors of ALL together (irrespective of age) for cross-sectional anthropometric analysis.

A summary of growth studies in ALL (Table 2.1) shows that only Berry et al (1983) assessed discrete age groups separately.

TABLE 2.1.

ALL GROWTH STUDIES LITERATURE REVIEW

STUDY	NO OF PATIENTS	CONTROL GROUP	METHOD OF STUDY	CRITICISM
Sunderman (1969)	21	Normal centiles	Individual growth curves	No cranial radiation group
Swift (1978)	14	Normal centiles	Individual growth curves	Small sample
Shalet (1979)	26	Normal values	Comparison of means of height velocity, standing height	Children at different stages of pubertal development studied together. No cancer control
Griffin (1980)	65	Normal centiles Solid tumour	Group mean height-for-age SD curve	All ages studied together from diagnosis

Table 2.1 continued

STUDY	NO OF PATIENTS	CONTROL GROUP	METHOD OF STUDY	CRITICISM
Wells (1983)	9	ALL No cranial RT	Ranking of height centile Ranking of height velocity	Small patient sample Collective assessment of all ages
Berry (1983)	127	Normal children same age	Linear regression analysis of growth rate Separate analysis of different age groups	No cancer control
Sainsbury (1985)	86	Growth standards Tanner & Whitehouse	Change in percentage height-for-age and weight-for-height	All ages assessed together in retrospective cross-sectional analysis.

Table 2.1 continued

STUDY	NO OF PATIENTS	CONTROL GROUP	METHOD OF STUDY	CRITICISM
Robinson (1985)	187	Population standards (NCHS)	Mean height percentiles	Collective assessment
Berglund (1985)	10		Means S.D. scores	Collective assessment Small sample

These workers found that children diagnosed under the age of 4 showed marked growth retardation in subsequent years. Three studies which assessed all ages collectively (Wells) (Sainsbury) (Griffin) found decreased height velocity during treatment, without post-therapy 'catch-up'. Two found no significant growth delay (Shalet 1979) (Swift) in populations studied collectively.

Because of the confusion in the literature and in order to assess the incidence and severity of effects on growth in our own leukaemia survivors, a longitudinal growth study of survivors of childhood leukaemia was carried out.

2.2 AIMS

a. To document the growth patterns of ALL survivors attending the Oncology Service of the Red Cross War Memorial Children's Hospital.

b. To compare the effects of different forms of treatment on the physical growth of children with cancer.

2.3 PATIENTS AND METHODS

2.3.1 Patients

All long-term survivors of acute lymphoblastic leukaemia were studied. Long-term survivors were patients who were disease free at the time of study and off all treatment for at least two

years. Thirty patients met these criteria. Ten were boys and 20 were girls (Figure 2.1).

FIGURE 2.1

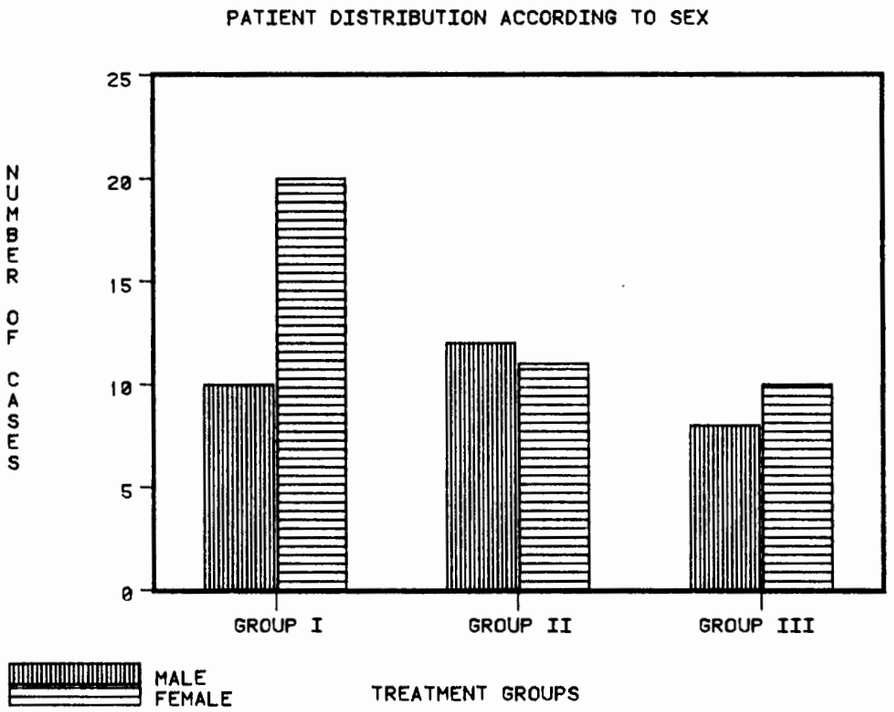


FIGURE 2.2

The distribution of social classes 1-5 (Davie) in each group is shown in Figure 2.2. Age at diagnosis ranged from 2 to 11,5 years (Table 2.2).

The diagnosis of acute lymphoblastic leukaemia was made on the basis of clinical findings, peripheral blood picture and bone marrow morphology (see Chapter 1). At diagnosis, all but one patient (No 26) had normal cerebrospinal fluid at lumbar puncture. Two patients had evidence of meningeal relapse of leukaemia during treatment (No 2, No 26).

Treatment of acute lymphoblastic leukaemia was given according to the St Jude Children's Hospital 'Total VII' protocol (Simone 1972) (Figure 2.3). Induction of remission was attained with prednisone, vincristine and L-asparaginase. Central nervous

TABLE 2.2

ALL PATIENTS : TOTAL DRUG EXPERIENCE

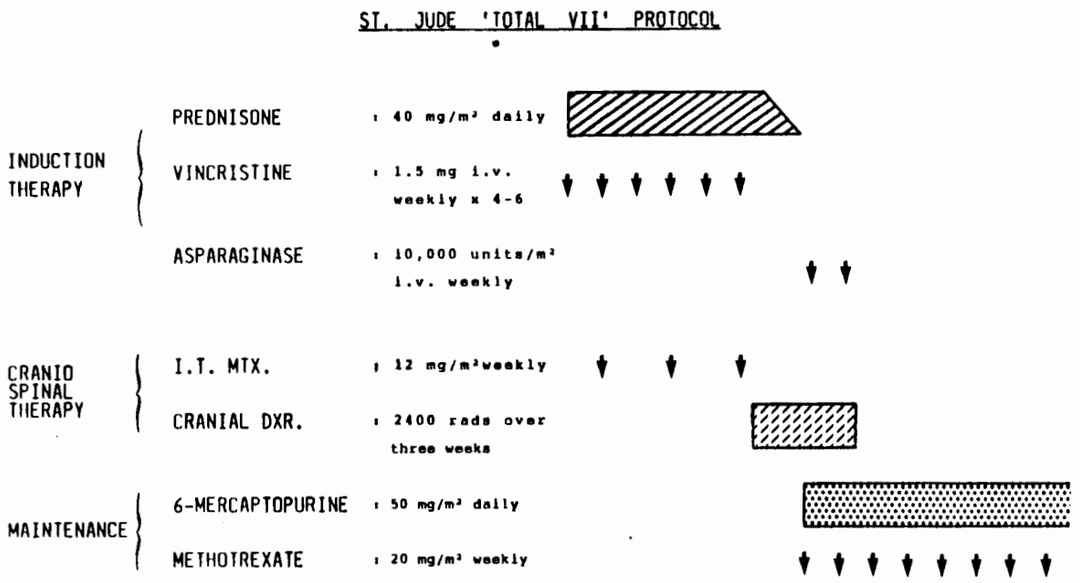
PAT NO	AGE DIAGN (yrs)	VINC (ug)	LASPAR (mean) (thous units)	IT MTX (mg)	ORAL MTX (mg)	IV MTX (mg)	IV CYTOSAR (mg)	IT CYTOSAR (mg)	THIO (mg)	HYDROX (mg)	IV CYCLO (mg)	ORAL CYCLO (mg)	DAUNO/ ADRIA (mg)	6 M-P (mg)	PRED (mg)
1	4,23	4,5	0	35	2077	0	0	0	0	0	0	0	0	39800	1680
2	5,50	15,8	0	171	4595	200	1020	1020	0	0	900	10450	71/118	99515	4110
3	6,75	72,2	16	178	1177	0	1136	0	21440	17600	1145	0	700/	17300	2020
4	11,50	12,6	0	68	3612	0	0	0	0	0	0	225100	210/	92100	1800
5	2,26	2,3	50	0	1350	0	3000	0	0	0	0	0	0	30240	5500
6	4,5	5,0	35	7,5		0	0	0	0	0	0	0	0		1120
7	7,09	10,4	78	50	1737	0	0	0	0	0	0	0	0	30725	1800
8	6,08	10,4	12	23,5	1767	0	0	0	0	0	0	0	0	24750	1680
9	2.53	9.6	12	53	2										
					855	0	0	0	0	0	0	0	0	43625	1920
10	3,86	9,3	14	40		0	0	0	0	0	0	0	0		1830
11	3,10	5,4	12	32,2	1550	0	0	0	0	0	0	0	0	25000	960
12	5,9	98,8	0	0	0	135	300	0	0	0	800	15000	90/	35000	4800
13	3,15	4,5	72,5	0	1800	0	0		0	0	0	0	0	30000	990
14	2,92	7,4	0	30	3265	0	0	0	0	0	0	0	0	49075	740
15	6,65	6,0	15	54	1660	0	0	0	0	0	0	0	0	21500	1200
16	2,70	4,0	0	30	2368	0	0	0	0	0	0	0	0	36050	700

Table 2.2 continued

PAT NO	AGE DIAGN (yrs)	VINC (ug)	LASPAR (mean) (thous	IT MTX (mg) units)	ORAL MTX (mg)	IV MTX (mg)	IV CYTOSAR (mg)	IT CYTOSAR (mg)	THIO (mg)	HYDROX (mg)	IV CYCLO (mg)	ORAL CYCLO (mg)	DAUNO/ ADRIA (mg)	6 M-P (mg)	PRED (mg)
17	5,14	5,6	18	60	2912	0	0	0	0	0	0	0	0	51300	1640
18	5,57	16,4	0	55	1482	177	350	0	0	0	3650	14250	75/	37635	4650
19	3,44	4,5	0	35	3010	0	0	0	0	0	0	0	0	52275	1440
20	5,17	12,5	15	48	2760	0	0	0	0	0	0	0	0	45975	2520
21	10,24	5,6	18	60	4002	0	0	0	0	0	0	0	0	54112	1400
22	8,4	16,0	28	188	5595	0	0	0	0	0	0	0		121825	3015
23	4,50	25,0	25	57	927	0	0	0	0	0	0	1100	0	16125	4900
24	3,55	8,1	12	42	1180	0	0	0	0	0	0	0	0	12150	1710
25	10,33	10,8	0	50	4185	0	0	0	0	0	0	0	0	64025	2100
26	5,1	18,4	0	185	13374	217	900	630	0	0	1600	82450	120/	78959	2945
27	3,44	6,0	0	63	1267	0	0	0	0	0	0	0	0	29537	2040
28	2,60	20,2	0	97,5	1840	0	6065	0	12540	66000	3960	0	392/	25550	1540
30	2,92	5,3	10	24	3148	0	0	0	0	0	0	0	0	43445	1200
31	8,80	6,7	0	50	3888	0	0	0	0	0	0	0	0	76675	1640

system 'prophylaxis' was provided by 2400 rad of deep x-ray therapy (250 kilovolt) therapy to the whole head and five doses of intrathecal methotrexate (12 mg/m²/dose). Maintenance chemotherapy consisted of daily 6-mercapto-purine and weekly methotrexate.

FIGURE 2.3



Drug treatment was not uniform. Details of each patient's drug experience is given in Table 2.2. Five patients received different doses of cranial radiation (Table 2.3). Of these, patients 5 and 13 received induction therapy at other hospitals. Patients 2 and 26 were given additional cranial radiation following meningeal relapse.

TABLE 2.3

RADIOTHERAPY SCHEDULES OF PATIENTS RECEIVING KILOVOLTAGE PROPHYLACTIC CRANIAL IRRADIATION

PAT NO	DOSE (rad)	MEV EQUIVALENT	NO OF FRACTIONS	DURATION (days)
1	2400	2808	15	20
2	2400	2080	10	15
	2340	2000	10	15
3	2400	2808	15	19
4	2400	2808	15	19
5	2400	2808	10	31
		2000 spinal	10	31
6	2400	2808	10	31
7	2400	2808	15	23
8	2400	2808	15	20
9	2400	2808	15	19
10	2400	2808	15	21
11	2400	2808	15	20
12	2400	2808	15	26
13	2000(Co)	1800	5	20
14	2400	2808	15	18
15	2400	2808	15	20
16	2400	2808	15	22
17	2400	2808	15	20
18	2400	2808	15	20
19	2600	3042	15	15
20	2400	2808	15	20
21	2400	2808	15	20
22	2400	2808	15	20
23	2400	2808	15	20
24	2400	2808	15	20
25	2400	2808	15	20

Table 2.3 continued

PAT NO	DOSE (rad)	MEV EQUIVALENT	NO OF FRACTIONS	DURATION (days)
26	2400	2808	15	24
	2000	2340	10	16
27	2400	2808	15	28
28	2400	2808	15	21
30	2400	2808	15	21
31	2400	2808	15	21

Radiation therapy dosage is given in rads of kilovoltage radiotherapy (delivered by deep x-ray therapy) and the calculated equivalent megavoltage dose (Mev)

Acute complications of treatment caused recurrent episodes of ill health. As an index of the impact of treatment on general well-being, review of patient charts provided the mean number of days for which treatment was withheld because of ill health and the mean number of acute infections during therapy (Table 2.4).

Growth of cancer patients were studied in two ways. Firstly by inspection and analysis of individual growth charts and secondly by collective assessment of growth in those patients who were prepubertal during the study period.

2.3.2 Comparison Groups:

Group I: This group consisted of patients diagnosed as having acute lymphoblastic leukaemia, who had received 2400 rads (Gcy) of cranial radiation.

Fourteen patients who were under 5 at diagnosis and who had not changed domicile during treatment were prepubertal during the study. Patients excluded from this group were: Patients 3, 4, 7, 8, 12, 15, 21, 22, 25, 31 because of age at diagnosis; patients 5, 15 and 26 because of alternative radiotherapy protocols (Table 2.3) and patients 20, 27 and 2 who changed domicile during treatment (see below).

TABLE 2.4

MORBIDITY ON TREATMENT

GROUP	DAYS OFF TREATMENT MEAN (RANGE)	NO OF INFECTIONS MEAN (RANGE)
I	53 (8-125)	10 (3-20)
II	8 (0-28)	4 (0-11)
III	31 (0-117)	6 (0-19)

Group II: Twenty-two children who had been treated for solid tumours with chemotherapy, but no radiotherapy. This group consisted of patients with Wilm's tumour, Non Hodgkins Lymphoma (NHL) and Neuroblastoma.

Patients with NHL had received a modified LSA-L2 drug protocol (Wollner), which included prednisone, vincristine, daunorubicin, asparaginase, oral and intrathecal methotrexate and cyclophosphamide.

Patients with Wilm's tumour had received vincristine and actinomycin. Because they had Stage I disease at diagnosis, Wilm's tumour patients in group II received no radiotherapy to the renal bed.

Patients with neuroblastoma were treated with vincristine, cyclophosphamide and daunorubicin.

Fourteen of these children were under 5 at diagnosis and provided a control group II: Children with cancer, who had been treated with cytotoxic chemotherapy but not radiotherapy, and who were prepubertal during the study period.

Group III: Seventeen children who had advanced Wilm's Tumour were treated with nephrectomy, chemotherapy and radiotherapy. Chemotherapy consisted of vincristine and actinomycin. More advanced cases were also given adriamycin or cyclophosphamide. Radiotherapy was given as kilovoltage (250 kv) deep x-ray therapy, 3000 - 3500 rads (Gcy) post-operatively to the renal bed. This field included the lumbar spine.

Fourteen children in this group were under the age of 5 at diagnosis and provided a further control group III: Children with cancer who had received chemotherapy and radiation to a site other than the head, who were prepubertal during the study period.

Patients in Group I received chemotherapy for 3 years as opposed to 1 -1½ years in the other groups. They also had more treatment-related morbidity (Table 2.4).

Sex (Figure 2.1) and social class (Figure 2.2) distribution was similar in the three groups.

2.3.3 Method:

Heights and weights had been measured at clinic visits for calculation of body surface area, and were recorded in patient charts. Height in metres was measured on a wall-mounted stadiometer and weight in kilograms on a balance scale. For ease of calculation, decimal ages were used (Tanner 1966).

2.3.3.1 Height

A height-for-age standard deviation (SD) score was calculated for each measurement of stature taken. The S.D score is equal to the patient's height (x) at a given age minus the mean height of a reference population ($\bar{x}$) divided by the standard deviation of height-for-age (SD) in the reference population.

$$\text{SD Score} = \frac{x - \bar{x}}{S\,D}$$

The population described by Tanner and Whitehouse (Tanner 1966) served as reference.

A height-for-age SD score was calculated for each patient at diagnosis and every anniversary of diagnosis and plotted against time since diagnosis (Figures 2.4 - 2.10).

The mean SD score of each group was calculated annually for patients under 5 at diagnosis and plotted against years elapsed since diagnosis (Figure 2.11).

2.3.3.2 Weight-for-Height

Individual weight-for-height scores SD of all patients using the National Centres for Health Statistics/Centre for Disease Control (NCHS/CDC) population (NCHS) as reference were similarly calculated. Group mean weight-for-height scores for patients under 5 at diagnosis were calculated and plotted against years elapsed since diagnosis (Figure 2.12).

2.3.3.3 Quetelet Index

A Quetelet Index (Cone), a measure of ponderosity derived by dividing height by the square of weight, was calculated for each pair of height and weight measurements. Group mean Quetelet indices for patients under 5 at diagnosis were calculated at diagnosis and at each anniversary of diagnosis and plotted against time (Figure 2.13).

2.3.3.4 Weight-for-Age

Weight-for-age SD scores, using the NCHS/CDC population (NCHS) as reference, were calculated for each measurement of weight, in patients under 5 at diagnosis. Group mean weight-for-age SD scores were then calculated at diagnosis and at each anniversary of diagnosis. Mean SD scores were plotted against years from diagnosis (Figure 2.14).

2.3.3.5 Statistical Analysis

The statistical significance of change in height-for-age and in weight-for-height within each group was calculated by means of the student 't' test for paired samples with unknown population standard deviation (Colton).

2.4 RESULTS

2.4.1 ALL patients

2.4.1.1 Height-for-age

2.4.1.1.1 Individual Growth Records (Figures 2.4 - 2.10)

With the exception of patients 2, 11 and 18 who showed increased height-for-age, and patient 21 who showed no change, all patients showed an initial fall in height-for-age during the first year of treatment. Patient 2 changed domicile to be near treatment. Increased height-for-age probably represents a growth spurt in response to better nutrition (from the rural Koo Valley, as a farm labourer, to St Joseph's home, a church hostel).

Patient 18 was on non-standard therapy (BCG vaccinations) prior to institution of St Jude Total V protocol. He only received cranial irradiation three years after diagnosis.

Patient 21 was 10.2 years at the time of diagnosis. His lack of deceleration of statural growth may be accounted for by the pubertal growth spurt. The non-conformity of patient 11 is unexplained.

FIGURE 2.4

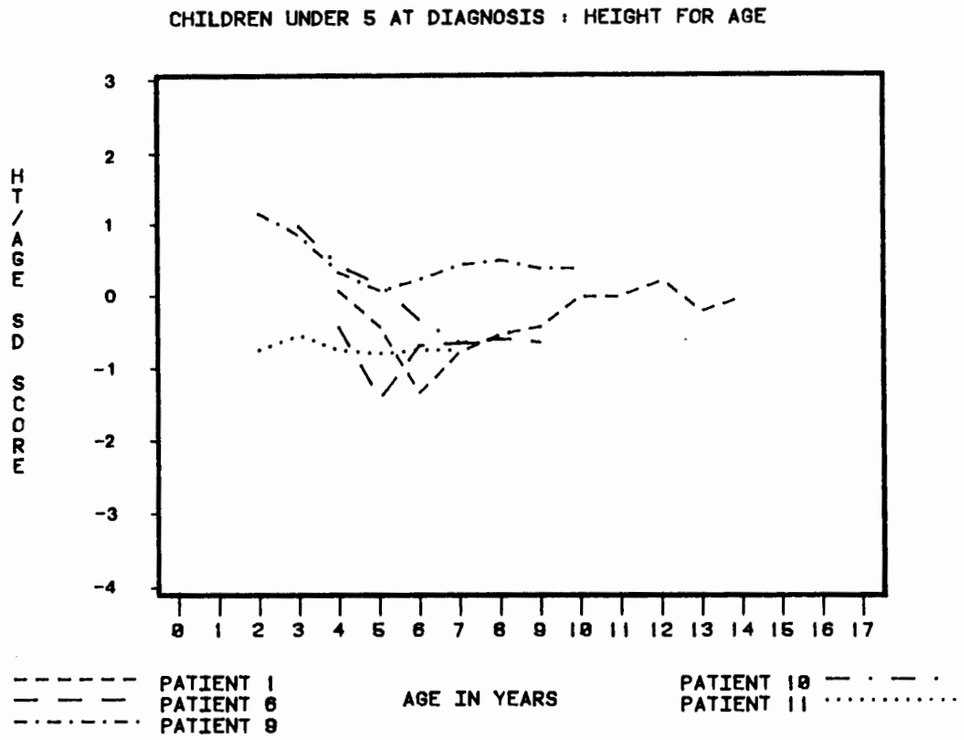


FIGURE 2.5

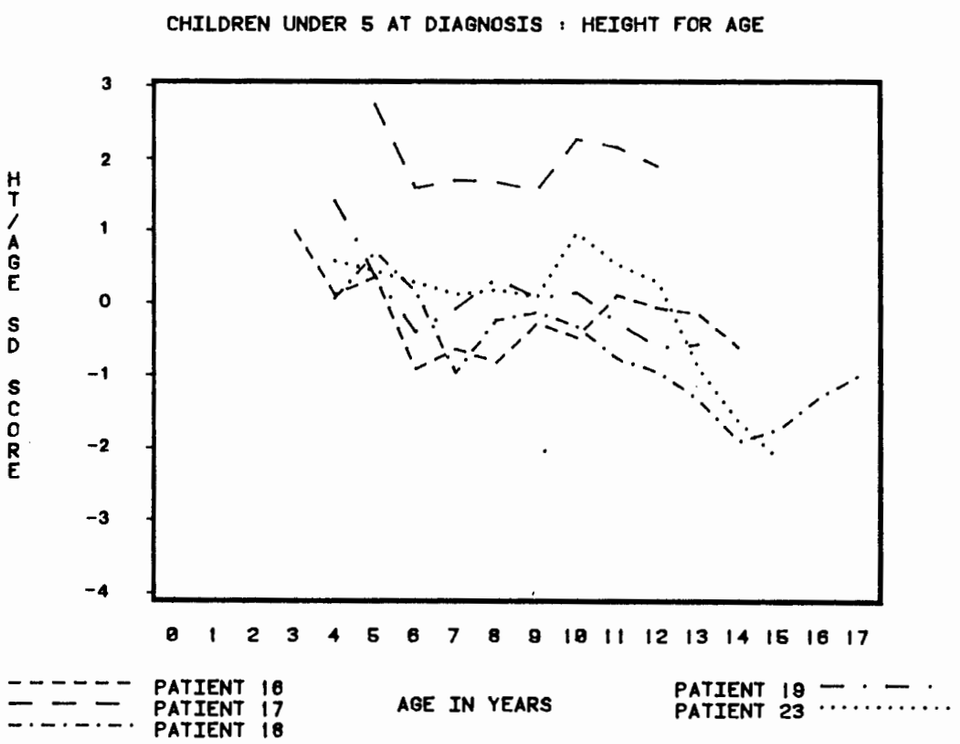


FIGURE 2.6

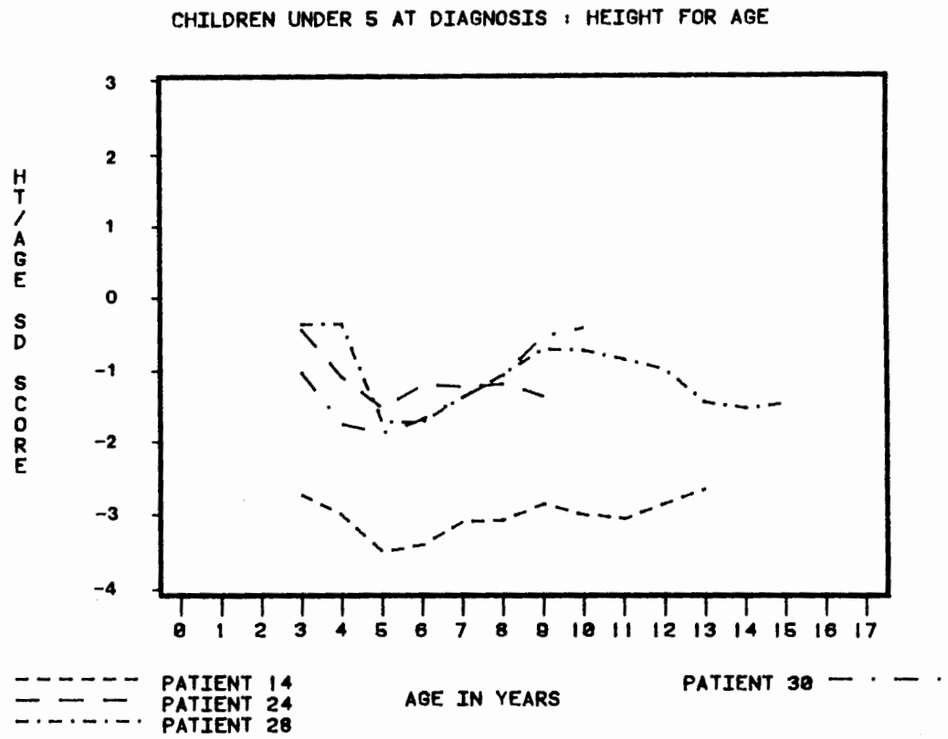


FIGURE 2.7

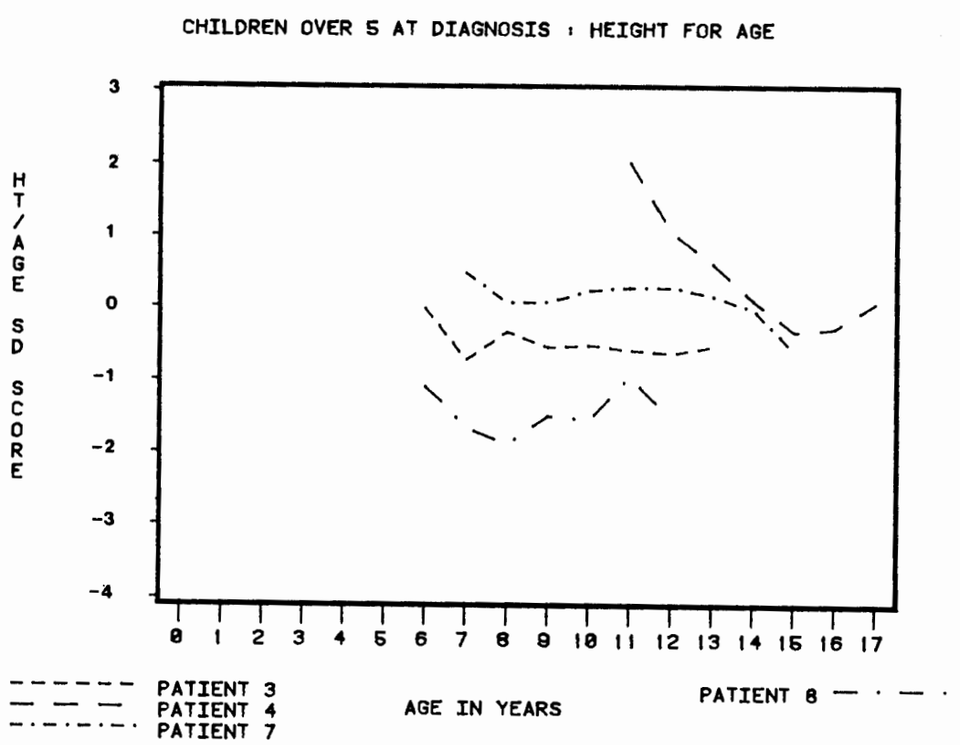


FIGURE 2.8

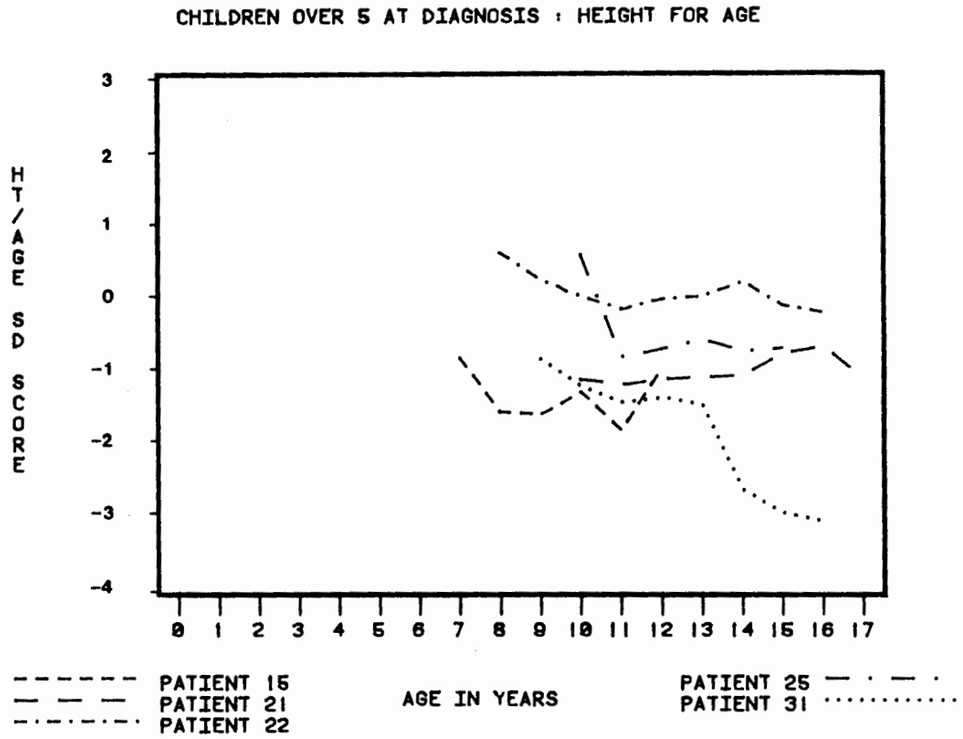


FIGURE 2.9

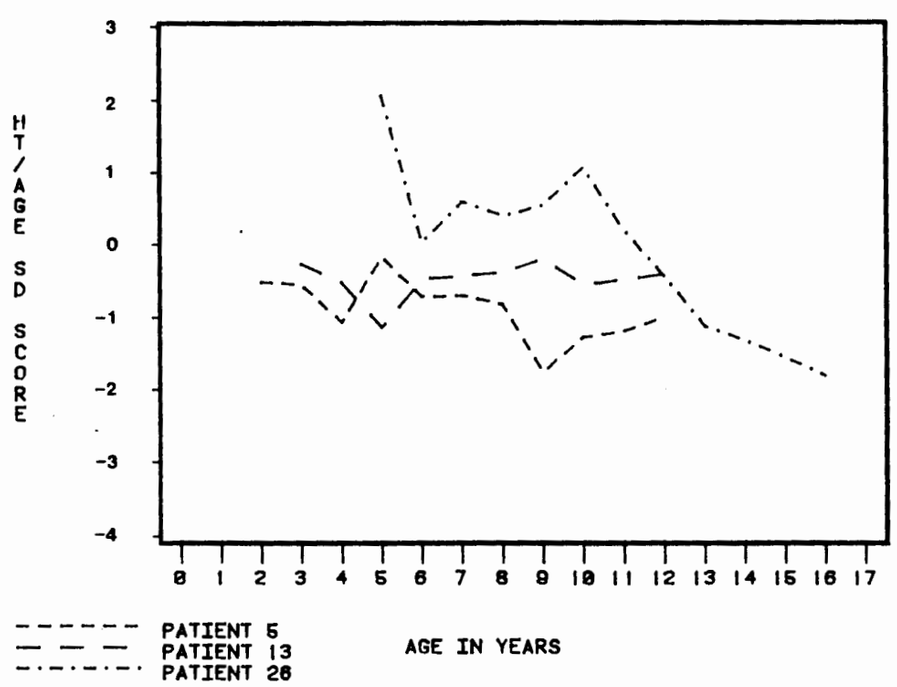
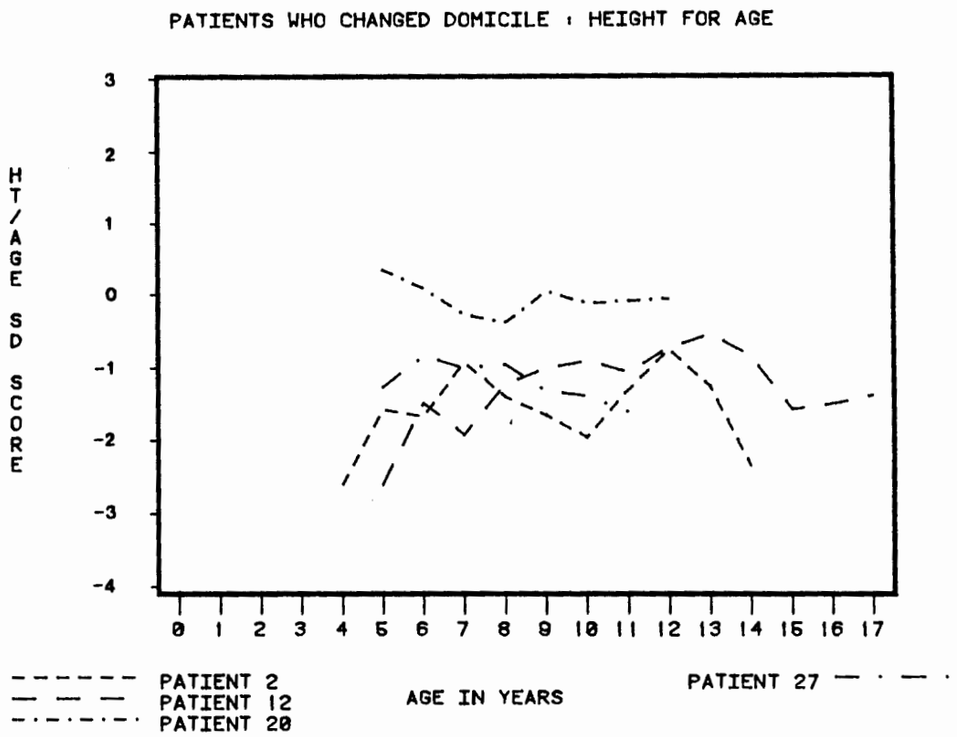


FIGURE 2.10


PATIENTS WHO CHANGED DOMICILE : HEIGHT FOR AGE
HT/AGE SD SCORE
3
2
1
0
-1
-2
-3
-4
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
AGE IN YEARS
PATIENT 2
PATIENT 12
PATIENT 20
PATIENT 27

2.4.1.2 2 Mean Height-for-Age (Figure 2.11) in children under 5 at diagnosis.

At the time of diagnosis, mean height-for-age did not differ significantly from that of the reference population (Tanner 1966). A fall in height-for-age was statistically significant by 1 year after diagnosis and remained so over the six year period of study (Table 2.5). After treatment had stopped, there was no 'catch-up' growth, but the rate of statural growth returned to normal.

FIGURE 2.11

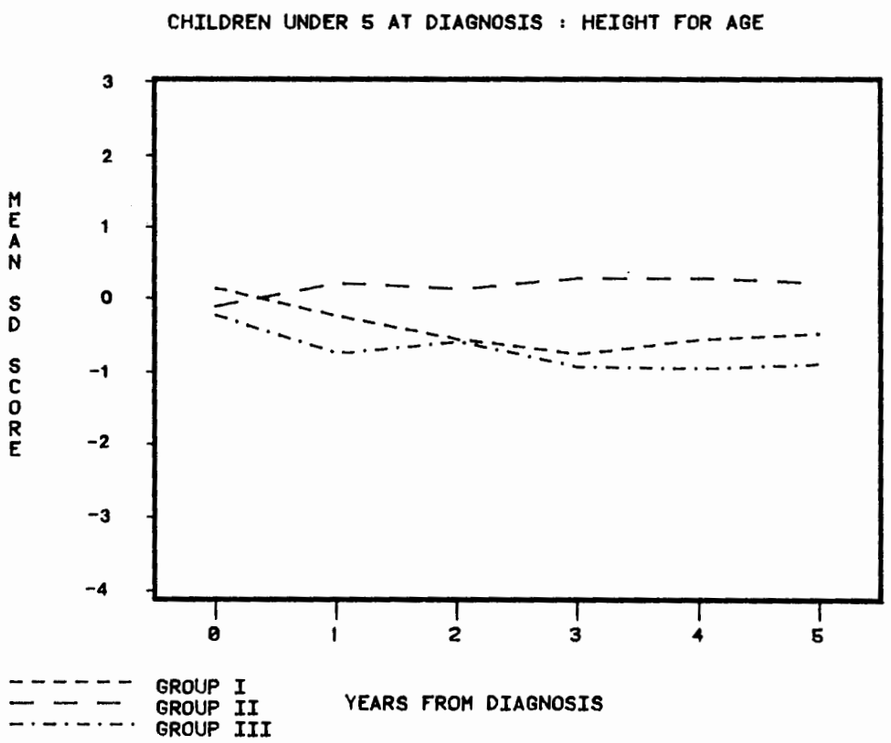


TABLE 2.5

GROUP I : STATISTICAL SIGNIFICANCE OF CHANGE IN HEIGHT-FOR-AGE FROM DIAGNOSIS IN ALL PATIENTS UNDER 5 AT DIAGNOSIS

YEARS	(n)	MEAN Ht/Age SD	$\bar{d}$ SD FROM DIAGNOSIS	t	p
0		0,19	-		
1	15	-0,19	-039	3,02	<0,01
2	15	-0,50	-0,69	4,93	<0,001
3	15	-0,70	-0,90	6,88	<0,001
4	12	-0,50	-0,81	6,79	<0,001
5	11	-0,42	-0,61	4,69	<0,001

2.4.1.2 Weight-for-Height

2.4.1.2.1 Individual Growth Records (see Appendix VI)

In all but patients 5 and 7 weight-for-height rose over the time of study. Patient 5 received non-standard therapy (2000 rads to the spine) which may have affected her weight gain (see Figure 2.12 Group III). Patient 7 showed a minimal decrease in weight-for-height.

2.4.1.2.2 Mean Weight-for-Height in children under 5 at diagnosis (Figure 2.12)

At diagnosis the mean weight-for-height of this group was significantly below the population mean. Mean weight-for-height one year after diagnosis was significantly higher than at diagnosis and remained so throughout the period of study (Table 2.6).

FIGURE 2.12

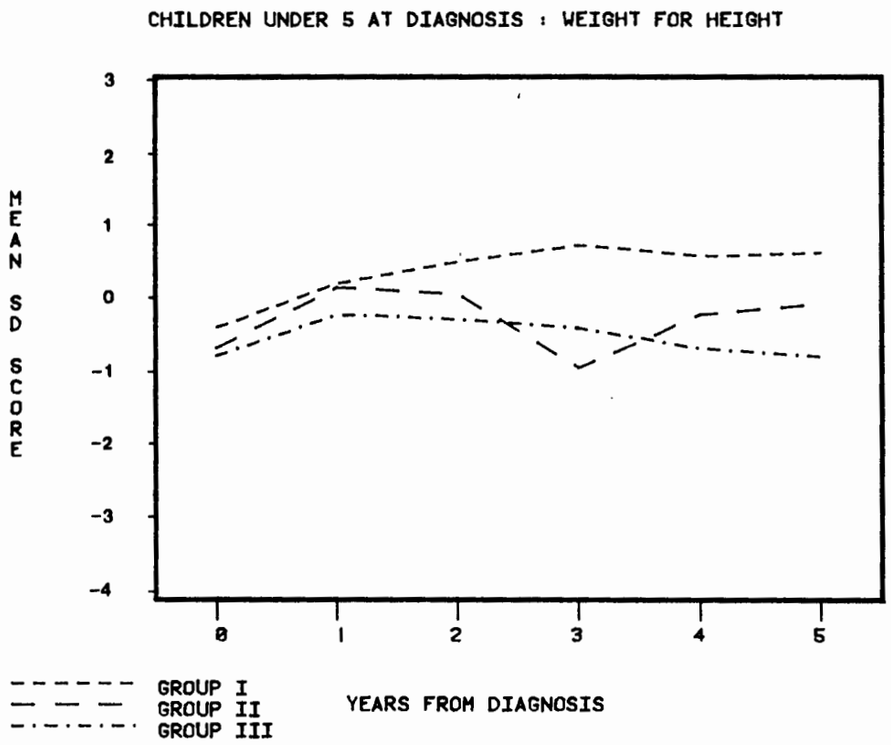


TABLE 2.6

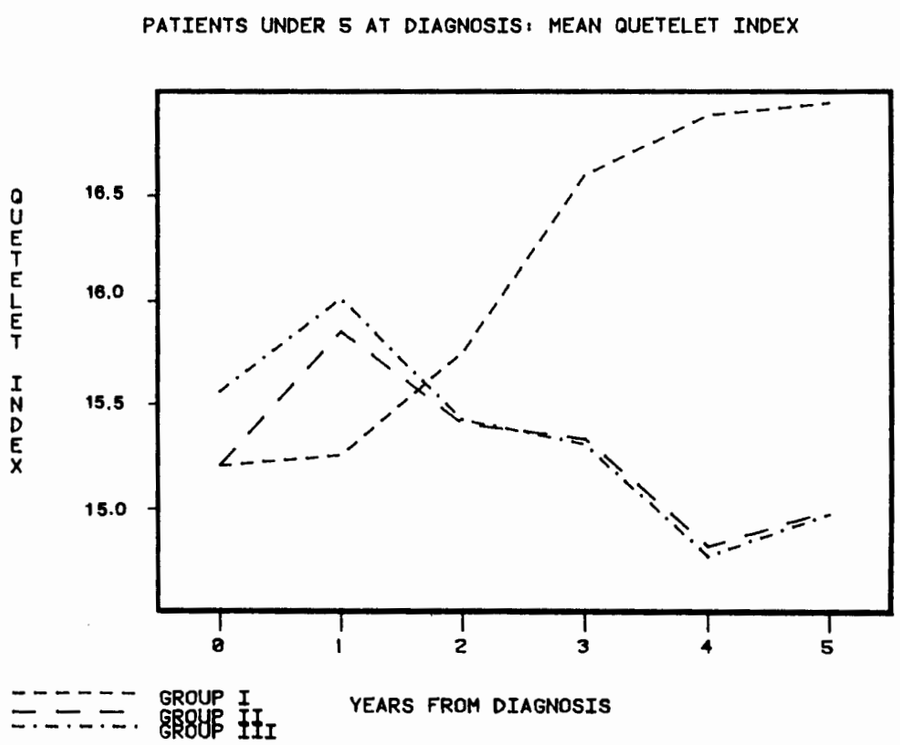
GROUP I : STATISTICAL SIGNIFICANCE OF CHANGE IN WEIGHT-FOR-HEIGHT FROM DIAGNOSIS IN ALL PATIENTS UNDER 5 AT DIAGNOSIS

YEARS	(n)	MEAN Wt/Ht SD	$\bar{d}$ SD FROM DIAGNOSIS	t	p
0	15	-0,35	-	-	-
1	15	0,24	0,59	2,75	$<0,01$
2	15	0,53	0,77	4,20	$<0,001$
3	15	0,75	1,29	5,25	$<0,001$
4	14	0,60	1,11	4,66	$<0,001$
5	12	0,65	1,06	3,99	$<0,001$

2.4.1.3 Quetelet Index (Figure 2.13) patients under 5 at diagnosis

Mean Quetelet index increased progressively in Group I throughout treatment and after treatment had stopped.

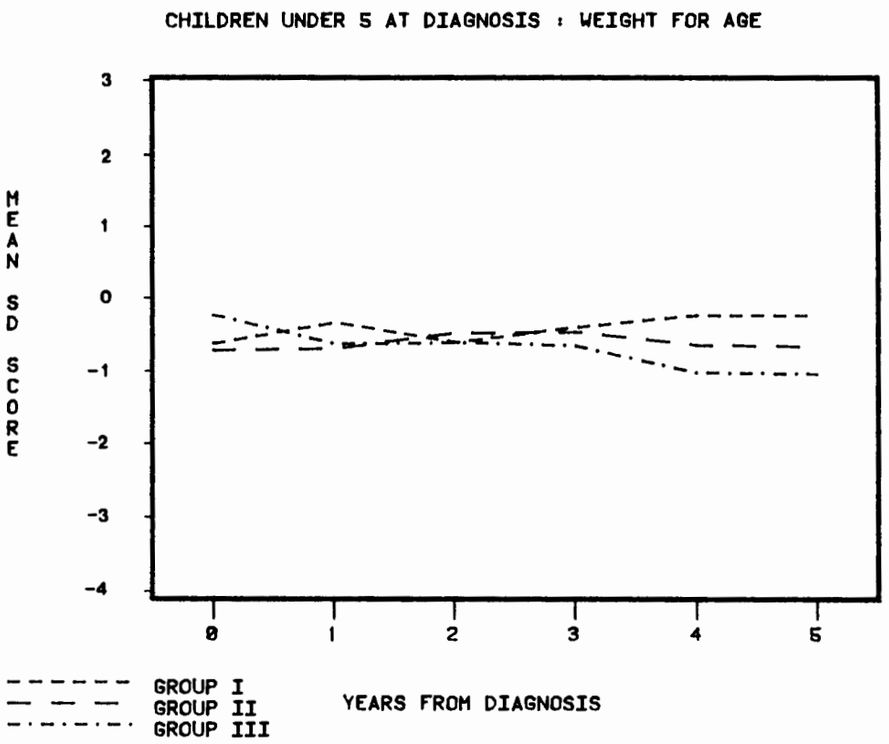
FIGURE 2.13



2.4.1.4 Weight-for-Age (Figure 2.14)

Mean weight-for-age rose in group I during the first year of treatment, fell during the second year and then rose slowly after therapy was stopped.

FIGURE 2.14



2.4.2 Group II Children with Solid tumours

2.4.2.1 Height-for-Age

In children with solid tumours treated with chemotherapy alone, there was no significant change in mean height-for-age during the period studied (Figure 2.11) (Table 2.7). A trend toward lower height-for-age during the year of treatment, was reversed by a growth spurt following the end of treatment.

TABLE 2.7

GROUP II : STATISTICAL SIGNIFICANCE OF CHANGE IN HEIGHT-FOR-AGE FROM DIAGNOSIS

YEARS	(n)	MEAN Ht/Age SD	$\bar{d}$ SD FROM DIAGNOSIS	t	p
0	14	-0,05			
1	14	0,26	-0,255	2,28	NS
2	14	0,18	-0,177	1,12	NS
3	14	0,33	-0,325	1,54	NS
4	14	0,33	-0,325	1,75	NS
5	13	0,26	-0,255	1,42	NS

2.4.2.2 Weight-for-Height

In this group of children no significant change in weight-for-height occurred from the time of diagnosis to the end of study (Figure 2.12) (Table 2.8), although the mean weight-for-height had returned to the reference population mean by the end of the study.

TABLE 2.8

GROUP II : STATISTICAL SIGNIFICNCE OF CHANGE IN WEIGHT-FOR-HEIGHT FROM DIAGNOSIS

YEARS	(n)	MEAN Wt/Ht SD	$\bar{d}$ SD FROM DIAGNOSIS	t	p
0	14	-0,62			
1	14	-0,18	+0,50	1,85	NS
2	14	0,09	+0,73	2,03	NS
3	14	-0,9	+0,56	1,49	NS
4	14	-0,18	+0,49	1,31	NS
5	14	-0,03	+0,59	2,14	NS

2.4.2.3 Quetelet Index

The group mean Quetelet index changed very little throughout the study (Figure 2.13).

2.4.2.4 Weight-for-Age (Figure 2.14)

There was no significant change in weight-for-age during the period studied.

2.4.3 Group III Children Treated with Radiation to the Renal Bed

2.4.3.1 Height-for-Age

In patients with Wilms tumour treated with chemotherapy and post-nephrectomy radiation to the renal bed, there was a significant decrease in height-for-age during treatment. There was a compensatory growth spurt for 1 year at the end of treatment which was followed by a further fall in height-for-age. Height velocity returned to normal at the end of the study. (Figure 2.11) (Table 2.9).

TABLE 2.9

GROUP III : STATISTICAL SIGNIFICANCE OF CHANGE IN HEIGHT-FOR-AGE FROM DIAGNOSIS

YEARS	(n)	MEAN Wt/Ht SD	$\bar{d}$ SD FROM DIAGNOSIS	t	p
0	14	-0,18			
1	14	-0,69	-0,65	3,2	$< 0,01$
2	14	-0,53	-0,58	2,49	$< 0,05$
3	14	-0,88	-0,89	3,92	$< 0,01$
4	14	-0,90	-0,98	5,02	$< 0,001$
5	12	-0,83	-1,10	3,33	$< 0,01$

Growth impairment appeared confined to the spine. In all these patients, sitting height was below -2 S.D. for age and marked trunk shortening was visible.

2.4.3.2 Weight-for-Height

There was a steady and statistically significant increase in weight-for-height during the first two years in children under 5 at diagnosis, which attained significance 2 years after diagnosis. At the end of the five year follow-up weight-for-height had returned to prediagnosis levels (Figure 2.12) (Table 2.10).

TABLE 2.10

GROUP III : STATISTICAL SIGNIFICANCE OF CHANGE IN WEIGHT-FOR-HEIGHT FROM DIAGNOSIS

YEARS	(n)	MEAN Wt/Ht SD	$\bar{d}$ SD FROM DIAGNOSIS	t	p
0	14	-0,73	-	-	-
1	14	-0,18	+ 0,57	3,43	< 0,01
2	14	-0,25	+ 0,48	2,21	< 0,05
3	14	-0,37	+ 0,30	1,58	NS
4	14	-0,64	+ 0,08	0,29	NS
5	12	-0,75	- 0,08	0,25	NS

2.4.3.3 Quetelet Index

The mean Quetelet index dropped slightly during the study (Figure 2.13).

2.5 DISCUSSION

2.5.1 Statural Growth in Leukaemia Survivors

Leukaemia survivors in this study grew at a reduced height velocity during the three years of therapy (Figure 2.11). There was an insignificant acceleration in statural growth at the end of treatment which was not enough to produce the 'catch-up' growth which is characteristic of return to health after a chronic illness (Prader). After treatment a normal rate of statural growth was resumed.

Loss of height-for-age occurred uniformly throughout the group, so that although in terms of absolute height loss the change was small, it was statistically significant by one year from diagnosis (Table 2.5). In comparison with the mean height-for-age at diagnosis (+ 0,19 SD) the loss in mean height-for-age remained statistically significant throughout the study.

In absolute terms, the loss of height represented by a mean height-for-age SD score of -0,61 would be approximately 4,5 cm in a mature male and 4 cm in a mature female (Tanner 1966).

It is expected that mean adult stature in this group will be reduced.

2.5.1.1 Comparison of Statural Growth in Group I with Group II and III (Figure 2,11)

All three groups showed a slowing of statural growth from diagnosis. This was most evident in groups II and III during the first year of treatment. In group I, deceleration of statural growth continued throughout the three year treatment period.

In group II there was an increase in height SD score after the first year, with patients still on treatment. In group III there was a slight increase in height SD after one year. This was when chemotherapy was stopped.

It is apparent from the SD scores in group II that malignant disease and chemotherapy have a negative influence on statural growth. This effect is statistically small and is probably not associated with a significant decrease in the final adult height.

Stature was significantly affected by treatment in Group III which included deep x-ray therapy to the lumbar spine. Slowing of statural growth following irradiation of the spinal column is related to impaired endochondral ossification in vertebral bodies (Dawson) (Katzman). Scoliosis, secondary to flank muscle wasting or unilateral vertebral body damage, may further contribute to short stature (Littman). These effects were clinically evident in our patients. Trunk shortening relative to body length and mild scoliosis were frequent. Sitting heights were not recorded in patient charts, but in a group of

14 patients, with a mean age of 11,5 years and a mean 9,8 years from the time of spinal radiation, most recent mean sitting height SD was -1,93 ($\pm$ 1,6). Damage to the spinal column during deep x-ray therapy to the renal bed was the likely major contributory cause of short stature in group III.

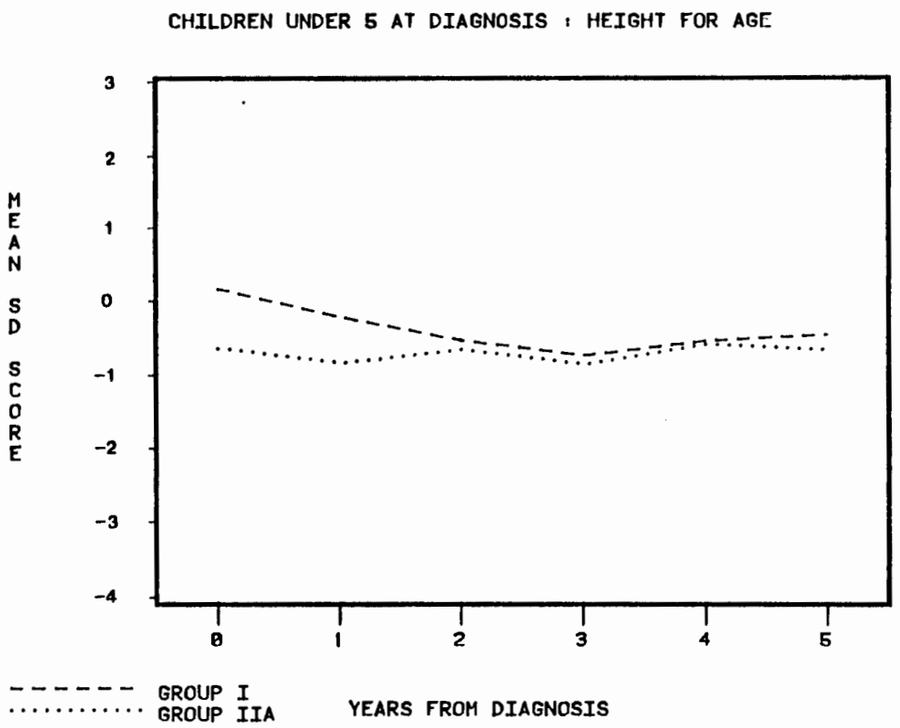
As a result of slower growth during the three years of therapy, children in group I, who received cranial irradiation and chemotherapy, had a significantly lower mean height-for-age SD score at their most recent examination than they had at diagnosis, and a significantly lower height-for-age SD score than the mean of the standard population.

The rate of fall in height-for-age SD score was constant throughout treatment and not restricted to the first 6 months of therapy, when cranial radiotherapy was administered. Neither one of the comparison groups provides an adequate control against which to assess the effect of cranial irradiation on growth in isolation. The only study in which such a control group was available (Wells et al 1983) found that patients receiving cranial irradiation had lower height velocities during therapy than normal subjects or leukaemic patients not receiving cranial radiation. These authors feel that cranial irradiation and not leukaemia or chemotherapy causes reduced growth.

A subgroup of 6 children in group II had Non-Hodgkins lymphoma diagnosed under the age of 5 years. They received intensive chemotherapy (LSA_2 protocol) for three years including intrathecal methotrexate, but were not given cranial

irradiation. Apart from not receiving cranial irradiation, their treatment was very similar to that of the children in group I. Mean statural growth of these children is reflected in Figure 2.15. There was some reduction in mean height-for-age SD score during treatment but after 5 years it was the same as at diagnosis.

FIGURE 2.15



This small subgroup (Group IIA) (Figure 2.15) was the best control group available in this study for determining the effect of cranial irradiation on statural growth. A comparison of growth in Groups I and IIA suggests that cranial irradiation may contribute significantly to growth retardation during and following treatment.

These findings regarding height-for-age in ALL are similar to those of previous studies (Swift) (Griffin). Children treated with whole head irradiation grew abnormally slowly during therapy. A normal rate of statural growth was regained once treatment has stopped. There was no compensatory growth spurt off treatment and ultimate stature will therefore be reduced. This is in contrast to 'catch-up' growth seen as a normal event in children recovering from a chronic illness or starvation (Prader).

Slowing of growth may not be wholly attributable to malignant disease or chemotherapy alone, because children with solid tumours, treated with intensive chemotherapy (Group II), showed statural growth within normal limits. More severe morbidity on treatment (Table 2.4) may have contributed to the slower growth in Group I, but children given equally intensive therapy (subgroup IIA) did not experience such marked inhibition of growth.

Hypothalamic/pituitary dysfunction resulting from cranial irradiation is a possible cause of growth failure in children treated for ALL (Dacou-Voutetakis) (Shalet 1981). Abnormalities of growth hormone secretion are frequent after cranial irradiation. This issue is discussed in depth in Chapter 3.

The lack of 'catch-up' growth in the group and failure of the adolescent growth spurt in some patients (see below) may occur because of abnormal hypothalamic-pituitary control of growth hormone release (see Chapter 3).

Increasing weight-for-height ratios favour an endocrine cause for stunting rather than other treatment-related factors, such as anorexia, emotional stress, malabsorption or hepatic dysfunction.

Patients treated for ALL received corticosteroids for 4-6 weeks during induction therapy (Figure 2.3). This therapy, while producing transient weight gain and growth hormone suppression (Blodgett) (Elders), should not produce long-term stunting or increased ponderosity.

2.5.1.2 Individual Statural Growth Records (Figures 2.4 - 2,10)

It may be seen from individual SD records, that the fifteen patients in group I had growth patterns that paralleled one another very closely.

Some other individual growth curves were instructive. Patient number 2 (Figure 2.10) gained in statural height from the time of diagnosis up to the end of treatment, but his height velocity slowed at the end of treatment. This was opposite to the trend observed in group I. This patient came from an extremely poor rural environment, where he herded sheep. To achieve adequate care, he was institutionalized for the three years of treatment. His increased rate of growth during treatment was possibly the result of better nutrition. He went back to his poor environment at the end of treatment, and slowed in statural growth. A subsequent growth spurt started at 11,5 years of age and stopped 2 years later. This represented his pubertal growth spurt. Patient no 12 (Figure 2.10) was also institutionalized

for treatment and had a similar growth record. These growth curves suggest that the effect of adequate nutrition overrides the negative effects of disease and treatment in previously undernourished patients .

Patient No 18 (Figure 2.5) only received cranial irradiation 1,6 years after diagnosis and the start of therapy. A fall in height-for-age coincided with his cranial irradiation. In this patient, the diagnosis of leukaemia was made at 5,5 years of age. Between 5 and 10 years after diagnosis (11,5 - 15,5 years old) his statural growth showed a steady decline, suggesting failure of pubertal growth.

Patient 26 (Figure 2.9) received two doses of cranial irradiation and a course of reinduction therapy because of CNS relapse. The second course of treatment was given 5 years after diagnosis. Her growth chart shows a recurrence of the fall in height-for-age following retreatment. Her ultimate height-for-age SD score was 4 standard deviations below its prediagnosis level.

Although mean height-for-age records suggest that the average real height loss is small, individual growth charts show that several children may be severely stunted. Their short stature became more apparent when they were seen with their immediate family members in group photographs or in the clinic. Management of growth disorders during and after the treatment of ALL must clearly be individualized.

2.5.1.3 Management of Growth Disorders

Since following cranial irradiation this is based on endocrine considerations this will be discussed in the next chapter.

2.5.2 Weight-for-Height and Quetelet Index

In the study of patients under 5 years old at diagnosis, only Group I (children surviving leukaemia) showed a steady increase in weight-for-height (Figure 2.12). With two exceptions an increase in weight-for-height was observed in all individual growth records as well. This increase in ponderosity is reflected in the steady increase in the mean Quetelet index in Group I.

Since children in Group I were under the age of 5 at diagnosis, increase in ponderosity over the five years of study could not be accounted for by the physical development of puberty, when increasing muscularity (in boys) or adiposity (in girls) might have had the same effect.

Physical examination of these children suggested obesity to be the cause of increasing weight-for-height. This observation was not substantiated by measurements of skinfold thickness, since these had not been carried out longitudinally.

In a previous study, a similar observation of obesity in a cohort of leukaemia survivors was made (Sainsbury). The authors of this report thought obesity to be the consequences of parental cosseting of their ill children. This explanation seems unlikely, because weight-for-height did not increase in Group II.

High dose steroid therapy is likely to cause an increase in weight-for-height and obesity (Blodgett) (Elders) if given in prolonged courses. Leukaemia survivors received steroid therapy for one month, which could not have caused the sustained increase in weight-for-height observed.

Obese children are generally taller than thin children of the same age. The presence of obesity in children of short stature may indicate an endocrine cause for stunting (Tanner 1972). While the children in Group I fall within the normal centiles for stature, their progressive increase in ponderosity in the presence of impaired statural growth is anomalous when compared to normal fat children. Whereas normal growth velocity attained at the end of treatment implies adequate growth hormone secretion, relative growth hormone deficiency during the period of cranial irradiation may account for the decreased growth velocity and increased obesity during this time. Relative growth hormone deficiency may contribute to obesity in children with isolated growth hormone deficiency (Tanner 1972). The subject of relative growth hormone deficiency in leukaemia survivors is examined further in Chapter 3.

Hypothalamic hyperphagia and obesity was described in at least 14 children with near terminal leukaemia before the introduction of pretreatment for silent meningeal leukaemia (Barak). Leukaemic damage to the hypothalamus was confirmed at autopsy in most of those patients. Such damage is not likely to have occurred in Group 1 patients, all of whom had clear CSF at diagnosis (see Section 1.2.5).

The psychosocial consequences of obesity in leukaemia survivors has never been assessed. Some aspects of this problem will be discussed in Chapter 7.

Weight-for-height and the Quetelet index remained relatively stable throughout the study in patients from Group II. This suggests that neither endocrine nor non-endocrine factors alter weight-for-height ratios in non-head irradiated survivors. The fall in weight-for-height in Group III was thought to reflect muscular and subcutaneous wasting of the flank, which followed radiotherapy to the renal bed.

2.5.3 Methodology

2.5.3.1 Errors in measurement

Errors in measurement of height were evident in some patient records. Errors were most frequent at diagnosis and during induction therapy if patients were ill and were measured supine. In a minority of patients initial measurements were well in excess of subsequent measurements. In such cases, initial measurements were adjusted by reference to growth standards (Tanner and Whitehouse) (NCHS). Anthropometric measurements during treatment were generally taken for estimation of surface area and drug dosage. Techniques were not necessarily as careful as they would have been for an anthropometric study. Because this study was longitudinal and because inferences were based on trends rather than cross-sectional assessment, the impact of inaccuracy in individual measurement would have been reduced.

2.5.3.2 Missing Values

In many instances children had not been measured near an anniversary of birth or a half-year. In such cases the SD score of height-for-age or weight-for-height was calculated by extrapolation between two measurements as is the practice in anthropometric surveys (Tanner 1951). Calculations were simplified by the use of decimal dates (Tanner 1966).

2.5.3.3 The Standard Deviation Score

The standard deviation score (SD score) has supplanted the use of centiles and other comparative devices in recent anthropometric studies because of its ease of application.

In a normally distributed sample, the SD score has a mean of 0 and an SD of 1. Because of the adolescent spurt, height SD scores between the ages of 10 and 16 in girls and 12 and 18 in boys do not have the simple interpretation which is valid at other ages.

SD scores of 1 and 2 correspond approximately to the 75th and 97th centile and SD scores of -1 and -2 to the 25th and 3rd centiles of height-for-age.

CONCLUSIONS

Children treated for acute lymphoblastic leukaemia manifest an abnormal growth pattern. This is characterized by a reduced height velocity during treatment and a failure of 'catch up' growth. Eventual adult stature is likely to be reduced, in spite of normal height velocity

after treatment has been stopped. This abnormal pattern of growth may be modified by environmental factors in individual patients as well as by the pubertal growth spurt.

Children treated for acute lymphoblastic leukaemia exhibit an increase in weight-for-height during and after therapy. This appears to be on the basis of failure of statural growth as well as increasing weight-for-age since both were shown to change during the period of study.

CHAPTER 3

ENDOCRINE SEQUELAE OF ACUTE LYMPHOBLASTIC LEUKAEMIA AND ITS TREATMENT

3.1 INTRODUCTION

Endocrine dysfunction may be a long-term complication of acute lymphoblastic leukaemia and its treatment. The hypothalamus, pituitary and thyroid glands are at risk in cranial irradiation. They have not been shown to be damaged by chemotherapy. Certain forms of chemotherapy may damage gonadal function.

3.1.1 Hypothalamus and Pituitary

Earliest knowledge of the endocrine consequences of cranial irradiation followed attempts to influence gynaecological disease by radiation of the hypophysis (Lawrence). The first studies on the effects of pituitary irradiation of animals were carried out in Germany, and took the form of histological examination of the brains of sacrificed animals (Strauss) and measurements of their growth (Brunner). It was learnt that histologic changes occur in the pituitary (Brunner) (Strauss) and that there is some suppression of growth after irradiation of the whole head (Brunner). Doses of irradiation were not given.

This knowledge was extended by later workers and confirmed in the first study reported in the English literature. Lawrence (1937) selectively irradiated hypophyses of rats using a total of 2500 rads in three fractions. He noted temporary growth retardation, atrophy of the target organs for pituitary hormones (thyroid, adrenals, ovaries) and histological abnormalities in the pituitary. He could not exclude the

possibility that hypothalamic damage was the basis of anterior pituitary malfunction.

Until the work of Arnold (1954) little attention had been paid to the possible effects of radiation on the hypothalamus even though, in radiating the pituitary during the animal experiments mentioned above, the ventral portions of the hypothalamus would unavoidably have been irradiated as well. Arnold irradiated the hypophyseal region of adult monkeys with 23 megavolt x-rays, in doses between 375 rad and 14,000 rad (equivalent to 225-8400 rad of 250 kilovoltage x-rays). Radiation was delivered in a single dose. He found selective damage in the supraoptic and paraventricular nuclei of the hypothalamus, in doses above 1500 r mev (900 rad kv) in animals sacrificed 6 months after radiation. In these experiments the endocrine consequences of irradiation were not studied.

The first clinical report of post-radiation hypopituitarism was of a patient who had been treated for nasopharyngeal carcinoma (Tan). She had received two courses of 400 kv x-ray therapy to a total dose of approximately 9000 rads and developed arrested growth, amenorrhoea and hypothyroidism. Larkins and Martin (1973) reported on two further adults who had received 3000 and 6500 rads of 250 kv x-rays for extracranial tumours. Both patients developed delayed hypopituitarism several years later. The second patient had a normal thyroid stimulating hormone (TSH) reponse to thyrotropin releasing hormone (TRH) and a normal cortisol response to vasopressin, suggesting that hypopituitarism was due to primary hypothalamic damage.

Samaan et al (1975) reported a series of 15 patients over 16 years old who had received between 5000 and 8000 rads from various x-ray sources (cobalt 60, 22 Mev, 250 kv) for nasopharyngeal cancer. Twelve patients had evidence of hypothalamic dysfunction, 7 of primary hypopituitarism and 3 of primary hypothyroidism (some patients had more than one endocrine pathology). These findings indicated that depending on dose, abnormalities of pituitary function could be due to either hypothalamic or pituitary damage.

Pituitary function after cranial irradiation of children was first studied by Shalet et al (1975). This group found impaired growth hormone (hGH) responses to insulin-induced hypoglycaemia following cranial irradiation. Children with impaired hGH responses also had elevated basal TSH levels and exaggerated TSH secretion after TRH. Growth hormone responses fell progressively with time after radiation. Affected children had short stature (cross-sectional assessment) and retarded bone ages. They had normal responses to luteinizing hormone releasing hormone (LHRH). Dosages of cranial irradiation were not reported. Children were considered to be growth retarded, but longitudinal growth data were not reported. Affected children were labelled growth hormone deficient on the basis of response to insulin hypoglycaemia. Growth velocity was not discussed.

Impairment of growth hormone response to pharmacologic stimuli was confirmed by other workers (Fuks) (Harrop) and it was suggested that clinical follow-up of patients given cranial irradiation should include endocrine assessment. It was

recommended that when such patients presented with growth failure, they might benefit from hGH replacement therapy.

In a further study, Shalet et al (1976(c)) reported on patients who had received between 2700 rads and 5000 rads of cranial irradiation (250 kv DXR). Bone age was uniformly retarded. It was not possible to comment on growth rate, but retarded growth was apparent. Growth hormone response to hypoglycaemia was depressed, but cortisol responses were normal. There was no correlation between hGH peak levels and degree of growth delay. The delay in expression of hypothalamo-pituitary damage was ascribed to gradual development of post radiation endarteritis. It was thought that chemotherapy given with radiotherapy may have sensitized nervous tissue to the effects of radiation. A dose of under 2900 rad (DXR) was considered relatively safe with respect to late effects on hGH secretion (Shalet Clin Endocr 1976).

Richards et al (1976) reported on pituitary function of 8 patients after radiotherapy for extracranial tumours. All had received over 4000 rads to the hypothalamo-pituitary area and had a retarded rate of growth. All but one had impaired hGH responses to insulin hypoglycaemia, arginine and L-dopa, with normal prolactins and normal TSH responses to TRH, normal cortisol responses to hypoglycaemia and normal LH and FSH responses to LRH. One patient had TSH, ACTH and gonadotropin deficiency.

Dickinson et al (1978) found doses of cranial irradiation over 2400 rad (source of radiation not given) to be associated with

severe growth suppression and impaired hGH response to pharmacological stimuli (insulin hypoglycaemia and arginine infusion). Patients given under 2400 rads of cranial irradiation had a normal hGH response to arginine, but a blunted response to insulin hypoglycaemia. Since arginine acts directly on the pituitary to stimulate hGH release (Cavagnini), these workers postulated that cranial irradiation up to 2400 rads might damage the hypothalamus, while sparing the pituitary gland. They also made inferences based on the group mean peak hGH levels after stimulation tests, which are of doubtful clinical value.

In a follow-up study, Samaan et al (1975) demonstrated endocrine deficiency in 62 of 65 patients receiving 2400-7000 rads to the hypothalamus and 2000-7500 rads to the pituitary. They confirmed primary hypopituitarism in 25 patients, but gave no data to indicate radiation thresholds beyond which such damage ensued. Thirty-nine patients showed high basal prolactin levels, suggesting a high incidence of hypothalamic damage, but once again, a radiation threshold was not indicated.

Shalet (1982(a)) equated a blunted hGH response to pharmacologic stimuli with growth hormone deficiency, and advocated hGH replacement therapy in children who had abnormal responses to hGH stimulation tests after radiation.

Effects of cranial irradiation used as 'CNS prophylaxis' in acute lymphoblastic leukaemia on hGH secretion were first reported in 1974 (Dacou-Voutetakis). These authors reported a

decrease in spontaneous nocturnal secretion of hGH immediately after radiation, which recovered within 6 to 12 months. Radiation dose was 2400 rad from a cobalt-60 source. Shalet et al (1976(b)) found delayed bone age and suppression of hGH response to hypoglycaemia and Bovril in 15 survivors of ALL at least 3 years after irradiation. Growth was impaired in this group, but 12 had also received spinal irradiation. Children who had received 2500 rads (DXR) in 10 fractions had lower peak hGH levels than those who had received 2400 rads in 20 fractions. In a group of patients reported by van Mühlendal et al (1976) who had received 850 to 1800 rad of cranial irradiation from a cobalt-60 source, there was no abnormality of spontaneous nocturnal hGH secretion, and peak hGH respones to insulin induced hypoglycaemia were also normal.

A further report by Shalet et al (1977) supported previous findings of abnormal hGH secretion in reponse to pharmacologic stimuli. Patients had received 2500 or 2400 rads (DXR) of cranial radiotherapy. The subjects in this study had received spinal irradiation which may have accounted for elevated basal TSH levels and an augmented TSH response to TRH in some (because of thyroid damage). Peak cortisol response to hypoglycaemia was impaired in some subjects but none was clinically hypothyroid or showed signs of adrenocortical failure. Prepubertal girls in the study had biochemical evidence of primary ovarian failure. In a later study (1979) Shalet and co-workers reported normal growth velocity in the same group of children although the mean standing height-for-age of the group was significantly below normal.

Only a minority of these children had clinical growth hormone deficiency manifest by a declining growth rate. Growth hormone stimulation tests with insulin and arginine confirmed the findings of Samaan et al (1975) and supported the hypothesis that hypothalamic radiation injury was the likely cause of an impaired hGH response. Bone age was not significantly delayed in these patients.

Romshe et al (1984) studied a heterogeneous group of 9 patients treated with cranial irradiation, who subsequently experienced a decreased growth velocity. Six of these clinically hGH deficient patients had normal arginine and L-dopa stimulation of hGH, but only 2 had normal responses to insulin hypoglycaemia. Pulsatile secretion of hGH was significantly depressed, and the number of spontaneous pulses over 5 ng/ml was similar to that of patients with isolated hGH deficiency and to that of irradiated primates (Chrousos). A study by Blatt et al (1984) confirmed disturbance of spontaneous hGH secretion in long-term survivors of ALL. Her subjects had a diminished amplitude and frequency for hGH pulses over 24 hours when compared with normal children. Normal children secreted more hGH at night than during the day, but this diurnal variation was lost in ALL survivors. Two children had normal hGH responses to insulin-induced hypoglycaemia but had a diminished total daily hGH output.

Diminished pulsatile secretion was also demonstrated in a subsequent study (Kirk) and associated with growth failure which was particularly severe in younger children and those tall for age at diagnosis.

Following the development of synthetic growth hormone releasing factor (GRF) two groups have demonstrated peaks of hGH secretion in response to GRF in patients who had previously been shown to have radiation-induced suppression of hGH release (Shalet 1982(a)) (Lustig). These studies support the hypothesis that cranial irradiation in children can lead to hypothalamic GRF deficiency, presumably secondary to radiation injury of hypothalamic GRF-secreting neurons.

3.1.2 The Thyroid Gland

Radiation-induced thyroid dysfunction occurs after irradiation of the head and neck. It is possible that cranial irradiation as given in ALL may affect thyroid function. Clinically obvious hypothyroidism is rare, but biochemical hypothyroidism (elevated TSH and decreased T_4) has been reported following neck irradiation (Shalet 1982(b)). Minimal thyroid dysfunction is indicated by normal basal TSH and T_4, but an exaggerated TSH response to thyrotropin releasing hormone (TRH) (McFarlane 1983). Patients under 20 may be more susceptible to the effects of radiotherapy.

An increased incidence of thyroid cancer has been noted in patients given radiotherapy for tinea capitis. The latent period between irradiation and thyroid cancer is 10-30 years (Haselow). Children appear to be particularly at risk for malignancy (Hempelmann). Thyroid cancer after high dose external radiotherapy (over 2000 rads) is very uncommon, presumably because thyroid cells are damaged beyond further mitotic capacity (Schimpff) (Gray) (Li 1975).

3.1.3 The Gonads

Gonadal function is affected by alteration in hypothalamo-pituitary function, as discussed above, as well as by direct cytotoxic effect of radiation or chemotherapy.

Cranial irradiation as given in ALL is not known to have any effect on testis or ovary. The alkylating agents (cyclophosphamide, busulphan, chlorambucil, melphelan) are the major group of drugs causing gonadal damage, though vinblastine and cytosine arabinoside have also been incriminated. Gonadal damage is dependent on total dose. It is not known whether duration of therapy is relevant (Siris) (Shalet 1982(b)).

In male children and adolescents, chemotherapy may affect germ cells to cause azoospermia, reduction in testicular size and infertility. It is not clear whether such infertility is reversible. Characteristically such patients should have an elevated follicle stimulating hormone (FSH) level, a raised or normal luteinizing hormone (LH) level and a normal plasma testosterone level. Leydig cell damage may be associated with gynaecomastia and a low plasma testosterone. Boys given chemotherapy alone have normal basal LH and FSH, normal responses to stimulation with luteinizing hormone releasing hormone (LHRH) and human chorionic gonadotrophin (HCG) but boys given testicular radiotherapy for extramedullary relapse have both Leydig and germ cell damage (Carrascosa) (Leiper).

In females cytotoxic germ cell damage is age dependent, as the number of oocytes decreases with advancing age. Recovery has

been documented and is time dependent. Ovarian failure presents as amenorrhoea, oligomenorrhoea, hot flushes and infertility (Shalet 1982(b)).

3.2 THE CURRENT STUDY

It has become clear that therapy of ALL demands close follow-up of endocrine function. The aims of this study were:

1. To assess the prevalence and severity of growth hormone, hypothalamo-pituitary-adrenal, thyroid and gonadal abnormalities in a group of ALL survivors.
2. To assess the effect of cranial irradiation on endocrine function by comparing the ALL survivors with a group of children surviving Non-Hodgkins lymphoma.

3.2.1 Patients

Thirty-one long-term survivors of ALL were in the care of the Oncology Service of the Red Cross War Memorial Children's Hospital at the time of the study. Twenty-two of these patients were studied. Two patients relapsed before they could be studied (8,10), 4 were excluded because of distance from the hospital (2, 6, 11, 22) and 3 (4, 5, 23) would not give consent for hypothalamo-pituitary functon tests.

Patients and treatment received are listed in Tables 2.2 and 2.3. The study patients ranged from 8 to 17,5 years in age. Eight patients were pre-pubertal and 14 were at various stages of puberty (see below). There were 9 males and 13 females in this sample.

A control group of 10 patients with non-Hodgkins Lymphoma (NHL) consisted of 6 boys and 4 girls with an age range of 6,5 to 21 years. Four of these patients were pre-pubertal (see below). This group had been treated according to the LSA-L2 protocol (Wollner). Details of treatment received are given in Table 3.1. Central nervous system prophylaxis consisted of intrathecal methotrexate. This group received no cranial irradiation. One child with ALL had received treatment according to the NHL protocol (Patient 29) and was not given cranial irradiation.

3.2.2 Method

Children were admitted for a morning of tests on a weekend or during a school holiday and on a date coinciding with a scheduled clinic visit. Hypothalamo-pituitary function tests were arranged toward the end of the overall study so that parents and children were familiar with the investigator.

The object and exact nature of the test procedures were explained to the children and their parents. Written consent (see appendix 1) was obtained prior to testing.

Serum growth hormone and plasma cortisol were measured before and during an insulin tolerance test. Insulin hypoglycaemia was produced by rapid injection of 0,15 units/kg of soluble insulin 30 minutes after an intravenous line had been established and after basal blood samples had been taken. Venous blood for the estimation of growth hormone and glucose was drawn at 20, 30, 45, 60, 90 and 120 minutes and for the

TABLE 3.1

NHL PATIENTS : TOTAL TREATMENT EXPERIENCE

PAT NO	VIN-CRISTINE (mg)	IV LASPAR (thou)	IT MTX (mg)	ORAL MTX (mg)	IV CYTOSAR (mg)	THIO-GUAMINE (mg)	HYDROXY-UREA (mg)	IV CYCLO PHOSPHAMIDE (mg)	DAUNORUBICIN/ ADRIAMYCIN (mg)	PREDNISONE (mg)
32	24,0	28	182	570	11590	26540	144000	9840	690/0	1800
34	80,4	15	148,5	330	5890	12460	96000	6360	439/44	1120
35	24,8	13	88,5	195	5020	7200	21600	4100	332/40	840
37	36,6	12	94,5	320	6465	10920	82000	4810	393/0	1020
39	40,8	22	127	450	9060	12360	22000	6750	520/0	1860
40	40,3	18	176	490	10065	17220	30000	7800	560/0	1740
41	42	20	1258	400	11600	14880	90000	7300	560/0	1740
42	42,3	12	154,5	310	5580	10560	74000	5850	333/0	2250
43	52,0	24	176,0	690	12415	24400	176000	1105	802/0	1600
45	44,0	20	138,3	335	6280	13920	99999	8350	555/0	2460
46	42,2	12	120,5	180	3800	7680	60000	3280	240/60	930
47	39	20	146,8	320	5300	11200	76800	5800	480/0	1080
48	12,6	10	54	80	2740	3520	12000	1650	163/0	1260

estimation of cortisol at 20, 30, 45 60 and 90 minutes after the injection of insulin. Blood was spun down immediately and stored at -15° centigrade. Tests were run with routine batches in the relevant laboratories.

Growth hormone was measured by radioimmunoassay in the Medical Biochemistry Laboratory at the University of Cape Town (UCT), Medical School. A second antibody separation technique was followed, using a commercially available kit produced by Serono Diagnostics. The kit hGH standard is calibrated against the international hGH standard preparation WHO 66/217. Results were reported in nanograms (ng) per ml. One ng equals 2 micro international units (uIU) of WHO 66/217. The assay range was 0-20 ng/ml. Levels above this were reported as 20 ng/ml.

Glucose was measured in the Chemical Pathology Laboratory of the Red Cross War Memorial Children's Hospital. A Beckman glucose chemistry module was used which assays by means of an oxygen rate method, employing a Beckman oxygen electrode (Kadish). In addition, patients were monitored at the bedside by means of dextrostix (Ames) tests of each blood sample.

Cortisol was measured in the Steroid Laboratory at the UCT Medical School, by direct immunoassay using an Amerlex cortisol RIA kit.

At the time of the insulin tolerance test, a thyrotropin-releasing hormone (TRH) and a luteinizing hormone/follicle stimulating hormone-releasing hormone (LH/FSH-RH) test were

carried out. TRH was given intravenously in a dose of 3 ug/kg body weight to a maximum of 200 ug and LHRH in a dose of 100 ug/m^2 body surface up to a maximum of 100 ug. Basal blood samples were taken for the measurement of serum LH, FSH, prolactin, thyroid stimulating hormone (TSH), thyroxine (T_4), triiodothyronine (T_3) and serum oestradiol and testosterone. At 20 and 60 minutes after TRH and FSH/LH-RF administration, samples were taken for measurement of TSH, LH and FSH.

Free T_3 and T_4 were measured by Amerlex M kits in the Radioisotope Laboratory at Groote Schuur Hospital.

Serum LH and FSH were measured in the Gynae Endocrine Laboratory of the UCT Medical School using Amerlex-M radioimmunoassay kits. Luteinizing hormone WHO 1st IRP (68/40) and FSH WHO 2nd IRP (78/549) were used as standards. Oestradiol was measured in the same laboratory by the radioimmunoassay described by Abraham.

Prolactin and TSH levels were measured in the Radioisotope Laboratory of the Department of Chemical Pathology at the UCT Medical School. Prolactin was measured with a kit from Serono Diagnostics calibrated against the WHO 1st IRP 75/504 standard preparation. TSH was measured with an Amerlex-M TSA RAI kit, which is calibrated against the WHO 1st IRP 68/38 standard preparation.

Results of growth hormone stimulation tests were plotted individually using a graphing programme on a Tectronix 4025 computer and a Tectronix 4662 plotter.

The proportion of abnormal to normal results in the ALL group were compared with that in the NHL group for each test. Statistical significance was calculated by Chi-square test.

Mean stimulated hormone levels were not compared between the groups. Although the test results were quantitative, normal or abnormal responses were decided by whether or not the patient's hGH levels rose above a certain threshold. Growth hormone stimulation tests by insulin-induced hypoglycaemia may therefore be considered to be qualitative. It is suggested that comparisons of mean hGH levels between groups are more appropriate in measurements of physiological stimuli (such as during sleep).

All patients underwent X-ray assessment of the pituitary fossa. Bone age was estimated, using the atlas of Gruelich and Pyle and the TW_2 method (Tanner 1975). Plain skull x-ray films were taken of the pituitary fossa to exclude local disease. Pubertal stage was assessed according to the Tanner standards (Tanner 1976).

Mean difference between patient's chronological and bone age was calculated within in each group and statistical significance of difference within the group was tested by means of a paired 't' test. The difference in bone and chronological age was also assessed in the light of the child's height-for-age SD score at the time of bone age assessment, and peak hGH levels following stimulation.

3.3 RESULTS

3.3.1 Bone Age

Bone age was in advance of chronological age in 10 out of 21 survivors of ALL. In 6 of these patients, bone age was advanced despite a height for age SD score well below the mean (Table 3.2). Six others had retarded bone ages associated with height-for-age SD scores below the mean. In 5 patients bone age and chronological age agreed. Mean bone age was 0,18 years in advance of chronological age. This difference was not statistically significant. In NHL survivors there was agreement between chronological and bone age in 5 patients, retarded bone age in 4 (all but one with height-for-age SD score below the mean) and 1 patient with advanced bone age and a height for age SD score above the mean. There was no statistical significance between the groups in respect of bone age advance or delay.

3.3.2 Pituitary Fossa

X-rays of the pituitary fossa were normal in all subjects.

3.3.3 Pubertal Developement

Normal progression of sexual maturation was observed in all subjects. Mean age of menarche was similar in females of both groups at 12,5 years.

Two females who did not have endocrine assessment (patients 3 and 4) have been delivered of healthy infants after normal full-term pregnancies. They were 18 and 24 years old and 6 and

TABLE 3.2

BONE AGE, MOST RECENT HEIGHT/AGE SD SCORE AND PEAK GROWTH HORMONE CONCENTRATION

PAT NO	CHRONOLOGICAL AGE (YRS)	BONE AGE (TW_2)	BONE AGE (GRUELICH AND PYLE)	HT/AGE SD SCORE	PEAK GH ng/ml
1	11,5	10,75	11	0,03	4,79
2	17,0	18,0	18-19	-3,98	3,82
7	11,5	12,0	13	0,18	10,41
9	7,75	8,5	9	0,52	9,29
12	16,75	15,5	15,5	-1,46	20
13	11,25	12,0	12,0	-0,62	6,35
14	9,0	9,5	9,5	-2,98	20
15	11,25	12,0	12	-0,96	11,07
16	10,5	11,0	11,0	0,13	9,44
17	9,5	9,0	7,0	2,13	13,84
18	16,6	15,5	15,0	-0,95	2,06
19	12,0	12,25	12,5	-0,58	8,64
20	9,25	10,0	10	0,14	7,69
21	16,0	16,0	15,5	-1,00	12,46
23	14,1	16,0	18	-1,82	20
24	7,2	7,5	6,5	-1,39	7,05
26	16,5	15	15	-2,00	0,60
27	10,4	9,25	9,5	-1,33	2,86
28	14,0	14,5	13,5	-1,57	4,37
29	8,5	9,0	9,0	-0,67	6,18
30	7,5	8,0	6,5-7	-1,04	6,97
31	16,25	16,0	16	-3,0	14,8
32	15,5	15,0	14,0	-0,65	20
34	8,75	8,75	8,75	0,07	20
35	9,5	9,5	9,5	0,70	16,76
37	10,6	10,0	8,5	-1,38	31,7

Table 3.2 (continued)

NO	CHRONOLOGICAL	BONE AGE (TW_2)	BONE AGE (GRUELICH) AND PYLE)	HT/AGE SD SCORE	PEAK GH ng/ml
40	12,5	13,0	12,5	-0,87	5,85
41	14,5	15,5	14	1,21	39,3
42	8,0	6,0	5,5	-2,21	13,6
46	5,5	7,0	6,0	-1,28	2,18
47	13,5	14,5	13,5	-1,00	15,64
48	6,0	9,0	7,0	0,72	8,54

9 years off therapy respectively.

Testicular biopsy before stopping maintenance chemotherapy is a relatively recent adaptation of ALL treatment protocols. Five boys in the study group (patients 1, 9, 21, 27, 29) and 1 not studied (No 11) underwent testicular biopsy. All had normal Leydig and germ cells on histologic examination. Patient 29 had a leukaemic infiltrate of the testis and was treated.

3.3.4 Growth Hormone Regulation

Growth hormone responses to insulin tolerance tests in ALL survivors are shown in Table 3.3 and Figures 3.1 to 3.4. Responses were classified as abnormal when below 7 ng/ml, intermediate between 7 and 10 ng/ml and normal above 10 ng/ml.

Thirteen of 21 ALL survivors had an impaired hGH response to adequate insulin hypoglycaemia (Table 3.3). Of these, 10 had frankly abnormal responses and 3 had intermediate responses. Eight ALL survivors had a normal hGH response to insulin induced hypoglycaemia. In the group of 10 NHL survivors, 2 patients had frankly abnormal responses. There were 7 normal responders (Table 3.4, Figures 3.5 and 3.6).

The proportion of abnormal responders to hGH stimulation in the group of ALL survivors is significantly greater than in the control group ($X^2 = 6{,}29 < {,}01 \quad p < 0{,}05$).

TABLE 3.3

ALL PATIENTS : GROWTH HORMONE RESPONSE (ng/ml) TO INSULIN INDUCED HYPOGLYCAEMIA

								GLUCOSE (mmol/l)	
PAT NO	0 MIN	20 MIN	30 MIN	45 MIN	60 MIN	90 MIN	120 MIN	0 MIN	MINIMUM
1	5,92	2,12	2,49	3,87	4,17	4,79	1,64	4,9	1,3
2	1,37	3,82	3,58	3,15	3,41	2,86	2,49	4,4	1,5
7	3,87	9,80	10,41	7,52	5,25	4,12	3,99	4,9	1,3
12	0,3	2,36	6,57	20	13,09	9,13	5,37	4,6	0,9
13	0,3	0,3	0,87	6,35	4,99	2,2	1,64	3,9	1,6
14	0,3	0,3	6,07	20	20	8,86	2,7	4,7	1,3
15	0,3	11,2	10,71	11,07	6,34	5,25	2,49	4,4	1,2
16	5,72	9,44	8,48	5,92	4,46	1,74	1,25	4,9	2,1
17	0,3	0,3	1,47	6,1	9,85	13,48	9,19	5,0	1,4
18	0,3	0,3	0,3	1,13	2,06	1,70	1,01	5,4	1,5
19	3,22	5,34	8,64	7,46	5,94	2,47	1,42	5,0	1,7
20	3,22	1,41	2,14	5,84	7,69	7,09	2,06	4,2	1,5
21	0,3	3,15		7,04	12,46	0,83		4,1	0,8
23	1,63	2,19	4,35	20	20	8,67	3,86	5,4	1,4
24	0,3	0,80	3,67	4,32	7,05	5,3	5,07	4,3	1,6
26	0,3	0,3	0,3	0,3	0,54	0,60	0,42	4,3	1,5
27	0,81	0,3	0,3	1,52	1,80	2,49	2,86	5,0	1,1

Table 3,3 continued

								GLUCOSE (mmol/l)	
PAT NO	0 MIN	20 MIN	30 MIN	45 MIN	60 MIN	90 MIN	120 MIN	0 MIN	MINIMUM
28	3,06	3,75	3,99	4,37	3,71	2,71	2,87	6,2	2,1
30	1,78	0,59	4,82	6,97	5,25	2,45	0,93	4,7	1,6
31	0,3	0,83	1,52	6,46	14,85	8,78	2,49	4,4	3,0

FIGURE 3.1

A.L.L. PATIENTS: GROWTH HORMONE RESPONSE TO HYPOGLYCAEMIA

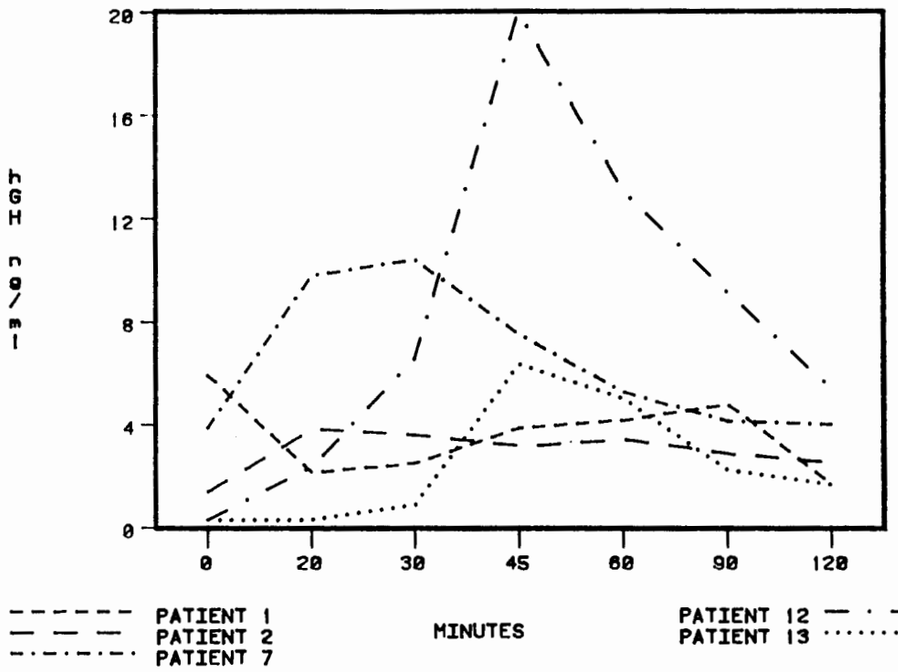


FIGURE 3.2

A.L.L. PATIENTS: GROWTH HORMONE RESPONSE TO HYPOGLYCAEMIA

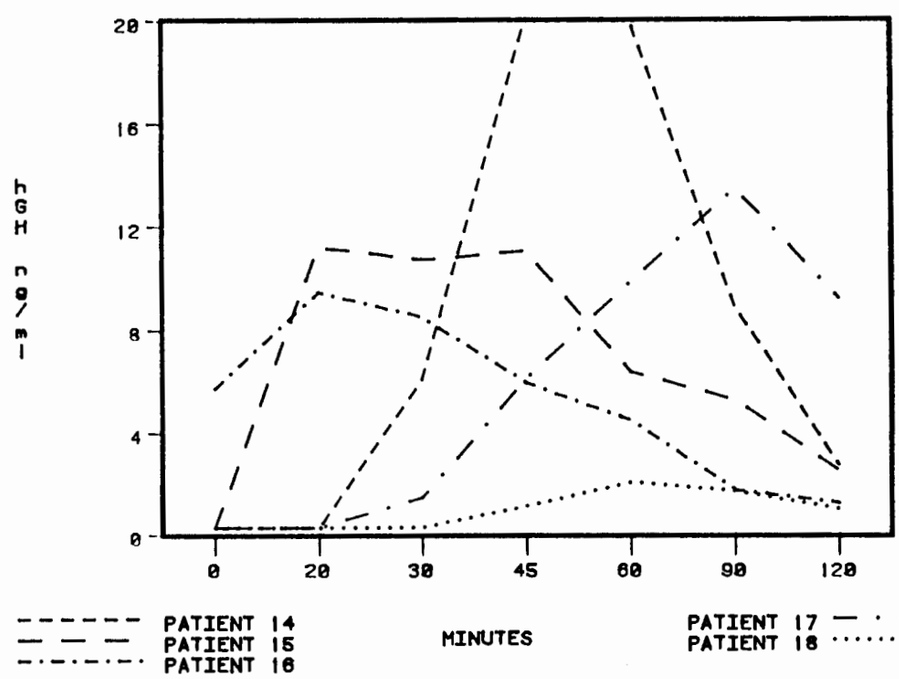


FIGURE 3.3

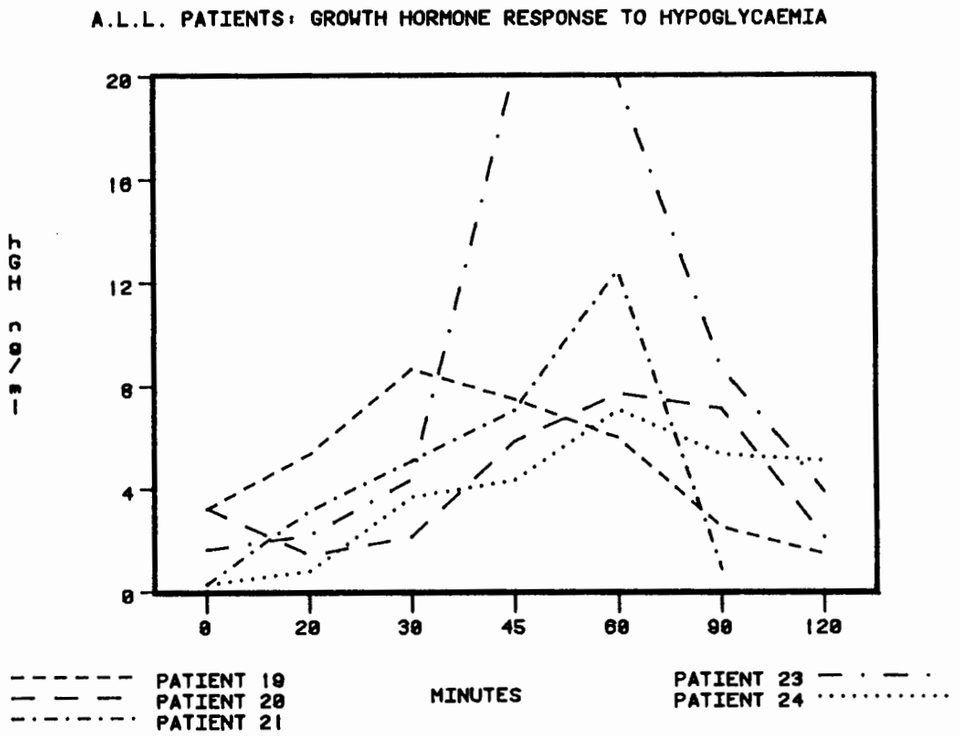


FIGURE 3.4

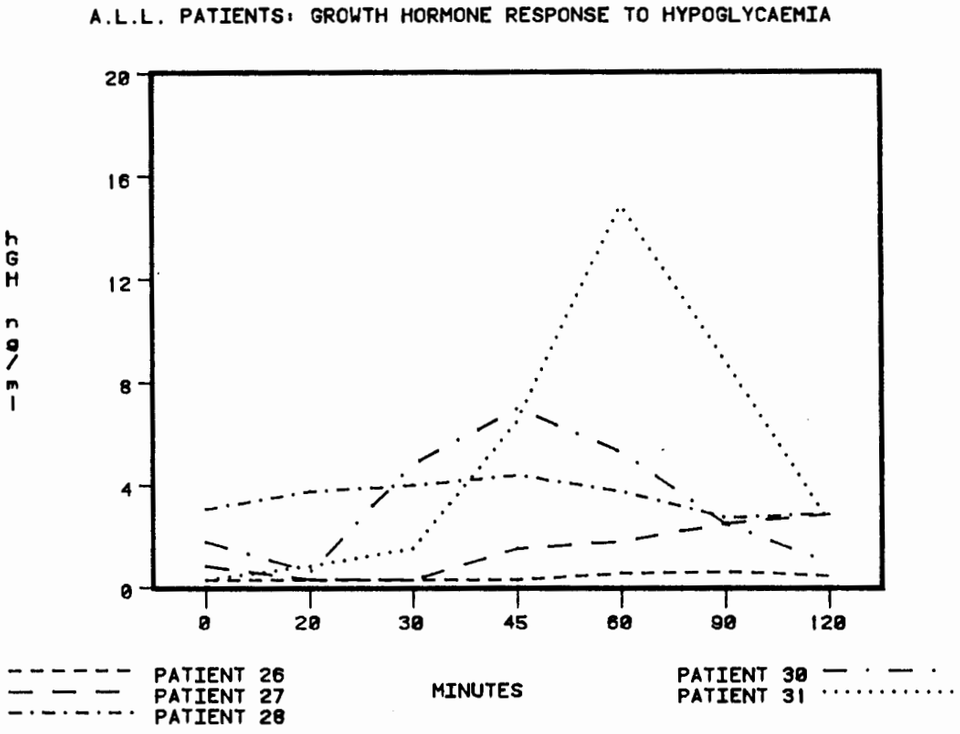


FIGURE 3.5

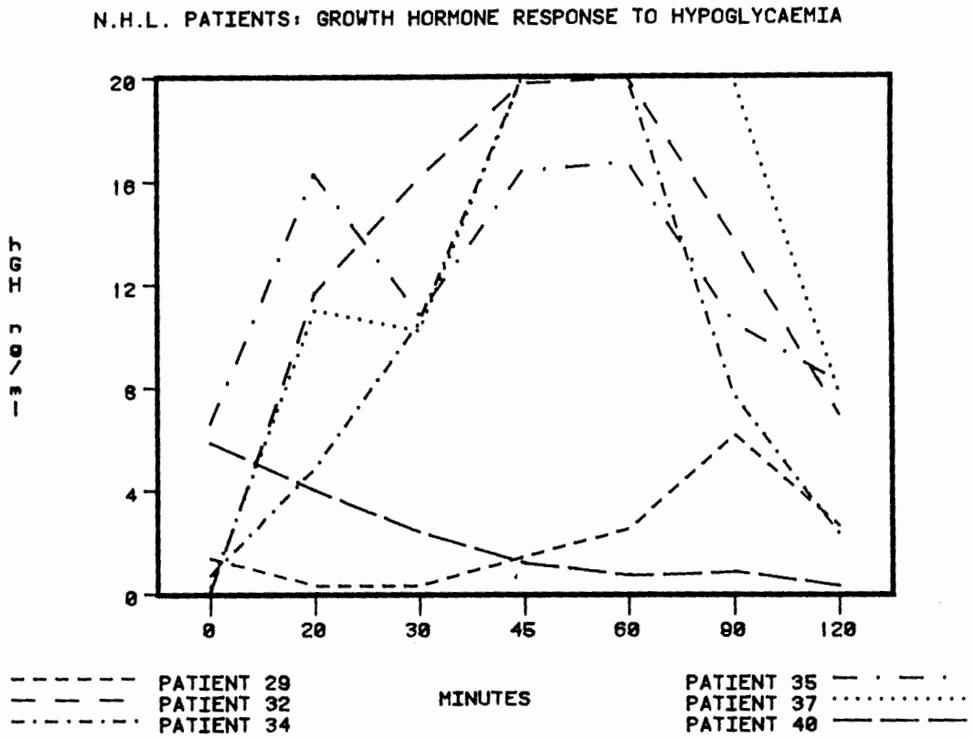


FIGURE 3.6

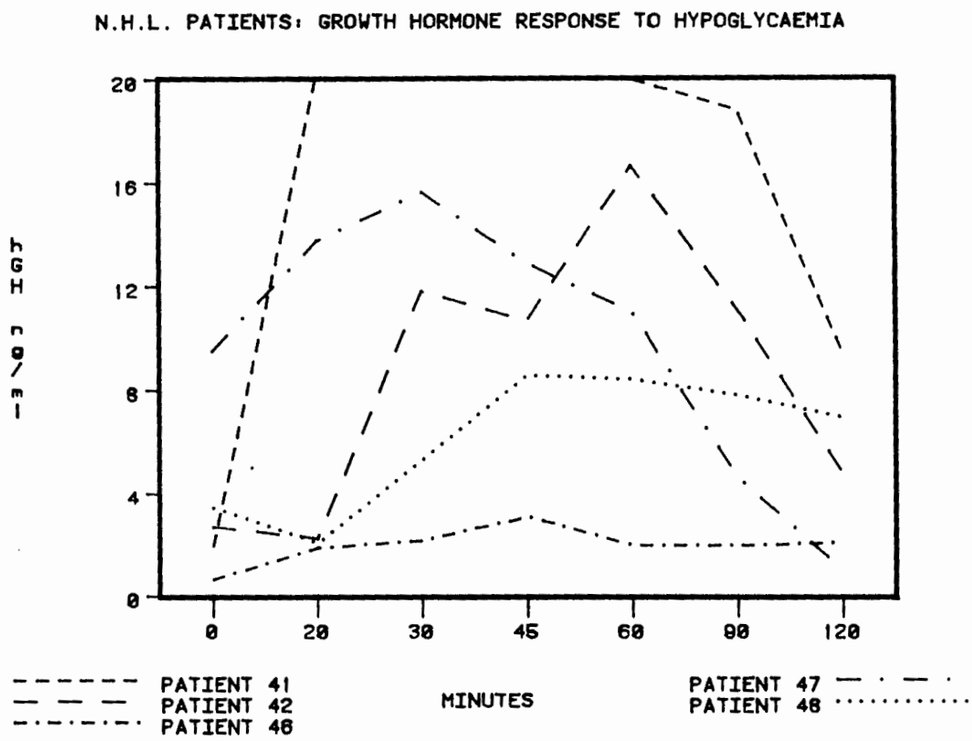


TABLE 3.4

NHL PATIENTS : GROWTH HORMONE RESPONSE (ng/ml) TO INSULIN INDUCED HYPOGLYCAEMIA

								CLUCOSE (mmol/l)	
PAT NO	0 MIN	20 MIN	30 MIN	45 MIN	60 MIN	90 MIN	120 MIN	0 MIN	MINIMUM
32	0	11,66	16,14	19,77	20,29	13,84	6,94	4,5	1,6
34	0,72	4,9	10,52	20	20	7,69	2,29	4,8	2,0
35	6,61	16,3	10,84	16,44	16,76	10,49	8,23	4,5	1,7
37	31,7	11,0	10,2	26,5	27,8	25,0	7,8	4,7	2,0
40	5,85	4,0	2,38	1,18	0,70	0,85	0,3	5,4	2,4
41	22,0	26,1	35,5	37,9	39,3	18,8	9,4	4,0	1,9
42	11,8	2,7	2,24	10,65	16,65	11,05	4,74	4,5	1,2
46	0,67	1,9	2,18	3,1	1,97	1,97	2,1	3,7	1,3
47	9,52	13,76	15,64	12,87	10,99	4,58	0,98	4,9	1,6
48	3,47	2,07	5,28	8,54	8,38	7,77	6,91	4,8	1,6

3.3.5 Thyroid Studies

Normal free T_3 values in the RIA laboratory at Groote Schuur Hospital are 3,3 - 8,1 pmol/l and normal free T_4 values are 6,3 - 22,8 pmol/l. All subjects were euthyroid in terms of clinical features and free T_3 and T_4 levels (Tables 3.5 and 3.6).

Normal resting TSH values in the UCT Medical school RIA laboratory are 0-6 micro IU/l. Normal stimulated values (after TRH) are double resting values, but not in excess of 15 uU /ml. TSH responses to TRH are reported in Table 3.5 and 3.6. In the group of ALL survivors, 1 patient (No 30) had a low peak of 4,2 uU/l, but this was double a resting TSH of 2,1 uU/l. Four ALL survivors had exaggerated TSH responses to TRH (7, 15, 20, 24). The single ALL survivor who had received spinal irradiation (No 13) had a basal TSH of 2,6 uU/L and a stimulated level of 14,6 uU/l. In the group of NHL survivors all patients had normal resting TSH values, but two patients (32, 47) had exaggerated TSH responses (Table 3.6). There were no statistically significant differences between the two groups in respect of results obtained from these tests.

3.3.6 Hypothalamo-pituitary-adrenal Axis

Normal resting morning values for cortisol in the steroid laboratory of the UCT department of Chemical Pathology are 140 - 700 nmol/l. Normal stimulated values are an increase of 220 nmol or a maximal value above 550 nmol/l (Shalet 1976).

TABLE 3.5

ALL PATIENTS: TSH RESPONSE TO TRH (micro U/ml)

PAT NO	0 MIN	20 MIN	60 MIN	T4 (pmol/l)
1	3,2	17,5	10,1	14,5
2	3,7	15,5	7,5	14,9
7	6,2	24,2	15,8	14,8
9	2,7	16,8	9,5	11,4
12	1,6	7	4,3	15,9
13	2,6	14,6	10,1	11,3
14	4	15,3	9,2	14,9
15	2,3	27,7	19,9	14,4
16	2,6	20,1	8,7	14,0
17	3,4	17,1	10,2	14,6
18	2,2	11,5	4,8	16,1
19	4,5	16,5	16,7	13,4
20	3,6	35,5	18,1	14,2
21	2,7	12,1	9,2	20,8
23	2,4	10,8	12,1	16,6
24	3,8	25,2	11,8	19,1
26	2	7,8	4,7	10,5
27	4,1	13,7	10,9	15,8
28	2	17,8	8,3	14,2
30	2,1	4,6	4,2	14,7
31	2,2	12,1	8,3	18,6

TABLE 3.6

NHL PATIENTS : TSH RESPONSE TO TRH (micro U/ml)

PAT NO	0 MIN	20 MIN	60 MIN	T4 (pmol/l)
29	4,9	10,1	8,4	17,6
32	2,1	21,7	12,6	11,7
34	2,6	11,2	6,5	20,6
35	3,9	17,2	13,7	12,6
37	3,3	18,8	13,0	10,9
40	3,8	17,4	12,7	10,8
41	1,7	14,3	10,2	12,2
42	4,8	18,1	14,1	12,7
46	3,2	18,2	14,0	16,7
47	3,6	30,4	24,7	16,3
48	1,3	7,1	4,9	17,6

All subjects tested had normal basal plasma cortisol levels. Tables 3.7 and 3.8 illustrate cortisol levels in response to insulin hypoglycaemia in ALL and NHL survivors. Five patients (16, 23, 26, 28, 31) had flat response curves, but 3 of these (23, 26, 28) had relatively high basal levels. Three patients in the NHL group had flat response curves (32, 41, 47), but 2 of these had relatively high basal cortisol levels (41,47). A high cortisol level at the start of the stimulation test makes the response to hypoglycaemia difficult to interpret.

The results were not significantly different between the two groups.

3.3.7 Hypothalamo-pituitary-gonadal axis

Basal LH and FSH values during puberty (Winter) are:

Pubertal Stage (Tanner)	FSH uIU/l	LH uIU/l
1	4,1 ± 0,3	9,5 ± 0,5
2	5,7 ± 0,5	9,5 ± 0,5
3	7,1 ± 0,6	16,7 ± 1,4
4 and 5	8,7 ± 0,6	34,1 ± 4,5

Oestradiol values in prepubertal children are between 100 and 200 pMol/l. After puberty, values vary with the ovulatory cycle. In prepubertal children LH/FSH-RH evokes a greater and earlier FSH than LH response. During puberty, a striking increase in LH responsiveness to LH/FSH-RH develops and in adults LH response exceeds FSH response (Huang).

TABLE 3.7

ALL PATIENTS : CORTISOL RESPONSE TO INSULIN INDUCED HYPOGLYCAEMIA

(nmol/l)

PAT NO	0 MIN	20 MIN	45 MIN	60 MIN	90 MIN
1	309	316	451	473	461
2	575	558	483	459	791
7	70	380	500	640	540
12	446	387	667	722	634
13	399	636	628	492	
14	421	368	507	601	632
15	402	380	521	613	471
16	324	275	417	345	211
17	254	239	426	616	609
18	523	297	542	541	263
19	556	409	531	629	452
20	544	329	584	713	385
21	189	138	446	504	608
23	644	462	446	626	620
24	422	606	865	859	720
26	552		586	486	398
27	437	499	723	873	765
28	714	515	325	290	299
30	321	508	638	700	410
31	230	201	158	181	139

TABLE 3.8

NHL PATIENTS: CORTISOL RESPONSE TO INSULIN INDUCED HYPOGLYCAEMIA

(nmol/l)

PAT NO	0 MIN	20 MIN	45 MIN	60 MIN	90 MIN
29	294	233	448	575	509
32	273	313	396	450	318
34	593	762	877	638	731
35	342	536	627	713	606
37	324	309	461	630	417
40	388	410	263	250	209
41	551	441	581	634	437
42	453	339	938	943	651
46	343	490	610	638	415
47	546	690	537	465	378
48	211	235	810	706	356

Results of gonadotropin stimulation tests, oestradiol and testosterone levels are given in Tables 3.9 and 3.10.

Two girls (20, 30) in the ALL group had a precocious response to LH/FSH-RH. By the age of 11,25 years all but one ALL subject (patient 23, a girl with normal development of secondary sex characteristics) had an adult response to FSH/LH-RH. In the NHL group all patients had responses appropriate for age and pubertal stage.

Oestradiol in females and testosterone in males were appropriate for pubertal stage in all subjects.

3.3.8 Prolactin

Normal values range between 0-15 ng/ml in premenopausal women and 0-9 ng/ml in men (RIA laboratory, UCT Medical School). No subjects in either group had elevated prolactin levels (Table 3.9 and 3.10).

3.4 DISCUSSION

3.4.1 Abnormality of growth hormone secretion

3.4.1.1 Growth Hormone Regulation by the Hypothalamus

The secretion of growth hormone (hGH) is episodic and influenced by many stimuli, including psychic factors, endogenous sleep rhythms and exercise.

TABLE 3.9

ALL PATIENTS : HYPOTHALAMO-PITUITARY-GONADAL AXIS

PAT NO	ALL PATIENTS: LH RESPONSE TO LH/FSH RH (mIU/ml)			ALL PATIENTS: FSH RESPONSE TO LH/FSH RH (mIU/ml)			TESTOSTERONE (nmol/l)	OESTRADIOL (pmol/l)	PROLACTIN (ng/ml)
	0 MIN	20 MIN	60 MIN	0 MIN	20 MIN	60 MIN			
1	5,5	57,8	39,5	4,4	7,9	7,5	19,5		14,5
2	17,9	141,9	92,1	13,9	26,2	30	22,5		14,7
7	25,3	195	126	15,4	33,4	32,3		213	14,8
9	2,6	12	11,7	1,6	2,3	5,1	1,2		
12	5,7	58,3	59,1	6,2	9,8	11,6	27,2		15,9
13	1,6	17,8	18,8	4,3	12,3	19,3		100	11,3
14	2,6	30,6	24,9	10,5	27,9	30,4	4,7		14,9
15	13,7	132,1	105	3,6	8	11,6			14,4
16	15,6	99,1	76,3	2,0	6,9	8,5		523	1,40
17	1,6	12,6	12,4	5,9	15,8	25,5		242	
18	6,1	31,3	19,5	7,1	11	13,2	19		
19	14,7	50,6	33,6	12,6	15,7	18,8		32,9	13,4
20	14,8	100,9	84,9	11,8	32,9	33,3	199		
21	12,3	41,3	41,1	6,3	11	12,6	25		20,8
23	13,2	14,2	14,8	13,2	14,2	14,8		227	16,6
24	2,6	21	17,7	3,9	17,3	21,7		157	19,1

Table 3.9 continued

PAT NO	ALL PATIENTS: LH RESPONSE TO LH/FSH RH (mIU/ml)			ALL PATIENTS: FSH RESPONSE TO LH/FSH RH (mIU/ml)			TESTOSTERONE (nmol/l)	OESTRADIOL (pmol/l)	PROLACTIN (ng/ml)
	0 MIN	20 MIN	60 MIN	0 MIN	20 MIN	60 MIN			
26	5,9	21,8	23,1	11,4	18	20,1		100	10,5
27	2,6	14,2	11,5	2,5	11,7	16,8	1,0		15,8
28	7,8	25,3	24	5,7	8,9	10,6		223	14,2
29	2,6	9,7	7,2	1,6	4,7	6,8	1,4		17,6
30	2,6	56,9	43,8	1,7	17	27,7		154	14,7
31	8,7	34,3	23	12,0	16,4	17,8	21,1		12,1

TABLE 3.10

NHL PATIENTS : HYPOTHALAMO-PITUITARY-GONADAL AXIS

PAT NO	NHL PATIENTS: LH RESPONSE TO LH/FSH RH (mIU/ml)			NHL PATIENTS: FSH RESPONSE TO LH/FSH RH (mIU/ml)			TESTOSTERONE (nmol/l)	OESTRADIOL (pmol/l)	PROLACTIN (ng/ml)
	0 MIN	20 MIN	60 MIN	0 MIN	20 MIN	60 MIN			
29	2,6	9,7	7,2	1,6	4,7	6,8	1,4		17,6
32	18,7	86,6	56,2	44,5	65,7	62,3	20,7		1,3
34	2,8	6,5	6,7	1,9	4,0	5,7	0,8		6,7
35	2,6	14,1	22,9	10,2	22,9	43,3		186	4,4
37	8,4	14,4	104,7	16,0	46,9	52,3		248	9,6
40	9,6	83,1	62,5	9,3	16,3	17,4	6,2		7,2
41	9,0	96,5	62,7	9,7	19,1	17,1	11,7		7,2
42	2,6	9,8	9,1	1,4	4,8	8,1	0,8		7,1
46	2,6	5,2	5,7	1,7	3,6	5,2	1,0		6,7
47	11,6	17,8	20,8	11,8	43,6	38,6		216	12,6
48	2,6	14,5	12,5	1,2	20,0	38,0		100	13,9

Regulation of hGH secretion by the anterior pituitary is an example of open-loop, non-homeostatic control. Secretion is stimulated by growth hormone releasing factor (GRF) and inhibited by somatostatin. Both GRF and somatostatin are produced in the hypothalamus and reach the anterior pituitary via the hypophyseal portal system. The predominant influence of the hypothalamus on the release of hGH is stimulatory. Pituitary stalk section leads to inhibition of basal and stimulated hGH levels.

Growth hormone releasing factor is produced in the arcuate and ventromedial nuclei (VMN) of the hypothalamus. Regulation of GHRF release is partly by negative feedback of hGH and somatomedin C on the arcuate nucleus and partly by neural input from the limbic system. The hippocampus is believed to be responsible for bursts of hGH secretion during sleep. The basolateral nucleus of the amygdala relays excitatory impulses to the VMN of the hypothalamus, which produces GHRF in response to stress.

Impulses from the corticomedial nucleus of the amygdala inhibit GHRF release. Stimulatory impulses are mediated by cholinergic, alpha-adrenergic and dopaminergic stimuli. Inhibitory impulses are mediated by beta-adrenergic stimuli.

Glucoreceptors in the VMN influence secretion of hGH in response to falling blood glucose levels. This is part of the hypothalamic role in the control of feeding. The VMN integrates glucoregulatory hormones during eating and regulates feeding activity and the sensation of satiety.

In hypothalamic damage following radiation, the control of hGH secretion is always the first affected (Shalet 1982(a)). Damage to hGH regulation also appears to occur at relatively lower doses than does damage to other hypothalamus-controlled hormone systems (Samaan 1979).

3.4.1.2 Tests of Growth Hormone Release

Understanding of the consequences of cranial irradiation was retarded by early assumptions that growth hormone release could be equated with growth hormone deficiency (Shalet 1977). It was three years before the same authors (Shalet 1979) restated their findings following a longitudinal growth study of their original subjects. Abnormal responses to hGH stimulation after cranial irradiation indicate hypothalamic perturbation and not growth hormone deficiency.

Since the first observations of physiologic fluctuations of hGH, it has been accepted that basal levels of hGH have no significance and that response to some form of hGH stimulation has to be measured to assess hGH status.

For clinical use, hGH stimulation tests may be divided into screening tests (outpatient procedure) and confirmatory tests.

a. Preliminary Tests

Strenuous exercise is a physiologic stimulus to hGH secretion. After a workload on a bicycle ergometer or climbing stairs, hGH rises above 6 ug/ml in 72-91% of

normal controls (Buckler) (Okada). Since hGH stimulation is catecholaminergic, improved consistency of results may be obtained by combining L-dopa and exercise (Liberman). The combination frequently causes side-effects of pallor, nausea and vomiting.

Deep sleep is a physiological stimulus to intermittent bursts of hGH secretion (Quabbe) (Takahashi). Growth hormone levels above 5 ug/ml are reported in 70-100% of controls, 60 to 90 minutes after the onset of sleep. Hospital admission and uncertain timing of deep sleep without EEG monitoring are disadvantages of this method.

L-dopa has been used for hGH stimulation in children (Coller) (Liberman), with positive results in 60-90% of controls. Side effects (nausea and vomiting) are frequent and 4 to 6 blood samples are needed because timing of the hGH surge is uncertain.

Clonidine is an alpha adrenergic agent widely used to treat hypertension. One hundred percent of controls have positive responses (Gil-Ad) but because of a scatter of the hGH peak, at least 7 blood samples may be needed. All children fall asleep or feel drowsy.

Other screening tests are available (Bovril-Grant) but are either unreliable or more difficult to perform (Milner 1982).

b. Confirmatory Tests

A fall in blood glucose is a major physiologic stimulus to hGH release, and is the basis for the pharmacological stimulus of insulin-induced hypoglycaemia (Roth). This is widely used as the ultimate test of hGH response. 74% to 100% of controls respond normally with a serum hGH concentration of more than 20 uU/l (1 uU = approximately 0,5 ng/ml). Negative results may be due to interfering factors (see below).

Many amino acids stimulate hGH (Knopf). Infusion of arginine, ornithine or glycine are comparable with insulin hypoglycaemia in terms of sensitivity and specificity (Milner 1982). Arginine together with insulin hypoglycaemia has a lower false negative rate. Arginine-mediated hGH release results from direct action on the pituitary gland (Romshe) and may produce false positive results when hGH deficiency is primarily due to hypothalamic and GHRF failure.

Glucagon injected intramuscularly (Mitchell) has a higher false negative rate than insulin induced hypoglycaemia. The false negative rate may be reduced by adding propranalol, but false positives then occur.

Vasopressin, pyrogen, adrenocorticotrophic hormone (ACTH), melanocyte stimulating hormone (MSH), amphetamine, fructose, metyrapone, cyclic AMP cyproheptadine, metoclopramide, gamma-amino-butyric acid and sulpiride

stimulate hGH release but side effects and problems of specificity and sensitivity prevent their general use.

Centres with available manpower are able to measure daytime (Romshe) or nocturnal (Chrousos) pulsatile secretion of hGH. The number of peaks above 5 ng/ml distinguishes normal from abnormal secretion (Miller). The advantages of measuring physiological events over responses to pharmacological stimuli are obvious.

c. Factors Interfering with hGH Stimulation

Obesity (Roth 1963b) diminishes hGH response to hypoglycaemia, to exercise and to arginine infusions and to growth hormone releasing factor (Williams).

Fear of venepuncture and pain may be stressful enough to elevate hGH levels at zero time in tests (Frohman). The hGH peak may then be blunted. Venous lines are usually established 30 minutes before administration of the stimulus.

Emotionally deprived children frequently grow poorly. They have delayed bone age and an impaired hGH response to stimulation (Powell). Emotional deprivation may be difficult to differentiate from hypopituitarism.

Hypothyroidism may blunt responses to hGH stimulation (Katz). Thyroid stimulating hormone releasing hormone (TRH) suppresses hGH release, but not in conjunction with other pituitary function tests (Sack 1985).

The hGH response may be blunted in delayed puberty and increases in boys and girls during normal puberty (Illig).

d. The Test Used in this Study

Clearly, measurement of physiological hGH secretion is preferrable to measurement of the response to some pharmacological stimulus. In the present study the means to measure pulsatile hGH secretion were not available. Growth hormone stimulation by insulin-induced hypoglycaemia was chosen because of the relative paucity of side effects, safety under controlled conditions and familiarity with the test. A further major advantage with this test was that blood glucose could be measured so that the adequacy of the stimulus to hGH secretion was known.

3.4.1.3 Results of the Present Study

Results of the present study support the hypothesis that cranial irradiation is at least partly the cause of abnormal hGH secretion. It is also possible that damage is caused by the combination of radiation and methotrexate therapy or radiation and some other form of chemotherapy. In the case of methotrexate, there is good evidence that it causes synergistic damage with radiotherapy (Bleyer 1981). It is also evident from this study that methotrexate alone, given either orally or intrathecally is not associated with abnormalities of hGH secretion. CNS damage due to intravenous methotrexate alone has been described (Bleyer 1978) but it is not known whether this damage has any effect on hGH secretion.

Results from this study do not indicate a specific site of damage, since the hypoglycaemic stimulus to hGH secretion acts via the ventromedial nucleus (VMN) of the hypothalamus and a normal response requires integrity of VMN, hypothalamo-pituitary portal tract and pituitary. Growth hormone response to arginine infusion (Romshe) and early reports of response to GRF (Ahmed) (Lustig) indicate that injury caused by radiation is probably localized to the hypothalamus. A lack of blood brain barrier in the hypothalamic area makes it vulnerable to synergistic damage by radiation and methotrexate. Delayed effects on the hypothalamus may also be a consequence of end artery radiogenic arteritis (Price and Birdwell) leading to mineralizing microangiopathy.

It would have been desirable to assess our patient's response to GHRF, but this was not available at the time.

The proportion of ALL survivors with abnormality of hGH secretion is higher in this study than in most previously reported series (Table 3.11). The reason for this may lie in a difference in the radiotherapy schedule given to patients in the present study. Patients reported by the Manchester group (Shalet, 1976, 1977) were treated with a cobalt 60 4Mev source (Co^{60}) whereas patients reported by Swift et al (1978) were treated with a lower dose of 250 kv x-rays (DXR). Our patients were treated with 2400 rads of DXR in 15 fractions (Table 3.12).

TABLE 3.11

GROWTH HORMONE ABNORMALITY IN ALL SURVIVORS

AUTHOR (year)	RADIATION DOSE		MODE	NO SUBJECTS	ABNORMAL hGH RESPONSE
	rads	rets			
Shalet (1976)	2400-2500	900-1070	CO^{60}	13	4
v Mühlendahl (1976)	850-1800	?400- 670	DXR	22	0
Schirivo (1976)	2400	?	DXR	9	5
Shalet (1977)	2400-2500	900-1070	CO^{60}	26	13
Swift (1978)	2000-2500	1000	DXR	8	2
Blatt (1984)	2400	960	23 Mev	8	3(2)
This study	2400	850- 950	DXR	21	13

rets = Total dose . $N^{-.24}$. $T^{-.11}$ (Ellis)

Where total dose is in rads

N = Number of fractions

T = Time elapsed during treatment course

DXR = 250 kv x-ray source

CO^{60} = Cobalt 60 (4 mev) source

23 mev = 23 megavolt radiation source

According to Ellis (1969) total radiotherapy dose, number of fractions and overall treatment time may be used to calculate a quantity called the normal standard dose (NSD) (Orton). This quantity represents the biological effect of a given treatment and is expressed in rad equivalent units (ret units) (Rubin).

According to this formula, patients treated by Shalet et al received 1070 rets and those treated by Swift et al 1000 rets. Shalet's patients without hGH abnormality received 900 rets. Patients in the current study were given 850-900 rets.

3.4.2 Catch-up Growth After Cranial Irradiation

Head irradiated rats show diminished GH secretion despite a normal periodicity of GH secretory pulses (Mosier 1985a). Growth is retarded, and does not respond to GH treatment (Mosier 1967) although somatomedin levels are normal. Irradiated rats have normal or increased tibial epiphyseal width instead of a decrease, which would be expected in GH deficiency (Evans). Decreased GH secretion after head irradiation contrasts with increased GH secretion in rats during catch-up growth following starvation (Mosier 1976b). Failure of catch-up growth occurs in rats following head irradiation, but head-irradiated rats will exhibit catch-up growth after subsequent starvation (Mosier 1983). This catch-up growth occurs without an increase in GH secretion (Mosier 1986). It seems therefore that head irradiation has a specific effect on catch-up growth which is time related to the radiation event. It may be that irradiation acts by altering some central control of catch-up (Mosier 1986) in rats.

Stunted statural growth after cranial irradiation for ALL is the consequence of failure of catch-up growth (Swift) (Griffin) (see section 2.4.2. and Figure 2.10) rather than a failure in growth rate. This is in contrast to catch-up growth normally seen after illness or starvation (Prader). It would be expected that bone age in hGH deficient children would be decreased (Tanner 1975) but in the present study, the majority of subjects had an advanced bone age (see section 3.3.1 and Table 3.2). Similar findings are reported in previous studies (Shalet 1979) (Swift 1978) although their authors did not comment on these facts. It may be that abnormalities of growth seen following the treatment of ALL are due to some central effect of radiation which alters the control of catch-up growth in these children. How this might lead to advancement in bone age and therefore a potential loss of statural growth is unclear.

3.4.3 Hypothalamic Obesity

The ventromedial nucleus (VMN) of the hypothalamus is part of a localized neuronal system which is sensitive to changes in blood and tissue glucose levels. The VMN registers rising blood glucose levels and when stimulated leads to satiety. This action is opposed by the lateral hypothalamus, which is sensitive to falling blood glucose levels and stimulates a feeding drive. In experimental animals, destruction of the VMN leads to unopposed hyperphagia. This is accompanied by obesity, a reduction in spontaneous activity and stunted growth (Bray).

Hyperphagia is the primary factor in the development of obesity of rats with VMN destruction (Tepperman). Rapid increase in weight is followed by a plateau. Inactivity and slowed metabolism contribute only minimally to weight gain.

In patients with hypothalamic disease or damage, hyperphagia and hyperinsulinism are manifest. Their metabolic rate and fat metabolism are normal. Depending on the cause of hypothalamic injury there may be a variety of other hormonal abnormalities (Bray).

In the present study, weight-for-height, weight-for-age and the Quetelet index increased significantly in children treated with cranial irradiation (see section 2.4 ii, iii and iv and Figures 2.17, 2.18 and 2.19) over the five years after diagnosis.

It is interesting that a specific defect in the glucostat, namely impaired hGH response to hypoglycaemia, occurs in the same group of leukaemia survivors. This suggests that this area in the hypothalamus may be the site of localized damage following radiation.

3.4.4 Therapy for Radiation-Induced Short Stature

Treatment of isolated growth hormone deficiency of childhood with replacement hGH has become routine, and apart from recent fears of slow-virus disease from cadaver hGH, has generally been satisfactory. Children given cranial or craniospinal irradiation for brain tumours suffer the effects of several

factors which may reduce their eventual height. If one factor, i.e. hGH deficiency, is more amenable to treatment, replacement therapy is urgent and mandatory.

Most longitudinal growth studies in ALL survivors (Shalet 1979) (Griffin) (Swift) indicate a normal rate of statural growth, which is a clinical sign of adequate hGH activity.

Pharmacological stimuli of hGH release evoke inadequate hGH responses in a large proportion of leukaemia survivors. These poor responses should perhaps be seen as an indication of hypothalamic dysfunction with relative GRF deficiency rather than growth hormone deficiency. Abnormalities of pulsatile hGH secretion in the face of a normal growth rate (Chrousos) (Blatt) should be interpreted in the same way. Abnormalities of hGH secretion do not necessarily indicate treatment with hGH.

True growth hormone deficiency with associated growth failure clearly merits hGH therapy (Milner 1986). Therapy should continue until epiphyseal closure in children with post-irradiation growth failure, since hGH deficiency in such cases has been shown to be permanent (Clayton).

It has been shown that ALL survivors have a transient reduction in nocturnal hGH secretion immediately after radiotherapy, which subsequently recovers (Dacou-Voutetakis). This reduction in hGH secretion occurs at the same time as the most marked

statural growth delay seen in longitudinal studies (Griffin) (Swift). It may be that hGH supplementation at this time would be beneficial since eventual statural loss is the consequence of failure to regain this growth, as is demonstrated by this study and others (Griffin).

Mosier et al (1967) (1985) failed to show any advantage of hGH supplementation in head irradiated rats which showed no 'catch-up' after radiation. The same rats responded with normal 'catch-up' growth after starvation. In rats the growth pattern after radiation appears to be the consequence of a 're-setting' of some central mechanisms which regulates growth. It may therefore be that children who grow at a normal rate after cranial irradiation will grow no better on growth hormone.

Clinical trials in children treated with hGH for growth failure after cranial irradiation for a miscellany of diseases (Shalet) (Winter) show accelerated growth during the first year of hGH replacement therapy. A disturbing report by Winter et al (1985) indicated that head irradiated children responded less well to hGH than a control group with isolated hGH deficiency. The head irradiated group also showed an increased rate of epiphyseal maturation and a disproportionate advancement in bone age during therapy. The poor growth rate in the irradiated group together with the increased rate of skeletal maturation would result in decreased growth potential and stunting of growth refractory to therapy. In addition, premature puberty as seen in some of our patients, and also

reported by others (Winter) (Brauner)as a possible sequel to cranial irradiation may further advance bone age and limit ultimate stature. A tendency to advanced bone age seen in our study and seen but not commented on in other data (Swift) would also be a relative contra-indication to hGH therapy.

In leukaemia survivors with short stature and premature puberty it may be possible to allow optimal growth by blocking the progress of puberty with LHRH analogues.

3.4.5 Testicular Function

Leydig cell function, normal progression of puberty and testosterone levels are not affected by leukaemia chemotherapy (Shalet 1982(b)) (Blatt) (Drinnan) (Carrascosa). Germinal cells and testicular tubular function may be affected (Lendon) (Müller) (Kuhadja) by combination chemotherapy although late recovery is likely (Lendon). The effects of alkylating agents are predictable and severe if used as adjunctive therapy (Lenz) (Penso).

Following radiotherapy of the testis for extramedullary relapse, both Leydig- and germ cell damage (Rawley) (Carrascosa) may be severe.

In this study Leydig cell function, as assessed by a normal progression of puberty, age appropriate testosterone levels and basal gonadotropin levels in keeping with pubertal stage, was normal. In the testicular biopsies available, germ cell

function was normal. Normal gonadal function and fertility may therefore be predicted.

Three boys at risk of infertility because of cyclophosphamide therapy were patients 1, 12 and 18. As expected all three passed through normal puberty, had appropriate testosterone levels and LH and FSH responses to LH/FSH RH.

3.4.6 Ovarian Function

Ovarian failure, manifest by elevated serum FSH level has been documented in prepubertal girls given combination chemotherapy (including cyclophosphamide) for acute leukaemia (Shalet 1982), but the incidence may be low (Siris).

All patients in this study passed through a normal puberty. There was no evidence of primary ovarian failure in the patients tested and the only child treated with cyclophosphamide, although not assessed hormonally, had a normal baby when aged eighteen.

Normal ovarian function with normal fertility may therefore be predicted for these patients.

3.4.7 Thyroid Function

Exaggerated TSH response to TRH is a hormonal marker for minimal thyroid damage. It has been postulated (Shalet 1979) that 'scatter' from cranial radiotherapy may be the cause of

3.4.8 Adrenal Function

Deficient cortisol response to insulin hypoglycaemia in both patients and controls may be technical, since high basal cortisol levels indicate a response to the stress of venepuncture and possible depletion of pituitary ACTH early in the test. It must be emphasized that as a group these patients have severe negative associations of pain, nausea and malaise with venepuncture and intravenous infusions as experienced during treatment.

There is no evidence from other studies that treatment of ALL or NHL has late effects on the hypothalamo-pituitary- adrenal axis (Shalet 1977) (V Muhlendahl).

3.4.9 Prolactin

Prolactin secretion by the pituitary gland is regulated by hypothalamic inhibition. Inhibition is mediated by prolactin inhibiting factor (P.I.F.). Elevated serum prolactin levels are therefore a marker of hypothalamic damage due to tumour or other physical injury (Tolis). Normal prolactin values in ALL survivors with impaired hGH respones to hypoglycaemia but apparently normal control of gonadotropin, corticotropin and thyroid stimulating hormone release, indicate the selectivity of radiation damage to the hypothalamus. This is in contrast to the multisystem damage to hormonal control seen following surgery or tumour-related destruction (Shalet 1977).

3.5 CONCLUSION

Growth deceleration during therapy accounts for overall loss in height-for-age in the majority of leukaemia survivors. At the end of treatment growth rate returns to normal. Because of failure of catch-up growth, prediagnosis centiles of height-for-age are not regained.

In a minority of patients growth failure may have its onset years after the end of therapy. Regular measurement of stature in ALL survivors is therefore mandatory.

Growth deceleration and failure of catch-up growth may be the consequence of perturbation of hypothalamic function, most probably due to cranial irradiation. Changes in weight-for-height and development of relative obesity constitute circumstantial evidence favouring hypothalamic injury.

Unless growth velocity is abnormal, growth hormone stimulation tests are unnecessary in leukaemia survivors. If growth velocity remains below the 25th centile (Milner 1986) standard hGH stimulation tests are indicated (Milner 1982).

Replacement therapy with hGH is indicated in those patients with reduced height velocity. Growth hormone treatment may accelerate statural growth in patients with a normal height velocity but treatment related short stature. The decision to treat such patients should be weighed against evidence that hGH may hasten closure of epiphyses and eventually cause further

stunting (Winter).

Testicular and ovarian function are normal in the absence of radiotherapy to these organs. Parents may be reassured that pubertal development and reproductive function are normal in survivors of acute lymphoblastic leukaemia.

Thyroid function tests should form part of long term follow-up of ALL survivors. Hypothyroidism and thyroid tumours may occur.

Adrenal function is normal in survivors of ALL and assessment need not be part of long term follow-up.

CHAPTER 4

INTELLECTUAL FUNCTION IN SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKAEMIA

4.1 INTRODUCTION

Whole head irradiation and intrathecal methotrexate were added to the treatment of acute lymphoblastic leukaemia (ALL) as a life saving strategy (Pinkel) (George) when it became clear that meningeal relapse had become the leading cause of death in marrow remission (Evans) (Hardisty 1967).

From the outset, there was concern (Soni) that this central nervous system 'prophylaxis' might have adverse effects on the developing intellect. Assessment of the effects of treatment on intellectual function presented several problems, which still confound the design of present studies. Although the optimal way to detect development of intellectual deficit is by prospective study at diagnosis, children with leukaemia are often very ill, either from the primary disease or from effects of induction therapy and results of initial intelligence tests would be affected. Furthermore, because ALL has its peak incidence in the pre-school age group, age specific instruments have to be used to measure intelligence. Results of these tests correlate relatively poorly with results of different, age appropriate tests which must be used in follow-up assessments (Rosenberg) (Clarke) (Eysenck). Most studies have therefore relied on retrospective cross-sectional assessment of groups of ALL survivors (Table 4.1). This technique introduces a further major problem: That of finding an appropriate control group.

4.1.1 Neuropsychological Studies in ALL Survivors (Table 4.1)

TABLE 4.1

STUDIES OF NEUROPSYCHOLOGIC FUNCTION AFTER LEUKAEMIA + C.I.

	PRINCIPAL AUTHOR	DESIGN	NO	CONTROL GROUP(S)	DESIGN ERRORS	INSTRUMENTS	FINDINGS
1	Soni (1975) St Jude (Memphis)	a. Prospective	14 19	Self test retest Solid tumour	Sill on treatment	Standford-Binet WISC-R Frostig	No difference detected
		b. Retrospective	5 9	Non irradiated ALL	Small size	Bender Gestalt	
2	McIntosch (1976) (Yale)	Retrospective	18	None	No controls Not pre-tested On treatment IV MTX maintenance	Stanford Binet Merrill-Palmer McCarthy Scale WISC-R	Abnormalities in 8/11 symptomatic patients. Over half had major neurological problems
3	Eiser (1977) (G.O.S.)	Retrospective Correlative	15	Normal age sex socially matched	Normal children as controls. Retrospective, small numbers remedial teaching	McCarthy Scales WISC Burt (reading) scale 'Teachers report'	Children beginning treatment under 5 particularly poor on qualitative, memory and motor skills, not verbal or reading

Table 4.1 continued

	PRINCIPAL AUTHOR	DESIGN	NO	CONTROL GROUP(S)	DESIGN ERRORS	INSTRUMENTS	FINDINGS
4	Eiser (1978) (G.O.S.)	Retrospective Correlative	28	No radiation Late radiation Early radiation	Small numbers Not aged matched retrospective	WISC Burt reading	No difference between 1 + 2 in overal IQ 3 significantly lower IQ than 1 + 2. No verbal scale difference.
4	Obetz (1979) Mayo Clinic	Retrospective Cross section	33	IT MTX alone IT + IV MTX	No sibling/normal controls	Stanford-Binet Bayley scales Wechsler Beery Battery	No significant difference between 3 treatment groups
6	Eiser (1980) (G.O.S.)	Retrospective	40	Normal children age and social match 16 solid tumours age and social match	No sibling controls. 11 remedially taught leuks	1. Shortened WISC-R 2. Burt reading 3. Memory (Williams and WAIS paired association)	ALL treated groups lower on all subtests. Younger ages at treatment did worst

Table 4.1 continued

	PRINCIPAL AUTHOR	DESIGN	NO	CONTROL GROUP	DESIGN ERRORS	INSTRUMENTS	FINDINGS
7	Goff (1980) (St Jude)	Retrospective (survivors include Soni's patients)	37 18	Post induction age matched, newly diagnosed ALL	15 patients had had complications which might have affected IQ scores No controls for 8 patients over 16	WISC WRAT Reitan battery Halstead battery	Lower mean IQ in irradiated group. Memory and attention problems, dyspraxia visual/ spatial problems
8	Moss (1981) (N.C.I.)	Retrospective correlative (test retest)	24	1. 24 healthy sibs 2. ALL survivors - no CNS prophylaxis 3. 10 Siblings of control group 2	1. Some on treatment 3. Retrospective	WISC-R Bender Gestalt WPSSI WAIS 16 plus	Irradiated patients lower full scale, verbal and performance scores. Younger at treatment, lower IQ.
9	Meadows (1981) Philadelphia (Penn U)	Prospective	23 (18) 6 5	Self: test retest ALL Wilms tumour	1. Testing intervals not standardized 2. Older + poor comparison group 3. Different tests used in follow-up.	Stanford Binet WISC McCarthy scales Beery	Significant impairment in 33% at 36 month test: VMI, problem solving and memory. Greatest IQ fall in younger children.

Table 4.1 continued

	PRINCIPAL AUTHOR	DESIGN	NO	CONTROL GROUP	DESIGN ERRORS	INSTRUMENTS	FINDINGS
10	Ivnik (1981) (Mayo Clinic)	Retrospective	19	ALL, No radio-therapy	No normal controls Tested early Small numbers	WISC, WRAT Draw-A-Man	Few meaningful differences.
11	Gutjahr (1981) (Mainz)	Retrospective Prospective	36 20	Unknown Self	Controls not specified	Not specified	"Reflectivity" Slowing tempo improved after stopping treatment
12	Stehbens (1981) (Iowa)	Retrospective	38	Haemophilia patients	Patients still on treatment	WISC-R	Low V/high P younger patients performed less well
13	Stehbens (1983) (Iowa)	Prospective Longitudinal	14 17	Solid tumour	One year interval Still on Rx	WISC-R WRAT WPPSI	All treated under 8 had IQ declines
14	Pavloski (1983) (Beunos Aires)	Retrospective	19	Leukaemics given IT MTX but no irradiation	2 years after diagnosis, still on treatment No normal controls	WISC Stanford-Binet Bender Gestalt	Irradiated patients had lower I.Q.'s
15	Twaddle (1983) Newcastle	Retrospective	23	Sibs Solid tumour + sibs	Retrospective	British Ability Scales (BAS)	Reduced IQ in Cranial RT Less so in ST group

Table 4.1 continued

	PRINCIPAL AUTHOR	DESIGN	NO	CONTROL GROUP	DESIGN ERRORS	INSTRUMENTS	FINDINGS
16	Jannoun (1983) (G.O.S.)	Retrospective	129	Healthy sibs	Retrospective	BAS S Binet WISC-R WAIS	Decrease of IQ but within normal range. Worse under age 3
17	Rowland (1984) (Sloan-Kettering)	Retrospective	33	Leukaemics given IT + IV MTX or IT MTX alone	Early in treatment No normal controls	WRAT Halstead/Reitan	RT lower I.Q. and WRAT independent of age and time from diagnosis
18	Robison (1984) (CCSG)	Retrospective	50	0	No controls	WISC-R 7 years from diagnosis	Lower I.Q. in females, longer treatment younger age at RT

	PRINCIPAL AUTHOR	DESIGN	NO	CONTROL GROUP	DESIGN ERRORS	INSTRUMENTS	FINDINGS
19	Pfefferbaum-Levine (1984) (M.D. Anderson)	Retrospective	18 14	Leukaemics not given RT	Small numbers No normal controls	Weschler Beery WRAT	Absence of effects on non-intellectual language-based skills. Poor spatial skills
20	Whitt (1984) (North Carolina)	Retrospective	8	Leukaemics given IT MTX alone	Small numbers No normal controls	WISC-R WRAT	No significant difference
21	Lansky (1984) (Illinois)	Prospective	21	Leukaemics given no RT	No normal controls	IQ Test .	Decreased I.Q. in RT Lower school attendance
22	Stehbens (1984) (Iowa)	Prospective at diagnosis, 1 year, 3 years	12	Solid tumours	No sibling or normal controls	WISC-R WRAT	Significant decline in ALL verbal and full scale I.Q.
23	Copeland (1985) (M.D. Anderson)	Retrospective	25	Leukaemics given IT MTX alone	No normal controls retrospective	WISC WAIS Beery VMI	RT group significantly worse. Poor V.motor, Spatial memory

4.1.1.1 I.Q. Tests

Soni and colleagues were the first to study ALL survivors who had been treated with cranial irradiation (1975). These workers assessed a small group of survivors both prospectively (14) and retrospectively (5). No significant effects of treatment could be detected on I.Q. testing (Stanford-Binet and WISC-R). Their findings may have been biased by the small sample, the fact that children were still on treatment when tested and sub-optimal conditions during the first test. In the retrospective study, controls were not adequately matched for age or social class.

McIntosh and colleagues (1976) assessed 18 survivors of leukaemia who had received cranial irradiation and intravenous methotrexate. More than half these patients had some severe neurological deficit. Only neurologically symptomatic survivors underwent neuropsychologic testing, with a variety of I.Q. tests. Eight of 11 had abnormal results. There was no control group.

Eiser and Lansdown (1977) (1978), were the first to demonstrate I.Q. deficit following cranial irradiation, particularly in children under 5 at diagnosis. This was a retrospective study and numbers were small. The control group consisted of normal children who were matched for age, sex and social class, so that the effects of cancer and chemotherapy might have been interfering variables. More specific findings from a subsequent study by Eiser (1980) indicated a lower I.Q. score,

poor verbal comprehension, poor perceptual organization and difficulties with concentration span in all survivors, particularly those under 5 at the time of radiotherapy. The interpretation of this study is difficult because of a lack of suitable controls and pretest remedial teaching in 11 of the ALL survivors.

Goff (1980) studied a group of 37 ALL survivors which included patients previously studied by Soni (1975). Controls were newly diagnosed leukaemics in remission, who were tested before radiotherapy. Mean I.Q. in irradiated children was significantly lower. Test patterns suggestive of memory deficit and distractibility indicated possible reasons for academic failure. Obvious difficulties in this study lie in the choice of controls with poor matching for age and social class.

A further difficulty in longitudinal prospective study of intellectual function in ALL survivors was demonstrated by Stehbens (1981) who found a marked verbal-performance (V-P) I.Q. discrepancy (low verbal, high performance) in 38 recently diagnosed paediatric oncology patients (of whom 19 had ALL). Increasing cumulative doses of prednisone and vincristine therapy correlated with the V-P discrepancy. Meadows (1976) had earlier found the opposite, i.e. high verbal and low performance IQ scores in ALL survivors. Relatively small numbers may have biased findings in both groups.

Moss (1981) demonstrated that 24 ALL survivors given cranial irradiation had a significantly lower mean I.Q. than their healthy siblings. In children radiated at a younger age, the I.Q. discrepancy was greater. Survivors of ALL who had not been given cranial irradiation had I.Q.'s not significantly different from their siblings. Some of the subjects given radiation were still on treatment whereas the non-irradiated group were much older at the time of testing. The wide age range required the use of several different I.Q. tests.

Meadows et al enlarged on their previous study in 1981 and reported a significant I.Q. drop in a prospective study. Younger children and those with a high initial I.Q. were most severely affected. The most severe effects were only manifest three years after radiotherapy. Specific deficit was most serious in areas of problem solving, general memory and visual motor integration (VMI). Children were first studied when preschool and later retested with different instruments, making interpretation of this study difficult.

The failure of Ivnik et al (1981) to find few if any meaningful differences between irradiated and non-irradiated ALL survivors may relate to the short interval between radiotherapy and testing, small numbers and the fact that both test groups were given potentially neurotoxic therapy (cranial irradiation and IV methotrexate). Both groups scored slightly below the average for healthy untreated children of similar age.

Walther et al (1981) studied 56 survivors of ALL both prospectively and retrospectively. These children had received 1800 r in cranial irradiation. Testing procedures were not specified, but no I.Q. deficit or any evidence of 'minimal brain dysfunction' was found. Concentration span and auditory memory were impaired. In a letter to the Lancet (1981) they disagreed with Meadows et al (1981) who had reported significant decline in cognitive abilities and widespread, severe neuropsychological difficulties. Slowing in 'psychomotor tempo' during treatment, Walter et al thought, could account for poor I.Q. scores on speed rather than power tests. Their patients had also improved with time and they felt Meadows et al might have tested their patients too soon.

Stehbens et al (1983) reported on a prospective study of 14 children with ALL and 17 with solid tumours. ALL survivors under 8 at diagnosis had falls in I.Q. but, possibly because of small numbers, the change was not significant. Once again V-P discrepancy was noted. Children were still on treatment and only one year post radiotherapy.

Pavlovsky et al (1983) found a higher incidence of low I.Q. scores (compared with values for normal children) than previously reported. There were no normal controls in this study.

Twaddle et al (1983) demonstrated an effective intellectual deficit after treatment in a group of 23 ALL survivors.

Siblings were used as controls for this group and for 19 patients treated for various solid tumours. In ALL survivors intellectual deficit was not apparent immediately after radiation, but became progressively more evident with time. Patients fell within a wide age range and subgroups were too small for statistical analysis. Some patients were still on treatment when tested. Jannoun (1983) also compared I.Q. results of survivors (129 children) with siblings (67) and found that although survivors were functioning within the normal range, I.Q. scores were significantly lower than those of their siblings. Patients treated under the age of 3 years had significantly lower I.Q.'s than patients given the same treatment at an older age, or healthy children matched for age, sex and parental occupation. This study included patients previously tested by Eiser.

Rowland (1984) reported on a retrospective study of 36 ALL survivors given cranial irradiation, comparing them with 35 patients given IV and IT methotrexate and 33 given IT methotrexate alone. Children given radiotherapy had significantly lower I.Q. scores, independent of age at diagnosis or time elapsed from diagnosis. No normal controls were tested and some children were only one year from CNS 'prophylaxis'.

In an uncontrolled study (1984) Robinson found a mean fall in I.Q. significantly below population norms in 50 long-term survivors more than eight years after cranial irradiation. I.Q. scores were lower in subgroups given higher doses of

cranial irradiation, concommitant intrathecal chemotherapy and longer maintenance therapy. Girls and patients given radiotherapy at a younger age also had lower mean I.Q. scores. Some of these findings are questionable because of the lack of controls, but suggest a more defined I.Q. deficit in long-term survivors.

Pfefferbaum-Levine (1984) analysed neuropsychological function of a small number (18) of ALL survivors given cranial RT and compared them with ALL survivors who were not irradiated. Significant differences were found between the two groups on full scale and verbal I.Q. scores, mathematical and constructional skills and memory for spatial material.

Whitt et al (1984) examined a small number of ALL survivors no longer on treatment and compared I.Q. results of those given cranial irradiation (8) with those given other forms of 'prophylaxis' (10). No differences were found between groups, but as a whole, mean I.Q. of all 18 patients was lower than the population mean. The small numbers studied and the lack of normal controls call these findings into question.

Lansky et al (1984) studied school attendance and achievement as measures of ALL survivors' abilities to learn and keep pace with their peers. A prospective study assessed 41 survivors treated with cranial irradiation and 21 given intrathecal methotrexate alone. Patients receiving 'prophylactic' radiation at an early age showed a uniform reduction in school grades when grades from the year prior to diagnosis were

compared with grades three years after diagnosis. Siblings and matched normal children were used as comparisons. The lack of change in full scale I.Q. scores in children treated with cranial irradiation may have related to the relatively poor correlation between instruments of testing for young children and age appropriate tests used in longitudinal follow-up.

In a later study Stehbens (1984) revised his previous findings (1981) (1983) and reported declines in ability and achievement in ALL survivors treated with cranial irradiation. This suggests that intellectual problems are more clearly expressed the longer children survive after radiation.

In a retrospective follow-up study of patients previously described (Pfefferbaum-Levine) Copeland (1985) found a general lowering of scores in tests of visual-motor and fine-motor skills, spatial memory, arithmetic achievement and in verbal, performance and full IQ scores of ALL survivors irradiated during treatment. Although scores were generally lower in this group, abnormality was more pronounced for non-language skills. CNS irradiation reduced performance regardless of the age at which leukaemia was diagnosed.

The weight of evidence is therefore that cranial irradiation as used in the therapy of acute lymphoblastic leukaemia leads to long-term and permanent intellectual deficit. Damage is more severe in younger children and may be delayed in expression. A threshold dose below which this damage might be avoided is not known.

4.1.1.2 Tests of Visuomotor Integration (VMI)

Soni et al (1975) used the Marianne Frostig Developmental test of visual perception (Frostig) on young children, and the Bender Gestalt test as scored by the Koppitz developmental system (Koppitz) on older children to assess VMI. There were no differences in either test between treatment groups (Table 4.1)nor any change during prospective study. Goff (1980) who saw the same patients at a later date did not reassess VMI.

Moss (1981) used the Bender Gestalt test to measure VMI. He showed significantly more perceptual-motor errors in patients given cranial irradiation than in sibling controls. Meadows (1981) used the Beery-Buktenica Developmental test of visual motor integration (Beery) and found moderate to severe impairment in VMI in the majority of children treated with cranial irradiation. Despite abnormal VMI, some childen had normal range IQ scores. Neither initial IQ scores nor a fall in I.Q. during study were predictive of performance in specific functional categories.

Ivnik (1981) found lower mean VMI scores (Beery) in children after cranial irradiation, but the difference was not statistically significant. As mentioned previously, many of these patients were tested soon after treatment. Walter et al (1981) used Frostig and Bender Gestalt tests and found relatively minor abnormalities in children given 1800 rad of whole head irradiation. Pfefferbaum-Levine (1984) used the Beery VMI test, and found no significant difference between

long-term survivors who had received cranial irradiation and those who had not.

Whitt (1984) performed the Beery VMI on a small group of ALL survivors and showed no significant difference between children who had been given cranial irradiation and those who had not, although the former had lower mean developmental quotients. The whole group of survivors scored significantly lower than average when compared with age adjusted normal values.

Lansky et al (1984) used a Bender Gestalt test on a total of 62 patients and found that both patients who had received cranial irradiation and non-irradiated leukaemia survivors had normal Bender Gestalt scores.

Copeland et al (1985) used the Beery VMI test and showed a significant difference between radiated and non-irradiated patients.

Although there is a considerable variation in results, several authors have observed abnormalities of VMI in long-term survivors of ALL (Moss) (Meadows) (Copeland). 'Normal' findings from certain studies may be accounted for by sample size (Soni) (Whitt) (Lansky) or timing of the test soon after treatment (Ivnik) (Soni).

4.1.2 Aim of the Present Study

The aim of the study described in this chapter was to investigate a high rate of school failure among survivors of

acute lymphoblastic leukaemia attending the Oncology Clinic of the Red Cross War Memorial Children's Hospital.

4.1.3 Hypothesis

It was hypothesized in view of the weight of evidence in the literature, despite errors of design in specific studies (Table 4.1) that cranial irradiation was an important cause of poor intellectual function and consequently of school failure.

4.1.4 Design of the Present Study

The ideal design to test such a hypothesis would have been prospective, measuring intellectual ability before and at intervals after irradiation, with a non-irradiated control group assessed in the same way. Such a design would have to discount effects of chemotherapy and synergism between radiation and chemotherapy.

A difficulty with prospective study is the peak incidence of lymphoblastic leukaemia in childhood between 2 and 5 years of age (Miller). Intelligence tests appropriate at this age are not age appropriate at follow-up assessment, because aptitudes they measure are not the same as those assessed by later tests (Piaget) (Clarke). Results are therefore not comparable. If prospective assessment were limited to older children in whom the initial test could be re-used, the children most at risk would be excluded.

A further problem is that children presenting with leukaemia are ill and not likely to perform optimally in any test.

Baseline assessment would therefore underestimate I.Q. and subsequent measurements would not give a true reflection of decline in I.Q. If the first test is performed when the child is in remission, possible effects of chemotherapy may already have occurred.

For these reasons, few investigators have found prospective study to be a realistic option in assessing the effects of treatment on intellectual function in leukaemic children.

For the present study, a cross sectional design was chosen, using sibling controls to exclude socio-economic variables. An additional control group, consisting of children surviving other forms of cancer (which had not required cranial irradiation as part of treatment) and their siblings was used to exclude effects of chronic illness and hospitalization.

It was recognized that this design could not assess the specific effects of cranial irradiation in isolation, since patients in the control group, apart from those with non-Hodgkins Lymphoma, had received treatment which differed from that of acute leukaemia in more than just this respect (see section 4.2.2).

For the purpose of this design, it was also assumed that acute leukaemia, in the absence of clinical or CSF evidence of meningeal leukaemia, has no long-term effects on the central nervous system (see Section 1.2.5).

4.2 PATIENTS AND METHODS

4.2.1. Patients

All long-term survivors of acute lymphoblastic leukaemia were potential subjects for study (see section 2.3). Of 30 long-term survivors, 5 were not tested. Two of these would not consent to study (patients 4 and 5), two could not be tested because of the distance between their homes and the hospital (patient 6 and 12) and one relapsed before testing was possible (patient 10).

Patients were between 7,5 and 18 years old at the time of testing, with a mean age of 11,87 years. They were between 3,8 and 11,2 years (a mean of 7,8 years) from diagnosis. There were 9 boys and 16 girls in the study group. Eleven were of the white ethnic group and 15 were so-called Coloureds. All patients were either English or Afrikaans speaking at home and at school and all were tested in their school language.

Treatment received by these patients is detailed in Tables 2.2 and 2.3

The object and nature of the tests to be performed were explained to the children and their parents and written consent was obtained prior to testing (see Appendix I).

4.2.1. Controls

Subjects surviving acute lymphoblastic leukaemia were tested along with their siblings. Where possible, a sibling of the same sex as the patient was selected. If this was not possible, the sibling closest in age to the leukaemia subject was tested.

Fourteen siblings were available for testing. Their ages ranged between 5,3 and 17,5 years (mean 10,45 years). Eleven were of the same sex as the leukaemia subject and 3 were of opposite sex. A further 6 siblings had school records available for comparison.

This group of siblings was considered to be an appropriate comparison group for IQ testing, which matched the leukaemic subjects for variables such as socio-economic class, child rearing practices and language, since they had been reared in the same household.

All long-term survivors of solid tumours were potential control subjects, having had cancer and chemotherapy, but no cranial irradiation. These patients formed a heterogeneous group (see Table 2.4). Patients surviving non-Hodgkins Lymphoma had received chemotherapy similar to that given to leukaemic patients, had also been treated with intrathecal methotrexate but had not had any cranial irradiation (details of treatment in Table 3.1). Patients surviving Wilms tumours had received chemotherapy alone, with or without radiotherapy to the lumbar region (see Section 2.3).

Patients from the leukaemia and solid tumour groups came from a similar range of socio-economic backgrounds (see Figure 2.2).

4.2.3 Method

Tests were done during school holidays and on Saturday mornings, where possible to coincide with follow-up clinics. IQ and Bender Gestalt tests were carried out in the same office by one psychometrist, who had extensive experience of testing chronically ill children (A.E.M.). All tests were performed without knowledge of the subject's health status.

4.2.3.1 I Q Test

The Senior South African Individual Scale (Madge) was administered to each subject in his or her home language. The SSAIS is similar in construction to the Wechsler intelligence scale for children (WISC). It consists of 9 subtests, 5 of which are verbal and 4 non-verbal:

1. Vocabulary (VOC). A picture test with 20 vocally presented stimulus words. Perception of an auditory stimulus and integration with a visual stimulus is tested.
2. Comprehension (COMPRE). Ten questions that deal with a variety of every day activities and situations, largely social in nature. Items are arranged in increasing order of difficulty. The aim of this subtest is to measure commonsense judgement in social situation and awareness of moral and social norms.
3. Verbal Reasoning (V.REAS). Ten items form a similarities test, the first two requiring completion of a simple

analogy. Performance depends on the ability to differentiate between essential and superficial similarities and to generalize and think abstractly.

4. Problems (PROB). Fifteen verbally administered, timed arithmetical problems. This is mainly a test of concentration ability. Success is dependent on training and therefore reflects level of school achievement.
5. Memory (Mem). A test of recall of meaningful verbal material (a simple 'story') presented vocally. It measures immediate auditory recall and auditory attention span.
6. Pattern Completion (PAT COMPL). This requires free completion of 12 partially completed designs. Time for completion is included in scoring. Visual orientation, ability to concentrate and reasoning by means of analogy are measured.
7. Block design (Blocks). Eight two-dimensional designs to be reproduced with multi-coloured blocks within time limits. This Koh's type test measures the ability to solve problems in spatial relationships and requires visual perception and visual-motor coordination skills.
8. Absurdities (ABSURD). This is similar to Wechsler's Picture Completion subtest, but contains incongruities as well as omissions. Perception, cognition, judgement and delay of impulse enter into performance.
9. Form Board (FORM B). An adaptation of the Leake-Smith Form Board. The test is based on the time taken to complete each figure. The test is considered to measure qualitative aspects of intelligence and of temperament factors in the solution of concrete problems.

Point scales are used, so that the same test item can be applied to all age groups. Performance is indicated by standard scores or normalized scale scores. In the present study, power-plus-time scores were recorded for all subjects.

This test has not yet been standardized for socalled 'coloured' children. Individual scores could therefore not in any way be interpreted as intelligence quotients. In reporting, results were therefore referred to as verbal-, non-verbal- and full scale intelligence scores. These scores represent performance in terms of the 'White' standardization. The only significance attributed to these scores was the difference between scores obtained by the patient (experimental) and sibling (control) groups.

It is difficult to know how so called 'coloured' children should best be tested for intelligence. Many come from a 'culture of poverty' and would be expected to perform less well on the S.SAIS. As an interim measure, until we live in a 'normal' society with equal opportunity, a culture specific assessment based on developmental progress (Piaget) may offer the best estimate of intelligence.

Despite a lack of normative data for more than half of the population studied, the application of the S.SAIS was justified on the basis that the sample consisted of urbanized children only. This would minimize cultural differences, which would be most significant in the vocabulary, comprehension, verbal reasoning, memory and absurdities tests. Cultural factors were

further minimized because inferences were only drawn from inter-sibling differences. Siblings would have been exposed to similar socio-cultural influences. Differences in performance would reflect the extent of differential integration of the same environmental stimuli by a sibling pair.

Results were analysed by student 't' test to detect statistically significant differences between comparison groups at the 5 per cent confidence level.

4.2.3.2 Visual Perception/Visuomotor Coordination

A Bender Visual Motor Gestalt test was administered to all patients and available siblings. These tests were scored according to the Koppitz developmental system (Koppitz). A test result was considered to be abnormal when the subjects error score was higher than that allowed for his or her age. Chi-squared analyses of relative proportions of abnormal results were carried out to detect statistically significant differences between groups.

The Marianne Frostig Developmental Test of Visual Perception (Frostig, 1966) and the Beery Developmental test of Visual Motor Integration (Beery) were performed on age-appropriate patients. Age equivalent scores were compared between groups. Statistical testing was by chi-squared analysis.

Siblings were not given visual perception tests, because it was difficult to arrange these on Saturday mornings and school holidays. It was considered unreasonable for these children to miss school on acount of this study.

4.2.3.3 School Achievement

A history of school achievement was taken from all patients and available siblings. School achievement was compared between groups and differences were statistically assessed by chi-square test.

4.3 RESULTS

4.3.1 I Q Tests

Test scores of leukaemia survivors with available siblings are recorded in Table 4.2. Test scores of their siblings are recorded in Table 4.3. In leukaemia patients mean full scale score was 78,4, compared with 99,3 in their siblings. This is a statistically significant difference ($t = 3,54$, $p < 0,01$). Leukaemia patients with like-sexed siblings had a mean full scale score of 77, compared with a mean of 100,1 for their siblings. This difference was statistically significant ($t = 3,68$, $p < 0,01$).

Differences between patient and sibling groups were statistically significant for verbal, non-verbal and full scale scores whether the patient was compared with a like- or opposite sex sibling (Table 4.4).

In all subtests mean patient scores were lower than mean sibling scores (Table 4.4). Differences were statistically significant (within the set confidence limits) for vocabulary,

TABLE 4.2

S.S.A.I.S. SCORES : LEUKAEMIA PATIENTS (WITH AVAILABLE SIBLINGS)

PAT NO	AGE RT	AGE TEST	VOCAB	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMP	BLOCKS	ABSURD	FORM B	NON-VER	FULL SCALE
1*	4,3	11,5	9	10	7	6	9	85	6	7	7	10	81	81
7*	7,1	12,0	11	10	14	6	12	105	11	11	9	0	99	102
8	5,9	9,7	12	11	6	7	8	89	9	5	10	7	74	81
9*	2,6	7,6	10	9	7	4	10	84	5	5	6	7	69	74
13*	3,3	10,7	11	15	12	8	11	110	11	9	12	11	104	109
14*	2.9	11,2	8	4	6	4	8	69	5	9	9	7	81	72
15*	6,6	11,2	12	9	7	10	7	91	10	11	9	8	95	92
16*	3.8	11.0	11	10	8	5	7	85	7	5	7	9	78	80
17	5,0	9,5	12	11	14	8	8	106	8	8	7	13	92	101
21	10,1	15,5	6	9	11	7	5	81	12	8	8	10	96	88
23*	3,7	14,6	4	6	3	11	8	71	3	2	3	9	58	62
24*	3,6	7,6	7	6	6	10	5	75	6	4	9	8	76	73
26*	5,2	16,4	4	7	3	5	0	54	3	3	6	10	67	55
28	3,3	14,2	6	6	5	4	4	62	4	5	4	8	65	60
31*	8,8	16,8	6	4	6	2	5	60	2	0	0	7	44	47
Mean*	4,72	11,87	8,45	8,18	7,09	6,45	7,45	80,8	6,23	6	7	8,6	77,45	77
S.D.	1,98	3,03	2,87	2,71	3,36	2,91	3,52	17,34	3,19	2,38	3,28	1,36	16,21	18,86
Mean	5,08	11,96	8,60	8,46	7,66	6,46	7,13	81,8	6,46	6,13	7,06	8,06	78,6	78,46
S.D.	2,23	2,93	2,92	2,97	3,51	2,58	3,62	17,00	3,24	3,22	3,91	1,66	16,65	17,48

* = like sex siblings

TABLE 4.3

S.S.A.I.S. SCORES : LEUKAEMIA SIBLINGS

PAT NO	AGE TEST	VOC	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMPL	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
1*	14,0	12	7	6	9	10	89	5	9	7	11	85	86
7*	9,4	11	13	12	9	9	105	13	10	7	6	92	99
9*	11,0	16	15	13	13	15	129	10	11	14	3	95	115
13*	12,4	12	10	10	6	12	99	12	9	12	11	118	109
14*	8,9	17	8	7	10	14	106	11	11	16	19	129	118
15*	13,0	12	14	11	8	12	107	11	8	9	16	106	108
16*	5,3	15	13	16	10	13	122	13	13	12	11	115	120
17	11,7	10	11	11	6	5	88	10	10	4	17	100	93
21	17,5	14	8	13	5	4	75	3	7	3	10	69	69
23*	7,4	13	6	8	10	13	98	9	8	9	9	90	94
24*	10,7	9	5	5	5	6	71	8	5	5	8	74	69
26*	10,6	10	11	10	11	12	102	13	13	10	9	108	105
28	7,5	20	11	13	11	14	124	11	12	13	15	118	124
31*	9,6	10	6	6	3	7	72	6	5	13	11	90	78
Mean*	10,21	12,45	9,81	9,45	8,6	10,8	100	10,09	9,27	10,36	1036	100,7	100,1
S.D.	2,5	2,58	3,6	3,42	2,87	4,16	17,5	2,81	2,71	3,35	4,36	16,09	16,72
Mean	10,45	12,86	10,13	10,06	8,33	10,53	99,6	9,53	9,4	9,6	11,06	98,93	99,26
S.D.	3,05	3,04	3,29	3,15	2,77	3,52	198,0	3,04	2,50	3,83	4,2	16,84	17,68

* = like sex siblings

TABLE 4.4

S.A.I.S. SCORES : PATIENT-SIBLING DIFFERENCE : LEUKAEMIA GROUP

PAT NO	VOCAB	COMPRE	V.REAS	PROBL	MEM	VERB	PAT COMP	BLOCKS	ABSURD	FORM B	NON Verb	Full Scale
1*	-3	+3	+1	-3	-1	-4	+1	-2	0	-1	-4	-5
7*	0	-3	+1	-3	+3	0	-2	+1	+2	+3	+7	+3
8	0	-3	-4	-2	-4	-18	+1	-5	0	-3	-21	-21
9*	-6	-6	-6	-9	-5	-45	-5	-6	-8	+4	-16	-41
13*	-1	+5	+2	+2	-1	+11	-1	0	0	0	-14	0
14*	-9	-4	-1	-6	-6	-37	-6	-2	-7	-12	-48	-46
15*	0	-5	-4	+2	-5	-16	-1	+3	0	-8	-11	-16
16*	-4	-3	-8	-5	-6	-37	-6	-8	-5	-2	-37	-40
17	+2	0	+3	+2	+3	+18	-2	-2	+4	-7	-4	-8
21	+2	+1	-2	+2	+1	+6	+9	+1	+5	0	+30	+19
23*	-9	0	-5	+1	-5	-26	-6	-6	-6	0	-32	-32
24*	-2	+1	+1	+5	-1	+4	-2	-1	+4	0	+2	+4
26*	-6	-4	-7	-5	-12	-48	-10	-10	-4	+1	-41	-50
28	-14	-5	-8	-7	-10	-70	-5	-7	-9	-7	-53	-64
31*	-4	-2	0	-1	-2	-12	-4	-5	-13	-4	-46	-31

Table 4.4 continued

	VOCAB	COMPRE	V.REAS	PROBL	MEM	VERB	PAT COMP	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
Mean d*	-4	-1,63	-2,36	-2	-3,72	-19,09	-3,27	3,27	-3,3	-1,91	-21,8	-23,09
SD+	2,22	3,47	3,69	4,19	3,92	10,70	4,03	4,03	5,04	4,6	19,74	20,79
t	4,12	1,55	2,12	1,58	3,14	3,05	2,69	2,69	2,17	1,37	3,66	3,68
p	0,01	NS	NS	NS	0,01	0,02	0,05	0,05	NS	NS	0,01	0,01
Mean d	-3,6	-1,66	-2,46	-1,8	-3,4	-18,1	-2,2	-3,26	-2,46	-2,53	-19,2	-21,86
SD	4,58	3,17	3,77	4,07	4,3	25,2	4,76	3,77	5,41	4,3	23,56	23,87
t	3,04	2,02	2,56	1,71	3,06	2,78	1,79	3,34	1,76	2,27	3,15	3,55
p	0,01	NS	0,05	NS	0,01	0,02	NS	0,01	NS	0,05	0,01	0,01

* = like sex siblings

memory, pattern completion and blocks between like-sex siblings and for vocabulary, verbal reasoning, memory, blocks and form board between patients and mixed-sex siblings (Table 4.4).

Test scores of solid tumour survivors with available siblings, are recorded in Table 4.5. Test scores of their siblings are recorded in Table 4.6. In solid tumour patients, mean full scale score was 96,5 compared with 98,4 in their siblings. This difference is not statistically significant. Solid tumour patients with like-sex siblings had a mean full scale score of 99,4 compared with 99,5 in their siblings. There was no significant difference between these values (Table 4.7).

Mean verbal, non-verbal and subtest scores were not significantly different between the solid tumour group and their siblings (Table 4.7).

Because the SSAIS is standardized for 'white' South African children, total IQ scores of white leukaemia survivors (Table 4.8) could be compared with IQ scores of white solid tumour survivors (Table 4.9). The mean IQ of this group of leukaemia survivors was 95,27 ($\pm$ 18,87) compared with 116,2 ($\pm$ 14,2) in the solid tumour survivors. This difference is statistically significant ($t = 3,20$, $p < 0,01$).

TABLE 4.5

S.S.A.I.S. SCORES : SOLID TUMOUR PATIENTS WITH SIBLINGS

PAT NO	AGE TEST	VOC	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMPL	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
34*	9,2	9	13	14	12	9	107	11	14	6	9	99	104
35	9,6	14	11	15	15	13	123	14	13	11	13	118	123
39	15,9	11	4	9	5	5	75	12	10	12	6	99	84
40	13,6	3	9	4	5	7	67	7	6	7	5	71	64
42*	8,5	6	5	5	6	2	61	3	6	3	9	67	59
43	13,8	20	15	17	10	7	124	12	12	14	15	122	126
44*	14.9	9	11	14	9	7	98	5	10	1	15	83	90
46	8,3	9	10	7	12	8	92	8	7	11	12	95	94
48	6,1	11	7	8	8	6	84	7	7	6	6	74	77
51*	10,4	12	13	14	10	7	106	16	13	12	14	125	116
52*	16,2	10	12	11	14	10	107	11	14	14	15	106	108
53	7,2	11	9	10	11	8	90	14	13	14	11	120	108
55	10,9	6	4	7	7	3	65	6	5	5	5	63	61
56	10,2	13	16	15	12	13	124	15	14	11	14	124	127
58*	15,2	14	15	12	11	10	115	12	12	11	11	109	114
61*	13,6	14	11	12	12	11	112	10	11	15	10	109	112
62*	12,3	9	6	6	6	8	76	9	7	10	12	95	83
64	15,4	6	5	3	5	6	76	11	8	5	14	95	74
66*	16,8	13	12	10	11	9	105	11	12	12	12	111	109

Table 4.5 continued

	AGE TEST	VOC	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMPL	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
N = 9													
Mean*	13,01	10,6	10,88	10,8	10,1	8,22	98,55	9,77	11	9,33	11,88	99,7	99,4
S.D.	3,07	2,73	3,29	3,56	2,71	2,63	18,0	2,78	2,87	4,89	2,36	16,9	18,6
N = 19													
Mean	12,00	10,52	9,89	10,15	9,53	7,94	95,42	10,21	10,21	9,47	10,94	98,89	96,47
S.D.	3,32	3,86	3,82	4,11	3,13	2,94	20,76	3,50	3,12	4,11	3,43	19,73	22,23

* = like sex siblings

TABLE 4.6

S.S.A.I.S. SCORES: SOLID TUMOUR : SIBLINGS

PAT NO	AGE TEST	VOC	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMPL	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
34*	12,6	8	10	15	7	6	92	7	10	7	10	88	89
35	10,3	17	18	18	16	11	140	17	18	17	15	116	148
39	10,3	15	11	12	10	10	109	15	16	10	18	133	122
40	11,6	7	5	2	2	4	55	4	4	2	10	62	53
42*	10,0	10	5	2	3	5	62	4	7	4	8	69	67
43	11,0	16	12	11	8	8	105	14	14	10	15	122	114
44*	6,8	6	7	4	10	8	76	7	6	7	9	80	75
46	5,6	6	9	9	10	8	86	7	6	4	6	69	76
48	11,0	12	7	9	10	7	91	8	10	7	12	94	91
51*	14,1	9	15	8	11	10	102	16	13	16	17	138	120
52*	13,7	14	12	12	9	10	107	6	7	4	12	80	85
53	10,6	10	11	15	12	12	112	12	15	12	9	113	114
55	12.9	5	8	4	4	4	62	7	8	5	9	78	66
56	12,9	13	16	17	17	13	133	17	12	12	15	127	134
58*	13,7	14	15	10	13	11	116	16	15	13	17	136	128
61*	9,6	11	10	11	15	11	109	15	14	10	13	120	115
62*	16,0	4	7	6	5	8	69	5	7	8	6	74	68
64	10,2	11	7	4	4	3	68	11	12	9	14	109	94
66*	14,4	14	10	9	8	9	98	16	14	14	11	125	111

Table 4.6 cntinued

PAT NO	AGE TEST	VOC	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMPL	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
Mean*	13,0	10,6	10,6	10,88	10,11	8,11	98,5	9,77	11	9,33	11,88	100,4	99,5
S.D.	3,07	2,73	3,29	3,37	2,71	2,66	18,06	3,83	2,87	4,89	2,36	17,1	18,84
Mean	11,76	10,9	10,63	10,47	9,68	8,05	97,26	10,52	11,2	9,05	12,1	102,94	98,42
S.D.	2,78	3,41	3,65	4,56	3,98	3,06	23,79	4,18	3,72	4,53	3,07	23,22	26,83

* = like sex siblings

TABLE 4.7

S.S.A.I.S. SCORES : SIBLING - PATIENT DIFFERENCE SOLID TUMOUR GROUP

PAT NO	VOCAB	COMPRE	V.REAS	PROBL	MEM	VERB	PAT COMP	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCORE
34*	+1	+3	-1	+5	+3	+15	+4	+4	-1	-1	+11	+25
35	-3	-9	-3	-1	+2	-17	-3	-5	-6	-2	-28	-25
39	-12	-2	-2	-5	-3	-34	-3	-6	+2	-12	-33	-38
40	-4	+4	+2	-13	+3	+12	+3	+2	+5	-4	+9	+11
42*	-4	0	+3	+3	-3	-1	-1	-1	-1	-1	-2	-8
43	+4	+3	+6	+2	-1	+19	-2	+2	+4	0	0	+12
44*	+3	+4	+10	+5	-1	+22	-2	+4	-1	+6	+3	+15
46	+3	+1	-2	+2	0	+6	+1	+1	+7	+6	+26	+19
48	-1	0	-1	-2	-1	-7	-1	-3	-1	-6	-20	-14
51*	+3	-2	-6	-1	-4	+4	0	0	-4	-3	-13	-4
52*	-4	0	-1	-2	+1	0	+5	+7	0	+3	21	+23
53	-1	-2	-5	-1	-4	-16	+2	-2	+2	+2	+7	-6
55	+1	-4	+3	+3	-1	+3	-1	-3	0	-4	-13	-5
56	0	0	-2	-5	0	-9	-2	+2	-1	-1	-3	-7
58*	0	0	+2	-4	-1	-1	-4	-3	-2	-6	-27	-14
61*	+3	+1	+1	-3	0	+3	-5	-3	+5	-3	-11	-3
62*	+5	-1	0	+1	0	+7	+4	0	+2	6	+21	+15
64	-5	-2	-1	+1	+3	+8	0	+4	+4	0	-14	-20
66*	-1	+2	+1	+3	0	+7	-5	-2	-2	+1	-14	-2

Table 4.7 continued

PAT NO	VOCAB	COMPRE	V.REAS	PROBL	MEM	VERB	PAT COMP	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCORE
Mean d*	0,66	0,77	1	0,77	-0,55	5,55	-0,44	0,66	-0,44	0,22	-1,22	5,22
SD±	3,2	1,92	4,24	3,41	2,06	8,7	3,97	3,53	2,60	4,14	16,64	14,35
t	0,61	1,20	0,70	0,67	0,80	1,91	0,33	0,56	0,51	0,15	0,21	1,09
p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mean d	-0,63	-0,21	0,10	0,21	-0,36	1,10	,0,52	-0,10	0,63	-1	-4,21	-1,42
SD±	4,08	3,06	4,14	3,17	2,16	13,44	3,02	3,46	3,33	4,57	17,23	17,0
t	0,67	0,29	0,10	0,28	0,72	0,35	0,75	0,12	0,82	0,95	1,06	0,36
p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

* = like sex siblings

TABLE 4.9

S.S.A.I.S. I.Q. SCORES : WHITE SOLID TUMOUR PATIENTS

PAT NO	AGE TEST	VOC	COMPRE	V.REAS	PROB	MEM	VERB	PAT COMPL	BLOCKS	ABSURD	FORM B	NON VERB	FULL SCALE
35	9,6	14	11	15	15	13	123	14	13	11	13	118	123
39	15,9	11	11	9	5	5	75	12	10	12	6	99	84
43	13,3	20	15	17	10	7	126	12	12	14	15	122	126
47	13,9	17	14	12	12	12	122	18	13	11	14	127	127
51	10,4	12	13	14	10	7	106	16	13	12	14	125	116
52	16,2	10	12	11	14	10	107	11	14	4	15	106	108
56	10,2	13	16	15	12	13	124	15	14	11	14	124	127
58	15,2	14	15	12	11	10	115	12	12	11	11	109	114
61	13,6	14	11	12	12	11	112	10	11	15	10	109	112
66	16,8	13	12	10	11	9	105	11	12	12	12	111	109
73	10,3	14.	11	15	13	9	115	11	10	9	15	108	113
75	12,3	12	14	14	15	17	129	19	17	14	17	146	141
$\bar{x}$	13,14	13,6	12,91	13	11,66	10,25	113,25	12,58	12,58	11,33	13	117	116,6
S.D.	2,57	2,67	1,83	2,37	2,7	3,25	14,54	3,77	1,92	2,83	2,92	12,68	14,2

4.3.2 Visual Perception

4.3.2.1 Bender Gestalt Test (Tables 4.10 to 4.13)

There were significantly more abnormal scores among leukaemia survivors than among siblings of survivors.

Bender Gestalt Test

	Normal	Abnormal	Total
Leukaemia patients	11	12	23
Leukaemia siblings	11	4	15
	22	16	38

An analysis of proportions indicates that a higher than expected number of leukaemia survivors had abnormal Bender Gestalt tests ($X^2 = 3,58$; $0,05 < p < 0,10$) than siblings tested but that the difference was not significant at the 5 percent level of confidence.

Similar proportions of solid tumour survivors and their siblings had abnormal Bender Gestalt tests, but significantly more leukaemia survivors had abnormal tests than had solid tumour survivors.

TABLE 4.10

BENDER GESTALT : LEUKAEMIA PATIENTS

NO	AGE AT TEST	BENDER SCORE	EXPECTED SCORE	NORMAL/ ABNORMAL	'BRAIN INJURY' SCORE
1	11,5	5	0-3,6	A	4
2	17,5	2	0	A	2
7	12,0	0	0	N	0
8	9,6	3	0-3,3	N	3
9	7,5	9	1,2-8,4	A	6
13	10,6	0	0-3,6	N	0
14	11,1	5	0-3,6	A	4
15	11,1	3	0-3,6	N	4
16	11,0	6	0-3,6	A	5
17	9,5	2	0-3,5	N	1
18	16,6	0	0	N	0
19	12,25	0	0	N	0
20	10,0	6	0-3,3	A	4
21	15,5	0	0	N	0
22	16,5	0	0	N	0
23	14,9	10	0	A	7
24	7,5	7	1,2-8,4	N	6
25	18,0	1	0	A	0
26	16,5	3	0	A	5
27	10,0	6	0-3,3	A	5
28	14,6	6	0	A	3
30	7,8	9	1,4-8,0	A	7
31	16,75	2	0	N	0

TABLE 4.11

BENDER GESTALT : SIBLINGS OF LEUKAEMIA PATIENTS

NO	AGE AT TEST	BENDER SCORE	EXPECTED SCORE	NORMAL/ ABNORMAL	'BRAIN INJURY' SCORE
1	14	1	±0	N	2
7	9,3	7	0-3,5	A	6
8	7,75	6	1,4-8,0	N	6
9	11,0	5	0-3,6	A	4
13	11,5	0	0	N	0
14	9,0	0	0-3,5	N	0
15	13,9	0	0	N	0
16	5,4	10	10-17	N	0
17	11,6	5	0-3,6	A	4
21	18,0	0	0	N	0
23	7,5	8	1,2-8,4	N	8
24	10,9	4	0-3,6	A	1
26	10,6	2	0-3,6	N	0
28	8,0	4	0,1-7,3	N	0
31	9,6	2	0-3,3	N	1

TABLE 4.13

BENDER GESTALT : SOLID TUMOUR SIBLINGS

NO	AGE AT TEST	BENDER SCORE	EXPECTED SCORE	NORMAL/ ABNORMAL	'BRAIN INJURY' SCORE
34	12,6	0	0	N	0
35	10,25	0	0-3	N	0
39	10,3	2	0-3	N	0
40	11,7	2	0-3	N	2
42	9,9	0	0-3	N	0
43	10,9	2	0-3	N	0
44	6,75	6	2-10	N	4
46	8,3	5	1-7	N	0
48	11,0	3	0-3	N	2
51	14	0	0	N	0
52	13,6	0	0	N	0
53	10,6	4	0-3	A	0
55	12,9	1	0-3	N	0
56	11,9	0	0	N	0
58	13,6	0	0	N	0
62	13,7	0	0	N	0
62	15,9	0	0	N	0
64	13,1	0	0	N	0
66	14,6	5	0	A	4

Bender Gestalt Test:

	Normal	Abnormal	Total
Leukaemia patients	11	12	23
Solid tumour patients	24	4	28
	35	16	51

($X^2 = 10,27$ $p < 0,01$).

Fifteen of 23 leukaemia survivors (65%) had one or more errors on testing such as are made by patients with organic brain injury (Koppitz). Twenty-five percent of solid tumour survivors made such errors.

Bender Gestalt 'Brain Injury' Errors

	Absent	Present	Total
Leukaemia patients	8	15	23
Solid tumour patients	20	8	28
	28	23	51

Significantly more leukaemia survivors have such indications of 'brain injury' on Bender Gestalt testing ($X^2 = 8,42$, $0,001 < p < 0,01$)

There is a high incidence of such errors among siblings of leukaemia patients (8 of 15).

4.3.3.2 Marianne Frostig Test of Visual Perception (Table 4.14)

Ten leukaemia survivors were within the age range for this test.

Visuomotor Integration (VMI)

Four patients (9, 12, 27, 30) had results indicating VMI delay. In six, results were age appropriate (10, 11, 24) or advanced for age (8, 17, 20). These findings (apart from patient 20) were in keeping with available Bender Gestalt scores.

Other Categories

All patients scored below age norms for all other subtests (see table).

No controls were given these tests.

4.3.3.3 Beery-Butenika Test of Visuomotor Integration (Table 4.15)

Twenty leukaemia survivors were within the age limits for this test. Only 3 (patients 7,10,11) scored appropriately. All other subjects had indications of VMI immaturity. Ten of these results were in agreement with Bender Gestalt findings (including four patients - 9, 12, 27 and 30 - which were abnormal for all three tests). Five patients with VMI immaturity had normal Bender Gestalt scores. Of these, 2 also had normal VMI on the Frostig test (patients 8, 17).

No controls were tested.

TABLE 4.14

FROSTIG: ALL SURVIVORS UNDER 10 YEARS OLD AT TESTING

NO	AGE AT TEST	TESTS				
		VMI	FIGURE GROUND	FORM CONSTANCY	POSITION IN SPACE	SPATIAL RELATIONS
8	9,75	10+	6,5	5,5	5,5	8,25
9	6,75	4,5	3,5	6,25	4,75	4,75
10	7,0	7,0	4,75	9,0	5,5	8,25
11	7,6	7,5	6,5	6,5	5,5	7,0
12	10,0	7,3	8,3	7,0	7,0	8,3
17	9,5	10+	5,75	6,75	6,23	7,5
20	8,5	10+	5,75	6,75	6,25	6,5
24	7,25	7,25	5,25	5,5	5,0	4,0
27	9,25	6,75	5,0	6,75	6,25	6,0
30	8,75	7,75	5,5	6,25	6,25	6,5

TABLE 4.15

BEERY BUTENIKA : DEVELOPMENTAL TEST OF VISUOMOTOR INTEGRATION : LEUKAEMIA PATIENTS

NO	AGE	BEERY AGE
1	10,8	9,3
3	14,5	10,25
6	7,25	5,5
7	11,75	12,0
8	9,75	6,6
9	6,75	3,2
10	7,0	6,8
11	7,7	8,7
14	10,2	6,8
15	11,25	6,2
16	11,25	7,2
17	10,5	7,2
19	12,25	7,2
20	8,5	5,5
21	15,0	9,3
24	7,25	5,5
27	9,25	6,8
28	14,25	5,8
30	8,75	4,0
31	15,6	10,25

4.3.4 School Records (Tables 4.16 to 4.18)

Twenty-two (74,2%) of 30 leukaemia survivors had failed one school grade or more. Eight (25,8%) had failed two grades and one had failed four times. Of the 8 who had not failed, 2 were experiencing difficulty at school (patients 11 and 19). One had dropped out of school early (patient 25) and one was pursuing commercial subjects.

Four (20%) of the 20 siblings of leukaemia patients and failed a class at school.

Four (30%) of 13 school-going survivors of Non-Hodgkins Lymphoma (NHL) therapy had failed a class, as had four of 23 school-going survivors of other solid tumours (17%) of the siblings of all these solid tumour survivors 26% (4 out of 19) had failed a class at school:

Diagnosis	Failed	No Failure	Total
Leukaemia	23	8	30
Non-Hodgkins Lymphoma	3	9	13
Other solid tumours	4	19	23
	30	36	66

A significantly larger proportion of leukaemia survivors had a record of school failure than had either NHL patients (x^2 = 6,82, $0,001 < p < 0,01$) or the whole group of solid tumour survivors ($X^2 = 18,3$, $p < 0,001$).

TABLE 4.16

SCHOOL RECORD : LEUKAEMIA PATIENTS

NO	AGE START	NO OF GRADES FAILED	PRESENT GRADE	TREATMENT DURING SCHOOL
1	6,0	1	5	Yes
2	7,0	2	4	Yes
3	6,0	2	6	Yes
4	6,0	0	12	Yes
5	6,0	1	6	No
6	6,0	1	1	Yes
7	6,0	0	6	Yes
8	7,0	1	3	Yes
9	6,0	2	1	Yes
10	7,0	1	2	Yes
11	6,0	0	2	No
12	6,0	1	6	Yes
13	6,0	1	5	No
14	6,0	4	3	Yes
15	5,0	1	5	Yes
16	6,0	2	3	No
17	6,0	0	4	Yes
18	6,0	0	11	Yes
19	6,0	0	6	Yes
20	6,0	2	2	Yes
21	6,0	2	9	Yes
22	5,0	0	11	Yes
23	8,0	2	6	Yes
24	6,0	1	1	Yes
25	6,0	0	10	Yes
26	6,0	2	9	Yes
27	6,0	1	4	Yes
28	5,0	1	7	Yes
30	6,0	1	1	No
31	7,0	1	7	Yes

TABLE 4.17

SCHOOL RECORD : SOLID TUMOUR - NON HODGKINS LYMPHOMA

NO	AGE START	NO OF GRADES FAILED	GRADE ACHIEVED	TREATMENT DURING SCHOOL
29	6,0	1	1	Yes
32	6,0	0	12	Yes
34	6,5	0	4	Yes
35	6,5	0	3	No
37	7,5	3	1	Yes
39	6,5	1	9	Yes
40	6,5	2	3	Yes
41	6,5	0	9	Yes
42	8,0	0	2	No
43	6,5	0	8	Yes
44	7,0	0	8	Yes
46	-	-	-	No
47	6,5	0	9	Yes
48	6,0	0	1	No

TABLE 4.18

SCHOOL RECORD : SOLID TUMOUR : WILMS

NO	AGE START	NO OF GRADES FAILED	GRADE ACHIEVED	TREATMENT DURING SCHOOL
49	6,0	0	7	No
50	6,0	0	7	No
51	6,5	0	5	Yes
52	6,2	0	10	No
53	6,4	0	1	No
54	7,0	1	3	No
55	6,5	2	4	Yes
56	6,0	0	5	No
57	6,5	0	9	No
58	6,5	0	9	No
59	6,0	0	6	No
60	-	-	-	-
61	7,0	0	3	No
62	6,3	0	6	No
63	6,3	0	11	No
64	6,0	1	8	Yes
65	6,5	1	4	No
66	6,0	0	11	Yes
67	-	-	-	-
68	6,5	0	10	No
69	-	-	-	-
70	6,5	0	4	No
71	-	-	-	-
72	6,0	0	4	No
73	6,3	0	4	No
74	6,0	0	3	No
75	5,8	0	7	Yes

Twenty-six of 30 leukaemia survivors were being treated while at school. Nine of 13 survivors of NHL and 5 of 23 survivors of other tumours had received treatment while at school.

Diagnosis	Treatment During School		Total
	Yes	No	
Leukaemia	25	5	30
Non-Hodgkins Lymphoma	10	4	14
Other solid tumours	5	18	23
	40	27	67

The proportion of leukaemic children treated while at school was not significantly different from that of children with NHL (X^2 = 0,47), but a significantly larger proportion of leukaemics were treated while at school than were children with other tumours (X^2 = 18,38, $p < 0,001$).

4.4 DISCUSSION

4.4.1 S.S.A.I.S. Test Results

Intersibling S.S.A.I.S. comparisons indicated a deficit in leukaemia survivors with respect to their healthy siblings. This was not the consequence of chronic illness or the effect of a prolonged course of treatment, since children surviving solid tumours had scores similar to those of their siblings.

This difference of approximately 18 points is biologically significant, but might still leave the child in the 'low normal' range and able to benefit from normal schooling, as indicated by the analysis of 'white' survivor I.Q.'s (Table 4.8).

Although socio-economic class should be similar for siblings, this is not always so, since a family's circumstances may fluctuate (Guilford). In lower socio-economic groups younger children might score lower on I.Q. tests until they have been at school long enough to learn the tasks required to perform well in these tests (Piaget). These are possible sources of bias in a sibling controlled study. In this sample, there were similar numbers of controls older and younger than their leukaemic siblings.

The expected I.Q. correlation between relatives depends on the number of genes they share (Erlenmeyer-Kimling). In non-twin siblings a correlation of about 0.5 is expected. Although the difference in correlation between same and opposite sex non-twin sibling pairs is trivial (Bouchard), sex differences may be a source of bias in small samples. In the present study for example, male patient-female sibling comparisons (patients 17,21) yielded unexpected results and a female patient-male sibling comparison (patient 28) gave an unusually large full scale deficit.

In a previous study, Twaddle et al (1983) corrected the sibling score for an expected intersibling correlation of 0.5. These

authors found an I.Q. deficit in leukaemia survivors. A similar statistical maneuvre was carried out on I.Q. data from this study and yielded unchanged conclusions. Twaddle et al used non-sex matched sibling controls.

This study showed no significant difference between verbal and non-verbal score deficits as was previously described by Stehbens (1981) and Pfefferbaum-Levine (1984). The deficit was global, with negative trends in all subtests but with more marked effects on verbal reasoning, abstract language and memory and in the use of spatial concepts (form board and blocks). The deficit in memory was previously reported by Eiser (1977), Goff (1980), Meadows (1981) and Copeland (1985). Visual-spatial deficits were also reported by Goff, Meadows and Pfefferbaum-Levine, and correlated well with results of visual perceptual tests (see below).

It is not surprising that S.S.A.I.S. findings are in keeping with poor school performance among leukaemia survivors, since the prediction of scholastic ability has always been the major purpose of intelligence tests (Richardson) (Cattel).

The present study sample was too small to assess the effects of age at the time of irradiation on subsequent I.Q. There was a trend to suggest that younger children fared worse, but the correlation coefficient of -0,336 was not statistically significant for the number of patients compared. In previous studies, Eiser (1977), Moss (1981), Meadows (1981), Stehbens (1981) (1983), Jannoun (1983) and Robinson (1984) all found

younger children more severely affected by 'prophylactic' cranial irradiation for leukaemia than older children.

Of 11 White children (for whom the SSAIS is standardized) cranial irradiation was given under the age of 5 years in 5, and over the age of 5 in 6. Four out of the five under age 5 had low I.Q. scores and one had a normal I.Q. score. Five of the six over age 5 had normal I.Q. scores. The difference in the proportion of children with low I.Q. scores within these two groups is statistically significant ($X^2 = 7,34$, $0,001 < p < 0,01$). In this subgroup therefore, children under 5 at radiation are demonstrably worse off.

4.4.2 Bender Gestalt Test

The majority of leukaemia survivors had abnormally high error scores for age, indicating perceptual immaturity. This was not purely the consequence of socioeconomic deprivation, since sibling controls had significantly fewer errors. Illness early in life with loss of school and other learning opportunities was not the only cause, because children surviving solid tumours had significantly fewer errors.

Certain errors in the Bender Gestalt test have been found more frequently in 'brain-injured' children than in those with other causes of perceptual problems (Koppitz). These errors were more frequently made by leukaemia survivors than any of the other groups tested. The significance of these findings will be discussed in Chapter 5.

The high rate of errors specific for 'brain injury' among children surviving non-Hodgkins Lymphoma is interesting, since these children received intrathecal methotrexate as part of therapy. This treatment modality is known to be a cause of organic brain injury, but more so in combination with cranial irradiation and intravenous methotrexate (Bleyer).

4.4.3 Marianne Frostig Developmental Test of Visual Perception (Frostig) and Beery-Butenika Test of Visuomotor Integration (Beery)

The majority of leukaemia survivors had indications of serious visual perceptual disturbance. Findings on the Frostig and Berry tests were uncontrolled, but correlated well with results of the Bender Gestalt test, which was carried out on sibling and solid tumour controls.

Visual perceptual tests measure maturation of specific perceptual abilities. Uniformly retarded perception is seen in mental retardation, social deprivation and with neurological handicap (Frostig). Findings in the leukaemia group are in keeping with the I.Q. deficit demonstrated, but it is possible that other factors contributed to low scores.

Nursery school attendance, nursery school programmes and socio-economic class are important determinants of the rate of maturation of visual perception (Frostig). Among children from poor socio-economic background, such variables are related to a low level of school readiness and a high rate of failure in the first grades at school. Among leukaemia survivors,

particularly those diagnosed in the pre-school years, poor scores in tests of visual perception may have been contributed to by loss of school and nursery school experience due to treatment related illness (Eiser 1980b) (see Table 2.5)

Step-wise acquisition of perceptual skills is a child's main developmental task between 3 and 7 years of age, after which intellectual development becomes the primary task (Piaget). The presence of visual-perceptual disturbance in the majority of leukaemia survivors in this study and in others (Moss) (Meadows) (Copeland) suggests a developmental failure, either preceding the illness or because of the illness and treatment-related side effects during the preschool years.

It appears that childhood leukaemia survivors are at high risk of general visual-perceptual disability because of the early age of onset and specific treatment of the disease. Children with such severe perceptual disturbances are often unable to overcome their handicap by intellectual means and therefore fail academically (Frostig).

There is also an impressive correlation between perceptual disability and neurological handicap, and the Frostig test has been used in a battery of tests for the diagnosis of brain damage. This correlation will be examined in the folloiwng chapter (Frostig, Lefever).

4.4.4 School Record

Leukaemia survivors had a significantly higher rate of school

failure than any other group studied. Several factors may have interfered with the learning process and had a bearing on school failure.

The child with leukaemia experiences interruptions with schooling due to illness and treatment side-effects (Table 2.5). Rates of absence are highest during the first 6 months after diagnosis (Eiser, 1980b) when therapy is the most intensive. As soon as therapy stops, school attendance improves substantially. In children falling ill immediately before starting school the effects of treatment related illness are most severe and early school failure more likely, although some children failed lower grades even though treatment was complete before they started school (Table 4.18).

Interrupted schooling is not the sole cause of school failure, since children with NHL and solid tumours were also treated while at school, without academic failure (Table 4.19).

Visual-perceptual immaturity, and delay in visuomotor integration among leukaemia survivors, leading to a lack of school readiness, may explain their high rate of failure in the first grades at school (Table 4.18).

Children surviving leukaemia had relatively low I.Q.'s in comparison with their siblings, although those who could be compared with population norms (Table 4.8) had a mean I.Q. in the low normal range. An I.Q. of this order would not necessarily be associated with early school failure, but would rather predict limited achievement in later grades.

Children who are socio-economically deprived are less likely to be school ready (Piaget) since they are less likely to have acquired basic skills in early life. A similar proportion of leukaemia survivors come from a poor socio-economic background as did patients in other treatment groups, so that this does not explain perceptual delay or early failures at school in this group.

Emotional adaptation is an important prerequisite for success at school and interaction with teachers and peers. This aspect is addressed in Chapter 7 and, as will be seen, is not of significance among leukaemia survivors.

It appears therefore that many factors contribute to early school failure among leukaemia survivors. Loss of schooling (Lansky) difficulties with visuomotor integration, retardation in the development of visual perception and moderate IQ deficit all play a role.

CONCLUSION:

The results of this study indicate that there are significant differences in intellectual function between children surviving ALL and their healthy siblings. That such differences are not present between other cancer survivors and their siblings, indicates that the cause of intellectual deficit lies in ALL and its treatment. It is not possible to isolate any one therapeutic modality as a cause of intellectual deficit, but the combination of cranial irradiation and intrathecal methotrexate is implicated.

Cranial irradiation causes immediate damage to myelin sheaths, manifest as an elevation of CSF myelin basic protein (Ganji). There are no clinical signs of this early damage, although

Furthermore, a significantly larger proportion of leukaemia survivors have visual-perceptual deficiencies. It is proposed that visual perceptual problems and illness in preschool years lead to a lack of school-readiness, which is a major cause of school failure in early grades.

Management of young leukaemics should include routine assessment of intelligence and visual perception. Visual-perceptual problems should be treated where possible and absences from school should be minimized to improve achievement in early grades.

Parents and teachers should be warned of the possibility of school problems in early grades and should be careful not to base their academic expectations of the leukaemia survivor on achievements of an older sibling.

Until an effective alternative is found, cranial irradiation will remain part of the therapeutic regimen of acute lymphoblastic leukaemia. Since 1979, the cranial irradiation dosage has been reduced to 1800 rad (Nesbit). Children who were given this dose are now approaching the time when its long-term effects may be assessed, but so far, these are not known. If severe late effects are seen, therapeutic trials of lower radiotherapy doses or other therapeutic combinations may become necessary.

CHAPTER 5

NEUROLOGICAL SIDE-EFFECTS OF LEUKAEMIA THERAPY

5.1 INTRODUCTION

A number of treatment modalities used in childhood ALL are potentially neurotoxic (see Chapter 1). Signs of neurotoxicity may be acute, subacute or delayed in onset. These forms of neurotoxicity may persist as 'late effects' of leukaemia therapy in the nervous system.

5.2 LITERATURE REVIEW

5.2.1 Acute Neurotoxicity

Vincristine is the most common cause of acute neurotoxicity. This presents as a peripheral neuropathy and a myopathy. Less commonly vincristine may cause the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and lead to coma (see section 1.4.1).

L-asparaginase and cytosine arabinoside may cause acute encephalopathy (sections 1.4.2 and 1.4.3) while intrathecal methotrexate administration may cause an arachnoiditis (section 1.4.5).

Apart from cytosine arabinoside induced coma (section 1.4.3) these forms of acute toxicity resolve without sequelae.

Cranial irradiation causes immediate damage to myelin sheaths, manifest as an elevation of CSF myelin basic protein (Ganji). There are no clinical signs of this early damage, although children may have mild symptoms of nausea, vomiting, headache,

drowsiness and anorexia (Sheline). If high individual radiation fractions are avoided, these symptoms do not occur, except in children with meningeal leukaemia at diagnosis (Oliff).

There is also an immediate radiation effect on the electroencephalographic wave form in the shape of an arousal pattern (Garcia) but this has not been correlated with any clinical signs.

5.2.2 Subacute Neurotoxicity

Subacute manifestations of radiation neurotoxicity are frequent, (Garwicz) beginning weeks after CNS 'prophylaxis'. Patients become drowsy, complain of nausea and malaise (McIntosh) and may also present with anorexia, irritability, fever, dysphasia, ataxia and transient papilloedema (Bleyer 1981). This constellation of symptoms has been called the 'somnolence syndrome' (Freeman). Symptoms may be more severe in children under 3 years old at the time of radiotherapy. The syndrome lasts from 1 to 3 weeks when 1800 - 2400 rads have been given.

The 'somnolence syndrome' is associated with diffuse slowing on electroencephalography (Garwicz) (Chi'en) which returns to normal on follow-up (Garwicz). Changes in cerebrospinal fluid composition also occur. A CSF pleocytosis is occasionally present.

The CSF proiein pattern suggests partial breakdown of the blood-CSF barrier with a prominent increase in CSF albumen (Similä) (Siemes) (Stephani) and Alpha-2 macroglobulin (Rating).

The somnolence syndrome may not be as unimportant as first thought (Freeman) but may be predictive of longterm neurological sequelae (Chi'en).

Intrathecal methotrexate may cause myelopathy or encephalopathy some weeks after the start of therapy. Symptoms are more common in patients receiving therapy two or more times a week and may be related to duration and concentration of methotrexate in the CSF (Bleyer 1983). When intrathecal methotrexate is added to cranial irradiation, a more severe form of 'somnolence syndrome' is produced (Bleyer 1981).

L-asparaginase and cytosine arabinoside are rare causes of subacute neurotoxicity described in sections 1.4.2 and 1.4.3.

5.2.3 Delayed Neurotoxicity

5.2.3.1 Introduction

Delayed neurotoxicity is the most serious cause of late effects on the nervous system.

Following radiation of the head, mineralizing microangiopathy (Price and Jamieson) may lead to clinical signs years after radiotherapy. Signs are presumably due to vascular

insufficiency, although cerebral necrosis as a consequence of post-irradiation vasculopathy is rare at doses used in the management of acute lymphoblastic leukaemia (Bleyer, 1981).

Delayed cerebral sequelae are more common when cranial irradiation and intrathecal methotrexate are given together (Bleyer 1981). Three mechanisms are likely explanations for observed additive, possibly synergistic effects of these two modalities:

a. overlapping mechanisms of cytotoxicity - both inhibit macromolecular synthesis and DNA repair
b. methotrexate as a radiosensitizer, increasing sensitivity of brain cells to radiation
c. radiotherapy altering the distribution kinetics of methotrexate so that more antifolate penetrates certain areas of the brain.

The latter mechanism may act by effects on the blood brain barrier, the choroid plexus, the ependymal barrier or on individual cells (see also sections 1.4.5 and 1.4.6).

The clinical manifestations of delayed neurotoxicity include neuroendocrine and intellectual effects, which have been discussed in previous chapters. In this chapter further manifestations of structural damage are described.

5.2.3.2 Neuropsychological Tests

Some neuropsychological tests will discriminate between subjects with normal brains and those with known structural

damage (Brouwers 1985). Cortical mechanisms performing specific functions are arranged assymmetrically, allowing tests of such functions to localize cortical damage. Non-verbal learning and memory are affected by right hemispheric injury (Springer) (Reed).

Sorting, attentional and fluency tasks are affected by frontal lobe abnormalities (Stuss). Brouwers (1985) was able to correlate structural cerebral damage seen on computerized tomographic scanning (CT scan) of leukaemia survivors with specific neuropsychological deficit. Earlier Goff (1980) had found a pattern of distractibility in leukaemia survivors, but did not attempt to correlate this with specific anatomical lesions.

These studies suggest that specific testing will identify the anatomical causes of neuropsychological disturbances in leukaemia survivors. The pattern of abnormality is unlikely to be uniform, but would vary from patient to patient, depending on individual cerebral damage patterns.

5.2.3.3 Neurological Examination

Eye-hand coordination, visuo-spatial skills and fine motor function may be affected in more general 'minimal brain injury'. Rowland (1984), Pfefferbaum-Levine (1984) and Copeland (1985) used the Halstead Reitan battery of tests (Reitan) to assess these abilities in leukaemia survivors, and found a higher incidence of abnormalities in children given cranial irradiation than in controls. Previously Ivnik (1981) had found such abnormalities in all leukaemia survivors.

5.2.3.4 Neurophysiological Tests

Electro-encephalography

EEG tracings during the 'somnolence syndrome' show diffuse slowing (McIntosh 1973) (Freeman) (Garwicz). Background EEG frequencies remain below normal for at least four years afterwards (Ch'ien 1979). Seizure disorders occur more frequently in ALL survivors who have had the 'somnolence syndrome' than in those who have not. Seizures are usually tonic-clonic grand mal attacks (Ch'ien). Tonic and focal seizures occur less commonly.

Other authors have noted abnormal EEG tracings in ALL survivors who had been given cranial irradiation (Obetz) (Pavlovsky) but such abnormalities are not found consistently and do not indicate the severity of CNS damage (Kramer).

Ochs et al (1984) reviewed the progress of 1289 leukaemia survivors and found 132 (10%) to have experienced one or more seizure. Thirty six of these patients had seizures as a consequence of tumour lysis syndrome (9 patients), thrombocytopaenic cerebral haemorrhage (11 patients), viral encephalitis or febrile convulsions (13 patients) or L-asparaginase induced cerebral thrombosis (3 patients). In the remaining 96 patients with unexplained convulsions, seizure rates were much higher in patients who had received prolonged repeated intrathecal methotrexate or moderate doses of intravenous methotrexate in addition to 'prophylactic' cranial irradiation, than in those who had received only irradiation

plus 5 doses of intrathecal methotrexate. Patients who received higher doses of intravenous methotrexate or who developed meningeal leukaemia which was treated with intrathecal methotrexate had further increased susceptibility to seizures.

Survivors of childhood ALL have a higher seizure rate than the general population (Ochs), particularly when they have had the 'somnolence syndrome' (Ch'ien), have been treated for meningeal leukaemia (Bleyer 1973) or with intravenous methotrexate (Ochs).

Visual evoked response (VER)/brainstem auditory evoked response (BAER)

The optic and auditory pathways fall within the field of radiation in CNS prophylaxis. Subclinical injury to these pathways occurs in various disorders and may be detected by measurement of visual (VER) and auditory evoked response (BAER). A single report of a VER study in leukaemia survivors has reported a radiation-related abnormality persisting in one third of long-term survivors (Russo). The abnormality is similar to that seen in multiple sclerosis (Mizrahi) and may be the consequence of demyelination.

5.2.3.5 Computerized Tomographic (CT) Brain Scans (Table 5.1)

Specific findings characterize brain CT appearances in children surviving ALL and therapy for the CNS. These include ventricular dilatation and/or a widened subarachnoid space (interpreted as cerebral atrophy), calcification in the basal

TABLE 5.1

LITERATURE REVIEW : COMPUTERIZED TOMOGRAPHIC APPEARANCES OF THE BRAIN IN ALL

	AUTHOR	DATE	PATIENTS	TREATMENT	CT FINDINGS	CONCLUSION
1	Bjorgen	1977	1	CI 2000 rad high-dose intra ventricular MTX	Left frontal high density mass	Acute necrotising cerebritis at p.m. (methotrexate induced)
1	McIntosh	1977	25 6 months - 6 years from diagnosis	CI 2400 rad 2 Mev 5 x IT MTX	10 subcortical intracerebral calcification: basal ganglia, internal capsule, frontal white matter	Worse with more IV MTX or IT Ara C Ataxia, seizure disorders perceptual motor disability
3	Peylan-Ramu	1978	32 19-76 months from diagnosis	IT MTX IT Cytosar CI 2400 rad Mev	53% abnormality ventricular dilatation sulci widened calcification hypodense white matter	Mild CNS dysfunction not correlated with CT findings Normal CT in control group with ALL

Table 5.1 continued

	AUTHOR	DATE	PATIENTS	TREATMENT	CT FINDINGS	CONCLUSION
4	Day	1978	27 17-55 weeks from diagnosis	CI 2050 rad DXR 11 x IT MTX	4 with obvious sulci	No evidence of brain damage
5	Arnold	1978	7 with ALL 1 year or more after diagnosis	CI 2000 - 2400 rad IT MTX	Dilated ventricles + subarachnoid spaces Parenchymal lesions	Uncontrolled study suggests more damage with higher doses of CI and IT MTX
6	Enzmann	1978	25 with ALL	Cranial irradiation IT MTX	10 abnormal scans dilated ventricles and widened sulci	Autopsy in ventricular dilatation: mild neuronal loss, gliosis, mild demyelination. Worse in younger patients
7	Kingsley	1978	41	CI 2400 rad 5 x IT MTX	Dilated ventricles + sulci (13) Necrotizing leukoencephalopathy (4)	Necrotizing leukoencephalopathy All had meningeal leukaemia Atrophy related to duration of illness

Table 5.1 continued

	AUTHOR	DATE	PATIENTS	TREATMENT	CT FINDINGS	CONCLUSION
8	Schwenk	1978	4		Atrophy in 2. Acute haemorrhage (1). Diffuse cerebral infiltrate (1)	Investigation of seizure Acute complications detected
9	Gastaut	1978	40 with leukaemia		6 cerebral infiltrate 1 cerebral atrophy	CT to detect CNS leukaemia at diagnosis
10	Wendling	1978	Case report	2400 rads CI 5 x IT MTX	Periventricular hypodensity resolving on serial scans	Investigation of headache 90 days after diagnosis - papilloedema. No focal deficit
11	Kolmannskog	1979	19 2-64 months after CNS prophylaxis	IV high dose MTX + IT MTX (6-8)	1 abnormal scan: focal lesion	Fewer abnormalities when no cranial irradiation Associated acute hemiplegia
12	Oliff	1979	23	16 - CI + IT MTX (x30) 5 - no CI	7 ventricular dilatation 3 IC calcification No CT lesions	Association between ventricular dilatation and low hGH on stimulus

Children who are socio-economically deprived are less likely to be school ready (Piaget) since they are less likely to have acquired basic skills in early life. A similar proportion of leukaemia survivors come from a poor socio-economic background as did patients in other treatment groups, so that this does not explain perceptual delay or early failures at school in this group.

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It appears therefore that many factors contribute to early school failure among leukaemia survivors. Loss of schooling (Lansky) difficulties with visuomotor integration, retardation in the development of visual perception and moderate IQ deficit all play a role.

CONCLUSION:

The results of this study indicate that there are significant differences in intellectual function between children surviving ALL and their healthy siblings. That such differences are not present between other cancer survivors and their siblings, indicates that the cause of intellectual deficit lies in ALL and its treatment. It is not possible to isolate any one therapeutic modality as a cause of intellectual deficit, but the combination of cranial irradiation and intrathecal methotrexate is implicated.

Table 5.1 continued

	AUTHOR	DATE	PATIENTS	TREATMENT	CT FINDINGS	CONCLUSION
13	Kretzschmar	1980	28 ALL	CI 2400 rad IT MTX x 5	No change in ventricular dimensions in prospective study. Basal ganglion calcification in 1	Late CT appearance may not be due to cranial irradiation
14	Pedersen	1981	23 10-105 months after treatment	2400 rads CI (7) Intermediate dose IV MTX (4). IT MTX alone (12) CNS leukaemia (2)	Prospective study: progressive periventricular white matter hypodensity, subcortical calcification, ventricular + subarachnoid dilatation in 7 cases	Abnormalities developed on treatment only in children with CNS leukaemia. Leukoencephalopathy caused by CI + large doses of methotrexate
15	Allen	1981	17 ALL	CI + MTX (7) IT MTX (10)	No ventricular dilatation No white matter hypodensity	Children with meningeal leukaemia have ventricular enlargement before treatment

Table 5.1 continued

	AUTHOR	DATE	PATIENTS	TREATMENT	CT FINDINGS	CONCLUSION
16	Duffner	1981	20 ALL with CNS leukaemia	IT MTX (13) IT MTX + CI	Wide sulci, ventricles. hypodense areas, calcification	High MTX levels in children with severe CT abnormalities
17	Shalen	1981	Case report	CI 2400 rad IT + ommaya Methotrexate	Symmetrical white matter enhancement	Coagulative necrosis of deep white matter. Demyelination, reactive astrocytosis, disseminated necrotizing leukoencephalopathy
18	Esseltine	1981	26 longterm survivors over 4 years from diag-	14 CI + IT MTX (x8) 12 IT MTX (x8) 2400 rads Mev	6 abn 3 abn ventricular dilatation, prominent sulci and intracerebral calcification	35% abnormal scans No neurological deficit Calcification and ventricular dilatation More with CI and IT MTX
19	Stephani	1983	64 ALL/NHL	Berlin Protocol	Widening of cortical sulci	Children over 10 had more CT abnormality

Table 5.1 continued

	AUTHOR	DATE	PATIENTS	TREATMENT	CT FINDINGS	CONCLUSION
20	Carli	1985	72 ALL off therapy. 3-9 years after CNS prophylaxis 20 normal controls	2400 rad in 550 neurets 8 Mev + IT MTX	Intracranial calcification (12) Widened sulci (8) Ventricular dilatation (3) Widened ventricles + sulci (9) 49% abnormality	Age under 5 at diagnosis Worst minor neurological deficit associated CT damage. Worse with higher biological RT dose
21	Brouwers	1986	23 ALL. 4-8 years off therapy	CI 2400 rads 6 Mev IT cytosar IT MTX (x30) up to 2000 mg/m^2	Serial CT scans. 1st follow-up reported by Peylan-Ramu 13 abnormal scans: ventricular dilatation and widened sulci; intracranial calcification	Neuropsychological tests of localized function predict specific CT scan abnormalities with 87% accuracy. Patients with intracerebral calcifications fare worst

ganglia and subcortical white matter (interpreted as the late consequences of leukoencephalopathy and mineralizing microangiopathy) and areas of hypodensity in the white matter.

The relationships between CT abnormalities, mineralizing microangiopathy, gliosis (Enzmann 1978) and necrotizing leukoencephalopathy (Kingsley) (Pedersen) (Shalen) have been established by autopsy follow-up.

CT abnormalities are more frequently seen and also more severe in patients with meningeal leukaemia (Kingsley) (Schwenk), perhaps because meningeal infiltration interferes with MTX dynamics and leads to prolonged and higher concentrations of this drug in the CSF (Bleyer 1973) (Duffner).

When children receive no cranial irradiation (Kolmannskog) such lesions are rare, but with standard radiation doses, a higher cumulative dose of MTX may be associated with more severe abnormality (Esseltine). There is also evidence that the combination of IT and IV methotrexate with cranial irradiation results in the most severe CT damage pattern (Bleyer 1981).

The reported incidence of CT abnormality also depends on how soon after treatment children are studied and may vary widely (Table 5.1). In series reporting on long-term survivors, rates of abnormality are similar: Peylan-Ramu (53%), Esseltine (35%), Carli (49%).

Neurological deficit was absent in most series studying patients retrospectively (Peylan-Ramu) (Day) (Esseltine). Carli et al reported some minor neurological deficit with higher doses of radiotherapy, but when children are investigated with anatomically specific neurophysiological tests, there was a close correlation between abnormal tests and CT scan lesions (Bouwers). In some studies, children were scanned because they presented with specific neurological symptoms (Kingsley) (Schwenk). These authors consequently report a higher proportion of abnormal results.

5.3 THE PRESENT STUDY

5.3.1 Aim

To identify the incidence, nature and effects of neurological injury in children surviving ALL and its treatment.

5.3.2. Patients and Methods

5.3.2.1 Patients

All survivors of childhood leukaemia were potential subjects for study (see Section 2.3). Of 30 long-term survivors 7 were not fully tested. Two (patients 4 and 5) would not consent to study. Four lived too far away to undergo CT scans (patients 2, 6, 11, 30) and 1 relapsed before testing (10).

Patients were between 7,5 and 18 years old at the time of testing (mean 11,8 years). They were between 3,8 and 11,2 years from diagnosis (mean 7,8 years).

5.3.2.2 Controls

Patients surviving solid tumours (see Section 4.2.2) provided controls for tests described below. This was a heterogeneous group (Table 2.4) but patients with Non-Hodgkins lymphoma, who had received intrathecal methotrexate and no cranial irradiation (Table 3.1) were, apart from being older at diagnosis (mean 7.3 years) an ideal control group against which to measure the effects of adding cranial irradiation to intrathecal methotrexate therapy.

Details of exclusions will be provided with the results.

5.3.2.3 Methods

Informed consent was obtained prior to the tests described here (see Appendix I).

a. History of neurological disturbance during treatment:

Patient records were reviewed for data on neurological deficit, seizure disorder or 'somnolence syndrome' during treatment.

b. Neurological function:

Each patient had a full neurological examination. Particular attention was given to detection of minor neurological abnormality, using the technique described by Touwen.

Visual acuity was assessed with a Snellen chart. Auditory function was assessed clinically and confirmed neurophysiologically (see below).

c. Neurophysiology:

Each patient had an electroencephalogram with standard

head leads performed on a Beckman Accutrace 16 recorder. Each patient had measurement of visual evoked response, using a photic stimulator which produced a flash stimulus at the rate of 1 per second. Responses were recorded and integrated with a Nihon Kohden MEB-3102 Neuropack physiological response recorder.

Visual evoked responses were recorded graphically after 100 summated flash stimuli. Recordings were performed in the waking state with the eyes open. Normal values for peaks and troughs in the neurophysiology laboratory were:

N_1 = 50 - 70 m/sec P_2 = 100 - 150 m/sec

P_1 = 60 - 85 m/sec N_3 = 145 - 200 m/sec

N_2 = 90 - 130 m/sec

Brainstem auditory evoked responses (BAER) were stimulated by a Nihon Kohden SS3100 acoustic stimulator. Summations of 2000 auditory stimuli were recorded graphically. Electrodes were placed on the vertex and ipsilateral mastoid, with a third electrode as ground. Normal values for wave peaks were:

Wave I	1,7 - 2,0 m/sec
Wave III	$\pm$ 4,0 m/sec
Wave V	$\pm$ 5,7 m/sec

Evoked responses were measured by a technologist (M.P.) who was unaware of the patients' treatment status.

d. Computerized tomography of the brain:

Brain CT scans were performed on an ELSCINT EXCEL 905 machine. This is a second generation scanner with a

matrix of 256 x 256 which provides spatial resolution of up to 1,0 mm. Two computer controlled collimators are used.

Scans were done at 25° angulation, with a slice thickness of 5 mm. No contrast medium was used. Scans were reproduced on single emulsion film. Scans were reported directly from film by two neuroradiologists (M.W.) (L.H.) who worked independently and had no prior knowledge of a patient's disease or treatment status. Ventricular size and sulcal width were assessed according to the standards of Enzmann and Lane (1977).

5.3.3 Results

5.3.3.1 Neurological Examination (Touwen) (Tables 5.2 and 5.3)

Neurological assessment is based on the system of examination for minor neurological dysfunction as described by Touwen (1979). Abnormality indicates a maturational lag in the neurological functions itemized in Tables 5.2 and 5.3, as each child was assessed against age specific norms of ability.

Children surviving ALL and its treatment showed significantly more neurological abnormality than the control group of children with solid tumours:

	Touwen Tests		
	Normal	Abnormal	Total
Leukaemia survivors	5	19	24
Solid tumour survivors	23	8	31
	28	27	55

($X^2 = 17,78$, $p < 0,001$)

For logistical reasons (these children lived long distances from the clinic), 14 solid tumour survivors were not neurologically assessed. There is no reason to believe that the rate of abnormality in untested survivors of solid tumours would be different from that in the group tested.

Children under 5 at the time of cranial radiotherapy were more frequently neurologically abnormal (X^2 = 5,36, p 0,05) but the majority of children over 5 (7 out of 11) were also neurologically abnormal (Table 5.2).

Motor abnormalities in the ALL group were present in every category tested, but were most frequently seen as poor fine motor coordination (17 patients) difficulties with fine movements (15 patients) and the presence of associated movements (15 patients) (see Table 5.2).

An important comparison is with survivors of NHL (patients 32-48). These children were given the same treatment as leukaemia survivors but received no cranial irradiation. They had significantly fewer neurological abnormalities on testing (Table 5.3)

	Touwen Test		
	Normal	Abnormal	Total
Leukaemia survivors	5	19	24
Non-Hodgkins lymphoma	10	4	14
	15	24	38

(X^2 = 8,97, p < 0,01)

TABLE 5.2

LEUKAEMIA PATIENTS : NEUROLOGICAL FUNCTION

NO	AGE AT DIAG-NOSIS	AGE TEST	SENSORI-MOTOR	POSTURE	BALANCE	FINE MOVEMENT	FINE COORDINA-TION	KINESIA	GROSS MOTOR	QUALITY OF MOVEMENT	ASSOCIATED MOVEMENT	VISUAL SYSTEM
1	4,0	11	N	N	A	A	A	N	A	A	N	N
7	7,0	11,0	N	N	N	N	N	N	N	N	N	N
8	6,0	10,0	N	N	N	N	N	N	N	N	N	N
9	2,5	7,5	N	A	A	A	A	N	A	A	A	N
10	3,5	7,0	N	N	N	A	A	N	N	N	A	N
11	2,9	7,5	N	N	N	N	A	N	N	N	A	N
12	5,1	16,5	N	N	A	A	A	N	A	N	A	N
13	3,1	10,0	N	N	N	N	N	N	N	N	N	N
14	2,8	11,5	N	N	N	A	A	N	A	A	A	N
15	6,4	11,0	N	N	N	N	A	A	N	N	N	N
16	2,5	10,8	N	A	N	A	A	A	N	N	A	N
17	5,0	9,5	N	N	N	N	N	N	N	N	N	N
18	5,5	16	N	N	N	A	A	N	A	N	A	A
19	3,3	12	N	A	N	A	A	N	A	N	A	N
20	5,1	8,5	N	A	N	A	N	N	A	N	N	N
21	10,1	15	N	N	N	N	N	N	A	N	N	N
22	8,2	16	N	N	N	N	N	N	N	N	N	N

Table 5.2 continued

NO	AGE AT DIAG-NOSIS	AGE TEST	SENSORI-MOTOR	POSTURE	BALANCE	FINE MOVEMENT	FINE COORINA-TION	KINESIA	GROSS MOTOR	QUALITY OF MOVEMENT	ASSOCIATED MOVEMENT	VISUAL SYSTEM
23	4,4	14	N	A	N	A	A	A	N	A	A	N
24	3,4	7,2	N	N	N	A	A	A	A	A	A	A
26	4,5	14	N	A	A	A	A	N	A	A	A	A
27	5,1	8,5	N	A	N	A	A	N	A	N	A	N
28	3,3	13,75	N	N	A	N	N	A	A	N	N	N
30	2,8	7,5	N	A	A	A	A	A	A	A	A	A
31	8,6	15,8	N	A	N	N	A	N	N	N	A	N

TABLE 5.3

SOLID TUMOUR PATIENTS : NEUROLOGICAL FUNCTION

NO	AGE AT DIAG-NOSIS	AGE TEST	SENSORI-MOTOR	POSTURE	BALANCE	FINE MOVEMENT	FINE COORINA-TION	DYS-KINESIA	GROSS MOTOR	QUALITY OF MOVEMENT	ASSOCIATED MOVEMENT	VISUAL SYSTEM
29	2,4	11	N	A	N	A	A	A	N	A	A	N
32	12,4	16,5	N	N	N	N	N	N	N	N	N	N
34	5,2	8	N	N	N	N	N	N	A	N	A	N
35	3,5	8,75	N	N	N	N	N	N	N	N	N	N
37	4,1	10	N	N	N	N	N	N	N	N	N	N
38	11,0	15	N	N	N	N	N	N	N	N	N	N
40	9,2	13	N	N	N	N	N	N	A	N	N	N
41	9,7	15	N	N	N	N	N	N	N	N	N	N
42	4,5	9,6	N	N	N	N	N	N	N	N	N	N
43	9,7	13	N	N	N	N	N	N	N	N	N	N
44	10,4	13	N	N	N	N	N	N	A	A	A	N
46	2,7	5,5	N	N	N	N	N	N	N	N	N	N
47	9,8	14,5	N	N	N	N	N	N	N	N	N	N
48	2,6	7,5	N	N	N	N	N	N	N	N	N	N
49	1,9	7,0	N	N	N	N	N	N	N	N	N	N
51	6,1	12,0	N	N	N	N	N	N	N	N	N	N

Table 5.3 continued

NO	AGE AT DIAG-NOSIS	AGE TEST	SENSORI-MOTOR	POSTURE	BALANCE	FINE MOVEMENT	FINE COORINA-TION	DYS-KINESIA	GROSS MOTOR	QUALITY OF MOVEMENT	ASSOCIATED MOVEMENT	VISUAL SYSTEM
52	2,7	15,0	N	N	N	N	N	N	N	N	N	N
53	2,0	8,0	N	N	N	N	N	N	N	N	N	N
54	0,8	10,8	N	N	N	A	N	N	A	N	N	N
55	1,4	10,75	N	N	N	N	N	N	N	N	A	N
56	1,0	11,0	N	N	N	N	N	N	N	N	N	N
58	4,4	12,0	N	N	N	N	N	N	N	N	N	N
59	0,6	9,2	N	N	N	N	N	N	N	N	N	N
61	1,9	8,0	N	N	N	N	N	N	N	N	N	N
62	1,9	7,0	N	N	N	N	N	N	N	N	N	N
66	11,7	16,0	N	N	N	N	A	A	N	N	N	N
64	12,7	14,75	N	A	A	N	N	N	A	N	N	N
70	2,1	7,5	N	N	N	N	N	N	N	N	N	N
72	3,2	10,25	N	N	N	N	N	N	N	N	N	N
73	0,25	10,0	N	N	N	N	N	N	N	N	N	N
74	4,2	11,5	N	N	N	N	N	N	N	N	N	N

This shows that minor neurological dysfunction occurs more often when cranial irradiation is added to the other modalities of leukaemia therapy.

Children with neurological dysfunction had a high rate of school failure (17 out of 19), but because of the design of the IQ study absolute IQ scores could not be correlated with neurological signs.

A history of somnolence, present in 73% of leukaemia survivors, did not predict neurological deficit. Five patients with a history of somnolence had no detectable neurological deficit and 6 with neurological deficit had not experienced the somnolence syndrome (Table 5.7).

There was no correlation between neurological status and EEG, VER or BAER results in any group.

There was a statistically significant association between neurological abnormality and abnormality seen on CT scan among leukaemia survivors (Table 5.7)

Leukaemia survivors	CT Scan		
	Normal	Abnormal	Total
Neurologically abnormal	3	14	17
Neurologically normal	4	1	5
	7	12	22

(X^2 = 10,09, $p < 0,01$)

TABLE 5.4

ALL PATIENTS: NEUROPHYSIOLOGICAL ASSESSMENT

NO	ELECTRO-ENCEPHALOGRAPHY	VISUAL EVOKED RESPONSE (VER)						AUDITORY EVOKED RESPONSE (BAER)						
								I		III		V		
		N_1	P_1	N_2	P_2	N_3		L	R	L	R	L	R	
1	Normal	38	-	55	106	145	Normal	2,5	2,5	5,3	5,3	7,6	7,3	Hearing loss
2	Normal	40	63	80	111	163	Normal	2,0	2,0	2,0	4,1	5,8	6,3	Abnormal
3	Normal	53	70	92	105	139	Normal	1,9	1,9	5,0	5,2	6,8	6,9	Abnormal
7	Normal	56	112	155	200	267	Abnormal	1,8	1,8	3,8	3,8	5,7	5,7	Normal
8	Mild generalized slowing bilateral posterior slowing	60	115	159	115	215	Abnormal	1,8	1,8	3,6	3,6	5,4	5,4	Normal
9	Normal (on anticonvulsants)	58	73	86	131	173	Normal	1,8	1,8	4,2	4,2	5,9	5,9	Normal
10	Marked bilateral posterior slowing	50	80	173	230	300	Abnormal	1,8	1,8	3,9	3,9	5,8	5,8	Normal
11	-													
12	Paroxysmal activity and phase reversal in both mid-temporal areas	54	72	86	113	143	Normal	1,7	1,7	4,1	4,0	5,7	5,7	Normal
13	Episodic L temporal focus	35	79	111	129	151	Normal	-	1,7	3,8	3,7	5,7	5,7	Normal
14	Normal	65	96	120	150	176	Abnormal	2,2	2,2	-	-	5,9	5,9	Normal
16	Normal	52	74	92	108	151	Normal	1,8	1,8	3,8	3,8	5,7	5,7	Normal

Table 5.4 continued

NO	ELECTRO-ENCEPHALOGRAPHY	VISUAL EVOKED RESPONSE (VER)						AUDITORY EVOKED RESPONSE (BAER)						
								I		III		V		
		N_1	P_1	N_2	P_2	N_3		L	R	L	R	L	R	
17	Paroxysmal activity of sharp and slow wave components on hyperventilation	50	99	158	204	260	Abnormal	1,8	1,8	3,8	3,8	5,8	5,7	Normal
18	Normal	50	84	130	180	229	Abnormal	1,9	1,9	4,2	4,2	5,9	5,9	Normal
19	Bilateral temporal cortical foci	43	84	121	150	165	Normal	1,9	2,0	4,0	3,9	5,7	5,7	Normal
20	Normal	41	-	75	104	171	Normal	1,7	1,8	3,8	3,8	5,7	5,7	Normal
21	Normal	40	55	71	89	130	Normal	2,2	2,2	4,2	4,2	5,8	5,8	Normal
22	Normal	46	79	139	183	218	Abnormal	1,7	1,7	4,0	4,0	5,8	5,8	Normal
23	Normal	27	50	69	92	129	Normal	1,9	1,9	4,0	4,1	5,8	5,8	Normal
24	Normal	35	61	92	127	203	Normal	2,2	2,2	4,3	4,3	6,3	6,3	Abnormal
25	Normal	55	107	172	206	221	Abnormal	1,8	1,8	3,8	3,8	5,7	5,7	Normal
26	Mild generalized theta slowing	58	109	159	204	260	Abnormal	1,8	1,8	3,8	3,9	5,7	5,7	Normal
27	Normal	50	75	99	133	162	Normal	2,0	2,1	4,2	4,1	5,9	5,9	Normal
28	Normal	46	94	122	-	152	Abnormal	1,8	2,6	4,0	4,0	5,9	5,9	Abnormal
30	Normal	47	86	125	-	160	Normal	2,0	-	3,7	3,7	5,6	5,6	Normal
31	Normal	45	-	72	113	151	Normal	2,2	2,2	4,1	4,1	5,7	5,7	Normal

TABLE 5.5

NHL PATIENTS : NEUROPHYSIOLOGICAL ASSESSMENT

NO	ELECTRO-ENCEPHALOGRAPHY	VISUAL EVOKED RESPONSE (VER)						AUDITORY EVOKED RESPONSE (BAER)						
								I		III		V		
		N_1	P_1	N_2	P_2	N_3		L	R	L	R	L	R	
29	Paroxysmal slow wave	47	79	111	138	169	Normal	1,7	1,9	3,9	3,9	5,6	5,7	Normal
34	Epileptic dysrhythmia marked bilateral posterior slowing	43	90	146	184	269	Abnormal	1,8	1,9	2,9	4,0	4,7	4,7	Normal
35	Normal	36	74	115	175	210	Abnormal	1,7	1,7	3,9	3,9	5,6	5,6	Normal
36	Normal	44	78	124	152	176	Normal	1,7	1,7	3,8	3,8	5,8	5,8	Normal
37	Normal	37	66	78	95	136	Normal	1,8	1,8	3,9	4,0	5,8	5,8	Normal
38	Normal	50	100	141	190	236	Abnormal	1,3	2,3	4,8	4,8	6,2	6,2	Impaired
41	Normal	50	80	107	130	176	Normal	1,8	1,7	3,9	3,9	5,8	5,8	Normal
42	General dysrhythmia. Paroxysmal spike and wave	43	66	81	106	145	Normal	1,8	1,8	3,9	3,9	5,8	5,8	Normal
43	Normal	55	82	120	133	170	Normal	1,7	1,7	3,8	3,8	5,6	5,6	Normal
44	Episodic right hemispheric slowing	64	92	151	-	220	Abnormal	1,6	1,6	4,4	4,4	6,4	5,8	Abnormal
46	Paroxysmal theta and delta components	49	88	157	½190	216	Abnormal	1,9	1,9	4,3	4,3	5,8	5,9	Normal
47	Normal	43	67	83	128	160	Normal	1,7	1,7	3,9	3,9	5,7	5,7	Normal
48	Mild bilateral posterior episodic slowing	67	108	176	250	277	Abnormal	1,7	1,7	3,8	4,0	5,6	5,7	Normal

TABLE 5.6

'OTHER' SOLID TUMOURS : NEUROPHYSIOLOGICAL ASSESSMENT

NO	ELECTRO-ENCEPHALOGRAPHY	VISUAL EVOKED RESPONSE (VER)						AUDITORY EVOKED RESPONSE (BAER)						
								I		III		V		
		N_1	P_1	N_2	P_2	N_3		L	R	L	R	L	R	
49	Episodic L cortical paroxysmal sharp-slow activity	40	50	71	100	138	Normal	2,0	2,0	4,0	4,0	5,7	5,7	Normal
51	Normal	44	60	73	101	140	Normal	1,5	1,5	3,8	3,8	5,6	5,7	Normal
52	Normal	32	54	78	104	149	Normal	1,7	1,7	4,0	4,0	5,7	5,7	Normal
53	Normal	40	58	82	105	133	Normal	1,4	1,4	3,8	3,8	5,6	5,6	Normal
54	Mild R poterior slow waves	55	90	110	155	200	Normal	Conductive hearing loss						
55	Episodic R temporal focus	41	63	71	98	139	Normal	2,0	2,0	4,0	4,0	5,7	5,7	Normal
56	Normal	30	-	63	96	158	Normal	1,9	1,9	3,8	3,8	5,7	5,7	Normal
57	-													
58	-													
59	Paroxysmal bursts with delta and theta components	49	59	78	114	163	Normal	1,7	1,8	4,0	3,8	6,3	6,2	Abnormal
60	Mild generalized slowing L temporal focus	50	80	107	130	176	Normal	Conductive loss (cold)						
61	Mild L hemispheric slowing	47	100	168	215	265	Abnormal	1,8	1,8	3,9	3,9	5,6	5,7	Normal
62	L hemispheric slowing episodic L temporal focus	52	91	160	247	298	Abnormal	2,0	2,0	4,1	4,1	5,8	5,8	Normal

Table 5.6 continued

NO	ELECTRO-ENCEPHALOGRAPHY	VISUAL EVOKED RESPONSE (VER)						AUDITORY EVOKED RESPONSE (BAER)						
								I		III		V		
		N_1	P_1	N_2	P_2	N_3		L	R	L	R	L	R	
63	-													
64	Normal	45	59	78	110	149	Normal	1,8	1,8	4,5	4,4	5,9	5,8	Normal
65	Bilateral episodic posterior slowing	50	78	124	180	211	Abnormal	1,8	1,8	4,0	4,0	5,6	5,6	Normal
66	Normal	49	63	72	111	163	Normal	1,9	1,9	3,9	3,9	5,3	5,3	Normal
67	-													
68	-													
70	Mild generalized theta slowing	59	106	132	186	219	Abnormal	1,8	1,8	3,7	3,7	5,6	5,6	Normal
72	Normal	51	69	82	115	160	Normal	1,4	1,4	3,9	4,0	5,5	5,5	Normal
73	Normal	66	104	155	160	215	Abnormal	2,0	2,0	5,0	4,0	5,7	5,7	Normal
74	Normal	41	60	79	102	130	Normal	1,8	1,8	4,0	4,0	5,8	5,8	Normal
75	-													

According to these results, neurological assessment would predict $\pm$ 94% of CT scan abnormalities, with a false positive rate of 13%.

5.3.3.2 CT Scan Appearances

Children exposed to cranial irradiation and intrathecal methotrexate have a significantly higher rate of CT scan brain abnormality than do children treated with intrathecal methotrexate and no cranial irradiation (Tables 5.7 and 5.8).

Within the leukaemia group, abnormalities did not correlate with CT scan changes, school records (Table 4.18) or visual perceptual problems (Table 4.10).

The significance of prolonged latencies in some patients in all groups is not clear. Abnormal results are not significantly related to radiation therapy.

Diagnosis	CT Scan		
	Normal	Abnormal	Total
Leukaemia	8	16	24
Non-Hodgkins lymphoma	11	2	13
	19	18	37

(X^2 = 11,05, p < 0,001)

TABLE 5.7

LEUKAEMIA SURVIVORS : NEUROLOGICAL ASSESSMENT

NO	AGE AT DIAGNOSIS	SOMNOLENCE	SEIZURE	ABNORMAL NEURO	ABNORMAL EEG	C T FINDINGS
1	4,3	Yes	Yes	Yes	No	Basal ganglion calcification. Right occipital subcortical calcification
2	6,5	Yes	No	-	No	Basal ganglion calcification. Bilateral subcortical calcification, dilated ventricles, prominent sulci
7	7,1	Yes	No	No	No	Normal scan
8	6,0	Yes	No	No	Yes	Normal scan
9	2,6	Yes	Yes	Yes	No	Extensive bilateral occipital and temporal subcortical calcification
10	3,6	No	No	Yes	Yes	Normal scan
12	5,9	Yes	No	Yes	Yes	Prominent sulci - widened
13	3,2	Yes	Yes	No	Yes	Normal scan
14	3,0	Yes	Yes	Yes	no	Bilateral basal ganglion calcification widened sulci
15	6,6	Yes	No	Yes	No	Widened sulci
16	2,7	Yes	No	Yes	No	Widened sulci prominent basal cistern
17	5,1	Yes	No	No	Yes	Widened sulci
18	5,5	No	No	Yes	No	Widened sulci
19	3,4	No	No	Yes	Yes	Normal scan
20	5,1	No	No	Yes	No	Widened sulci

Table 5.7 continued

NO	AGE AT DIAGNOSIS	SOMNOLENCE	SEIZURE	ABNORMAL NEURO	ABNORMAL EEG	CT SCAN FINDINGS
21	10,3	Yes	No	Yes	No	Widened sulci
22	8,3	Yes	No	No	No	Normal scan
23	4,5	No	No	Yes	No	Posterior subcortical calcification, biparietal widened sulci
24	3,6	No	No	Yes	No	Biparietal sulchal widening over upper cortex
25	10,4	Yes	No	-	No	Normal scan
26	4,6	Yes	Yes	Yes	Yes	Basal ganglion calcification; extensive bilateral subcortical and deep white matter calcification; cerebellar atrophy; biparietal widened sulci
28	3,5	Yes	Yes	Yes	No	Normal scan
30	2,9	Yes	No	Yes	No	-
31	8,8	Yes	No	Yes	No	Widened sulci

TABLE 5.8

NON-HODGKINS LYMPHOMA SURVIVORS : NEUROLOGICAL ASSESSMENT

NO	AGE AT DIAGNOSIS	SOMNOLENCE	SEIZURE	ABNORMAL NEURO	ABNORMAL EEG	CT SCAN FINDINGS
29	2,6	No	No	Yes	Yes	Left anterior temporal, biparietal widening of sulci
32	12,4	No	No	No	Yes	Normal scan
34	5,2	No	No	Yes	No	Normal scan
35	3,5	No	No	No	No	Normal scan
37	4,1	No	No	No	No	Normal scan
38	11,0	No	No	No	No	-
39	11,0	No	No	-	No	-
40	9,25	No	No	Yes	No	Normal scan
41	9,7	No	No	No	No	Normal scan
42	4,5	No	No	No	Yes	Normal scan
43	9,7	No	No	No	No	Normal scan
44	10,4	No	No	Yes	Yes	Normal scan
46	2,7	No	No	No	Yes	Normal scan
47	9,8	No	No	No	No	Normal scan
48	2,6	No	No	No	Yes	Biparietal sulchal widening

TABLE 5.9

'OTHER' SOLID TUMOURS NEUROLOGICAL ASSESSMENT

NO	AGE AT DIAGNOSIS	SOMNOLENCE	SEIZURE	NEURO ABNORMAL	EEG ABNORMAL	NO CT SCANS PERFORMED ON THIS GROUP
49	1,9	No	No	No	No	-
51	6,1	No	No	No	No	-
52	2,7	No	No	No	No	-
53	2,0	No	No	No	No	-
54	0,8	No	No	Yes	No	-
55	1,4	No	No	Yes	Yes	-
56	1,0	No	No	No	Yes	-
58	4,4	No	No	No	No	-
59	0,6	No	No	No	No	-
61	1,9	No	No	No	Yes	-
62	1,9	No	No	No	Yes	-
64	12,7	No	No	Yes	No	-
66	11,7	No	No	Yes	No	-
70	2,1	No	No	Yes	No	-
72	3,2	No	No	No	No	-
73	0,25	No	No	No	No	-
74	4,2	No	No	No	No	-
75	6,1	No	No	No	No	-

There was no significant difference in the incidence of CT scan abnormality in children given cranial irradiation under or over the age of 5, but children under 5 had a more severe pattern of damage. Of the 6 patients with intracerebral calcification, 5 were under 5 at diagnosis (Table 5.7).

Abnormalities on CT scan are associated with a history of school failure in leukaemia survivors.

Leukaemia	CT Scan		
	Normal	Abnormal	Total
School failure	4	14	18
No school failure	4	2	6
	8	16	24

($X^2 = 6{,}07$, $p < 0{,}05$)

Two patients with widened sulci on CT scan (17 and 18) who were over 5 at the time of cranial irradiation have had no problems at school. Patient 18 recently matriculated at a commercial high school.

Of the four patients with a normal CT scan who had a record of school failure, all had failed only one early grade and have since made good progress (see Table 4.18).

All patients who had failed more than once (2, 9, 14, 16, 20, 21, 23, 26) had abnormal CT scans. Four of these had subcortical calcification and one had basal ganglion calcification.

5.3.3.3 Neurophysiological Assessment

a. EEG

Thirty-two percent of leukaemia survivors had an abnormal EEG trace (Table 5.4). This was not significantly different from the rates of abnormality in either the NHL or 'other' solid tumour group (Table 5.8 and 5.9).

An abnormal EEG did not correlate with BAER or VER abnormality (Table 5.4). There was a negative correlation between EEG and CT abnormalities. A patient with an abnormal EEG was significantly less likely to have an abnormal CT scan than a patient with a normal EEG (X^2 = 5,0, $p < 0,05$) (Table 5,7).

The EEG does not appear to be a useful instrument in the assessment of treatment late-effects in leukaemia.

b. VER and BAER

There was no significant difference in rates of VER and BAER abnormalities in any of the three comparison groups (Tables 5.4, 5.5 and 5.6).

5.4 DISCUSSION

5.4.1 Neuromotor Abnormalities

Neuromotor sequelae of 'CNS prophylaxis' are milder than and distinct from physical signs of the leukoencephalopathy which follows treatment of overt meningeal leukaemia.

In the latter, the neurological syndrome is the consequence of treatment with intravenous methotrexate given in high dose (Price and Jamieson) (McIntosh) (Ch'ien) together with prolonged courses of intrathecal methotrexate (Bleyer 1981) and cranial irradiation. Damage may be more severe because of the change in CSF dynamics due to meningeal leukaemia, which leads to very high levels of CSF methotrexate (Bleyer 1973). Signs of leukoencephalopathy include dementia, cranial nerve lesions, ataxia, tetraplegia (Kay), seizures, loss of consciousness (Hendin) (Pizzo) and abnormalities of posture and tone (Campbell).

Following 'CNS prophylaxis' for presumed subclinical meningeal infiltration, signs of neuromotor abnormality are far more subtle, and indeed have not been detected on standard neurological assessment (Soni) (Moss). Specific examination and testing will detect a poorer performance of tests measuring motor speed (Ivnik) (Rowland) (Copeland), fine motor skills (Copeland) and gross motor coordination (Carli) (Stephani) among leukaemia survivors given cranial irradiation in comparison with selected control groups.

Findings in the present study based on an examination for signs of minor neurological dysfunction (Touwen) agree with those in the literature. This suggests that a concise neurological examination is an adequate replacement for formal neuropsychological testing in the detection of neuromotor abnormality. This assessment could be carried out by the attending paediatrician-oncologist, rather than by a psychologist.

In this study, the neurological assessment was a better predictor of school failure and I.Q. deficit than any neurophysiological instrument or neurological investigation. This finding is in keeping with previous studies, where neuromotor abnormalities were significantly associated with I.Q. deficit (Rowland) (Copeland).

Enzmann and Lane (1977) found the severity of neurological signs roughly proportional to the severity of CT scan abnormality, but neurological examination has otherwise been normal in children with abnormal CT scans (Peylan-Ramu) (Esseltine). In this study, abnormal CT scans are significantly associated with minor abnormalities of neurological function (Touwen). This association has not been reported before, but is in keeping with the cerebral insult of cranial irradiation (and intrathecal methotrexate) which is as diffuse as the insult of asphyxia neonatorum. The variability of clinical signs is not unexpected because of the heterogeneity of CT scan appearances.

As with other diffuse insults to the brain, younger children would be expected to be more vulnerable (Dobbing). In this study, children under 5 at this time of treatment had both more frequent neurological abnormality and more severe damage on CT scan.

5.4.2 Visual Evoked Response (VER) and Brainstem Auditory Response (BAER)

Yaar et al (1980) reported abnormal VER 15 years after low dose cranial irradiation (140 rad DXR) for tinea capitis. Abnormality consisted of shortened latency of the first positive deflection (P1) of the VER. This was interpreted as evidence of subcortical damage perhaps as a result of reduced dendritic arborization in immature brains (a direct effect of irradiation) or secondary to astrocytic or endothelial damage (a delayed effect of irradiation). Russo et al (1985) described abnormal VER's in leukaemia survivors. Their patients had prolonged latencies, which were interpreted as a sign of subclinical demyelination due to cranial irradiation. Neither group described clinical correlates of these neurophysiological abnormalities.

The proportion of patients with abnormal visual evoked responses in each of the three treatment groups in this study was similar. This is contrary to the findings of Yaar and Russo and also indicates that IT MTX therapy is not a cause of abnormal VER's. The rate of abnormal results might be explained by the considerable variation in VER's in response to flash stimuli (Cobb) both among individuals and laboratories (Mizrahi).

The nature of abnormalities seen among our patients (prolonged latencies) is characteristically that of inflammatory or demyelinative optic neuropathy (Asselmann) (Halliday). Atypical VER wave forms characteristic of neurodegenerative disorders (Harden) were not seen.

Abnormalities of VER did not correlate with school failure or IQ deficit in the present study. This is in keeping with the findings of Engel who reported no correlation between VER peaks and the Bender Gestalt test or WISC scores. Workers who have found such a correlation (Ertl) have based their hypotheses on the study of brain damaged children in whom there would be a high rate of I.Q. deficiency irrespective of neurophysiological abnormality.

VER abnormalities did not correlate with CT scan abnormalities in our study. Where the relevant sensory pathways are affected, VER is a good predictor of CT abnormalities (Nlazy) but this does not seem to be the case in our patients.

BAER findings in our patients were of as little predictive value as visual evoked responses, but were of assistance in the objective assessment of hearing in younger children. The incidence of conductive hearing loss because of chronic middle ear disease in our sample is probably similar to that of the general population (no exact population figure is available).

5.4.3 Electro-encephalogram

This study suggests that electroencephalogram (EEG) is an inappropriate instrument in the assessment of neurological status among longterm leukaemia survivors. These findings are similar to those reported elsewhere (Kramer).

Carli (1985) and Stephani (1983) both report a poor correlation between EEG and CT scan findings, while Schwenk (1978) found

the CT scan to be a better indicator of pathology in acute meningeal relapse presenting with seizures.

5.4.4 Computerized Tomography

This study shows that significantly more longterm survivors treated with cranial irradiation and intrathecal methotrexate (leukaemia patients) have abnormal CT scans than do those treated with intrathecal methotrexate alone (lymphoma patients). This finding is similar to that of studies assessing longterm survivors by similar means (Peylan-Ramu) (Brouwers) (Esseltine) (Oliff). Rates of cerebral atrophy and intracranial calcification are also similar to those reported by these authors.

Intracerebral calcification, suggesting leukoencephalopathy and/or mineralizing microangiopathy (Price and Birdwell) (Kingsley) was seen more frequently in younger children, as reported by Carli (1985).

The frequency of diagnosis of cerebral atrophy will depend on the design of the study, the state of nutrition of patients (Enzmann 1977) and, if patients are still on treatment, the therapeutic regimen. Although there are criteria available for assessment of ventricular dilatation and cerebral atrophy in children (Enzmann 1977), observer variability may account for some of the difference (0% (Day) to 53% (Peylan-Ramu)) in their reported incidence. Quality of resolution in CT imaging is not always reported, but it is likely that widening of sulci would have been seen less frequently with first generation scanners than with subsequent improved models.

In a prospective study of leukaemic patients a comparison between follow-up scans and a peri-diagnostic scan (Kretzschmar) is unlikely to detect real cerebral atrophy, since disease related anorexia (Enzmann 1977) and therapy with steroids (Benston) and other chemotherapeutic agents (Enzmann) all produce CT appearances of atrophy.

Late atrophy has been shown at autopsy (Enzmann 1978) to be associated with mild neuronal loss, gliosis and mild demyelination, worse in younger patients. This is in keeping with neuromotor findings reported above.

Children were treated with the same dose of cranial irradiation (2400 rad DXR) except for two: Patient 13 received 2000 rad (Cobalt 60) at 3,2 years of age - and had a normal scan. Patient 26 was given 4400 rads of DXR with another course of IT methotrexate - she had severe CT scan abnormality (Table 5.7).

No correlation could be found between abnormality or hGH stimulation and CT scan abnormality, such as has been described previously (Oliff). It is suggested that this lack of correlation reflects the heterogeneity of the cerebral insult of cranial irradiation and the variability of injury responses (Rubin and Cazaret).

5.5 CONCLUSIONS

Survivors of acute lymphoblastic leukaemia in childhood exhibit a variety of minor neurological abnormalities which are detectable by an appropriate clinical examination. These

abnormalities are associated with 'prophylactic' central nervous system irradiation.

Survivors of acute lymphoblastic leukaemia in childhood have a high incidence of intracerebral structural abnormalities which are detectable by computerized tomographic scanning. These abnormalities are associated with the minor neurological signs noted above.

Visual evoked response, brainstem auditory evoked response and electroencephalography do not contribute to the assessment of functional neurological abnormality in survivors of childhood leukaemia.

There is no correlation apparent between cerebral abnormalities an CT scan and abnormalities of hGH secretion in this group of survivors.

CHAPTER 6

FURTHER PHYSICAL LATE EFFECTS : CASE REPORTS AND LITERATURE REVIEW

6.1 INTRODUCTION

In some cases, a single organ or system may be affected by combined ALL therapy or by one specific chemotherapeutic agent. In this chapter, late effects in organs other than the endocrine and central nervous system are reviewed. Where such late effects occurred among the 31 ALL survivors, they are illustrated with a case report.

6.2 SECOND MALIGNANCY

6.2.1 Case Report Patient No 26 (T.S.)

This girl presented in February 1971, when she was 4½ years old. There was a one month history of pallor, easy bruising, listlessness and anorexia. On examination she was pale, with purpura on her face and trunk. She had axilliary adenopathy and a large liver and spleen.

Her haemoglobin concentration was 6,3 grams per 100 ml, the packed cell volume 18, white cell count 11,500 per cubic millimeter (76% blasts, 2% neutrophils, 22% lymphocytes). Examination of the bonemarrow confirmed leukaemia, labelled undifferentiated. A chest x-ray showed enlarged hilar glands but x-ray skull and cerebrospinal fluid were normal.

Remission was induced with vincristine (1,6 mg IV weekly) and prednisone (40 mg daily). During the induction period she had

epistaxis, melaena and haematuria and required three blood transfusions. She also had recurrent upper respiratory tract infections.

She then received consolidation therapy, consisting of courses of Daunorubicin, 6-mercapto-purine, methotrexate, cyclophosphamide and vincristine. Fourteen months after diagnosis she was given 2,400 rads of cranial DXR and 5 doses of intrathecal methotrexate (1,5 mg/m²) as 'CNS prophylaxis'. At this time she was 6 years old and also receiving oral methotrexate, cyclophosphamide and 6-mercapto-purine. She had by now had several minor infections and had also developed a herpes zoster infection in the distribution of the fifth cranial nerve (having had chicken pox at the age of 3).

Maintenance therapy (methotrexate, cyclophosphamide and 6 mercapto-purine) was discontinued in November 1974, three years and nine months from the start of treatment.

In October 1976, now 9 years and 7 months old and nearly 2 years after the end of treatment, she presented with a 3 month history of occasional headache. Her vision had been blurred for a month. Ophthalmoscopy confirmed papilloedema. There were no other neurological signs. A skull x-ray showed erosion of the pituitary fossa and posterior orbits, but a CT scan was passed as normal. Lumbar puncture confirmed meningeal relapse. Sheets of lymphoblasts were seen in the CSF. Bonemarrow was normal.

Her meningeal leukaemia was treated with a further 2000 rad of cranial DXR given in ten 200 rad fractions. She was also given 10 more weekly injections of intrathecal methotrexate (1,5 mg/m^2) and a reinduction course of prednisone and vincristine, followed by a further three years of maintenance chemotherapy.

Six weeks after her second course of cranial irradiation, she became drowsy, listless and anorexic. This period of somnolence lasted for four weeks.

From this time on, learning problems at school became serious. She also developed increasing obesity, in spite of dietary counselling. Height-for-age progress may be seen in Figure 2.9.

In May 1979 she had a convulsion associated with enuresis and a right sided hemiparesis. She was drowsy, dysarthric and dysphasic. An electroencephalogram showed left sided slowing with a left hemispheric focus. A CT scan of the brain showed cerebellar atrophy, cortical and insular atrophy and calcification of the basal ganglia, subcortical layers of both frontal and parietal lobes as well as of deeper white matter. These findings were unchanged at follow-up scan and were interpreted as evidence of leukoencephalopathy and mineralizing microangiopathy. Severe symptoms lasted for five months after which she made a gradual recovery, complete but for residual learning problems at school.

Maintenance chemotherapy was finally stopped in October 1979. In February 1983 two lesions were excised from her left temple and her neck below the occiput. Histological examination identified both as multicentric basal cell carcinoma, excised clear of the tumour.

6.2.2 Literature Review

The carcinogenic potential of radiation exposure among young survivors of atomic explosions is well known (Miller 1968). The cumulative probability of a second neoplasm in a field of therapeutic radiation is 4-17% over 20 years (Coleman) (Li). This is 20 times higher than for the general population. Carcinogenesis due to cytotoxic chemotherapy is also well described (Harris).

Spontaneous oncogenesis in susceptible patients (Meadows, 1980) and persistence of an environmental oncogen responsible for the first tumour further increase the likelihood of a second tumour in survivors of childhood cancer.

Second tumours following treatment of childhood acute lymphoblastic leukaemia occur in several tissues (Mosijczuk) (Zarrabi). These include Hodgkins disease, acute myeloid leukaemia (Secker) (Bohinjec), and various solid tumours. Because the number of cases reported in the literature remains small, it is not possible to say that these tumours are definitely treatment related (Zarrabi).

Acute myeloid leukaemia is the most common haematologic cancer following ALL (Zarrabi). Thyroid cancer and intracranial tumours (astrocytoma, glioma, meningioma and glioblastoma multiforme) (Rubinstein) (Judge) have arisen in the field of cranial irradiation. Late 'relapses' of ALL could be a second cancer. Proof of this would depend on precise cytogenetic, immunologic and cytochemical study of both leukaemias.

The patient described above had received 4,400 rad of orthovoltage (high kv) deep x-ray therapy in two separate courses. This total dose is in the range normally given for intracranial tumours. Basal cell carcinoma is well described at such a radiation dose (Soloway) (Hempelmann). Radiation-induced second tumours may occur more frequently with orthovoltage than with megavoltage radiotherapy (Haselow). Such tumours are much more likely to occur at the edge of the radiation field (Gray) such as in our patient, because of increased cell killing at higher doses of radiation in the centre of the field.

Other children in this study may yet develop secondary tumours because of the long latency period for solid tumour induction (Coleman).

6.2.3 Conclusion

The long and unpredictable latency of second tumours necessitates prolonged follow-up of survivors of all cancers. Young people tend to be migratory, so that there is a parallel need for a patient based information system and a national

cancer registry. These needs are becoming more urgent as children treated for cancer survive longer.

6.3. ANTHRACYCLINE CARDIOTOXICITY

6.3.1 Case Report : Patient No 3 (M.C.)

This child presented in April 1976 at 7½ years of age. She had been relatively well until 2 weeks before, when she developed swellings under the jaw, bleeding gums, a sore throat and nosebleeds.

At examination she was pale and had extensive adenopathy, scattered purpura, bruising and enlargement of liver and spleen. She had a tachycardia (120 beats/minute) a gallop rhythm and an ejection systolic murmur.

A blood count showed 9,900 white cells with 49% blasts. Haemoglobin concentration was 4,4 grams/100 ml and the platelet count was 9,000. Acute lymphoblastic leukaemia was diagnosed on marrow aspirate. The cerebrospinal fluid was clear. The heart was enlarged on chest x-ray but an electrocardiogram was normal.

Remission was induced with prednisone and vincristine. CNS 'prophylaxis' was given with intrathecal methotrexate and 2,400 rad of cranial DXR in twelve 200 rad fractions.

She remained in remission for 1 year and then relapsed on maintenance therapy. This was detected on routine blood count and marrow examination.

Remission was reinduced with Daunorubicin, thioguanine, cyclophosphamide and hydroxyurea. The last dose of anthracycline was given in May 1979, by which time she had received a total dose of 670 mg/m^2. All treatment was stopped in August 1980.

Regular chest x-rays and ECG's were performed at follow-up visits. Slight cardiomegaly was reported on 2 occasions while on anthracycline therapy. On one occasion her ECG showed intermittent right bundle branch block. X-rays and ECG following the completion of anthracycline therapy were within normal limits. Examination of the cardiovascular system remained normal throughout treatment.

In January 1981, 18 months after her last dose of Daunorubicin, she presented in cardiac failure. Chest x-ray confirmed cardiomegaly with left ventricular hypertrophy. Therapy with digoxin and hydrochloro-thiazide was started, with good effect. Eighteen months later, a follow-up ECG and chest x-ray were normal, but echocardiography showed a reduced shortening fraction of 14% and a systolic time interval of 0,48 sec. Her most recent echocardiogram (April 1983) confirmed persistently impaired left ventricular performance.

6.3.2 Literature Review

Early therapeutic trails demonstrated severe cumulative dose related cardiotoxicity as a major side effect restricting the use of anthracycline cytotoxics (Tan 1967) (Lefrak) (Ragab).

Anthracyclines damage the myocardial cell nucleus (Di Marco, 1964) (Ferrans) by intracalation with DNA (Di Marco 1975). Myocytic organelles, myofibrils (Lefrak) (Billingham), sarcoplasmic reticulum and mitrochondria (Burja) also show a characteristic damage pattern during antracycline therapy. Inhibition of mitichondrial respiratory enzymes (Lenaz) and of Na-K ATPase (Gonsalves) (Olson), chelation of divalent cations (Lenaz) and peroxidation of membrane lipid (Myers) are possible mechanisms of organelle injury.

Anthracycline cardiomyopathy rarely occurs below a cumulative total dose of 500 mg/m² (Halazun) (Hvizdala) although inidividual variation in susceptibility (Alexander) and 'risk factors' such as mediastinal irradiation (Merrill), concurrent cyclophosphamide treatment (Bhanot) age below 10 years (Prout) (Pratt) (Von Hoff) and antecedent cardiac disease (Praga) may contribute to myocardial failure at lower doses.

The relationship between cumulative anthracycline dose and histological evidence of myocardial damage is linear (Bristow) (Mason) but both cumulative dose and histological signs have a non-linear relationship with clinical signs and laboratory indices of pump failure. There is a distinct threshold effect at a cumulative dose of 500 mg/m² above which cardiac failure is very much more likely to occur.

Indices of ventricular function such as the systolic time interval (STI) (Rinehart) (Balcerzak), radionucleide

angiography ejection fraction (Alexander) (Singer) (Morgan) and echocardiographic shortening fraction (Biancaniello) will reflect myocardial of damage. Ejection fractions below 30% (Alexander) and shortening fractions below 10% predict imminent cardiac failure. Ventricular function may deteriorate after therapy has stopped, leading to delayed cardiac failure up to 12 months after the last dose (Biancaniello). Electrocardiographic changes have been reported during therapy (Weiss 1975) (Ragab) but are not of value in predicting myocardial failure (Pratt) (Praga).

Cardiac failure is often of sudden onset. Children may present with tachycardia, dyspnoea and hepatomegaly, in biventricular failure. They may respond poorly to digitalis and diuretics (Van Hoff). ECG changes of cardiomypathy (Weiss 1976) and enzyme elevation (Lefrak) occur late. Some patients recover sufficiently to come off therapy for cardiac failure, but in others, cardiac failure may persist (Gottdiener).

Children treated with cumulative doses of anthracycline in excess of 450 mg/m^2 require longterm cardiologic follow-up. Echocardiography is probably the optimal technique for follow-up in children (Biancaniello).

6.3.3 Conclusion

Cardiac failure in Patient 3 was predictable because of the cumulative anthracycline dose she received and only unusual because of the 15 month delay in onset. She remained on digitalis and diuretics for five years and 10 months and is

currently well off treatment.

6.4 LUNG DISEASE

6.4.1 Case Report

Patient 29 A.S

This child was born at home to a single mother. His birthweight was 3 kilograms. He was first seen at the Children's Hospital aged one month and treated for gastroenteritis and malnutrition. A diagnosis of miliary tuberculosis, based on x-ray and clinical findings was made at the age of 2 months. This was treated. He was next seen at 18 months of age with severe aspiration pneumonia after having ingested mineral turpentine.

In August 1977 at the age of 3,5 years he presented with sudden weight loss and back pain for the previous 2 weeks. He was pyrexial and had tender swollen thighs and a painful right hip. He had hepatosplenomegaly.

His haemoglobin concentration was 7,3 grams/100 ml, his white cell count was 10,800/mm^2 (no blasts) and his platelet count was 150,000/mm^2. A bone marrow aspirate was thought diagnostic of acute myeloid leukaemia. X-rays showed bony disease in the scapulae and lytic lesions in ribs and the left femur.

Remission was induced with Daunorubicin, cytosine arabinoside, prednisone and thioguanine. Maintenance therapy was continued for three years. During this time he had 10 episodes of

pneumonia involving all regions of both lungs, but most often the left lower lobe (5 episodes).

A testicular biopsy was done in August 1980, prior to stopping treatment. This revealed an acute lymphoblastic leukaemic infiltrate. Initial bone marrow slides were reviewed and the diagnosis changed to ALL.

He received a course of testicular radiation and was given a course of ALL induction therapy. He was not given cranial irradiation, but received 6 weekly IT methotrexate for 2 years. Maintenance therapy with 6-mercapto-purine and methotrexate was stopped in September 1982. During maintenance therapy he had four further episodes of pneumonia.

In March 1983 he was noted to have a productive cough. He was clubbed, hyperinflated and had palpable rhonchi cleared by coughing. Isolated crackles were audible in both lung bases. Bilateral bronchiectatic changes with numerous cysts were present on chest x-ray and were confirmed on bronchography.

6.4.2 Literature Review

Pulmonary damage as a consequence of cytotoxic chemotherapy was first described following treatment with busulfan in 1961 (Oliner). Since then the pulmonary toxicity of a variety of other cytotoxics has been recognised.

Methotrexate (Cooperative Study) (Lascari) 6-mercapto-purine (Bhat) (Sostman) and cytosine arabinoside (Haupt) (Ginsburg) are

drugs used in ALL treatment regimens which have produced specific pulmonary toxicity.

Methotrexate causes an acute pneumonitis. Patients present with shortness of breath, a non-productive cough and fever. A minority of cases have abnormal physical findings on chest examination. Chest x-rays taken early in the illness show an interstitial infiltrate which may progress to an alveolar infiltrate. Most patients recover within 6 weeks. Recovery may be enhanced by steroid therapy (Ginsberg). Few patients die of progressive pulmonary toxicity (Lascari).

Rare cases of 6-mercapto-purine related interstitial pneumonitis have been described (Bhat). Complete recovery is the rule.

Patients treated with cytosine arabinoside may develop an acute respiratory illness similar to that seen in methotrexate-related toxicity. At autopsy, some patients have an unexplained pulmonary oedema (Haupt).

Radiographic and pathological changes seen in cytotoxic induced pulmonary toxicity are characteristic and strikingly uniform (Ginsberg). They may progress to late pulmonary fibrosis. Damage caused by acute infections during therapy may contribute to the progression of injury.

Acute upper and lower respiratory tract infections are common in children on treatment for ALL. Sixty percent of leukaemia patients in the present study had upper respiratory tract

infections severe enough to cause a break in treatment. Eighteen per cent had one or more episode(s) of pneumonia. In a study analysing causes of death in remission for leukaemia, Simone (1972) found that 57% of deaths were due to pneumonia. These children had non-bacterial infections (Pneumocystis carini, Herpes simplex, cytomegalovirus and fungal pneumonias) suggesting that immunosuppression by chemotherapy had predisposed to infection.

Bronchiectasis has been described in leukaemia survivors (Kearney) who had recurrent upper and lower respiratory tract infections during treatment. In such cases the recurrent infections are probably the primary aetiological factor, although methotrexate and 6-mercapto-purine pneumonitis might contribute to damage.

6.4.3 Conclusions

The case record of patient 29 suggests that pre-existing lung damage would further predispose a child to suppurative lung disease during leukaemia treatment.

6.5 HEPATOTOXICITY

Although transient elevation of liver transaminases were frequently seen during treatment, none of the patients in this study exhibited persistent clinical features or laboratory evidence of chronic liver disease.

6.5.1 Literature Review

Methotrexate (Hersh), 6-mercapto-purine (Einhorn) and cytosine arabinoside (Katz) are the drugs of known hepatotocity which are used in the treatment of acute lymphoblastic leukaemia.

Cytosine arabinoside causes reversible acute elevation of liver transaminases and of bilirubin, but does not cause lasting damage (Katz). 6-Mercapto-purine induced hepatotoxicity usually occurs when the dose exceeds 2 mg/kg body weight. It may present as hepatocellular or obstructive liver disease (Einhorn). Cellular necrosis may occur but fewer than 1% of longterm survivors will have evidence of chronic liver disease (Topley).

Methotrexate therapy is commonly associated with elevated liver transaminases and lactic dehydrogenase (Hersh) (McIntosh). Hepatic fibrosis is more common in patients receiving daily methotrexate (Weinstein) but is rarely a cause of hepatic failure. Cirrhosis may occur in up to 24% of patients on daily methotrexate (Podurgiel), but may be avoided by giving this drug weekly.

Transfusion related disease is potentially a more serious cause of chronic liver disease in leukaemia survivors. In certain populations of leukaemia survivors a high incidence rate of hepatitis B (Vergagni) and non-A, non-B hepatitis (Locasciulli) are seen. These are more frequently associated with chronic liver disease than is direct drug toxicity (Malone). In the populations mentioned, a high incidence of hepatitis may be due

to local causes such as the incidence of hepatitis in the population at large. In a more recent study of a different patient population (Ratner) Hepatitis B virus infection was found to be the most important single cause of abnormal liver function during remission and conferred an adverse effect on prognosis in terms of leukaemia-free survival.

6.5.2 Conclusions

Chronic liver disease is rare in survivors of acute lymphoblastic leukaemia. When it occurs it is more likely to be the consequence of contamination of blood products than due to chemotherapy. Meticulous care should therefore be taken in the preparation and use of blood products during acute management.

CHAPTER 7

PSYCHOLOGICAL ADJUSTMENT IN SURVIVORS OF CHILDHOOD LEUKAEMIA

7.1 INTRODUCTION

Emotional and social growth in survivors of childhood cancer are as much part of a successful outcome of treatment as are normal physical and mental development. The assessment of quality of life among leukaemia survivors would be incomplete without some estimate of their later emotional adjustment.

This chapter reviews the literature on the psychosocial consequences of cancer in children and describes emotional and behavioural adjustment in a group of leukaemia survivors, as seen by their parents and teachers. The results of this study are discussed in the light of previous knowledge.

7.2 LITERATURE REVIEW

Concern about the psychological impact of childhood cancer has increased but its emphasis has changed with improved rates of survival. Whereas early authors discussed the problem of childhood cancer as that of the dying child, more recent workers have considered the child with cancer to have a chronic illness which he is expected to survive. Because of this change in prognosis, childhood cancer no longer presents a static problem. The patient, previously somewhat overlooked (Spinetta, 1978), has become more closely studied.

Because of the poor prognosis of leukaemia before 1970, long-term psychosocial adjustment was not perceived to be a problem by those caring for children with cancer. Early

subjects of psychological study were the child's conception and fear of death (Kübler-Ross) (Koocher, 1973). A major controversy was whether the child should be shielded from the illness and its possible consequences (Gogan, 1977) or whether these should be discussed openly (Lansky, 1974).

For the child the challenge has now changed from coping with approaching death to the stress of repeated invasive courses of therapy and repeated 're-entry' into school (Lansky 1975) (Eiser 1980) and society (Kagen-Goodheart) after each hospital admission. Physical consequences of therapy must be born in the short (Kuttner) and long term (Jaffe 1975) (Chessels 1983). Stopping chemotherapy at the end of the prescribed treatment protocol is a further stress (Kagen-Goodheart) as is the longterm uncertainty of prognosis (Cohen) (Koocher 1981).

Illness and treatment interfere with schooling, the child's main occupation and source of achievement (Kagen-Goodheart) (Eiser) (Lansky). Treatment side-effects may cause a deterioration of self-image leading to lowering of self-esteem, particularly in adolescence (Karon) when physical attractiveness and athletic ability are most important. Physical stigmata affect peer group relations, as do social myths about cancer, such as fear of contagion (Koocher 1981) which serve to isolate children with cancer from their normal peers (Pless).

Parental attitudes may affect the child's adjustment through overprotection (Pless) (Steinhauer) which may lead to a loss of the child's self esteem because standards and expectations are lowered. Particular parental coping styles (Spinetta 1978) (Harvey) may also retard the child's understanding of his illness by discouraging useful discussion.

There is little written about psychosocial adjustment to these stresses in survivors of leukaemia, although inferences may be drawn from studies of heterogeneous groups of longterm survivors of childhood cancer (Li and Stone) (Holmes) (Fergusson) (Koocher 1981) and from studies of children with other forms of chronic illness (Maddison) (Howarth), (Lavigne) (de Wet).

Holmes and Holmes (1975) found excellent adjustment among most survivors of childhood cancer, many of whom had succeeded in life beyond their pre-illness expectations. These findings were based on responses to a self report questionnaire and subjects were not assessed objectively. Li and Stone (1976) found potential for a high quality of life in survivors of childhood cancer. According to self reports, survivors were well adjusted, although this was not tested by psychological assessment.

Fergusson (1976) found symptoms suggesting mild maladjustment in 39%, and moderate psychological symptoms in 11% of a small group of survivors treated for malignancies between the ages of 2 and 5 years. On a range of psychological tests, half the children showed no evidence of residual problems.

In an intensive study of more than 100 patients, Koocher and O'Malley (1981) found that half the survivor group had mild symptoms of psychiatric maladjustment, with a good correlation between this assessment and scores from the instruments designed by Srole (1962), Koocher (1981) and Rutter and Graham (1968). Koocher and O'Malley found it difficult to identify an appropriate control group, and population norms for their instruments were not available. Despite these logistical problems it was possible, by comparing well and poorly adapted survivors, to identify certain factors which made a healthy psychological outcome more likely.

Children who had received a short course of treatment, with the minimum of side effects, who had had a relapse-free course and in whom cancer had it's onset in infancy or early childhood, had the best psychological prognosis. Survivors who demonstrated low self esteem, depression, persistent unresolved concern about the outcome of their illness and who had poor verbal skills were more likely to be poorly adjusted. In this analysis, children surviving leukaemia were not considered separately from the whole sample.

Parental coping strategies (Ray) (Kaplan) (Spinetta) are thought to play a major role in the child's adaptation to illness. Families with 'open' coping styles who inform sick children of their illness early, in an age-appropriate manner tend to have well adapted offspring. Contrary to expectations, children with visible stigmata do not demonstrate more maladaptive symptoms than those without visible evidence of their previous illness (Koocher 1981).

In their 1981 study, Koocher and O'Malley found that of all parental factors considered, only low socio-economic status correlated with a poor psychological outcome in the child. Outcome was unaffected by marital problems.

Armstrong et al (1982) showed that children still being treated for cancer exhibited more depression and anxiety than age and sex matched well children. This study used a personality inventory which showed that 26% of children with cancer were so symptomatic as to need psychiatric intervention.

In studies of chronically ill children (which may have some bearing on the outcome to be expected among leukaemia survivors), early studies (Howarth) (Pless) indicated significant and frequent psychological maladjustment among such patients. These findings have been refuted by the more recent studies of Tavormina (1976) (1981) and Lewis (1982). The latter investigator found that family functioning was a better predictor of child adjustment than the presence of chronic illness.

Although none of these studies was done on leukaemia survivors alone, some of their conclusions may be relevant to our patients:

1. The prediction of the psychological outcome in a leukaemia survivor is complex (Koocher)

2. Survivors with the minimum of late effects of therapy are more likely to adjust well (O'Malley 1979)
3. Children in whom disease is diagnosed during infancy and early childhood may do better (Koocher 1981)
4. Children with low verbal intelligence quotients may adapt less well (Koocher 1981)
5. Open parental coping styles may provide a better basis for late adjustment (Spinetta) (Ray) (Kaplan)
6. Children from lower socio-economic groups may have a poorer outcome (Koocher 1981).

7.3 THE PRESENT STUDY

7.3.1 Hypothesis

Because of the mean age of presentation, the intensity of treatment and the severity of acute and longterm treatment related side effects, survivors of ALL should exhibit a higher incidence of behavioural and emotional disorders than children surviving other forms of cancer, and a higher incidence than the population at large.

7.3.2 Patients and Controls

All longterm survivors of ALL (as previously described in Chapters 2, 3 4 and 5) were eligible for this study. Of 30 survivors, 23 were available for assessment. Three patients (No's 3, 5 and 25) had refused consent and 4 (No's 2, 4, 11 and 22) lived too far for a parent interview to be arranged. Patients 2, 3, 4 and 25 had also already left school. The mean age of the remaining group was 4,7 years at diagnosis and 11,9 years at assessment.

All longterm survivors of other forms of childhood cancer were eligible as controls. Subject to constraints of distance and consent, it was possible to assess 32 control subjects. In the control group, mean age at diagnosis was 4,7 years and at assessment was 10,7 years.

Patient and control groups did not differ substantially in sex distribution or in socio-economic background (see Figures 2,1 and 2.2).

7.3.3 Method

7.3.3.1 Logistics

Patients were informed of the study by letter in advance of a scheduled clinic appointment (see Appendix II). At the time of the clinic visit, the parent was seen with the child and the different parts of the study were explained in detail to both. Informed consent to the study was obtained (see Appendix I) and a time was arranged for the parent interview. The teacher questionaire was shown and each question it contained was explained, as was a letter which accompanied the questionnaire (see Appendix III). The parent was requested to deliver the questionnaire and explanatory letter to the class teacher in person. A reply-paid return-addressed envelope was provided with each questionnaire.

7.3.3.2 Teacher Questionnaire (Appendix IV)

The Rutter teacher questionnaire (Rutter 1967) was completed by class teachers of survivors from both groups whose parents had been interviewed. The scale consists of 26 brief statements about the child. The teacher has to mark whether the statement

applies 'certainly', 'somewhat' or does not apply to the child in question. These replies are given a weight of '2', '1' and '0' respectively. The sum of the scores gives a total of 0-52. A 'neurotic' subscore is obtained by the sum of scores on items 7 (often worried) 10 (often appears miserable), 17 (tends to be fearful) and 23 (has had tears on arrival). An antisocial subscore is derived from the sum of items 4 (often destroys), 5 (frequently fights), 15 (often tells lies), 19 (has stolen) and 20 (bullies other children).

Children with a total score of 9 or more are identified as showing disordered behaviour. Of these, those in whom the neurotic subscore exceeds the antisocial subscore are designated 'neurotic'. Those in whom the antisocial score exceeds the neurotic are 'antisocial' and when the subscores are equal an undifferentiated behaviour disorder is present.

In a random sample of children in the general population, Rutter (1967) found that 11 per cent of boys and 3,5 per cent of girls obtained scores greater than 9. When compared with findings on a standardized psychiatric interview, scores in excess of 9 correlated well with the presence of psychiatric disturbance.

7.3.3.3 Parent Interviews (Appendix V)

A standardized interview was conducted with a parent of each survivor to estimate the child's general adjustment in terms of behaviour and social relationships observed by the parent. The interview also contained a series of questions designed to

assess both the impact of the illness on the family and the style of coping employed.

Questions were based on the parent questionnaire by Graham and Rutter (1968) and a screening questionnaire developed by Rodgers (1974) for asessment of children with cystic fibrosis.

The interview consisted of 30 questions, asked in an open ended manner. This technique was followed to achieve spontaneity and to obtain a broader understanding of the parents frame of reference on each particular question. Probes were used with each question to direct more specific and concrete responses.

Answers were assessed in two major categories. The first related to parental and family attitudes toward the survivor and his illness, as well as their style of coping. This category included answers to questions 1, 7 a, b and c and 12 a, b, c and d. Answers were not scored, but were the basis of an assessment of the parental coping style and of the overall impact of this illness on the family.

The second category assessed answers to questions similar to those used in the Rutter parent questionnaire and was aimed at identifying neurotic or antisocial behaviour. The answer to each question was rated according to the severity of the problem in question. In each case if there was no difficulty, a score of '0' was recorded, if it was present to a mild degree, or infrequently occurred a score of '1' was given and if a problem was severe, or occurred frequently, it was given a

score of 2. Individual item scores were added to give a total score range of 0 to 40.

A neurotic subscore was obtained by adding the scores of items 2, 20, 8 and 17. An antisocial subscore was obtained by the sum of scores on items 4, 10, 14 and 16.

Children with a total score of 10 or more were designated as showing some behaviour disorder. Of children with a score in excess of 10, those with a higher score on neurotic than antisocial items were designated 'neurotic'. Those with a higher antisocial score were designated 'antisocial'. Children with equal neurotic and antisocial subscores were considered to have an undifferentiated behaviour disorder.

7.3.4 Results

7.3.4.1 Teacher Questionnaire

Twenty-two of 23 leukamia subjects were rated by their teachers (a 96% return). Three (15,6%) had abnormal scores (Table 7.1) all of which were designated 'neurotic' responses.

Teachers of 32 control subjects returned questionnaires. There were 7 (21,8%) abnormal scores of which 4 were designated 'antisocial' and 3 'neurotic' (Table 7.2).

There was no statistically significant difference between the two groups with respect to the incidence of abnormal scores on the Rutter teacher questionnaire ($X^2 = 0,26$).

TABLE 7.1

LEUKAEMIA PATIENTS : TEACHER AND PARENT QUESTIONNAIRES

PAT NO	TEACHER SCIRE	DESIGNATION	PARENT SCORE	DESIGNATION	SOC CLASS	COPING STYLE
1	9	Neurotic	8		V	Closed
6	7		4		I	Open
7	2		1		II	Open
8	3		3		V	Open
9	5		6		II	Open
10	2		10	Undifferentiated	II	Open
13	4		4		I	Open
14	6		9		V	Closed
15	7		7		I	Closed
16	6		2		II	Open
17	5		5		I	Closed
18	2		0		II	Open
19	6		5		I	Open
20	1		6		V	Open
21	5		1		V	Open
23	9	Neurotic	7		II	Open
24	5		3		III	Closed
26	1		14	Neurotic	II	Closed
27	2		2		V	Closed
28	7		15	Neurotic	I	Closed
30	13	Neurotic	3		IV	Closed
31	0		2		II	Open

TABLE 7.2

SOLID TUMOUR PATIENTS : PARENT AND TEACHER QUESTIONNAIRES

PAT NO	TEACHER SCORE	DESIGNATION	PARENT SCORE	DESIGNATION	SOC CLASS	COPING STYLE
29	13	Neurotic	14	Antisocial	V	closed
33	3		3		III	Open
34	7		9		III	Open
35	5		13	Neurotic	I	Open
37	14	Antisocial	14	Antisocial	V	Closed
39	0		7		II	Open
40	6		2		V	Open
42	10	Antisocial	4		IV	Closed
43	4		9		I	Open
44	2		5		IV	Open
46	6		6		II	Closed
47	5		5		I	Open
48	0		3		III	Closed
49	10	Neurotic	12	Undifferentiated	IV	Open
51	5		3		I	Open
52	2		3		I	Open
53	0		2		II	Open
54	25	Antisocial	7		V	Closed
55	28	Antisocial	10	Undifferentiated	III	Closed
56	0		0		I	Closed
57	6		5		I	Open
58	2		4		II	Open
59	4		5		IV	Open
61	0		5		II	Closed
62	5		1		II	Closed
64	3		1		III	Closed
66	0		1		I	Open
70	24	Neurotic	9		III	Closed
72	2		8		I	Open
73	3		5		I	Open
74	6		7		IV	Open
75	3		7		I	Closed

7.3.4.2 Parent Interview

Thirty-nine per cent of families with a leukaemic child had adopted a 'closed' coping style, compared with 40 per cent of families in the control group. Style of coping was not related to social class in either group.

Parents were either divorced or permanently separated in 6 families of leukaemic children and in 7 families in the control group. There was no statistically significant difference in the proportion of separations between the groups. None of the parents interviewed felt that the child's illness had been directly responsible for the break.

Eleven parents of leukaemic children reported depression in themselves or in a spouse during their child's illness (47%). Only one mother had received psychiatric care. In the control group, 56% of interviewees reported depression.

Forty-seven per cent of parents in both groups reported a significant economic effect of their child's illness on the family. This was independent of social class and related to a need to move home, decisions to decline promotion and transport costs. All these patients had received free medical treatment.

In the majority of cases, the mother was the parent interviewed (87% in leukaemics and control cases alike). In both groups, approximately 50% of mothers reported a lack of support from their spouse (this includes cases where the parents were divorced). Sources of support other than the spouse included

grandparents (39%), other relatives (13%) friends (13%), an employer (13%), other parents (13%) and the church (30%). These sources are not mutually exclusive. Doctors and other members of the oncology team were not specifically mentioned as sources of emotional support.

Three leukaemia survivors (13%) had abnormal scores on the parent interviews (Table 7.1). Two were rated 'neurotic' and one 'undifferentiated'. None of these abnormal scores correlated with abnormal scores on the teacher questionnaire.

Five control group subjects (15,6%) had abnormal scores on parent interview (Table 7.2). In four of these patients the abnormality correlated with an abnormal score on teacher questionnaire. Two patients were designated antisocial, two undifferentiated and one neurotic.

When leukaemia survivors and controls were considered together and all abnormal scores taken into account, a 'closed' coping style was significantly associated with evidence of psychosocial problems (Table 7.3).

Emotional outcome was not related to social class or to race.

TABLE 7.3

LEUKAEMIA PATIENTS AND CONTROLS : COPING STYLE AND PSYCHOSOCIAL ADAPTATION

COPING STYLE	ADAPTATION		TOTAL
	Normal	Abnormal	
'Open'	30	3	33
'Closed'	12	10	22
	42	13	55

($X^2 = 7,76$ $0,001 < p < 0,01$)

7.3.5 Discussion

This study employed the teacher questionnaire and parent interview as screening tests to detect psychosocial maladjustment in cancer survivors. Both instruments have been shown to be valid and relaible (Rutter 1967, 1968) (Rodgers 1974). Results of the two tests correlated well in the control group (Table 7.2) but not in the group of leukaemia survivors (Table 7.1). The parent interview is thought to be a better measure of emotional adjustment (Rutter 1970) because parents are best qualified to give an accurate account of the child's behaviour in all settings. The interpersonal relationship between the parent and interviewer is likely to enhance communication and clarity of the concepts involved, reduce misunderstanding and increase data validity (Rodgers). Standardization of the interview ensured systematic assessment of all important areas. Since the teacher questionnaire is acknowledged to be a relatively crude tool (Rutter 1970) more reliance was placed on data from the parent interview.

Results of this study indicated that, despite adversity, leukaemia survivors had no more behavioural or emotional problems than children surviving other forms of cancer. This finding is contrary to results of early studies (Howarth) (Pless), but because of the small sample size, findings may well be biased toward a favourable outcome.

In a study of school children in the Western Cape District Robertson et al (1986) found an incidence of behaviour disorder of 9,5% and 10,5% for 10 and 13 year olds according to the

Rutter teacher questionnaire. Twenty-one percent of 10 year olds and 17,6% of 13 year olds met criteria for behaviour disorder according to the Rutter parent questionnaire. Leukaemia survivors, therefore, had a similar incidence of behaviour disorder as seen in the population at large.

One explanation of such unexpectedly favourable behavioural outcome in survivors of malignant disease in childhood is that cancer may not be as devastating an experience to the patient as is popularly thought. According to Helson's adaptation level theory (Helson) judgements of discomfort and fear depend on whether the current stimulus exceeds or falls short of levels to which one has been accustomed by previous experience. Cancer survivors are frequently more satisfied with their lives than the population at large (Danoff) (De Haes) although they may have less sense of autonomy and more general worries about health (Schmale).

A major determinant of emotional outcome was the style of family coping, a finding in keeping with previous reports (Lansky 1974) (Koocher 1981). Improvement in prospects for emotional outcome may be the consequence of the modern open approach to cancer care. Because of the improvement in prognosis it has become easier for clinicians to provide the hope-filled truth about childhood cancer (Koocher 1981).

An interesting difference between the leukaemia and control groups was the preponderance of 'antisocial' behaviour patterns among control group children with abnormal scores. Physical

stigmata (surgical scars and truncal shortening) were present in all control group patients, but subtle (relative short stature, obesity) or absent in leukaemia survivors. It may be speculated that antisocial behaviour was related to physical stigmata which led to confrontation with the peer group (Plumb) (Pless) (Koocher 1981).

None of the parents reported 'rage attacks' in leukaemia survivors, which have previously been reported in the syndrome of hypothalamic injury (Bray) (Barak). In the light of the results of endocrine assessment (see Chapter 3) in these patients this is an interesting negative finding.

Contrary to the findings of Koocher (1981), low socio-economic class was not associated with a poor psychosocial outcome.

Contrary to the findings of Kagen-Goodheart (1977) and Koocher (1981) neither absence from school, nor verbal IQ deficit (Koocher 1981) were related to emotional maladaptation in leukaemia survivors.

7.4 CONCLUSION

Medical staff may assist emotional adjustment by open communication. They may also apply appropriate techniques to allay the fear and discomfort associated with regular visits to the oncology clinic for infusion of cytotoxics, venipuncture and other painful procedures (Kuttner).

It is important that oncology staff should keep educationists informed regarding the nature of a child's illness (Lansky) and possible short- and long-term consequences of treatment. The school is the child's workplace and his school work is as important to his self esteem as is an adult's work. School problems are frequent among leukaemia survivors (Chapter 5) so that close liaison with teachers (with parental consent) should be routine in an oncology service.

The incidence of behaviour disorder in this group of leukaemia survivors is no different from that in the general population, but remains a significant problem.

Although the causes of emotional and behavioural disorders in survivors of cancer are complex (Koocher 1981) and prediction of psychosocial outcome in survivors is difficult, it is possible to identify some of the children and families at risk of psychosocial disorder, by means of screening interviews.

Comprehensive oncology care should include assessment of all families admitted, to identify those at risk and in need of closer support.

CHAPTER 8

QUALITY OF LIFE IN SURVIVORS OF CHILDHOOD LEUKAEMIA

8.1 INTRODUCTION

The primary goals of therapy in ALL namely induction of remission, prolonged maintenance of remission and probable 'cure', have been attained. Now that survival of childhood ALL is the norm, treatment must be refined so that the least damaging curative regimens can be established. There are two important steps to the refinement of ALL therapy. The first is the identification of prognostic features which help to differentiate children requiring less intensive therapy. The second is the identification of those modalities of treatment most damaging in the long term, so that they may be modified in those children needing less intensive therapy.

Aims of a systematic assessment of late effects such as the present study are to demonstrate the range of damage following ALL and its treatment in many body systems and to identify patient- and treatment related factors which increase the likelihood of permanent damage.

To assist the oncologist in achieving an overall assessment of the quality of survival of childhood leukaemia patients a functional deficit score (FDS) was derived.

The proposed FDS differs from a quality of life score (QLS) in that it is not determined by the patient's subjective assessment of his or her own quality of life. The FDS is thought to be a more appropriate measure for assessment of overall outcome among cancer survivors, although the value of

the QLS in other settings is recognised.

8.2 AIMS

To document the overall late toxicity of an established ALL therapeutic regimen by means of a score which rates total residual damage in affected systems.

To compare overall residual deficit in patients treated for leukaemia with that in a group of children treated for non-Hodgkins lymphoma.

8.3 METHOD

8.3.1 Subjects

Subjects were the same as those described in earlier sections of this study. Not all scores were complete as certain subjects were excluded from particular categories of assessment for reasons stated earlier. Twenty one leukaemia survivors (Group 1) could be rated fully. Nine were incompletely rated.

Control subjects were drawn from patients surviving non-Hodgkins Lymphoma (NHL). Fourteen patients could be rated. This represented the entire available sample of such survivors.

Treatment in these groups was similar except that cranial irradiation was used as CNS 'prophylaxis' in leukaemic children and not in NHL survivors. Both groups received intrathecal methotrexate therapy.

8.3.2 The Instrument: Functional deficit score for leukaemia survivors (FDS).

Late effects of leukaemia and its therapy on the nervous system (Ivnik) (Rowland) (Ochs), intellectual function (Eiser 1980) (Copeland 1985) (Duffner), endocrine system (Shalet 1975) (Shalet 1981), growth (Shalet 1979) (Berry), liver (Einhorn) (Tapley) and heart (Billingham) (Ragab) and the danger of secondary neoplasia (Haselow) (Zarrabi) are well described in the literature. They have also been illustrated and discussed in this study.

More than one of these late effects may occur in an individual child and limit his or her available goals in a wide spectrum of achievement.

In order to make an overall assessment of late morbidity, all systems known to exhibit late effects were represented in separate categories of the FDS. These categories were somatic growth, intellectual function, neurological status and psychosocial adjustment. A fifth category gave a score for a miscellany of late effects in other systems which included cardiotoxicity, second tumour or late consequences of therapy-related infection.

Late effects were scored according to their functional consequences for the patient, rather than as abnormalities on laboratory tests (see Table 8.1). If a patient had no functional deficit in a given category, this was given a score of '0'. A mild functional deficit was scored as '1' and a

marked deficit causing symptoms and a handicap was scored as '2'. Patients with no late effects scored a total FDS of '0' whereas those with marked effects in all systems could score a maximum of '14' if all the miscellaneous late effects in category 5 were present.

8.3.3 Statistical Analysis

The statistical significance of the FDS difference between the test (leukaemia) and control groups was assessed by means of the 't' test for comparison of groups with independent means (Colton).

TABLE 8.1

LEUKAEMIA SURVIVOR FUNCTIONAL DEFICIT SCORE

1.	Growth	Normal height	0
		More than 1 SD below starting height	1
		Stalled growth (hGH deficient)	2
2.	Intellectual Function	No measurable deficit	0
		Mild deficit (IQ up to 10 points lower than sib, 1 class failed)	1
		Marked deficit (IQ more than 10 points below sib more than 1 class failed)	2
3.	Neurological Status	No deficit	0
		Deficit on specific examination	1
		Symptomatic	2
4.	Psychosocial Adjustment	No problem	0
		Mild behavioural symptoms	1
		Limiting symptoms	2
5.	Additional Deficit (second tumour, cardiac, respiratory)	No problem	0
		Deficit when specifically tested	1
		Symptomatic	2

8.4 RESULTS

8.4.1 Leukaemia Survivors (Table 8.2)

Seven of 30 leukaemia survivors had mild growth deficit as measured against their height for age at diagnosis. Only one patient (No 26) had stalled growth as a consequence of growth hormone deficiency. She had been given a total 4 400 rads of cranial irradiation, during induction (2 400 rad) and as treatment of a CNS relapse (2 000 rad).

Twenty-two of 30 survivors exhibited an intellectual deficit according to the criteria applied. In 10 of these children this was severe enough to lead to repeated academic failure. Although pretreatment IQ's were unknown, it was demonstrated that leukaemia survivors had a mean IQ significantly below mean sibling IQ (see Chapter 4). School failure, although it could have been caused by many other factors, was thought to be partly the consequence of treatment in these survivors.

Nineteen of 24 leukaemia survivors had clinically detectable signs of a neurological deficit. Only two of these patients had symptoms (of seizure disorder). Results of computerized tomographic scanning were not included in the neurological assessment.

Six of 22 leukaemia survivors had mild symptoms of maladjustment as reported by parents and teachers. In no case were these symptoms thought likely to limit the child in any way.

Two leukaemia survivors had other late effects. One patient (No 3) had limited exercise tolerance as result of anthracycline induced cardiotoxicity. One other patient had required excision of two basal cell carcinomata on the perimeter of the field of cranial irradiation (No 26).

The mean overall deficit score for the 21 patients with complete scores was 2,95 ($\pm$ 1,88). Only 2 patients (7 and 17) were entirely free of late effects. The maximum score of 9 was in patient No 26 who had suffered meningeal relapse and had undergone reinduction therapy.

TABLE 8.2

FUNCTIONAL DEFICIT SCORES IN LEUKAEMIA SURVIVORS

PAT NO	GROWTH	INTELLECT	NEUROLOGY	ADJUSTMENT	OTHER	TOTAL
1	0	1	1	1	0	3
2	0	2	-	-	0	(2)
3	0	2	-	-	2	(4)
4	1	0	-	-	0	(1)
5	0	1	-	-	0	(1)
6	0	1	-	0	0	(1)
7	0	0	0	0	0	0
8	0	2	0	0	0	2
9	0	2	2	0	0	4
10	1	1	1	1	0	4
11	0	0	1	-	0	(1)
12	0	1	1	-	0	(2)
13	0	1	0	0	0	1
14	0	2	1	0	0	3
15	0	2	1	0	0	3
16	1	2	1	0	0	3
17	0	0	0	0	0	0
18	1	0	1	0	0	2
19	1	0	1	0	0	2
20	0	2	1	0	0	3
21	0	2	1	0	0	3
22	0	0	0	-	0	(0)
23	1	2	1	1	0	5
24	0	1	1	0	0	2
25	1	0	-	-	0	(1)
26	2	2	2	1	2	9
27	0	1	1	0	0	2
28	0	2	1	1	0	4
30	0	1	1	1	0	3
31	1	2	1	0	0	4

Brackets indicate an incomplete score

8.4.2 Non-Hodgkins Lymphoma Survivors (Table 8.3)

Only one survivor of NHL had a deficit in somatic growth relative to growth status at the time of diagnosis.

A minority (42%) had some evidence of intellectual deficit, but only 2 of these 6 had had serious academic problems. Two (patients 35 and 48) had a potential IQ deficit on comparison with siblings but no academic problems. They were both female patients compared with male siblings.

Four NHL survivors (28%) had minor neurological abnormality detected on specific examination but were not symptomatic.

Four NHL survivors exhibited features of psychosocial maladaptation but only one child was markedly affected (Patient 29). There were other contributing causes evident on history. One child (Patient 29) had recurrent chest infections and bronchiectasis which preceded diagnosis and appeared to be aggravated during therapy.

The Mean FDS in this group was 1,61 $\pm$ 1,66 with a total score range of '0' to '6'.

The difference in FDS between leukaemia survivors and survivors of non-Hodgkins was statistically significant ($z = 2,108$, $p < 0,028$).

TABLE 8.3

FUNCTIONAL DEFICIT SCORES IN NHL SURVIVORS

PAT NO	GROWTH	INTELLECT	NEUROLOGY	ADJUSTMENT	OTHER	TOTAL
29	0	1	1	2	2	6
32	1	0	0	0	0	1
34	0	0	1	0	0	1
35	0	2	0	1	0	3
37	0	2	0	1	0	3
39	0	1	0	0	0	2
40	0	2	1	0	0	1
41	0	0	0	0	0	0
42	0	0	0	1	0	1
43	0	0	0	0	0	0
44	0	0	1	0	0	1
46	0	-	0	0	0	(0)
47	0	0	0	0	0	0
48	0	2	0	0	0	2

8.5 DISCUSSION

The functional deficit score (FDS) provided a useful summary of long-term damage in leukaemia survivors. Its application in the two comparison groups of ALL and NHL survivors emphasized the heavier burden of late effects in survivors of childhood leukaemia. Sub-category scores accentuated the high incidence of central nervous system-related late effects in this group.

The FDS should be reproducible in most oncology services. Although they are comprehensive, the subtests measure functional disorder without requiring sophisticated staffing or equipment.

Treatment related deficit in growth and intellectual function, can only be proved by longitudinal assessment. When longitudinal records are not available, assessment of these two categories is still advisable because of the high frequency of abnormality in survivor cohorts.

Minor neurological abnormality such as may be detected by appropriate clinical assessment (Touwen) is included in the FDS. It is not known to what extent such abnormalities are likely to affect the survivor's physical coordination and athletic and sporting ability. Seizure disorders represent a major neurological abnormality and would clearly limit the survivor's life.

Psychosocial adjustment was included as part of the comprehensive assessment of functional deficit, although it was recognised that factors other than ALL and its treatment contribute to psychological problems among leukaemia survivors. Psychosocial adjustment may correlate well with quality of life scores, since antisocial and neurotic behaviour may reflect dissatisfaction of the patient with his or her life situation. Indeed, investigation of psychosocial adjustment in children surviving leukaemia might fruitfully include an age appropriate measure of quality of life (Lansky 1985).

This functional deficit score was developed specifically for children surviving leukaemia. Treatment regimens for other neoplasms or other disease may be associated with a different spectrum of late effects. A similar rating of functional outcome might be based on the same principles, but would obviously address such different and specific late effects (Guyatt).

The pattern of late effects in ALL survivors indicated that central nervous system function was most severely affected. Comparison with NHL survivors suggests that cranial irradiation alone or in synergism with intrathecal methotrexate was the most damaging modality of treatment. Since 1979 a lower dose of cranial irradiation (1 800 rad) has been used in 'standard risk' ALL (Nesbit). It is too early to tell whether this dose has reduced the incidence and severity of late central nervous system effects. Assessment of such late effects would usefully include some comprehensive assessment rating such as the FDS.

The advantage of an instrument such as the FDS over a quality of life score in assessment of outcome (Clark) is that the latter is by definition subjective (Danoff) (De Haes) (Calman). Cancer survivors are generally better satisfied with life than expected (De Haes) perhaps because of adaptation to levels of discomfort and performance (Helson) which would be less well tolerated by the general population. It is inappropriate to use the QLS in an overall assessment of late effects, since clinical investigators are looking for objective evidence of remediable or preventable deficiencies.

8.6 CONCLUSION

It is suggested that all long term cancer survivors undergo comprehensive assessment of all systems known to exhibit late effects of treatment. Such assessment should be specific for each form of cancer and its treatment regimen. A summary of late effects such as the FDS is useful in comparing overall damage between groups.

Survivors of acute lymphoblastic leukaemia who have received cranial irradiation as part of central nervous system 'prophylactic' therapy exhibit a specific pattern of late effects. This pattern of damage, as has been illustrated by the present study, has lasting effects on growth, intellectual and neurological function.

It is suggested that longterm care of these survivors should, as a minimum requirement, include the functional assessment outlined in this chapter.

CHAPTER 9

FINAL CONCLUSIONS

The overall aim of this study was a comprehensive assessment of the nature and severity of the late effects of treatment in a group of children surviving acute lymphoblastic leukaemia.

A review of the literature written prior to effective treatment for leukaemia led to the conclusion that although lymphoblastic leukaemia could damage the organs it infiltrated, such damage was likely to cause late effects only if it was clinically overt at diagnosis and before treatment. In the absence of damage preceding treatment, late effects could be ascribed to treatment. Cranial irradiation, methotrexate, L-asparaginase and cytosine arabinoside are therapeutic modalities most likely to cause injury to the central nervous system. Vincristine damages the peripheral nervous system temporarily and anthracyclines cause cumulative dose-related cardiotoxicity.

A retrospective longitudinal assessment of growth in a group of leukaemia survivors demonstrated an abnormal growth pattern. There was a reduction of height velocity during treatment and a failure of 'catch up' growth, likely to result in reduced adult height. These abnormalities were seen to be modified by environmental factors and the pubertal growth spurt. Survivors of childhood leukaemia also showed an increase in weight-for-height during and after therapy which appeared to be the consequence of a loss in statural growth as well as increasing weight-for-age.

Assessment of endocrine function in leukaemia survivors indicated abnormalities in the regulation of growth hormone and thyroid stimulating hormone in some patients. These findings, together with the abnormalities of growth described above, suggest perturbation of hypothalamic function in leukaemia survivors, most probably due to cranial irradiation. Despite abnormal responses to growth hormone stimulation tests, children had grown at normal rates after treatment. In view of their normal height velocity, replacement therapy with growth hormone was not considered necessary. These children demonstrated advanced bone ages, which raised doubts about growth hormone therapy even if height velocity had been reduced, in the light of evidence that such therapy may hasten the closure of growth plates.

Survivors of childhood leukaemia were shown to have an intellectual deficit compared with their siblings and a high incidence of visual-perceptual defects. These findings were thought to explain the high incidence of school failure among these patients. Visual-perceptual problems are potentially remediable and early attention to them may improve school-readiness among young survivors. Cranial irradiation is the apparent cause of these problems but as yet an indispensable part of leukaemia therapy. The intellectual effects of lower doses of cranial irradiation are as yet unknown.

A variety of minor neurological abnormalities were detected among leukaemia survivors and thought to be related to preceding central nervous system 'prophylactic' chemotherapy and irradiation. These neurological abnormalities correlated with abnormalities of the central nervous system visualized by computed tomographic scanning. Neurophysiological tests did not contribute to the neurological assessment of leukaemia survivors.

Isolated examples of late effects specific to individual therapeutic agents were seen in this group of patients. Cases of second malignancy, cardiotoxicity and lung disease were described to illustrate the need for follow-up of cases specifically at risk.

Although psychological maladjustment in leukaemia survivors was not significantly more frequent than in survivors of solid tumours or in the population at large, a number of children were thought by parents or teachers to show signs of behavioural problems. Certain patterns of parental attitude and behaviour place their children at risk of psychological problems. Although the causes of emotional and behaviour disorders in cancer survivors are complex, families at risk may be identified by means of screening interviews.

A new instrument, the functional deficit score, was derived to reflect overall outcome in survivors of childhood leukaemia. This instrument included all categories of function assessed in this comprehensive study of late effects thought likely to be of consequence to the patient. The functional deficit score could distinguish between groups given different forms of central nervous system 'prophylaxis' and may be useful in assessing patients given lower doses of cranial radiotherapy in the future.

Although the number of patients in this study is relatively small, there is no study reported in which the assessment of late effects has been as comprehensive. It is suggested that long-term care of leukaemia survivors should include, as a minimum requirement, assessment of the elements of the functional deficit score.

DATE: _____

NAME: _____

PARENT OF: _____

I hereby give consent to my child being investigated by means of tests, the nature and risks of which have been explained to me by the doctors concerned.

I realise that these tests will not necessarily benefit my child directly, but that they may lead to a better understanding of the late effects of cancer treatment.

SIGNED: _____

WITNESSES: 1. _____

2. _____

DATUM: _____

NAAM: _____

OUER VAN: _____

Ek gee hiermee toestemming dat my kind ondersoek word deur middel van toetse, die aard en risikos waarvan aan my deur die betrokke dokters verduidelik is.

Ek besef dat my kind nie noodwendig by die toetse sal baat vind nie, maar dat die inligting wat bekom word mag bydra tot kennis omtrent die newe-effekte van kanker behandeling.

GETEKEN: _____

GETUIES: 1. _____

2. _____

APPENDIX II

RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL
and the
INSTITUTE OF CHILD HEALTH

Telephone Cape Town 69-8721
Ext. 497
Tel. Address: 'HOSFIL'

Rondebosch 7700
Republic of South Africa
Reference

Dear Parent,

As you know many children with cancer are now being cured. This success has brought about a number of new problems. Cancer and its treatment may cause permanent undesirable effects such as muscle wasting and slowing of growth, of which you may already be aware.

We plan to examine all children who have been cured of cancer under our care for these late effects. Tests will be carried out in our outpatient clinic, but may require a short admission in some cases. The tests are harmless and will give us a great deal of important information, which may be of practical value to your child and will be of great benefit to other children with cancer.

The complete list of tests (they will not be given to every child) is as follows:

1 Hormonal function - this will involve a blood test

2 Intellectual function - three tests, measuring general IQ and the use of the eye and ear in learning

3 Vision

4 Hearing

5 A special Xray of the head

6 Xrays of the wrist, chest and spine

7 Enchocardiogram (a test of heart function)

8 Behaviour - we would like permission to ask your child's teacher to fill in a questionnaire. You will be asked to complete another questionnaire describing your child at home and your child will need to complete a list of questions as well.

To do this survey we need your consent and co-operation. Please complete the enclosed form and return to us in the reply-paid envelope as soon as possible.

Yours sincerely

APPENDIX III

RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL
and the
INSTITUTE OF CHILD HEALTH

Telephone Cape Town 69-8721
Ext. 497
Tel. Address: 'HOSFIL'

Rondebosch 7700
Republic of South Africa
Reference

Dear

We are presently engaged in a survey, to establish whether children we have treated for a number of serious illnesses, have been left with any intellectual or behavioural problems.

As part of this study, we are asking the class teachers of these children to complete the questionnaire which accompanies this letter. As you can see, the questions are designed to find out about abnormal behaviour only.

I would be very grateful if you would complete the questionnaire according to the instructions, and return it to me in the enclosed addressed envelope.

If you have any queries, I would be happy to discuss them with you over the telephone.

Yours sincerely

DR P ROUX

APPENDIX IV

BEHAVIOUR QUESTIONNAIRE

TO BE COMPLETED BY TEACHERS

Below are a series of descriptions of behaviour often shown by children. After each statement are three columns: 'Doesn't Apply', 'Applies Somewhat' and 'Certainly Applies'. If the child shows the behaviour described by the statement place a cross in the box under 'Certainly Applies'. If the child shows the behaviour described by the statement but to a lesser degree or less often place a cross in the box under 'Applies Somewhat'. If, as far as you are aware, the child does not show the behaviour place a cross in the box under 'Doesn't Apply'. Please put ONE cross against each statement. Thank you.

STATEMENT	DOESN'T APPLY	APPLIES SOMEWHAT	CERTAINLY APPLIES	FOR DOCTOR'S USE ONLY
Very restless. Often running about or jumping up and down. Hardly ever still	☐	☐	☐	☐
Truants from School	☐	☐	☐	☐
Squirmy, fidgety child	☐	☐	☐	☐
Often destroys own or other's belongings	☐	☐	☐	☐
Frequently fights with other children	☐	☐	☐	☐
Not much liked by other children	☐	☐	☐	☐
Often worried, worries about many things	☐	☐	☐	☐
Tends to do things on his own - rather solitary	☐	☐	☐	☐
Irritable, Is quick to 'fly off the handle'	☐	☐	☐	☐
Often appears miserable, unhappy, tearful or distressed	☐	☐	☐	☐
Has twitches, mannerisms or tics of the face or body	☐	☐	☐	☐
Frequently sucks thumb or finger	☐	☐	☐	☐
Frequently bites nails or fingers	☐	☐	☐	☐
Tends to be absent from school for trivial reasons	☐	☐	☐	☐
Is often disobedient	☐	☐	☐	☐

STATEMENT	DOESN'T APPLY	APPLIES SOMEWHAT	CERTAINLY APPLIES	FOR DOCTOR'S USE ONLY
. Has poor concentration or short attention span	☐	☐	☐	☐
. Tends to be fearful or afraid of new things or new situations	☐	☐	☐	☐
. Fussy or over-particular child	☐	☐	☐	☐
. Often tells lies	☐	☐	☐	☐
. Has stolen things on one or more occasion	☐	☐	☐	☐
. Has wet or soiled self at school this year	☐	☐	☐	☐
. Often complains of pains or aches	☐	☐	☐	☐
. Has had tears on arrival at school or has refused to come into the building this year	☐	☐	☐	☐
. Has a stutter or stammer	☐	☐	☐	☐
. Has other speech difficulty	☐	☐	☐	☐
. Bullies other children	☐	☐	☐	☐

Are there any other problems of behaviour?

.....

.....

.....

GNATURE: .....

w well do you know this child?

ry well

derately well

t very well

THANK YOU VERY MUCH FOR YOUR HELP

APPENDIX V

PARENT INTERVIEW

1. How do you think your child is getting on _____

_____

2. Does he/she complain much of feeling sick, headaches or stomaches. _____

3. Would you describe him/her as a happy child, or does he/she sometimes worry or feel sad. _____

4. Is he/she obedient? _____

5. Who will he/she ask for advice with a problem? _____

6. How do your children get along with one another? _____

7. Do you think your child knows all about the illness he has had? (have you discussed death, has he always understood the need for treatment). _____

8. Are there any problems related to eating, sleeping, toilet habits? _____

9. Is there any problem with stuttering? _____

10. Does he/she lie or steal? _____

11. Does he/she suck a thumb or bite fingernails? _____

12. How has the family been affected by this illness (Discussion open, mother depressed, shared responsibility, material relationship. _____

13. Does he/she have many friends? _____

14. Is bullying a problem? _____

15. Is he/she generally alone in a group _____

16. Is fighting a problem? _____

17. What is the reaction to new experiences? _____

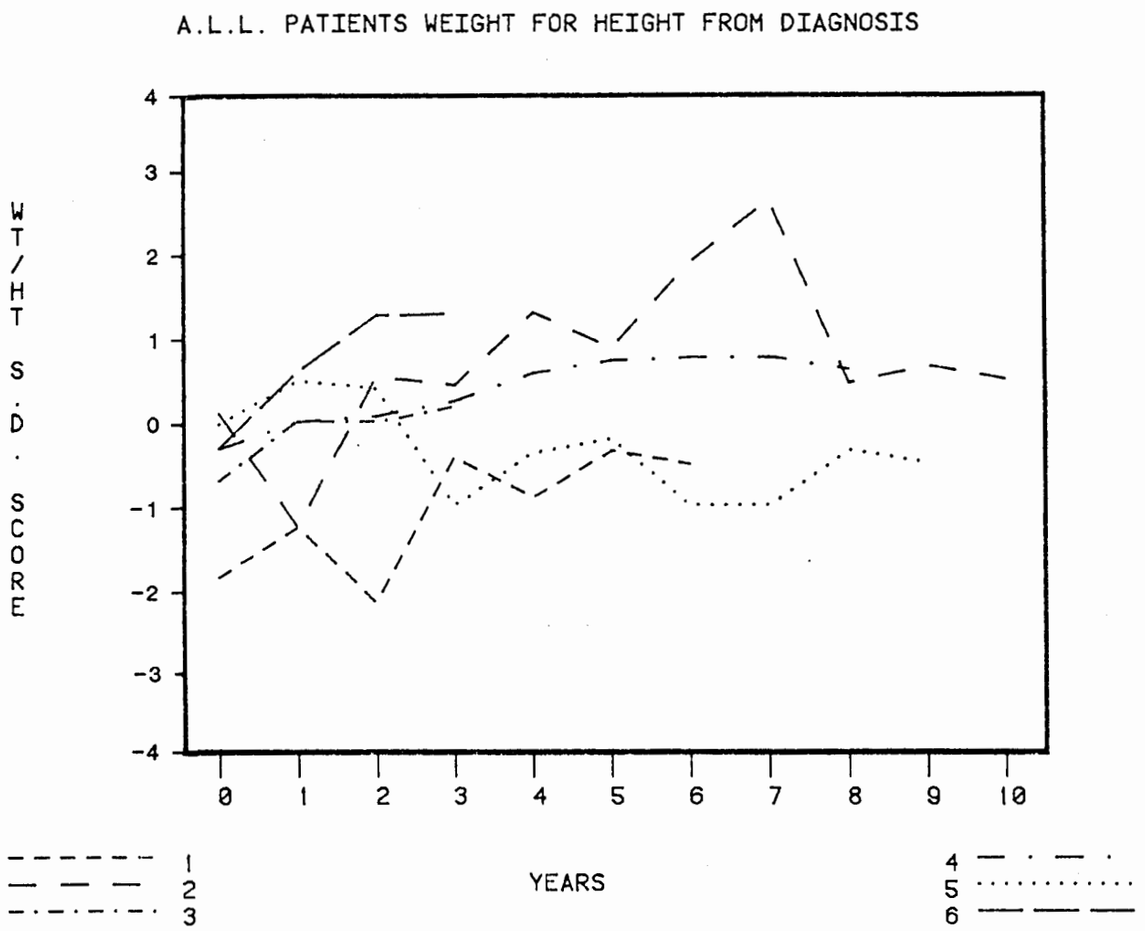
18. How are problems tackled? _____

19. How is responsibility accepted? _____

20. Is school seen as enjoyable, or is he/she often absent? _____

APPENDIX VI

FIGURE 2.16:


A.L.L. PATIENTS WEIGHT FOR HEIGHT FROM DIAGNOSIS
WT/HT S.D. SCORE
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-1
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YEARS
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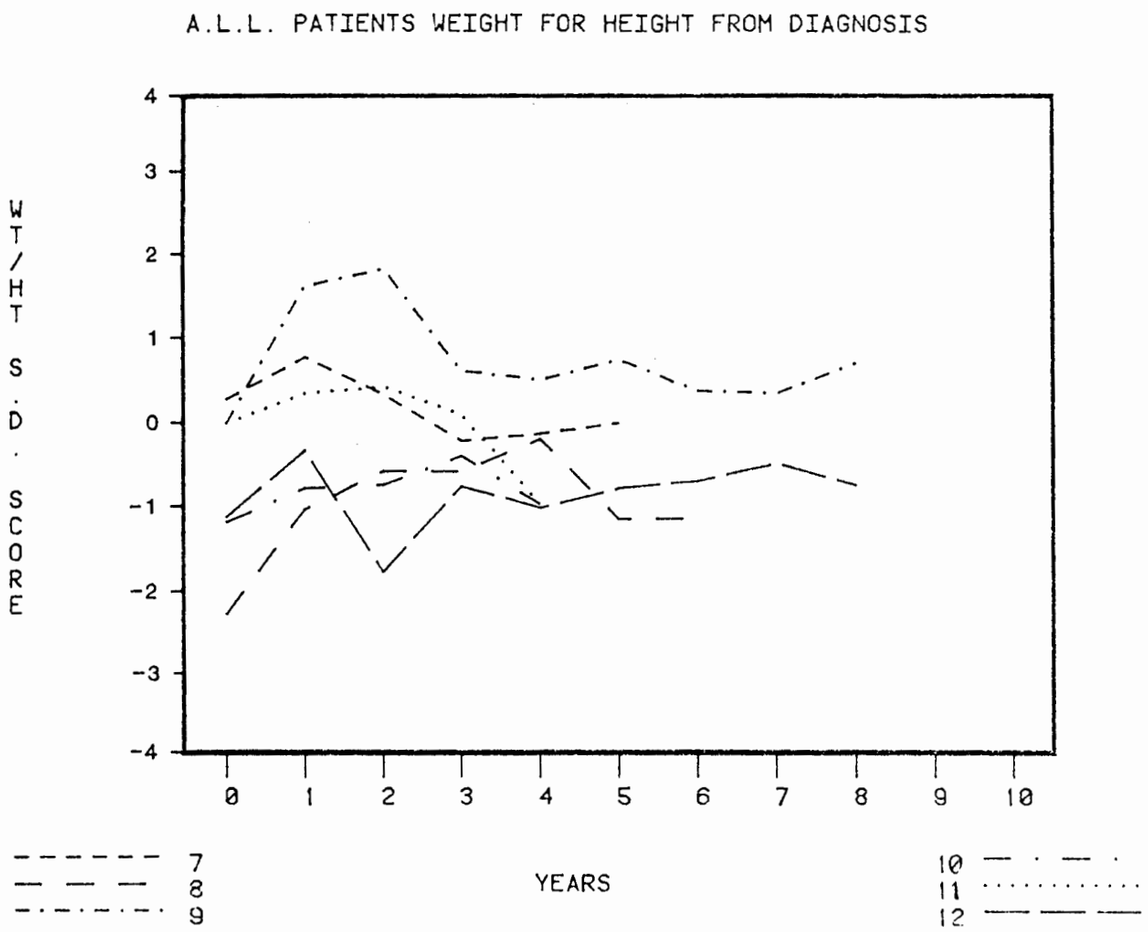
FIGURE 2.17: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WT/HT S.D. SCORE
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FIGURE 2.18:

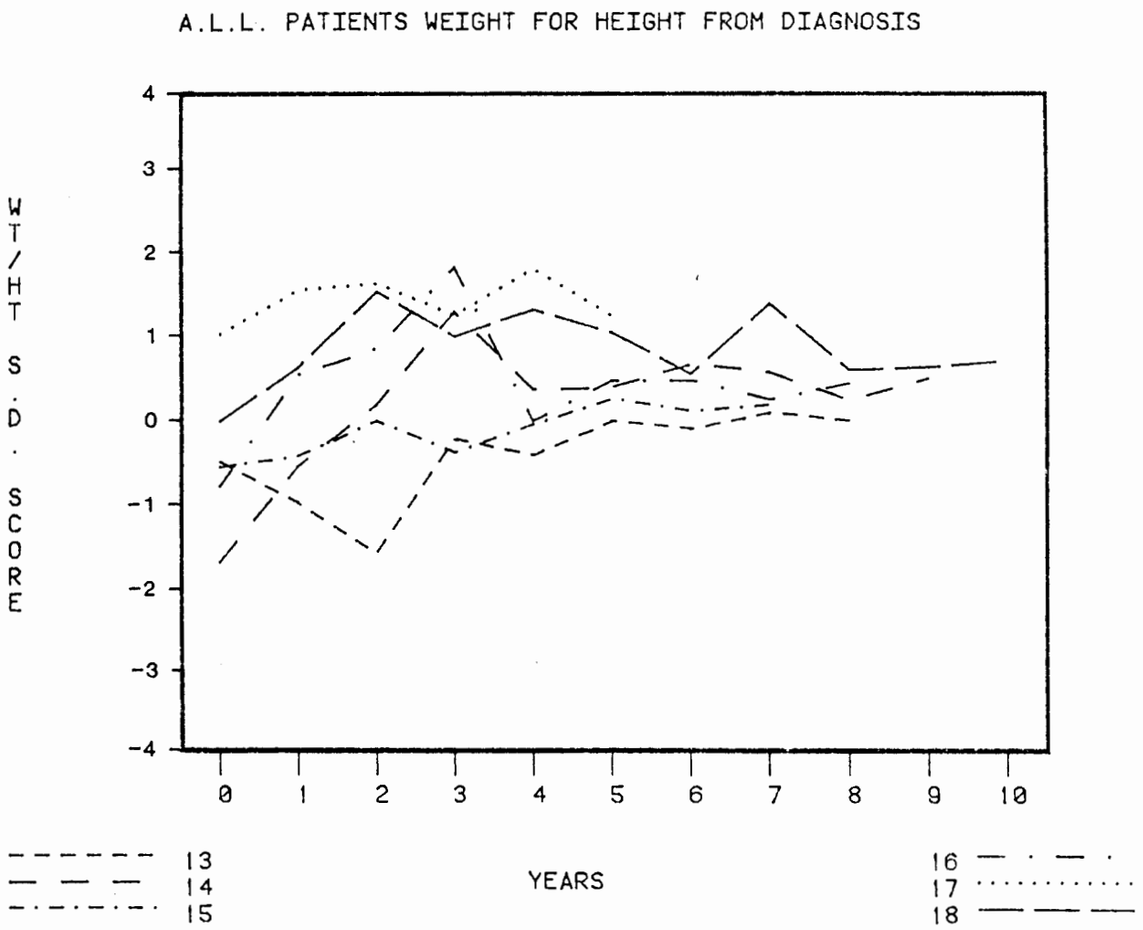
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FIGURE 2.19:

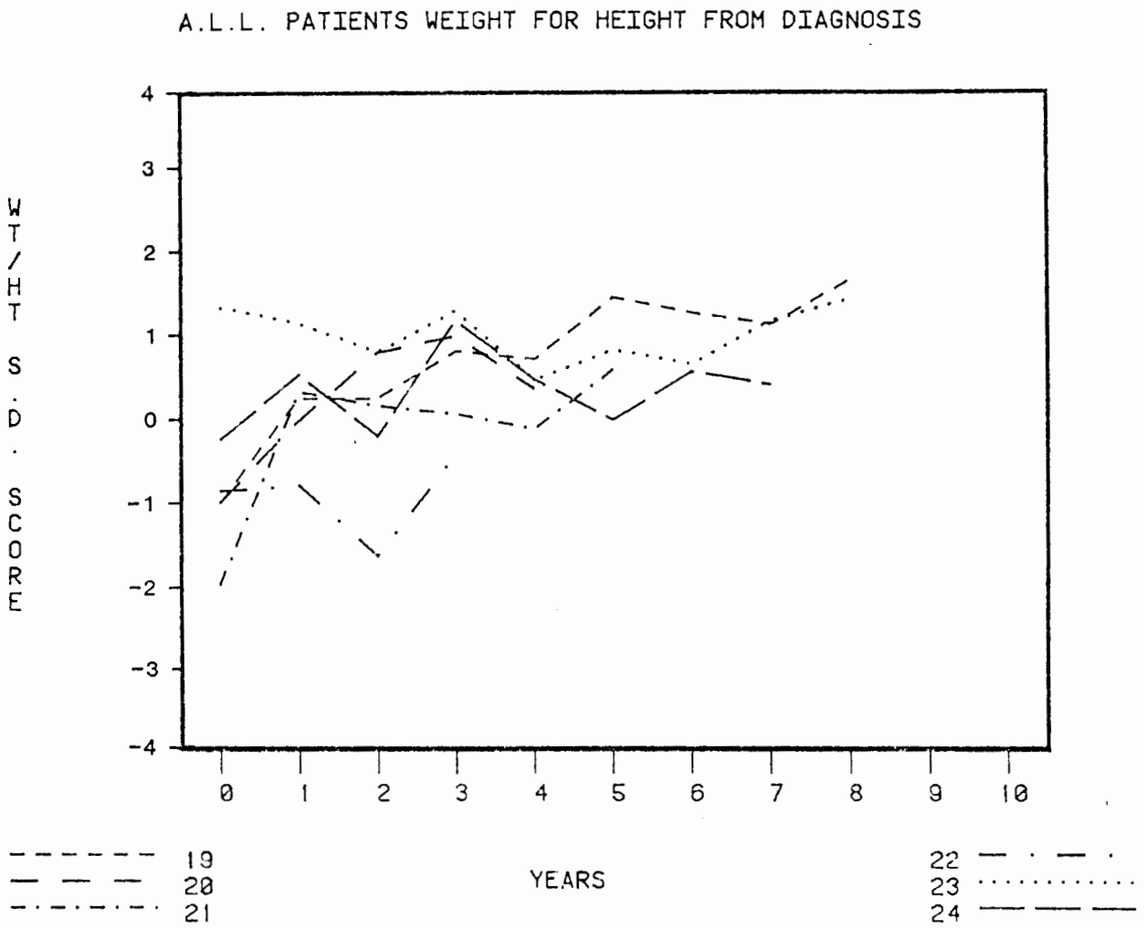
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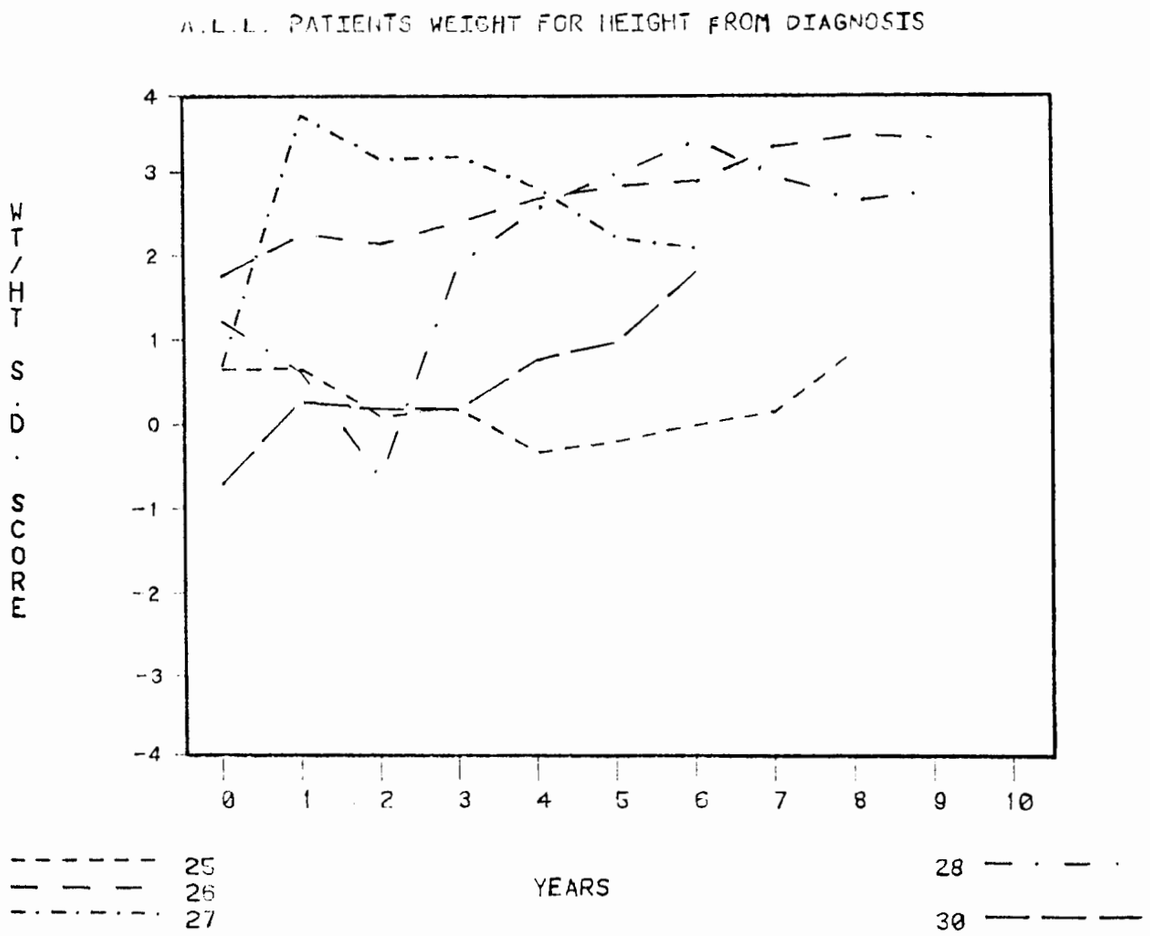
FIGURE 2.20:


A.L.L. PATIENTS WEIGHT FOR HEIGHT FROM DIAGNOSIS
WT/HT S.D. SCORE
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YEARS
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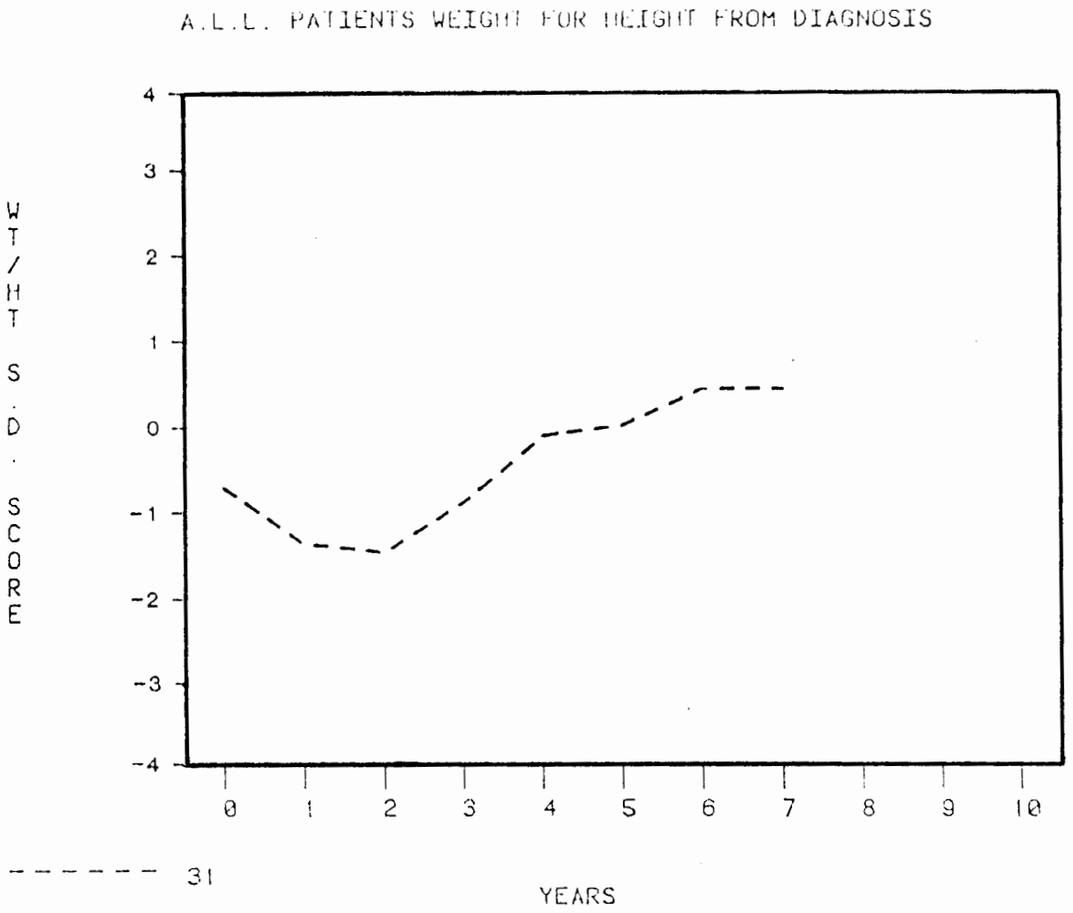
FIGURE 2.21:


A.L.L. PATIENTS WEIGHT FOR HEIGHT FROM DIAGNOSIS
WT/HT S.D. SCORE
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YEARS

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