Hand-Wrist Bone Age in Children Treated for Acute Lymphoblastic Leukemia

Mary Elizabeth Martin
University of Tennessee Health Science Center

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HAND-WRIST BONE AGE IN CHILDREN TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA

A Thesis
Presented for
The Graduate Studies Council
The University of Tennessee
Health Science Center

In Partial Fulfillment
Of the Requirements for the Degree
Master of Dental Science
From The University of Tennessee

By
Mary Elizabeth Martin, D.D.S.
May 2006
I would first like to thank Dr. Edward F. Harris for his constant leadership through, not only my three years in orthodontics, but also my four years of dental school at The University of Tennessee. Without his guidance and perseverance, my thesis would not have been possible. I must also express my sincere appreciation to Dr. Sue Kaste and Dr. Chris Rowland at St. Jude Childrens’ Research Hospital for their direction. It is my hope that my thesis will be among many more written as collaborations between St. Jude and The University of Tennessee’s Orthodontic department. Lastly, I appreciate the time and energy my committee members, Dr. William Parris, Dr. Quinton Robinson, and Dr. Edward Harris have committed to helping me refine and complete my thesis. Without their support, this project would not have been possible.

I would like to dedicate my thesis to both my family and my husband, David. I first became interested in dentistry at a young age from simply watching and admiring my father. I cannot express how fortunate I feel to have been given the opportunity to follow in my father’s footsteps. The constant support of my parents, my sister, and husband will always be my encouragement and source of aspiration to be the best orthodontist and person possible.
ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy of childhood, constituting 31 percent of all childhood malignancies. Treatment strategies to target ALL include chemotherapeutic agents, irradiation of the neck and/or spine, and bone marrow transplantation. The aggressive nature of anti-neoplastic therapies often produces numerous craniofacial and dental sequelae as well as additional harmful effects to the entire body. Cranial irradiation may adversely affect the hypothalamic-pituitary axis decreasing growth hormone production. Consequently, children with ALL may experience a transient or permanent reduction in growth iatrogenically. Hand-wrist radiographs are valuable for evaluating maturational status in children with ALL. These radiographs allow for the comparison of a child’s chronological age with relative “bone age.” OBJECTIVE: This study used hand-wrist radiographs to determine the maturational status of children treated with ALL. Bone age was compared to the child’s chronological age to determine the delayed, normal, or advanced tempo of growth. The null hypothesis was that anti-neoplastic therapies have no discernible effect on a child’s tempo of bone maturation. METHODS: Hand-wrist radiographs (n=108 films) of 73 children (39 boys, 34 girls) treated at St. Jude Children’s Research Hospital for ALL were evaluated to assess “bone age.” Mean chronological age at diagnosis was 4.54 years (sd = 2.81). The number of
films per child was highly skewed, since most were taken soon after the diagnosis of ALL (and, thus, close to the onset of treatment). Bone ages were scored for each of the 73 patients based on Greulich and Pyle’s 1959 standards (GP2), specifically the atlas method. RESULTS: We supposed that the combination of antimitotic drugs used to treat ALL would discernibly depress the childrens’ tempos of growth, so that BA-CA (bone age-chronological age) would become negative (and become larger during the course of treatment). We found no evidence of this in our study. In fact, since there was no depression of the rate of maturation during treatment, there was no need for a compensatory, or “catch-up,” phase. There was, then, no evidence that treatment for ALL had any effect on the progress of hand-wrist bone age towards maturity. There also was no detectable effect on the tempo of growth for those treated with cranial irradiation versus children with chemotherapy alone. In conclusion, treatment for ALL spares the tempo of growth as measured by HW bone age. This is a favorable outcome since treatment did not alter the duration of growth, so prognosis of normal adult status is good. This finding accounts for several prior studies that reported normal adult body dimensions (in the absence of radiation treatment) in subjects treated for ALL in childhood.
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Plot of chronological age against GP2 bone age for a girl (pseudo-record #1035)
Acute Lymphoblastic Leukemia (ALL) constitutes 31 percent of all childhood malignancies and now represents the most common malignancy of childhood. ALL strikes children primarily between two and ten years of age. However, it may also attack adolescents and adults. Higher rates of ALL have been found among populations in North America, Northern and Western Europe, and Oceania, whereas lower rates have been seen in Asian and African populations. Though the cause of ALL is not known, several substances or entities have been implicated to include: ionizing radiation, the used of drugs and chemicals, as well as various viruses.

As cure rates for children with ALL approach 80 percent, this sample provides an excellent means by which to examine anti-neoplastic treatment influences on growth and development. Chemotherapy and radiation (of the head and neck, as well as the spine) are commonly utilized in the treatment of ALL.

As radiation and chemotherapeutic agents often fail to differentiate between metabolically active normal cells and neoplastic cells, a patient’s overall tempo of growth is often adversely affected. Growth and development describe
the changes an individual progresses through from conception until death.

Growth is defined as a change in physical size of the organism as a whole or any of its parts. Development is defined as a change in proportion and/or an increase in complexity. Development indicates not only a change in shape of the entire body, but also individual anatomical structures.

Sonis et al. (1990) noted that an altered hypothalamic-pituitary function may result in decreased growth hormone production. Hypopituitarism has been shown to follow high-dose irradiation of both intra- or extracranial tumors (Tan and Kunaratnam 1966; Shalet et al. 1975; Richards et al. 1976). Several studies related the prevalence of diminished stature in children with ALL. However, these studies failed to demonstrate a decrease in the overall tempo of growth. Kirk et al. (1987) reported high rates of only diminished stature in children treated for ALL, however overall growth retardation was not demonstrated. Conversely, Clayton et al. (1998) concluded that while chemotherapy did contribute significantly to diminished stature in children with ALL, mean loss in the majority of children was not high enough to substantiate GH replacement therapy.

Bones in the skeleton may be analyzed throughout an individual’s life—from birth, through skeletal maturation, finalized with the end of life (Greulich and Pyle 1959). Chronological age, or a person’s age in calendar years, serves as the standard by which most laypersons gauge maturity. However, this
measurement often does not adequately reflect a person’s biological maturity or development, particularly when considering those periods of infancy or childhood. The framework or connective tissues of the body serve as a standard applicable to general body development. Skeletal or biological age, also termed “developmental age” and “physiological age,” reflects the level of maturity achieved by the individual (Todd 1937). Average bone or skeletal ages, then, illustrate the maturation status in which normal children, male and female, match up with their corresponding calendar or chronological age (Jimenez-Castellanos et al. 1996).

Hand-wrist radiographs are commonly used in the assessment of biological age because the hand and wrist are reasonably accessible and those vital organs particularly at risk to radiation damage are not in close proximity. A hand-wrist bone age serves as the measure by which a child’s chronological age may be compared. The child’s developmental status may be shown as delayed, normal, or advanced. Hand-wrist radiographs serve as an excellent measure to determine the effects of anti-neoplastic therapy.

The present study analyzed the hand-wrist radiographs of 73 children treated at St. Jude Children’s Research Hospital in Memphis, Tennessee for ALL. The number of films per child was highly skewed, ranging from one to four per child. The focus of bone age analysis centered on determining whether the
tempo of growth was retarded based on treatment with chemotherapy and/or radiation.
CHAPTER II

REVIEW OF THE LITERATURE

Introduction

Acute Lymphocytic Leukemia (ALL)—also known as Acute Lymphatic, Acute Lymphoblastic, or Acute Lymphogenous Leukemia—now represents the most common malignancy of childhood, constituting 31 percent of all childhood malignancies (Niemeyer and Sallan 1998; Berg et al. 2000). Figure 1 is a bar chart of the most common types of cancer in children under 15 years of age, with their percentage of total cases (Mirro 2000). While ALL accounts for nearly 75 percent of all leukemias in children, it accounts for less than one percent of all adult malignancies (Perkins et al. 1997; Berg et al. 2000).

The earliest descriptions of leukemia in the clinical setting were made independently by Bennett in Scotland and Virchow in Germany; each published his discovery in 1845. Their observations were based on a number of autopsies of patients with "enlarged spleens and purulent-appearing blood" in which microscopic analysis revealed a marked increase of "colorless corpuscles." Bennett suggested that the etiology of the increased white blood cell counts was due to inflammation, while Virchow preferred the term "weisses Blut," or white blood, that was later rephrased in Greek as "leukemia" (Perkins et al. 1997). The foremost breakthrough in cellular identification of the leukemias took place in
Fig. 1. Classes of cancer in children under 15 years of age, expressed as the percentage of total cases.

1891, when Paul Ehrlich established differential methods of staining and further categorized neutrophilic, eosinophilic, and basophilic granulocytes (Bennett 1990).

ALL strikes children primarily between two and ten years of age, with the peak age between two and three years. However, it can also attack adolescents and adults, with a substantial increase around 65 years of age (Berg et al. 2000). Figure 2 depicts overall incidence statistics by race and sex (Pui 1999). A survey by the Surveillance, Epidemiology, and End Results Program (SEER) showed that the incidence of ALL in the United States increased from 2.7 to 3.3 cases per 100,000 children aged 0 to 14 years old during the years 1973 to 1995. Latinos represent the highest rates of ALL for both boys and girls in the United States (Pui 1999). Each year, around 2,000 to 2,500 new cases of ALL are diagnosed in the United States (Niemeyer and Sallan 1998).

Significant geographic differences exist with regard to the incidence of ALL. Higher rates of ALL have been found among populations in North America, Northern and Western Europe, and Oceania, whereas lower rates have been seen in Asian and African populations. The highest rates of ALL in European males have been reported for Spain, whereas the highest rates for European females have been reported for Denmark (Pui 1999).

The cause of ALL is not known, though several explanations for an overall cause of leukemia have been explored. Numerous environmental factors
Fig. 2. Age-specific incidences for ALL by race and sex.

have been examined, including ionizing radiation, the use of drugs and chemicals, as well as various viruses. The incidence of leukemia was shown to be elevated in persons exposed to nuclear weapons in Hiroshima and Nagasaki, thus confirming the association between ionizing radiation and leukemia. Several chemical substances, such as benzene, chloramphenicol, and phenylbutazone, have also been linked to the disease. Additionally, several debilitating viruses have shown associations with leukemia. These include a statistical linkage of the Epstein-Barr virus with African Burkitt’s lymphoma, the human T-cell leukemia-lymphoma virus I (HTLV-I) with adult T-cell leukemia-lymphoma (ATL), and the HTLV-II virus with atypical hairy-cell leukemia (Perkins et al. 1997).

The Composition of Blood

ALL primarily targets lymphocytes in the bloodstream. A vital organ that delivers hemoglobin, oxygen, and other essential nutrients, blood also transports chemicals and hormones to various cells throughout the body. Blood is comprised of a variety of proteins that aid in nutrition, bodily defense, and hormonal regulation. Whole blood is composed primarily of three elements in a clear protein-rich medium known as serum or plasma: red blood cells, platelets, and white blood cells. Red blood cells represent roughly 45 percent of whole blood, with plasma contributing an additional 55 percent, and white blood cells
and platelets making up slightly below one percent (Ball and Lelek 2003). Hematopoiesis, the process of blood cell formation and development, is distinguished by a steady turnover of cells and is carried out by stem cells in the bone marrow (e.g., Bell and Hughes 1997). Bone marrow is a sponge-like, fatty material found within the confines of most bones. Red bone marrow, the marrow responsible for the production of blood cells, is found predominantly in the pelvis, sternum, ribs, skull and vertebral bodies in adults—and more broadly in children (e.g., Ball and Lelek 2003).

Blood cells are derived from pluripotent stem cells found in bone marrow, and they possess the ability to differentiate into a single cell lineage. Figure 3 delineates this stem cell hierarchy. The clinical manifestations of leukemia would be expected to reflect the level at which the malignant transformation took place (Mauer 1990).

Red blood cells, or erythrocytes, have an average life span of 120 days. Morphologically, these cells are biconcave discs without nuclei. These cells contain hemoglobin, an iron-rich protein that transports oxygen from the lungs to tissues and organs throughout the body. The blood is also responsible for carbon dioxide transport and elimination. A deficiency of red blood cells, known as anemia, can result in fatigue and weakness, nausea, as well as an increased temperature and pale discoloration of the skin. Anemia may be induced by a number of biological events, including nutritional deficiency,
Fig. 3. A scheme for blood cell derivation, differentiation, and proliferation.

harmorrhage, increased hemolysis, bone marrow transplants, infection, heredity or an acquired deficit (e.g., Bell and Hughes 1997).

Platelets, which are proteins essential to the blood clotting process, are also formed in the marrow and are descendents of megakaryocytes. These cells have an approximate life span of 5 to 10 days. A deficiency of platelets can result in spontaneous bleeding with blood loss into tissues and organs of the body. Excessive bruising of the skin often is seen with platelet deficiencies (Ball and Lelek 2003).

White blood cells, or leukocytes, are involved primarily in the host defense against disease-producing bacteria and parasites. The three main types of leukocytes—monocytes, granulocytes, and lymphocytes—fulfill separate and unique roles in the defense process. Monocytes are highly efficient and effective at recognizing and digesting foreign bodies (or antigens), and may also aid in long-term defense through antigen presentation to T-lymphocytes. The fully differentiated monocyte is referred to as a macrophage (e.g., Ball and Lelek 2003).

Granulocytes comprise neutrophils, basophils, and eosinophils. Neutrophils constitute the vast majority of the granulocyte population and are skilled at identifying and destroying bacteria and other harmful substances. As neutrophils are crucial in the defense against bacterial and fungal infections, suppression or absence of these cells leaves the body open to injury from viruses, bacteria, or other harmful parasites. Basophils are responsible for the
release of histamine during inflammation, while eosinophils target parasites and aid in the ingestion of an antigen-antibody compound (e.g., Ball and Lelek 2003).

Lymphocytes defend the lymphatic system and blood. The lymphatic system is an extensive network of vessels interconnected with small masses of lymphatic tissue termed lymph nodes. Lymph nodes lie along the network of lymphatic vessels and cluster primarily in the pelvis, neck, abdomen, and underarm. The spleen, which is located in the upper abdomen, the thymus, which lies beneath the sternum, and the tonsils and adenoids, which reside in the posterior throat, are also components of the lymphatic system. Tissue fluid carried throughout the lymphatic system, or lymph, is typically clear and watery in appearance, with the same consistency of blood plasma. The main functions of the lymphatic system are: absorption and transport of fat from the intestine to the venous system; formation of a defense mechanism for the entire body; and drainage of tissue fluid; as well as collection and transport of lymph from the tissue spaces to the venous system (Moore and Dalley 1999).

Lymphocytes are the second most numerous cells in the blood, comprising 20 to 44 percent of adult blood cells. Lymphocytes develop from multipotent hematopoietic stem cells that possess the means to mature into a range of different kinds of blood cells. These stem cells develop in the bone marrow and then differentiate into fully functional white blood cells. The common lymphoid progenitor cell may progress into T lymphocytes (T cells) or
B lymphocytes (B cells). T cells mature in the thymus, while B cells develop in the bone marrow (e.g., Bell and Hughes 1997).

Lymphocytes attack infection primarily through the production of antibodies, which fight germs and other harmful bacteria present with an infection. Upon presentation of specific antigenic stimuli, lymphocytes may transform into immunologically competent cells. This transformation is marked by an increase in size, due to an increase in RNA in the cytoplasm or DNA in the nucleus (e.g., Bell and Hughes 1997).

Cancer most commonly involves anaplasia, or the loss of a normal pattern of the growth of cells. Anaplasia is characterized by an increased variability in the appearance of cells. Anaplastic growth is common to nearly all tumors, benign or malignant. Furthermore, the degree of anaplasia may be important establishing prognosis of a tumor (Steen 2000).

The exact cause of leukemia, while currently deemed idiopathic, may arise from certain genetic events occurring at particular stages of stem cell development. The type of leukemia may then be linked to the genetic event and stem cell from which the flaw derived (e.g., Ball and Lelek 2003).

**Four Major Types of Leukemia**

Four major forms of leukemia are recognized: acute lymphocytic, acute myelogenous, chronic lymphocytic, and chronic myelogenous. The term “acute”
refers to leukemias that have a rapid onset and are characterized by an increased number of young cells. In contrast, the term “chronic” denotes a slower progressing disease, involving more developed cancer cells. Acute leukemias are most often fatal, while chronic leukemias follow longer courses of development. Lymphocytic leukemia involves cells of lymphoid origin, while myelogenous leukemia involves cells of myeloid origin (Ball and Lelek 2003). A classification of leukemia subtypes is listed below (Mauer 1990).

I. Acute
   A. Lymphocytic
   B. Nonlymphocytic
II. Chronic
   A. Lymphocytic
   B. Myeloproliferative disorders
      1. Chronic myelocytic leukemia
      2. Polycythemia rubra vera
      3. Essential thrombocytopenia
III. Myelodisplastic syndromes
IV. Miscellaneous chronic leukemias
   A. Hairy cell leukoplakia
   B. Adult T-cell leukemia
   C. Sézary syndrome
   D. Tγ-cell leukemia

ALL may be separated into three groups dependently on the apparent size of the constituent lymphoblasts. L1 lymphoblasts are relatively small and exhibit uniform structure and size among abnormal lymphoblasts. L2 lymphoblasts are larger in size and exhibit more structural and size variation, termed “structural heterogeneity.” L3 lymphoblasts are the largest in size and contain large voids, termed vacuoles. The L3 subtype, referred to as “Burkitt’s
type” because of its morphological similarities to Burkitt’s lymphoma, carries the worst prognosis of all subtypes (Perkins et al. 1997).

The L1 subtype is prevalent in childhood ALL, occurring in roughly 85 percent of all cases. The L2 subtype is most common in older people, while the L3 subtype represents only 1 to 2 percent of all ALL cases. These three subtypes may be further divided based on relative B or T cell similarities, demonstrated through a process called phenotyping. B lymphocyte lineage subtypes, which account for approximately 85 percent of ALL cases, are noticed by isolating cell surface markers on the leukemic blasts that match those of normal B lymphocytes. T lymphocyte lineage subtypes, which account for approximately 15 percent of ALL cases, are noticed by isolating cell surface markers on the leukemic blasts that match those of normal T lymphocytes. Detailed analysis of an ALL case often identifies surface antigenic or molecular markers that may aid in identification or classification of the specific disease type (Berg et al. 2000).

**Acute Lymphoblastic Leukemia**

**Symptoms**

Patients with ALL usually present with symptoms coincident with bone marrow invasion and deterioration (Perkins et al. 1997). Most often, this spread of leukemic cells is uncontrolled and extramedullary. The most common sites of
extramedullary ALL involvement are the central nervous system, lymph nodes, testes, liver, kidney and spleen. The central nervous system (CNS) and the testes often carry the highest clinical implications (Berg et al. 2000). Inherent anemia, thrombocytopenia, and neutropenia, or the depletion of red blood cells, platelets, and white blood cells, respectively, often manifest in signs of weakness and debility. Bleeding problems often range from mild complications such as petechiae, bruising, and mucosal bleeding, to severe problems such as GI bleeding and CNS hemorrhage. Hepato-splenomegaly and lymphadenopathy may also be noticed and attributed to lymphoblast engorgement (Perkins et al. 1997). Oral manifestations of ALL include swollen and bleeding gums, as well as relative periodontal infections (Greene 2002). Approximately 40 percent of childhood leukemia patients exhibit bone and joint manifestations, such as pain or sensitivity. Numerous patients, as high as 25 percent, can present with fractures or osteopenia most commonly of the long bones. These changes or symptoms are usually seen in areas of accelerated growth and development, such as the knees, wrist, and ankles. Niemeyer and Sallan (1998:1255) stated these symptoms, “may be the result of direct leukemic infiltration of the periosteum, periosteal elevation of underlying cortical disease, bone infarction, or expansion of the marrow cavity by the leukemic cells.” Overall signs and symptoms depend on a range of factors including age of onset, duration of treatment, and subtype of ALL.
Prognosis

“Progress in the treatment of ALL has been incremental, beginning with the development of effective therapy for CNS disease, followed by intensification of early treatment” (Pui 1999:1141). Cure rates for children currently are near 80 percent, while rates for adults approximate 30 to 40 percent. These high cure rates demonstrate the obvious progress that has been made in the treatment of ALL (Pui 1999).

Treatment Strategies

The current high and improving survival rates of ALL and other forms of cancer are due in large part to research efforts and improved treatment strategies (Goho 1993). When considering the treatment course for a person with ALL, physicians examine a number of factors: the ALL subtype, the composition of previous treatments and its successes or failures, levels of leukemic cells in the blood, the presence or absence of chromosomal aberrations, as well as the patient’s age and overall health (Wells et al. 1983). Treatment modalities may consequently differ significantly from person to person.

Many options exist for the treatment of acute lymphocytic leukemia. These include chemotherapy, radiation, and bone marrow transplantation. Physicians may use one therapy or combine methods to treat particular cases of
Multimodal therapy “creates synergistic and additive effects” not normally gained from the utilization of one therapy only (Goho 1993).

Chemotherapy

Chemotherapy is the treatment currently chosen for most types of acute leukemias. The first reported use of a chemical as an anti-neoplastic agent came from experiments with nitrogen mustard in a person with Hodgkin’s disease in 1942. Six years later, the discovery of remission induction by antifolates in ALL introduced chemotherapy as an anti-cancer agent. These chemotherapeutic principles have led to curative therapies for the acute leukemias and lymphomas, successful treatments for the chronic leukemias and multiple myelomas, and have supplied the conceptual foundation for contemporary medical oncology (Chabner et al. 1999).

As the malignant process is distinguished by uncontrolled cell proliferation, it is understandable that chemotherapy should target DNA replication (Chabner et al. 1999). Chemotherapeutic agents strive to prevent cancer cells from invading, multiplying, metastasizing, and destroying the host (Skeel and Khleif 2003). The majorities of efficient cancer agents either generate chemical lesions in DNA or interfere with the synthesis of DNA. The ultimate means by which cancer drugs produce cell death is uncertain. Destructive mechanisms may range from apoptosis, or programmed cell death, to progression
of death following mitosis. “While most antimetabolites and alkylating agents target DNA, other drugs attack the mitotic spindle \textit{(vinca alkyloids)}, inhibit protein synthesis (L-asparaginase) or induce cell differentiation \textit{(all-trans-retinoic acid)}” (Chabner \textit{et al.} 1999:186).

Chemotherapeutic drugs may be given orally, intravenously, or directly into a muscle. These medicines are systemic, and they are able to move freely through the bloodstream and body. Chemotherapeutic drugs are occasionally injected into the spine to access cerebrospinal fluid in the brain and spinal cord; this therapy is termed \textit{intrathecal chemotherapy} \textit{(e.g.,} Mirro 2000\textit{)}.

The cell cycle of cancer cells is essentially that of normal cells. Figure 4 depicts not only the approximate time spent in each phase of the cycle, but also the main function of each period (Skeel and Khleif 2003).

Chemotherapeutic drugs that target DNA may be classified as either specific or nonspecific in reference to a phase of the cell cycle, and are ultimately dependent upon their interference with the mitotic cell cycle. Figure 5 depicts the dynamics of chemotherapeutic interferences within the cell cycle (Goho 1993). Specific agents disrupt DNA synthesis \textit{(S phase)} or cell division \textit{(M phase)} (Goho 1993). Early treatments should comprise multi-drug chemotherapeutic doses large enough to kill the majority of the leukemic cell population. Agents commonly used in therapies are vincristine, prednisone, doxorubicin, methotrexate, asparaginase, and intrathecal cytosine arabinoside
Fig. 4. Cell cycle times for normal human cell tissues.

Fig. 5. Cell cycle with chemotherapy-specific and radiation-specific sites of action.

(Berg et al. 2000). Table 1 lists various chemotherapeutic agents with their associated clinical complications (Rodman and Reed 2000).

Nonspecific agents target cells in all phases of the functioning cell cycle, with the exception of inactive cells in the $G_0$ phase. These drugs crosslink DNA bases to disrupt DNA replication. These agents include alkylators (busulfan, chlorombucil, cyclophosphamide, melphalan, and nitrogen mustard), nitrosureas (BCNU, CCNU), antibiotics (actinomycin D, doxorubicin), DTIC, and cisplatin.

Since tumor cells replicate asynchronously, they are not all in susceptible phases during the initial chemotherapy exposure. Chemotherapeutic agents are eliminated rapidly, and a single dose does not affect tumor cells entering a susceptible phase at a later time. Furthermore, chemotherapy works on first order kinetics, in which only a percentage of cells are killed with each dose, leaving some undamaged cells. Chemotherapeutic agents are therefore administered in multiple (fractionated) doses so that tumor cells unaffected by the first dose are destroyed by following doses [Goho 1993:7].

Figure 6 depicts the effects of multiple dose chemotherapy on cancer cell numbers (Skeel and Khleif 2003).

As it aims to destroy cancer cells, chemotherapy often affects those normal cells or bodily organs that are undergoing reproduction at accelerated rates. Mucosal linings, such as those of the mouth and intestines, as well as the skin, hair follicles and bone marrow, are often affected. The overall goal involves selecting a chemotherapeutic agent that produces marked destruction
Table 1. Chemotherapy side effects.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Early Complications</th>
<th>Late and/or Delayed Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-asparaginase</td>
<td>Nausea and vomiting, allergic reactions (such as rashes or difficulty in breathing), temporary diabetes, change in mental status</td>
<td>Unknown</td>
</tr>
<tr>
<td>busulfan</td>
<td>Low blood counts; nausea, vomiting, and diarrhea</td>
<td>Loss of normal menstrual function; increased skin pigmentation, lung damage</td>
</tr>
<tr>
<td>carboplatin</td>
<td>Tiredness; low blood counts</td>
<td>Hearing problems; kidney damage</td>
</tr>
<tr>
<td>cisplatin</td>
<td>Hearing loss; nausea, vomiting, diarrhea; vein and tissue damage if drug leaks from vein</td>
<td>Hearing problems; kidney damage</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Nausea and vomiting; bladder damage; low blood counts; fluid retention; hair loss</td>
<td>Bladder cancer or secondary leukemia (rare); decreased fertility</td>
</tr>
<tr>
<td>cytarabine</td>
<td>Nausea and vomiting; mouth sores; low blood counts; fever; skin rashes; irritated eyes; seizures; diarrhea or liver damage (from high-doses)</td>
<td>Decreased fertility</td>
</tr>
<tr>
<td>daunorubicin, idarubicin, doxorubicin, epirubicin</td>
<td>Nausea and vomiting; hair loss; mouth sores; low blood counts resulting in anemia, bleeding or higher risk of infection; red-colored urine (not blood); skin burn if drug leaks out of vein; hair loss</td>
<td>Heart failure, skin or tendon deformities; pigmentation; secondary cancer</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Early Complications</td>
<td>Late and/or Delayed Complications</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>etoposide, teniposide</td>
<td>Nausea and vomiting; hair loss; mouth sores; low blood counts; allergic reactions</td>
<td>Secondary leukemia (uncommon)</td>
</tr>
<tr>
<td></td>
<td>(wheezing, difficulty in breathing, skin rashes swelling of lip); low blood pressure</td>
<td></td>
</tr>
<tr>
<td>hydroxyurea</td>
<td>Drowsiness; low blood counts; increased pigmentation; hair loss</td>
<td>Secondary cancer</td>
</tr>
<tr>
<td>ifosfamide</td>
<td>Hair loss; nausea and vomiting; bladder damage with bleeding; vein irritation; low</td>
<td>Increased skin color; kidney damage</td>
</tr>
<tr>
<td></td>
<td>blood counts; confusion, hallucinations</td>
<td></td>
</tr>
<tr>
<td>mercaptopurine</td>
<td>Nausea and vomiting; low blood counts; mouth sores; skin rashes; liver damage</td>
<td>Unknown</td>
</tr>
<tr>
<td>methotrexate</td>
<td>Nausea and vomiting; low blood counts; mouth sores; skin rashes</td>
<td>Seizures, intellectual impairment; kidney damage (from</td>
</tr>
<tr>
<td></td>
<td></td>
<td>high-dose treatment); liver damage</td>
</tr>
<tr>
<td>prednisone, prednisolone, dexamethasone</td>
<td>Temporary diabetes, high blood pressure, changes in mood or behavior, acne; increased appetite; weight gain; peptic ulcer; muscle weakness</td>
<td>Decreased growth; decreased bone density; joint destruction</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Early Complications</td>
<td>Late and/or Delayed Complications</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>thioguanine</td>
<td>Low blood counts; liver damage</td>
<td>Loss of normal menstrual function</td>
</tr>
<tr>
<td>thiotepa</td>
<td>Pain at injection site; low blood counts;</td>
<td>Secondary leukemia</td>
</tr>
<tr>
<td></td>
<td>dizziness; fever; hair loss</td>
<td></td>
</tr>
<tr>
<td>topotecan,</td>
<td>Diarrhea; low blood counts</td>
<td>Unknown</td>
</tr>
<tr>
<td>irinotecan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vincristine,</td>
<td>Constipation; weakness; numbness or</td>
<td>Skin or tendon deformities</td>
</tr>
<tr>
<td>vinblastine</td>
<td>loss of reflexes; skin burn if drug leaks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>out of vein; seizures; hair loss</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6. Effects of progressive bouts of chemotherapy on the number of cancer cells. Ideally, chemotherapy kills a constant proportion of the remaining cancer cells with each dose.

of cancer cells, while providing minimal damage to normal cells (e.g., Skeel and Khleif 2003).

Side effects of chemotherapeutic therapy range in severity among patients with ALL. As healthy marrow cells are destroyed along with tumor cells, various bleeding problems associated with diminished platelet counts, as well as anemia and infection may ensue. Therapeutic action on the intestines and their linings often induce nausea and vomiting as common side effects of ALL. Other symptoms of chemotherapy may include anaphylaxis, stomatitis as well as other oral complications, xerostomia, hair loss (alopecia), diarrhea, constipation, and/or an altered nutritional status due to a direct insult on the gastrointestinal tract (Tipton 2003).

Of particular importance to the dental profession are the symptoms of chemotherapy specific to the oral environment. Many of the drugs used in cancer therapies are cytotoxic to the oral mucosa, interfering specifically with the replication, growth, and maturation of epithelial cells. These toxic effects are expressed clinically by reduction, denudation, and ulceration of the mucosa surface. Immunosuppressive actions of chemotherapeutic agents cause the host to be particularly susceptible to bacterial, fungal, viral, and mixed infections. Myelosuppressive actions of these agents can trigger neutropenia and lymphocytopenia, or severe decreases in blood neutrophils and lymphocytes. The most common sites of oral infections are the lips and tongue, followed by
the buccal mucosa, gingiva, palate, oropharynx, and occasionally the major salivary glands (Dreizen and Brown 1983).

Radiation

Among the oldest and most efficient of cancer treatments, radiation therapy was recognized over a century ago for its ability to destroy both cancerous and healthy tissues (Merchant 2000). Radiation therapy targets cancer cells while trying to avoid damaging normal tissues or organs (e.g., Goho 1993). However, cells and structures lying within the radiation beam can be injured as well. While affecting rapidly dividing cancer cells more than normal cells, radiation therapy often also damages rapidly dividing healthy cells. Skin and hair are the tissues most noticeably affected by radiation treatment, which can also result in skin lesions, burning, redness, and possible hair loss (Greene 2002). Dentofacially, radiation can affect bone growth, including “microvascular injury, fibrous replacement of marrow spaces, osteocyte death, and periosteal damage” (Kaste et al. 1994:95).

Radiation may originate from either an internal or external source: external radiation produces deep penetrating gamma and X-ray photons, while internal radioisotopes generate gamma and X-ray photons and beta particles. These beta particles impair DNA and amino acids either directly by ionizing
critical structural molecules or indirectly by first ionizing intracellular water
used by the cells for vital processes (Goho 1993).

The ultimate effect of radiation therapy on an active tumor cell depends
on its position in the cell cycle during therapy. Cancer cells in the M, G$_1$, and G$_2$
phases of the cell cycle are actively involved in mitosis and often sustain the
most damage from radiation. All cancer cells, even those in the G$_0$ resting phase,
may be affected by high doses of radiation. Figure 5 depicts the effects of
radiation, as well as chemotherapy reviewed above, on cells at various stages of
the cell cycle (Goho 1993).

Radiation treatment also may be used to decrease tumor size, provide
palliative therapy, or treat inoperable malignancies. Therapy may be
multimodal, through a combination of substances or involve a single agent.
Commonly used radioactive agents include, but are not limited to: Cesium
(Cs$^{137}$), Cobalt (Co$^{60}$), Iodine (I$^{131}$), Phosphorus (P$^{32}$), Gold (Au$^{198}$), Iridium (Ir$^{192}$),
Yttrium (Y$^{90}$), and Palladium (Pa$^{109}$) (Howard 2002).

Effects of radiation therapy vary immensely, but depend on the area of
the body being irradiated as well as the schedule and dose of therapy. Side
effects may be either short-term, occurring within the first 90 days after
treatment initiation, or long-term, occurring after the initial 90 days. Short-term
effects may include tissue destruction similar to a burn, discoloration of the skin,
and/or weakness. Long-term effects may include tissue atrophy, scarring,
impaired growth, as well as cancers secondary to initial diagnosis (Merchant 2000).

Bone Marrow Transplantation

Bone marrow transplantation (BMT), a newer type of therapy, can be used in conjunction with chemotherapy to enhance eradication of cancer cells. BMT therapy begins with considerable doses of chemotherapeutic agents (with or without radiation) to eliminate the bone marrow in the patient’s body. Healthy stem cells are then provided by a donor (allogeneic BMT) or harvested from the patient’s own marrow (autologous BMT). A third type of transplant, a syngeneic BMT, involves an identical twin as a donor. The healthy marrow is then supplied to the patient intravenously, with the new marrow intended to replace the diseased marrow (Horwitz 2000).

Significant research is being devoted to the newer forms of BMTs, namely autologous transplants. After being removed from the patient’s body, the diseased marrow is treated with chemotherapeutic agents aimed at destroying cancer cells. The treated marrow is then frozen to ensure preservation. The patient then undergoes chemotherapy to kill all remaining cancer cells not removed in the marrow harvest. The bone marrow transplant is concluded with the treated marrow intravenously placed back into the patient (Horwitz 2000).
Progression of Treatment

Treatment for ALL, though largely dependent on the mode of therapy, age of onset, and subtype of the disease, often progresses through four main phases: (1) Remission induction therapy, the initial phase, uses chemotherapeutic agents to destroy a maximum number of leukemic cells while minimizing the “residual leukemic burden” (total number of leukemic cells in the body). (2) Consolidation or intensification therapy, the second phase, is used once the patient exhibits no sign of cancer and is in remission. This phase consists of large doses of chemotherapy to destroy remaining cancer cells. (3) Central nervous system (CNS) prophylaxis, the third phase, is often combined with consolidation-intensification therapy. This phase involves high dose therapy to both eliminate cancer cells in the CNS and prevent their spread to the spinal cord or brain. Radiation therapy may or may not be used. (4) Maintenance therapy, the fourth and final phase, spans the course of several years and exists solely to preserve remission of the disease (Silverman et al. 1995).
Treatment Effects on the Human Body

Effects on the Dentition and Oral Mucosa

Multimodal cancer therapy for pediatric head and neck tumors may be associated with significant developmental orofacial abnormalities (Berkowitz et al. 1989). Aggressive anti-neoplastic therapies, specifically chemotherapy and radiation often present significant detriment to the health and quality of life of long-term survivors of ALL (e.g., Kaste et al. 1997). As cure rates continue to rise, dentofacial complications from various therapies become increasingly relevant (Goho 1993).

The dental sequelae in patients treated for ALL are not surprising, because permanent teeth are undergoing active development during childhood, which is the time of peak incidence of ALL. Human dentitions, both primary and secondary, begin their development early in life (e.g., Arey 1965; Corliss 1976). The primary dentition commences at approximately 6 weeks of gestation and maintains growth through three years of age, at which point the roots have completely formed (Kraus and Jordan 1965; Lunt and Law 1974). The permanent dentition reaches its peak growth between the ages of four and six.

Illness, trauma, chemotherapy, and radiation therapy may each affect dental development at any point prior to complete maturation. The timing of the insult within the process of dental development is important. An
understanding of these dentofacial changes and exploration of their causes is essential so that suitable diagnosis and treatment, as well as future prophylaxis may be well planned. Still, because several therapies and agents are employed in a single patient’s treatment, the task of attributing a single dental abnormality to one specific agent or therapy is often impossible (Goho 1993).

Sonis et al. (1990) stated that current ALL treatments in children often produced developmental disturbances of the craniofacial skeleton and permanent dentition. The severity and degree of these disruptions depended on the child’s age at onset of ALL, dose of cranial radiation, and central nervous system treatment. Children receiving treatment prior to five years of age had the most severe dental defects, indicating that developing, immature teeth might be at an increased risk for developmental disturbances compared to mature teeth (Sonis et al. 1990).

Kaste et al. (1997) reported increased frequencies of hypodontia, microdontia, overretention of primary teeth, rampant decay, root stunting and taurodontism among the effects of ALL treatment. Additionally, Goho (1993) confirmed chemoradiation’s connection to congenital tooth agenesis, precocious apical closure, and coronal hypocalcification, in addition to microdontia and root shortening.

Kaste et al. (1997) evaluated the panoramic radiographs and clinical records of 423 ALL survivors to quantify the incidence, distribution, and
potential predisposing factors for dental abnormalities due to treatment for ALL. The following abnormalities were recorded during systematic examination of the panoramic radiographs: root stunting, microdontia, hypodontia, taurodontia, and over-retention of the primary teeth.

Hypodontia, or the incomplete development of a full complement of 32 permanent teeth, was noted in some children in a study by Kaste et al. (1997). Microdontia, the development of abnormally small teeth, occurred in about 20 percent of this sample. While fairly rare in the general population, microdontia of maxillary lateral incisors and of third molars occurred in nearly five percent of the ALL sample. Kaste et al. (1997:795) stated:

Hypodontia and microdontia can cause abnormal spacing and drifting of teeth, potentially resulting in poor dental alignment, malocclusion, and dysfunction of the temporomandibular joint. In addition, hypodontia or root stunting preclude adequate orthodontic anchorage and place these teeth at added risk for the damaging effects of gingival and periodontal disease.

Over-retention of primary teeth, the failure to shed primary teeth in a timely manner, occurred in roughly four percent of the sample. Over-retention of primary teeth involves not only the problem of retaining a primary tooth, but also the delayed eruption of the succedaneous tooth. Though controversial whether over-retention is due to chemoradiation, this abnormality is often associated with the following systemic conditions: Down syndrome, hypopituitarism, and hypothyroidism (Kaste et al. 1997). Goho (1993) reviewed
the overall effects of chemotherapy and radiation treatments and stated that any factor (or treatment modality) affecting dental development might also influence the relative progression of the ensuing teeth.

Extensive carious lesions present as frequent dental anomalies in children treated for cancer. Kaste et al. (1998) evaluated a retrospective sample treated for neuroblastoma, and noted that many of these patients had inadequate oral hygiene habits and increased carbohydrate intakes. Kaste et al. (1998:24) stated:

Dietary factors and parent permissiveness may also contribute to the increased dental caries in pediatric oncology patients. Frequently these children develop stomatitis and oral mucosal ulcerations. They may prefer sweet foods, thereby further promoting tooth decay. Medically compromised patients often require high carbohydrate diets in order to maintain caloric intake.

Extremely ill patients may not feel well enough to concentrate on their oral health. Additionally, young children depend on their parents for oral hygiene maintenance. Oral health and prophylactic care should be a chief priority when addressing treatment concerns for oncology patients (Kaste et al. 1998). It is necessary to have a comprehensive understanding of the patient’s medical status as well as any plans for cancer treatment.

Root stunting, though rare in the general population, occurred in nearly 25 percent of the same sample evaluated by Kaste et al. (1997). The most frequently affected teeth, the molars, were supposed to most frequently sustain damage because of their developmental status at the early age of treatment. As
the roots of the permanent molars had not developed fully before treatment was initiated, they were more frequently and severely affected by oncotherapy. In contrast, development of the permanent incisors, premolars, canines, and crowns of molars was nearly complete by the time treatment begun in most patients (Kaste *et al*. 1997).

Taurodontism, the presence of noticeably wider and lengthened pulp chambers, can occur in either the primary or permanent dentitions (Pindborg 1970). This anomaly is most often attributed to a “delay in the development and proper positioning of Hertwig’s epithelial root sheath after formation of the tooth crown resulting in the apical displacement of the pulpal floor and furcation areas” (Llamas and Jimenez-Planas 1993). Llamas and Jimenez-Planas (1993) suggest that genetic factors might affect the timely development of Hertwig’s root sheath in cases of nontreatment-related taurodontism. Commonly found in only one to 11 percent of the general population, taurodontism was identified in approximately 17 percent of the study. Within the sample exhibiting taurodontism, 98 percent were under the age of eight years old leading the researchers to speculate that cancer therapy in young patients might promote taurodontism. Clinically, teeth exhibiting taurodontism have markedly decreased root surface, are more susceptible to periodontal disease, and are less agreeable to orthodontic treatment (Kaste *et al*. 1997).
Root agenesis, or early apical closure, may be attributed to radiation therapy. While it represents a form of systemic therapy, chemotherapy would not simply affect one tooth class; instead, it would affect whichever teeth are undergoing crown-root formation. Goho (1993) reported a patient in whom early apical closure of the roots of the first and second molars correlated with root development at 4.0 to 4.5 years old, the age at which the child began anti-neoplastic therapy.

Effects of Radiation on the Head and Neck

The processes of enamel formation, \textit{amelogenesis}, and the process of dentin formation, \textit{dentinogenesis}, are affected by radiation directed at or near the mouth. Orofacial structures, including the teeth and mucosa, receive approximately half the radiation when located near the exposure, while radiation directed at distant structures provides no damage to the developing dentition (Goho 1993). Figure 7 depicts radiation therapy fields commonly used in the treatment of head and neck cancers (Berkowitz \textit{et al}. 1989). In the past, when dentofacial damage was anticipated, physicians commonly provided bilateral radiation to balance facial skeletal growth disturbances and preclude hemifacial hypoplasias (Goho 1993). Nwoku and Koch (1995) suggest that while the skin and mucosa are sensitive to radiation, both show extensive regenerative power, which probably explains why bone seems to suffer more injury than the epidermis.
Fig. 7. Common radiation fields used in the treatment of cancers of the head.

Overall damage depends on the dose delivered, regardless of the therapeutic means employed. Sonis et al. (1990) mentioned doses of 2,000 to 4,000 cGy in both animals and humans have been shown to induce tooth and root “dwarfism,” root foreshortening, hypoplasia, microdontia, and atypical root morphology. Prior to morphodifferentiation and mineralization, radiation treatments may result in arrest of the developing dental tissues. Equally, at later stages of development, dental malformations or arrested development have been observed (Sonis et al. 1990). Low doses of radiation may cause little or no damage to developing ameloblasts and odontoblasts, while high doses induce rapid cell death. Radiation affects cells in all stages of the cell cycle, whether proliferating or not. Dental development in humans has been revealed to sustain localized damage at 400R. However, the dose at which odontogenic cell death occurs unequivocally is still unknown (Goho 1993).

Effects of Chemotherapy on the Head and Neck

Chemotherapeutic effects depend on both the dose and the repetition of drugs. While radiation therapy affects cells in all stages of the cell cycle, chemotherapy only impacts actively dividing cells. Additionally, while radiation therapy damages only those cells in its path, chemotherapy is more extensive in its effects. Chemotherapy not only harms cells near or inside a tumor, it also affects cells and organs located far from the desired sites. The
following results of chemotherapeutic treatments have been documented: enamel defects, obstructed root development, and reduced dentin formation. Goho (1993) stated that eruption rates have shown no detrimental effects from chemotherapy.

Chemotherapeutic agents exhibit short half-lives and are eliminated quickly from the bloodstream. Consequently, effects on odontoblastic cells can be fatal, but are most often merely harmful (Goho 1993).

Endocrinologic Complications

As radiation and chemotherapeutic agents often fail to differentiate between metabolically active cells and neoplastic cells, numerous dental and craniofacial abnormalities have resulted from such anti-neoplastic treatments. However, Sonis et al. (1990) noted that an altered hypothalamic-pituitary function may result in decreased growth hormone production. Consequently, odontogenesis and craniofacial development might be adversely affected (Sonis et al. 1990).

When considering acute lymphoblastic leukemia, factors commonly affecting growth may include chemotherapy, irradiation, infection, poor nutrition, or the actual disease itself. “Cranial irradiation, leading to growth hormone (GH) deficiency, has been implicated as the main etiological agent in growth retardation following the treatment of brain tumors” (Clayton et al.
1988:460). Previous growth studies of ALL indicated that GH replacement therapy to be needed only when chemotherapeutic dose levels exceeded 2,400-2,500 cGy (Clayton et al. 1998).

Hypopituitarism has been shown to follow high-dose irradiation of both intra- or extracranial tumors (Tan and Kunaratnam 1966; Shalet et al. 1975; Richards et al. 1976). Smaller doses of cranial irradiation are often used in ALL, with hopes that these children sustain no considerable effects to the hypothalamic-pituitary axis. However, Schiliro et al. (1976) and Shalet et al. (1976) reported that these children may be at an increased risk of growth hormone (GH) deficiency, with their ultimate response in proportion to the “dose and fractionation of the irradiation” (Swinft et al. 1978:890). Additionally, Shalet et al. (1976) reported there may possibly be a progressive drop in GH response with increasing time after cranial irradiation. Interestingly, Kirk et al. (1987) noted that “idiopathic” GH deficiencies occur more commonly in males, so perhaps the male hypothalamus is more vulnerable to other abnormalities of GH regulation (1987:192). Lawrence et al. (1971:893) stated,

The site of radiation damage to the hypothalamic-pituitary axis is unknown. The pituitary is generally considered to be relatively radioresistant, probably because histological pituitary cell necrosis is rarely seen after irradiation. Radiotherapy may however alter pituitary cell function, increase permeability of the blood-brain barrier to potentially encephalotoxic drugs or damage the vasculoglial tissues of the hypothalamic-pituitary axis affecting the synthesis and release of hypothalamic releasing hormones.
Kirk et al. (1987) reported high rates of only diminished stature in children treated for ALL, however overall growth retardation was not demonstrated. Stature had decreased by more than one standard deviation in 32 percent of survivors at 4 years post-diagnosis and in 71 percent at 6 years post-diagnosis. Standard deviation scores were constructed as deviation measurements from the population mean. Kirk et al. (1987) also mentioned growth of younger children and those children especially tall for their age at diagnosis were more susceptible to reductions in overall stature.

Clayton et al. (1998) also evaluated changes in stature. 82 children treated for ALL were evaluated who achieved complete and continuous first remission following cessation of treatment. Forty-eight children received prophylactic cranial irradiation at a total dose of 1,800 cGy and 38 children received a dose of over 2,000 cGy. Chemotherapy spanned two to three years, with both groups of children showing a comparable decrease in height standard deviation. The greatest decrease in height occurred within the first year of diagnosis, whereas, height standard deviation scores of both groups increased significantly upon the completion of treatment. Clayton et al. (1998) concluded that while chemotherapy did contribute significantly to diminished stature in children with ALL, mean loss in the majority of children was not high enough to substantiate GH replacement therapy.
Swinft et al. (1978) noted the importance of a regular review of not only the neoplastic condition, but also detailed surveillance of growth and development. Endocrine investigation is essential only if growth and development are cause for concern.

Clinical Effects and Prophylactic Care

Orthodontic tooth movement, prosthetic replacement of missing teeth, periodontal health, endodontic procedures, and prophylactic home care may be compromised after therapies in children treated for ALL. The achievement of optimal dental health is increased if the clinician is mindful of dental development at the time of treatment as well as the type and quantity of treatment delivered (Goho 1993).

A panoramic radiograph, at minimum, should be obtained prior the beginning anti-neoplastic treatments. This radiograph enables clinicians to locate potentially vulnerable dental structures and establish a baseline of oral health specific to that patient. An additional panoramic radiograph should be obtained at the conclusion of treatment. This radiograph details damage to dental structures, allows for quantification of its severity, as well as aiding in an overall treatment approach to restore dental health (Goho 1993).

The prognosis for the correction of craniofacial abnormalities caused by anti-neoplastic therapies is guarded. Clinicians are often unable to formulate an
ideal treatment plan for these patients. Quite often then, treatment is compromised at the beginning. Sonis et al. (1990:2651) reported problems specific to mandibular growth potential:

Moreover, mandibular growth remains retarded, leaving patients with a skeletal disharmony between the two jaws. Conventional orthodontic correction of these problems often relies upon mandibular growth, although an attempt is made to retard maxillary growth therapeutically, allowing the mandible to “catch up” to the maxilla. Because the mandibles of our patients lacked intrinsic growth potential, correction may only be achieved with orthognathic surgery.

Human Growth and Development

Growth and development describe the changes an individual progresses through from conception until death. Growth is defined as a change in physical size of the organism as a whole or any of its parts. Examples of such growth may be an increase in height, an increase in weight, or an increase in arch circumference. Growth is not necessarily an increase, but may denote a decrease in size such as formation of the digits of the hand through selective cell death (apoptosis). When considering neoplastic conditions such as ALL, “growth is a sensitive measure of a child’s health and would thus be assumed to be affected in these children for multiple reasons: severe disease, irradiation of the skull, cytostatic treatment and perhaps poor nutrition” (Berglund et al. 1985:530).

Development is defined as a change in proportion and/or an increase in complexity. One such example includes the progression of fine motor skills and
dexterity throughout life. Development indicates not only a change in shape of
the entire body, but also individual anatomical structures.

Growth of the postnatal individual may be divided into four major
intervals: infancy, childhood, adolescence, and adulthood. Each interval is
distinguished by its own characteristic rate of growth. Figure 8 depicts velocity
of growth for these four intervals of growth (Tanner 1962).

Scammon’s Growth Curves

Richard Scammon (1927) described four main patterns of postnatal
growth. These four patterns, known as the “Scammon Curves” and
diagrammed in Figure 9, are: general (or somatic), neural, lymphoid, and
genital. These curves assume birth as the starting point (= 0%) and 20 years of
age as “maximal adult dimensions and size” (= 100%).

The general or “somatic” pattern of growth represents growth of the body
as a whole and encompasses such measurements as height, weight, *et cetera*.
This pattern has been divided into four parts: (1) a period of rapid growth in
infancy at 0 to 5 years of age; (2) fairly uniform increments during early and
middle childhood at 5 to 11 years of age; (3) a rapid parapubertal increase at 11
to 16 years of age; and (4) a final period of slower growth during late
adolescence and early childhood at 16 to about 35 years of age.
Fig. 8. Human growth velocity chart for somatic tissues partitioned into the four major intervals of postnatal growth. (Drawing provided by Dr. E. F. Harris.)
Fig. 9. Scammon’s four tissue-specific patterns of postnatal growth. The scheme is that size is standardized to 0% of adult size at birth and 100% of adult size occurs by 20 years of age. (Drawing provided by Dr. E. F. Harris.)
Tissues reflecting the neural pattern of growth include the brain and associated structures (cerebellum, pons, and medulla), the eyeball and the pineal gland. The two parts of the neural growth curve are: (1) a period of rapid growth subsequent to birth at 0 to 5 years of age; (2) a period of slow growth leading into maturity from age 6 forward. The human brain has achieved approximately 95 percent of its growth by age 7 or 8.

The lymphoid pattern of growth involves the weights of the thymus, adenoids, tonsils, mesenteric lymph nodes, as well as the number of Peyer’s patches in the small intestine and lymphoid follicles in the appendix. The three parts of the lymphoid curve are: (1) a rise of greater velocity in infancy and early childhood to an apex at puberty at 0 to 11 years of age; (2) a decrease in size from late childhood to adulthood at 12 to 20 years of age; and (3) maintenance of small size during adulthood commencing at age 20. Quite commonly the second phase fails to occur; that is, lymphoid tissues such as the adenoids and tonsils do not decrease adequately in size. This failure often presents problems for orthodontists and pediatric dentists, as these children may develop habits of mouth breathing which may adversely affect the dentition and related skeletal structures.

The genital pattern of growth encompasses the testis, ovary, epididymus, uterine tube, prostate, and seminal vesicles. The three parts of the this curve are: (1) a slow rise in infancy followed by a latent period at 0 to 13 years of age; (2) a
rapid increase from the prepubertal period, through adolescence into early maturity at 13 to 20 years of age; and (3) an extended period of maintenance throughout adulthood beginning at age 20. The rapid rise in the genital curve represents the increase various sex hormones which produce “sexual maturity” in both males and females.

Intervals of Human Growth

The many diverse tissues and structures of the human body have extremely different patterns of growth, as is illustrated by Scammon’s four growth patterns. Cells of organs, as well as the organ as a whole, are highly dependent on their environment for nutrient supply and removal. Organs may appear particularly vulnerable during stages of increased or important growth, such as rapid cell proliferation. These times of greatest vulnerability are termed critical periods. Critical periods are those times in a tissue’s life during which the opportunity for irreversible damage are greatest (Smith 1977).

The development of a particular organ or structure progresses through four distinct stages depicted in Figure 10. This figure is representative of total DNA and total protein content throughout life. These stages are: (a) hyperplasia, (b) a mixed period of hyperplasia (multiplicative growth) and hypertrophy (dimensional growth), (c) hypertrophy, and (d) maturity and aging. The most critical period of growth corresponds with the hyperplastic phase, in
Fig. 10. Stages of development in the growth and differentiation of an organ tissue. (Figure provided by Dr. E.F. Harris.)
which cells are mostly rapidly proliferating. The interval of hyperplasia and hypertrophy represents a “sub-critical” period.

As Scammon’s growth curves illustrate, the various different tissues and organs of the body develop and mature at various rates. Thus, these different structures possess separate critical periods and periods of maximum vulnerability. Figure 11 depicts the critical period for several major organs of the body.

**Physiologic Age Assessments**

Bones in the skeleton may be analyzed throughout an individual’s life—from birth, through skeletal maturation, finalized with the end of life (Greulich and Pyle 1959). “Maturational status can have considerable impact on diagnosis, treatment goals, treatment planning, and the eventual outcome of orthodontic treatment” (Moore et al. 1990:33). *Chronological age*, or a person’s age in calendar years, serves as the standard by which most laypersons gauge maturity. However, this measurement often does not adequately reflect a person’s biological maturity or developmental status, particularly when considering those periods of infancy or childhood. The majority of children may be seen as “average maturers,” with a strong association between their chronological and biological ages. Some children, however, may appear developmentally delayed, and these are termed “late maturers.” Conversely, “early maturers” is the term
Fig. 11. Critical periods for major organs and tissue systems. (Figure provided by Dr. E.F. Harris.)
that describes those children whose developmental growth precedes their chronological age (Tanner 1962).

The framework or connective tissues of the body serve as a standard applicable to general bodily development. The skeleton has been chosen in the past merely because radiographic technique provides “a ready, easily applicable and noninjurious method of determination. Skeletal age thus becomes a measure of bodily maturation and not a goal in itself” (Todd 1937:13). Skeletal or biological age, also termed “developmental age” and “physiological age,” reflects the level of maturity achieved by the individual. While a number of methods exist by which biological age may be assessed, two provide particular information to the dental profession. These methods are a “bone age” evaluation based on hand-wrist radiographic analysis and a “dental age” based on formation of the crowns and roots of developing teeth as seen radiographically (e.g., Demirjian 1978).

Average bone or skeletal ages illustrate the maturation status in which normal children, male and female, match up with their corresponding calendar or chronological age (Jimenez-Castellanos et al. 1996). Similar to the growth of organs in the human body, bones of the skeleton progress through their morphological development at different points in time. In the child, new (secondary) ossification centers appear over a span of time, and existing ones are
remodeled. Knowing initiation times and morphological changes of bones in the hand and wrist provide a means of relating skeletal age to chronological age.

The following excerpt was taken from Greulich and Pyle’s text, *Radiographic Atlas of Skeletal Development of the Hand and Wrist*:

The development of individual bones of the hand and wrist as well as those of other regions can be impaired by febrile and other illnesses and they seem to be especially vulnerable to such deleterious influences at certain stages of their differentiation. A hand-wrist film made of such a child before the affected ossification center or centers have made up their developmental deficiencies reveals the skeletal imbalance that the illness has produced. The hand-film can provide a record of past illnesses and a measure of the severity of their impact on the developing skeleton, a reflection of their impact on the total organism. Knowing the rate at which these skeletal deficiencies are corrected, as determined by subsequent X-ray examinations, is helpful in appraising the child’s progress toward complete recovery [Greulich and Pyle 1959:18].

Hand-wrist radiographs are commonly used in the assessment of biological age because (1) the hand and wrist are reasonably accessible, (2) those vital organs particularly at risk to radiation damage are not in close proximity, (3) there are several bones (19 diaphyseal bones, 8 carpals, plus the distal radius and ulna) by which developmental maturity may be measured. Technique involves placing the hand directly on an X-ray cassette, with fingers spread slightly apart. Source-to-film distance should be at least five feet. Figure 12 depicts the bones of the hand-wrist complex.
Fig. 12. Schematic of the hand-wrist bones as visualized on a dorsoventral radiograph. (Diagram provided by Dr. E. F. Harris.)
Development of Hand-Wrist Standards

Sydney Rowland was the first to mention use of hand-wrist radiographs in children (cited in Pyle et al. 1971). Rowland used radiographs to formulate indicators of skeletal maturity and published his description of the “shadows of the hand bones of a nine year old girl” on April 2, 1896. Just four months earlier, in late 1895, the scientific community had been introduced to the discovery of X-rays by the physicist Wilhelm C. Röentgen (Pyle et al. 1971).

A total of 29 bones exist in the hand-wrist complex by which a physiological age assessment may be made. Nineteen phalanges are present in the hand, three in each of the four fingers (proximal, middle, and distal), while only two exist in the thumb (proximal and distal). Each ray has one metacarpal, while the wrist has eight carpals. Each diaphysis has a corresponding epiphysis on the distal end of each metacarpal and the proximal end of each phalange. Thus, 21 epiphyses plus 8 carpals lends a total of 29 bones available for evaluation in a hand-wrist film.

In 1929, under the direction of T. Wingate Todd of Case Western Reserve University School of Medicine, the Brush Foundation began work on preliminary human growth and development studies. When the study began, there were no provisional standards by which to compare measurements. The project commenced in 1931, with three-month-old infants enrolled in the
study, and concluded in the summer of 1942. The children, ranged in age from three months to fourteen years (Greulich and Pyle 1959).

The children accepted for study were selected on the basis of their freedom from gross physical or mental defects on the promise of their parents to permit their continued participation until the completion of the project. Since, in addition, they were admitted only on application of a pediatrician, their families were somewhat above average in economic and educational status. All the children were White, all had been born in the United States, and almost all were of North European ancestry [Greulich and Pyle 1959:xii].

Children in the study were observed at three-month intervals during their first year after birth, at six-month intervals from twelve months to five years of age, and once a year thereafter. The series, published by Todd in 1937 as his *Atlas of Skeletal Maturation of the Hand*, included from two to twenty-one hand-wrist films made at consecutive examinations of each of 1,000 children. While it included information gathered from children in the Brush study, Todd also incorporated films that he and his associates had made of other children from various agencies and schools throughout the Cleveland, Ohio area (Greulich and Pyle 1959).

Greulich and Pyle undertook the task of updating and extending their own radiographic norms for skeletal age of adolescent males and females. Their work, first published in 1950, was based on the 1930’s work of T. Wingate Todd at Case Western Reserve University. When preparing their standards for skeletal age in their second edition, Greulich and Pyle (1959) included not only
Todd’s X-ray films through 1936, but also those which were obtained during the subsequent six years of the Brush study. Greulich and Pyle’s study arranged substantial groups of children chronologically to provide measurements they felt best represented children of that age. Their atlas differed from Todd’s in that it included fewer standards. “It is our opinion, that, after the age of five years, in both boys and girls, the skeletal development of the hand does not proceed rapidly enough to require standards at more frequent than approximately annual intervals except about the time of puberty” (Greulich and Pyle 1959:xiii). Figure 13 depicts an example of a hand wrist film used in assessment of skeletal age (Greulich and Pyle 1959).

Greulich and Pyle’s radiographic assessment of the hand-wrist complex involved two specific steps, the atlas and the bone specific methods. The atlas method involved comparing a hand-wrist film with the standard of the same sex and nearest chronological age. The film would then be compared with adjacent standards, both older and younger than the one is of the nearest chronological age. Finally, the standard which appears most closely to resemble the film in question is chosen. This first method is termed the atlas method (Greulich and Pyle 1959).

After selecting the appropriate GP2 standard via the atlas method, the examiner should proceed to make a more detailed comparison of the individual bones and epiphyses visible in them. The bones of the hand-wrist complex
Fig. 13. Example of a dorsopalmar hand-wrist radiograph. The fingers are relaxed. The radius is to the right (lateral) in this view. This particular example if of a 6 year-old American white boy. All of the epiphyses are mineralized, though that of the ulna is still small and sesamoid-shape. Seven of the eight carpals are evident; the pisiform, if forming, is superimposed to the palmar (anterior) of the triangular bone. (Figure provided by Dr. E. F. Harris.)
should be considered in a regular order. That is, one should begin at the distal ends of the radius and ulna, proceed next to the carpals, then to the metacarpals, and finally to the phalanges. Similarly, one should examine the carpals in a regular sequence—in their usual order: Capitate, Hamate, Triquetral, Lunate, Scaphoid, Trapezium, Trapezoid, Pisiform. This method is termed the bone-specific method (Greulich and Pyle 1959).

If an individual bone in the film to be assessed is in the same stage of development as the corresponding bone in the standard selected for the detailed comparison, it should be given the skeletal age that has been assigned to that bone in that standard. If it appears to be either less advanced or more advanced that its counterpart in that standard, it should be compared with the same bone in its adjacent standards. The proper skeletal age to be assigned to it is that which is given in the standard to the corresponding bone that shows the same degree of development. If none is found that corresponds exactly in developmental status with the bone to be assessed, its skeletal age should be estimated from that of those which it most closely resembles.

The developmental status of all bones of the hand to be assessed will occasionally correspond exactly to that of some one hand standard in this Atlas. When such is the case, the skeletal age of that standard is the skeletal age to be assigned to the child’s hand. If, however, its developmental status does not correspond exactly to that of any one standard but is, rather, intermediate between those of two adjacent standards, the age assigned to the film should be correspondingly intermediate between the ages of the two standards which it most closely resembles [Greulich and Pyle 1959:35-36].

In search of a standard appropriate for an independent study, Alice M. Waterhouse and Tavia Gordon (1963) found that S. Idell Pyle was preparing a
reference standard that included the hand-wrist complex. Her standards were based on the films of children enrolled in two growth studies conducted independently from 1929 to 1962 by the Brush Foundation of Cleveland, Ohio, and the Department of Maternal and Child Health in the Harvard School of Public Health in Boston, Massachusetts (Pyle et al. 1971). These standards for the hand and wrist were more complete chronologically than any other standard currently in use in 1964. Standards were arranged evenly at six-month intervals from ages three to thirteen years, and closely resembled the original standards set by T. Wingate Todd in 1937. The key difference was that Todd’s atlas included two separate series of films and age equivalents, one for males and one for females. Thus, in 1962, at the urging of Drs. W. W. Greulich and H. C. Stuart, Dr. Pyle was employed to prepare a single series of films that would provide standards for both sexes [as long as bone age equivalents for each sex were assigned to each bone.] Dr. Pyle’s study was included in the National Health Survey, and was supported by the National Center for Health Statistics (Pyle et al. 1971).

In constructing their standards for hand-wrist bone ages, Pyle et al. proposed two objectives: (1) to select representative films that would offer a variety of discernible features of developing hand-wrist bones—a series spaced at three, six, or twelve month, and (2) to relate these structures as accurately as
possible to the chronological level at which they usually appeared in the median position for the Cleveland boys and girls (Pyle et al. 1971).

Tanner et al. formulated two successive methods of estimating HW bone ages that were believed to be “more flexible and deriving from a more solid mathematical base than the Greulich-Pyle method” (1975:v). The first analysis, named TW1, was published in 1962 and the second analysis, labeled TW2, was published in 1975. The TW2 analysis was a follow-up to Tanner, Whitehouse, and Healy’s 1962 analysis in which “each bone of the hand and wrist was classified separately into one of eight or nine stages, to which scores were assigned” (Tanner et al. 1975:v). These scores were then added to provide the skeletal maturity estimate. The ordinal scale for rating the distal radius is depicted in Figure 14. Grade A represents the appearance of the diaphysis before any radiographic formation of the epiphysis is detectible. Grade B corresponds to the initial development of an ossification center in the cartilaginous precursor. Grades B through I depict progressive maturation and development of the epiphysis, ultimately ending with its capping and fusion with the diaphysis. Growth is completed at fusion, with the exception of minor remodeling that can occur at the subchondral articular surfaces. The TW2 analysis formulated by Tanner et al. was a revised version of the TW1 (Tanner et al. 1975).
Fig. 14. The eight-grade ordinal scale of maturation of the distal radius.

Fishman also formulated a scheme for assessing HW bone age that was published in 1982. His analysis was based on and involved a simplified approach to Greulich and Pyle’s 1959 standards (GP2 standards). He noted both the importance of hand-wrist films in measuring bone age and affirmed their clinical importance in applications relating to dentofacial diagnosis and therapy. He proposed four phases of bone maturation, located at six sites on the thumb, third finger, fifth finger, and radius. These sites are the adductor sesamoid of the thumb, the distal, middle and proximal phalanges of ray three, the middle phalanx of ray five, and the epiphysis on the distal end of the radius.

Fishman’s assessment is based on 11 grades of maturity, and these are depicted in Figure 15 as a flow chart by which the patient’s stage of development is reached. The following excerpt was taken from Pyle et al.’s A Radiographic Standard of Reference (1971:26):

The natural process of ossification begins in and spreads from specific sites in each bone, namely, its growth centers. Each expanding osseous mass in a cortex is surrounded by a vital, expanding cartilaginous ‘rim’ which is always differentiating ahead of the ossifying area until the bone attains its adult shape and size. Accordingly, all skeletal maturity indicators are preformed in cartilage. Since the cartilaginous portion of any cortex is translucent to X-rays, the entire growing bone is not shown in a radiograph.

Biological maturity is of importance to the dental profession. While average maturing children represent the norm, the clinician should recognize those children particularly late or early in their development. That is, those
Fig. 15. Fishman’s 11-grade scheme used to assess skeletal maturity from a hand-wrist radiograph. (Diagram provided by Dr. E. F. Harris.)
children fall outside the norms when their biological and chronological ages do not correspond. Additionally, certain dental treatments, particular orthodontics, often rely heavily on the individual’s growth potentials.

Effects on Human Growth and Development

With improved cure rates for acute lymphoblastic leukemia (ALL) and the increasing number of long-term survivors, it is important to determine whether clinically meaningful growth retardation occurs in these children and whether this adverse outcome is predictable and potentially preventable [Schriock et al. 1991:400].

Stature and Weight

Anti-neoplastic therapies have been evaluated for their effects on the overall tempo growth and development. Various research endeavors focused on the effects on bone age, while other studies concentrated on therapeutic effects on stature and weight.

Sklar et al. (1993) analyzed changes in height due to cranial irradiation for 127 children (68 females, 59 males) treated for ALL. Three treatment groups were studied: 38 patients who received no cranial irradiation, 36 patients who received cranial irradiation of 1,800 cGy, and 53 patients who received irradiation of 2,400 cGy. Mean age at diagnosis of the patients was 6.4 years (sd = 0.25 years). Results of the study indicated a significant overall decrease in height standard deviation scores (SDS) for all three treatment groups from diagnosis until the end of therapy and from the end of therapy until a final
evaluation. Patients in the 2,400 cGy treatment group had the greatest decrease in height SDS, followed by those patients in the 1,800 cGy group. Those patients who did not receive irradiation showed the least reduction in height SDS. Sklar et al. (1993) mentioned that younger age and female sex were closely associated with a significant decrease in height SDS for irradiated patients. A mean loss in height SDS nearly twice that seen for others with similar dose treatment was observed in female patients ≤ 4 years of age at diagnosis. Growth hormone replacement therapy was not recommended by these authors for most ALL patients. However, female patients less than 4 years old were shown to be at high risk of sustaining growth retardation (Sklar et al. 1993). Dalton et al. (2003) proposed that an earlier onset of puberty in females might improve height at the time of puberty because of acceleration in the rate of growth, but then might compromise final height by decreasing the time interval for growth.

Katz et al. (1993) evaluated final adult height of 109 patients treated for acute lymphoblastic leukemia between 1974 and 1981. Fifty-eight patients received no cranial irradiation, while 51 received 2,400 cGy of cranial irradiation. Prior to treatment, both groups had height distributions similar to those of the U.S. population. Mean age of the patients at diagnosis was 7.8 years (sd = 4.2 years). Final examination of the 51 patients who received cranial irradiation in addition to chemotherapy showed a mean height standard deviation score of -1.04, which corresponded to a median height reduction of 6.3 cm in females and
7.0 cm in males. In contrast, the 58 patients who did not receive cranial irradiation achieved final heights coincident with those of the U.S. population. In other words, this study found cranial irradiation to be significantly associated with short stature in adults, but that their sample treated with chemotherapy alone did not exhibit any long-term deficit.

“Obesity and short stature are commonly observed late effects of therapy for childhood acute lymphoblastic leukemia” (Dalton et al. 2003:2953). Dalton et al. evaluated the long-term effects of ALL treatment on height and weight for 618 children treated between 1987 and 1995 (2003). Three treatment groups were studied: intrathecal therapy alone, intrathecal therapy with conventional cranial irradiation, and intrathecal therapy with irradiation twice a day. Height and weight values were recorded at diagnosis and every six months thereafter. Body-mass index scores (BMI) were also calculated for each patient. Results showed that children younger than 13 years of age experienced a greater decrease in height and an increase in BMI compared with their older counterparts. Cranial irradiation was not shown to be an influencing factor. An increased chemotherapeutic intensity, as well as younger age, was significant risk factors for greater growth retardation. No statistically significant difference was seen in final heights between the irradiated groups and those who received no irradiation. Dalton et al. found that final height was compromised in ALL patients and further contributed to a relative increase in weight. They proposed
rather that as “patients became overweight for height; this seemed to be a result of relative height loss with normal weight gain rather than accelerated weight gain.” Additionally Dalton et al. (2003) suggested that subsequent weight gain could be due to corticosteroid therapy, as was suggested by Van-Dongen-Melman et al. (1995).

Precocious Puberty

As treatment of childhood acute lymphoblastic leukemia is now largely curing with the majority of children surviving into adulthood, there has been an increasing concern regarding the effects of therapy on reproductive potential and gonadal function in these children. Precocious or premature puberty, defined as “pubertal development beginning more than 2 SD before the mean age of the onset of puberty in the community,” has been reported after acute lymphoblastic leukemia (Quigley et al. 1989:143). Pubertal development commencing before 9 years of age in girls and 10 years of age in boys may be considered precocious (Quigley et al. 1989).

Quigley et al. examined pubertal status and plasma levels of various hormones in 45 children (20 girls and 25 boys) who had received combination chemotherapy with 24 cGy of irradiation to the cranium. Hormonal levels of sex steroids, as well as gonadotropin and inhibin, were assessed. Germ-cell damage (specified by increased plasma levels of follicle-stimulating hormone) was
apparent in both sexes. These findings were confirmed in the boys by the “absence of germ cells in the testicular biopsy specimens and by the small size of the testes for pubic-hair stage” (Quigley et al. 1989). Furthermore, plasma inhibin levels were measurable in only 44 percent of the pubertal girls, as compared with over 93 percent of normal pubertal girls. Despite evidence of apparent gonadal damage, the girls had an early menarche at a mean age of 11.95 (sd = 0.91) years, as compared with the Australian standard of 12.98 (sd = 1.11) years. Quigley et al. (1989) concluded that treatment for ALL may contribute to gonadal damage in both sexes; however, puberty will occur at a normal age or earlier in girls. Similarly, Greulich and Pyle (1959:8) stated that “in precocious puberty, the gonadal and related hormones are present abnormally early in quantities sufficient to cause the epiphyses of the various long bones to fuse before growth has continued long enough to permit the attainment of full normal adult stature.”

Brauner et al. (1984) remarked that gonadotropin deficiency can occur and prevent or disturb pubertal development. Brauner et al. evaluated 29 children with medulloblastoma (n = 14), head and neck tumors (n = 10), or acute lymphoblastic leukemia (n = 5) who had received cranial irradiation before seven years of age. These children were followed until the normal age of puberty. Six children (5 girls and 1 boy) had precocious puberty, with puberty beginning two months to 2.6 years after irradiation in the girls and after seven
years in the boy. One of these six children was a female who had been treated for ALL. Her therapy began at six years of age with a cranial irradiation dose of 2,400 Rad. Precocious puberty commenced at 7.5 years of age. Additionally, the child exhibited a relative growth hormone deficiency. None of the patients examined had invasive hypothalamic lesions, hydrocephalus, or increased intracranial pressure. Therefore, it was concluded that the precocious puberty can be considered a consequence of cranial (and hypothalamic and pituitary) irradiation (Brauner et al. 1984).

Treatment Influences on Bone Mass

ALL patients often experience impaired GH secretion following treatment with cranial irradiation. This GH decrease has been associated with a reduced bone mineral content. Similarly, long-term corticosteroid and methotrexate therapy has also been linked to reduced bone mass. Nysom et al. (2001) studied bone mass in 95 patients in first remission of ALL. Mean whole-body bone mineral content (BMC) and bone mineral density area (BMDA), both useful variables to predict the risk of fracture, were both decreased significantly posttreatment. “Reduced bone mass several years after childhood ALL appears to be caused by both reduced bone size and reduced size-adjusted bone mass” (Nysom et al. 1998:3757).
Regarding bone mass after childhood ALL, Atkinson et al. (1989) found reduced BMD\textsubscript{A} in the radius of 16 children 8 months after completion of treatment. The leukemia process was implicated as the underlying cause of reduced bone mass. The study later reported that bone mass was not significantly reduced at the diagnosis of childhood ALL (Atkinson et al. 1990).

Vertebral fractures and osteoporosis may well occur in children with newly diagnosed ALL (Newman et al. 1973; Samuda et al. 1987). In the past, these injuries were the result of infiltration and extension of leukemic tissues; however, they could also be an indirect result from a product of the malignant cells. Prostaglandin E, ectopic parathyroid hormone, and osteoblast inhibiting factor have been associated with the pathogenesis of bone loss (Newman et al. 1973; Samuda et al. 1987).

Gilsanz et al. (1990) also researched potential cases of osteoporosis in 42 patients treated for childhood ALL. The study utilized “quantitative computed tomography, a technique that accurately measures trabecular vertebral bone density, to establish or exclude the presence of osteoporosis in pediatric patients” (Gilsanz et al. 1990:238). Patients who had received cranial irradiation had significantly lower bone density than did untreated children in the normal population. Thus, the authors concluded that overall loss of bone density did not result from the disease or chemotherapy, but rather from the cranial irradiation (Gilsanz 1990).
Chapter Overview

This Review of the Literature provides an overview of Acute Lymphoblastic leukemia, including its numerous symptoms and treatments. Effort was made to mention iatrogenic effects of such anti-neoplastic therapies, as well as identifying radiographic methods to evaluate such harmful effects.

Acute Lymphoblastic Leukemia (ALL) represents the most common malignancy of childhood, comprising approximately 31 percent of all childhood malignancies (Niemeyer and Sallan 1998; Berg et al. 2000). Each year in the United States, around 2,000 to 2,500 new cases are diagnosed, with ALL predominately striking children between the ages of two and ten years (Niemeyer and Sallan 1998; Berg et al. 2000).

ALL attacks the immune system by invading the blood and bone marrow; however, metastasis is often seen in extramedullary sites such as the central nervous system, lymph nodes, and spleen. Symptoms of ALL commonly include anemia with inherent weakness and debility and joint pain, as well as specific oral manifestations such as swollen and bleeding gums, as well as periodontal infections.

Anti-neoplastic therapies often fail to differentiate between metabolically active and neoplastic cells. Consequently, treatment effects may often harm healthy tissues iatrogenically. Oral manifestations may include overretention of
primary teeth and delayed eruption of permanent teeth, as well as rampant
decay, microdontia, and root stunting.

Numerous methods have been reviewed by which an individual’s
skeletal growth and bone age may be assessed. Bone age, in contrast to an
individual’s chronological age, may properly reflect skeletal growth and
development. Due to reasonable accessibility and the availability of numerous
bones for evaluating maturity, hand-wrist radiographs are commonly used in
the evaluation of bone age. Hand-wrist radiograph analyses were proposed by

Treatment for ALL may also affect an individual’s overall growth and
development. Cranial irradiation had been shown to affect stature and weight;
height or stature is retarded, while weight centiles typically increase.
Individuals may also experience precocious puberty, or early-onset puberty
(defined as commencing at least two years before the mean onset of puberty in
the general population). Finally, treatment for ALL most often impairs growth
hormone secretion. Consequently, children often experience reduced bone mass
as well as fractures related to osteoporosis.
CHAPTER III

MATERIALS AND METHODS

Patient records were provided by St. Jude Children’s Research Hospital in Memphis, Tennessee. Institutional Review Board (IRB) approval was granted through both the University of Tennessee Health Science Center and St. Jude Children’s Research Hospital (XPD04-022). Cases were selected based on a diagnosis of acute lymphoblastic leukemia.

The data manager at St. Jude supplied a list of patients meeting a number of predetermined criteria. The following data for each patient were entered into an Excel spreadsheet: date of birth, diagnosis date, sex, initial examination date, treatment protocols in addition to dates, and GP2 bone ages for all available hand-wrist films. From these data, the following information was derived: chronological ages, hand-wrist bone ages, and relative tempo of growth (as delayed, normal or advanced). Overall demographics for the sample were as follows:

(1) All subjects had an initial diagnosis of acute lymphoblastic leukemia (ALL).

(2) This cohort of children was born no earlier than 1980 and no later than 2000.
Subjects had an ALL diagnosis date no earlier than 1985 and no later than 2003.

All subjects had at least one hand-wrist radiograph.

All subjects had a chronological age no older than 12 years old at initial diagnosis.

We chose not to eliminate patients based on nationality. Our sample represents a multicultural analysis of bone age in children with ALL. Children in our study had been brought to St. Jude from throughout the United States and various foreign countries. The majority of these children were white children of European extraction.

Subjects were treated according to one of two protocols, either exclusive chemotherapy or chemotherapy combined with cranial radiation.

Sample Characteristics

ALL is a disease that characteristically strikes young children as shown in Figure 16. This graph plots the age distribution of the patients studied here, by sex, and the median age at diagnosis is around four years of age for both sexes.

There were 73 children in this study (39 boys, 34 girls), each represented by at least one hand-wrist film. The number of films per child was highly skewed, though, since most films were taken soon after the diagnosis of ALL (and, thus, close to the onset of treatment). Of these 73 children, 53 had just
Fig. 16. Age-sequenced distributions of the children used in the present study. Each dot is a different individual.
one hand-wrist film, 10 had two films, 5 had three films, and 5 had four films. The total number of HW films was 108.

Mean chronological age at diagnosis was 4.54 years (sd = 2.81), with a range of 0.10 up to 11.02 years of age. Age at diagnosis did not differ between girls and boys (P = 0.15 by t-test).

**Collection of Hand-Wrist Bone Ages**

The focus of the bone age analysis centered on determining whether the tempo of growth in the patients with ALL was retarded based on treatment with chemotherapy and/or radiation. Bone ages were collected for each of the 73 patients based on Greulich and Pyle’s 1959 standards (GP2). All of the patients’ bone ages were assessed according to the GP2 atlas method, not the bone-specific method. We necessarily assumed that the GP2 standards were appropriate for our sample of predominately Caucasian children.

Bone ages were entered as decimal ages into a Microsoft Excel spreadsheet (Microsoft Corporation version 11.2). For example, a patient would be entered with a bone age of 11.5 years, but also a bone age of 138 months. Similarly, patients’ chronological ages were also calculated in decimal ages.

Data collected in the Excel file were imported into the JMP 5.0.2 statistical package (SAS Institute, Cary, NC). Following exploratory data analysis and verifying extreme values, routine descriptive statistics were calculated, with the
tempo of growth (BA-minus-CA) being the key measure. This is a mixed longitudinal study, but most of the data are tightly clustered near the onset of treatment. Consequently, while we made as much use as possible of the more informative repeated measures format of some of the data (with pairing design tests and model II ANOVA) sample sizes were critically small. More power was obtained from treating the data cross-sectionally, in which cases factorial ANOVA models were used. Methods are described in Rosner (2000). All of the tests were evaluated as two-tail at the conventional alpha level of 0.05.
CHAPTER IV

RESULTS

The purpose in this section was to test whether the treatment for ALL (chemotherapy and/or irradiation) significantly altered bone age. Specifically, bone age (BA) was evaluated for each child in this study using the Greulich-Pyle sex-specific standards from their second edition (Greulich and Pyle, 1959), commonly abbreviated as GP2. The central question was whether BA was depressed relative to chronological age (CA) as treatment progressed.

Our expectation was that the treatment of children with ALL using very potent drugs (with or without irradiation) would depress their tempos of growth, at least transiently. The hypothesized scenario is sketched in Figure 17. Because of the rapid onset of ALL, we expected that bone age at diagnosis would not have had an opportunity to become delayed relative to CA. Our supposition was that the sample of children would have bone ages equivalent to their CA because: (A) we supposed that children who subsequently contract ALL are growing normally, as a group, and (B) similarly, ALL is an acute-onset disease that is not known to affect BA prior to onset. Also, we supposed that the GP2 sex-specific bone standards (Greulich and Pyle 1959)—which are the only standards available (excepting those of the Tanner et al. 1975) are appropriate to
Fig. 17. Diagrammatic sketch of the author’s hypothesized relationships between CA and BA in children with ALL. The horizontal axis is chronological age, the vertical axis is bone age, and the origin is the onset of treatment for ALL. During phase “A,” soon after diagnosis, BA should be coincident with CA. We supposed that treatment would depress BA during phase “B,” but that there would be a recovery (compensatory) phase (“C”) after the completion of treatment.
this geographically heterogeneous sample of children with ALL. (Since we did not have access to the HW radiographs, it was not possible to evaluate the GP2 bone-specific standards or the TWII standards).

As sketched in Figure 17, we anticipated that BA would be equivalent to CA at the start of treatment within statistical limits. Specifically, we tested whether BA-CA differed statistically from zero. In fact, it is different. At diagnosis (we selected those HW BA readings taken within 1.0 year of diagnosis), BA is significantly delayed, at least in boys. There are no HW films prior to the onset of ALL, so we used those radiographs taken soon after the onset of ALL as being representative of these children’s baseline status. For girls, there was a sample of only 7 which yielded a test statistic of 0.1 and an associated P-value of 0.95 (two-tail). The average difference between BA and CA was 0.03 years (sd = 1.14). In boys, with a more informative sample size of 12, the t-test was 3.2 with an associated P-value of 0.0081 (two-tail). The average difference between BA and CA for these 12 boys was -0.71 (sd = 0.77) years. Half of the boys (6/12) had bone ages equal to or greater than the CA, but those with negative BA-CA differences ranged up to -2 years, and 4 boys had differences between -1 and -2 years, so the distribution clearly was centered below zero. Since the mean CA for these 12 boys averaged only 7.00 years, the mean BA-CA of -0.71 suggests a 10% delay.
There are at least two interpretations of these results. One is that ALL differentially selects children—at least boys—who are developmentally delayed. As will be seen, this seems unlikely. Moreover, it disagrees with prior findings. A second interpretation is that the GP2 standards—derived from Midwestern children primarily from the 1940s—are inappropriate for these children with ALL because the tempos of growth and progress towards maturation occur at different (and probably differing) rates.

We supposed that the combination of antimitotic drugs used to treat ALL (phase “B” in Fig. 17) would discernibly depress the children’s tempos of growth, so that BA-minus-CA would become negative (and become larger during the course of treatment). In fact, though, there is no evidence of this. There are several ways to tackle this issue statistically; we chose (1) to group the HW bone ages into time intervals using age at diagnosis as “time zero” and then (2) use one-way ANOVA to test for any difference across these intervals. We were not able to get information on when treatment ceased, so these age intervals span all ages up to a “catch-all” interval of “over 8 years” after diagnosis. HW films were not taken at any fixed interval, and the number of films varied appreciably among patients. The great majority of cases had only one film, though, so we treated these mixed longitudinal data as if they were cross-sectional. Analysis was performed separately for boys and girls since it seemed likely that the tempos of how the GP2 standards relate the children’s’
patterns of HW maturation are at least sex-specific. The results for the subset of boys are shown in Figure 18. Visually, it is apparent from this graph that treatment produced no obvious drop in bone age relative to CA.

In Figure 18, the diamond-shaped figure at each time interval defines the 95% confidence limits of the mean, and the middle line in the diamond is the mean. The grand mean is shown as the light horizontal line across the graph. It is evident that (1) the diamonds all overlap the grand mean and (2) all of the groups’ means are close to the grand mean. Consequently, there is no visual suggestion that the value of BA-CA exhibits any trend across time.

For the girls, indeed, there was a transient rise in the BA-CA values (Fig. 19, between about 0.5 and 2.0 years after diagnosis). This doubtlessly is due to the predominantly cross-sectional nature of the data since it can hardly be supposed that treatment is “protective” of bone age.

These visual impressions of “no change” are supported statistically. For the ANOVA of the females, the df were 9 and 35, F = 0.90 and the P-value was 0.5314. For the males, the df were 9 and 53, with F = 0.35 and the P-value was 0.9519. In this set of data, then, there is no suggestion that the chemotherapeutic treatment of ALL (with or without irradiation) affected the rate of progression of HW bone morphologies toward maturity. We had also anticipated that, following treatment, the children would experience a phase of catch-up growth (e.g., Caruso-Nicoletti et al. 1993). The depiction of this idea is sketched in
Fig. 18. Graphical results of examining BA-CA when the data are partitioned into intervals of time into treatment (data for boys alone). By analysis of variance, there was no significant difference among the 10 groups. Visually, there is no trend across time; the distributions neither increase nor decrease in the face of the serious stressors of chemotherapy.
Fig. 19. Graphical results of examining BA-CA when the data are partitioned into intervals of time into treatment (data for girls alone). By analysis of variance, there was no significant difference among the 10 groups. Visually, there is no trend across time; the distributions neither increase nor decrease in the face of the serious stressors of chemotherapy.
phase “C” of Figure 17. In fact, though, since there was no depression of the rate of maturation during treatment, there would be no need for a compensatory phase.

To confirm this, we tested the two “ends” of the data. Specifically, we tested whether the differences in BA minus CA at the start of treatment (within 1.0 year of diagnosis) was different from that of HW ages more than 6.0 years after diagnosis. (Again, we could not obtain information on when treatment ceased, so we used > 6.0 years after diagnosis as a conservative breakpoint.)

In both comparisons (for boys and for girls; Figs. 20, 21), the variability in BA-CA increased from pre- to posttreatment, but this is fully anticipated because the children had grown older and variability in this parameter increases with age (Garn et al. 1958, 1962). Inferentially, there was no difference across time; BA-CA did not change from soon after diagnosis to several years after treatment. In girls, the mean of BA-CA was 0.03 years for the set of HW examinations made within a year of diagnosis and 0.23 years for the set of readings taken more than 6 years after diagnosis. With 1 and 20 df and F = 0.15, the P-value is 0.7033. For the boys, the mean BA-CA was -0.71 years for the grouping of the examinations made within a year of diagnosis and -0.47 years for those in excess of 6.0 years after diagnosis. With 1 and 21 df and F = 0.24, the P-value is 0.6262. There is,
Fig. 20. Graphical results of examining BA-CA when just the data at the two extremes of time-in-treatment are compared (data for girls alone). By analysis of variance, there was no significant difference between the 2 groups.
Fig. 21. Graphical results of examining BA-CA when just the data at the two extremes of time-in-treatment are compared (data for boys alone). By analysis of variance, there was no significant difference between the 2 groups.
then, no evidence that treatment for ALL had any effect on the progress of HW bone age towards maturity.

For completeness, we also investigated whether the statistical power of a repeated-measures design would disclose any effect of treatment on bone age. We culled the data set for children with at least two HW films that were taken at least one year apart. Then BA-CA from the earliest film (closest to the diagnosis of ALL) was compared to BA-CA from the most recent film (when the child had been in treatment the longest). This resulted in a sample size of 17 pairs of BAs (sexes combined). There was some apparent change in the mean BA-CA with time, but the direction of the change was opposite what could be explained by treatment. Mean BA-CA was 0.43 years at the first examination and 0.16 years at the most recent examination. At face value, this change suggests that treatment is protective of bone age, which seems uninterpretable in light of the drugs’ known actions. On the other hand, this change across time is not significant statistically ($t = 1.95; \text{ df} = 16; P = 0.0693$).

This test would seem to be the most likely to find an effect of treatment on BA if one exists, and the results are negative. Indeed, the trends are not even in the anticipated direction. In sum, then, there seems to be no suggestion in the present data set that the tempo of growth as assessed through hand-wrist BA is at all affected by treatment for ALL.
There is a cautionary note in these results. If one were to ignore the bone ages from the early films, and, say, only test whether the most recent bone ages were affected (i.e., those BAs from children who were longest in treatment), the mean BA-CA is -0.19 (n = 73), which is suggestive that treatment for ALL does depress the rate of maturation—though not significantly (df = 72; t = 1.54; P = 0.1289). The error in this assumption becomes clear when it is recognized that the earliest films show that BA is even more “affected” (mean = -0.39 years; t = 2.44; P = 0.0203).

Our contention is that the bone age standards (GP2) produce the observed BA-CA discrepancies because the tempos of growth are different in the GP2 sample versus how quickly the children with ALL in the present study were maturing. Treatment for ALL has serious repercussions on the amounts of growth in the affected children (Kirk et al. 1987; Clayton et al. 1998; Dalton et al. 2003), but it appears to spare the tempo of growth as measured by HW bone age.
Acute Lymphoblastic Leukemia (ALL) is the most common malignancy of childhood, constituting approximately 31% of all childhood malignancies (Niemeyer and Sallan 1998; Berg et al. 2000). While ALL accounts for nearly 75% of all leukemias in children, it accounts for less than 1% of all adult malignancies (Perkins et al. 1997; Berg et al. 2000).

ALL strikes children primarily between two and ten years of age, with the peak age between two and three years. However, it can also attack adolescents and adults, with a substantial increase around 65 years of age (Berg et al. 2000). Current statistics from the Surveillance, Epidemiology, and End Results Program (SEER) reveals that the incidence of ALL in the United States increased from 2.7 to 3.3 cases per 100,000 children aged 0 to 14 years old during the years of 1973 to 1995. Each year, around 2,000 to 2,500 new cases of ALL are diagnoses in the United States (Niemeyer and Sallan 1998).

The cause of ALL is not known, though several explanations for an overall cause have been explored. Numerous environmental factors have been examined, including ionizing radiation, the use of drugs and chemicals, as well as various viruses. Several chemical substances, such as benzene,
chloramphenicol, and phenylbutazone, have been linked to the disease. Additionally, several viruses have shown associations with leukemia. These include a statistical linkage of the Epstein-Barr virus with African Burkitt’s lymphoma, the human T-cell leukemia-lymphoma virus I (HTLV-I) with adult T-cell leukemia-lymphoma (ATL), and the HTLV-II virus with atypical hairy-cell leukemia (Perkins et al. 1997).

The overall prognosis of patients with ALL is promising as rates of remission continue to increase. Survival rates for children are currently near 80 percent, which demonstrate the obvious progress that has been made in the treatment of ALL (Pui 1999). The current high and improving survival rates of ALL are due in large part to research efforts and improved treatment strategies (Goho 1993). When considering the treatment course for a person with ALL, a number of factors must be considered: the ALL subtype, the comparative success of previous treatments, levels of leukemic cells in the blood, as well as the patient’s age and overall health (Wells et al. 1983). Consequently, overall treatment may vary substantially from person to person.

Various options exist for the treatment of ALL, including chemotherapy, radiation, and bone marrow transplantation. Physicians may use one therapy exclusively or combine methods to treat particular cases of ALL. Multimodal therapy “creates synergistic and additive effects” not normally gained from the utilization of one therapy only (Goho 1993).
Chemotherapy is the treatment currently chosen for most types of acute leukemias. Chemotherapeutic agents target DNA replication in cells and strive to prevent cancer cells from invading, multiplying, metastasizing, and destroying the host (Skeel and Khleif 2003). While the ultimate mechanisms by which cancer drugs induce cell death are uncertain, the majority of efficient cancer agents are believed to either generate chemical lesions in DNA or interfere with the synthesis of DNA. Destructive mechanisms may range from *apoptosis* (programmed cell death) to progression of cell death following mitosis (Chabner *et al.* 1999).

While attempting to destroy cancer cells, chemotherapy often affects normal cells or organs that are undergoing cell reproduction at enhanced rates. Mucosal linings, such as those of the mouth and intestines, as well as the skin, hair follicles, and bone marrow, are often affected. The overall goal of a chemotherapeutic agent, though, is to produce marked destruction of cancer cells, while providing minimal damage to normal cells of the body (*e.g.*, Skeel and Khleif 2003). Side effects of chemotherapy may include anemia, nausea, anaphylaxis, stomatitis, xerostomia, hair loss (*alopecia*), diarrhea, constipation and/or an altered nutritional status due to gastrointestinal tract insult (Tipton 2003).

The antimitotic effect and toxicity of the drugs used in the treatment of ALL are quite apparent from the literature. Therefore, our hypothesis was that
although a person’s overall growth may not be affected by such agents, his/her *tempo* of growth could be affected significantly. Adult and adolescent stature has been shown to be greatly affected by anti-neoplastic treatments, particularly in combination with irradiation therapy. However, these findings reflected only changes in a person’s height (and often weight), not a patient’s tempo of growth as assessed from bone age. In the present study, the question was whether a patient’s rate of maturation was influenced by such treatment.

Tanner *et al.* (1975:1) stated,

> The concept of physical maturity, while familiar in general terms, does not suggest immediately a method by which it can be quantified, let alone measured. Maturity differs in an important way from a measurement such as stature, in that the normal growth process takes every individual from one common condition of being wholly immature to another of being wholly mature. It thus makes sense to measure maturity on, say, a percentage basis from 0 to 100. Stature lacks these common end points; a child who is ‘tall for his age’ may be so because he is more mature than his coevals, but he may simply be a tall child of average maturity, which will eventually be a tall adult. Stature and other ‘size’ measures can thus not be used to define maturity, except possibly in retrospect when the adult value is known.

A set of distinct events commonly occurring during growth are needed to properly define maturity. Examples of such events would be the eruption of a specific tooth, or (in females) the onset of menarche. One may then assume that an individual who has undergone a particular event is more mature than another which has not undergone the event. Furthermore, levels of maturity can
be assessed from “a series of events that always occur in the same sequence from a single event” (Tanner et al. 1975). Thus, in females, the sequence of breast development could serve to define a series of three specific events. A female with fully developed breasts is more mature than a female whose breasts are developing, and a female whose breasts are developing is more mature than a female whose breasts have not yet begun to develop. “Events of this kind are often referred to as developmental ‘milestones’, the name indicating the intention to define the distance an individual has traveled along the common road to full maturity” (Tanner et al. 1975:1).

Many series of events exist by which maturation may be measured. Examples may include eruption of the each tooth in the primary and permanent dentition as well as initial presentation and ossification of the bones of the hand and wrist. The difficulty in assessing maturity then becomes how to join the evidence from many sequences of events, many of which are often invariant (Tanner et al. 1975).

The best known method of assessing maturity by using the bones of the hand and wrist complex was developed by Greulich and Pyle in 1959. Their atlas, which presents a series of “typical” radiographs of children at some 30 points along the maturity scale, allows the user to match a given radiograph as well as possible to one stage. “The maturity recorded is then given by the age that characterizes the closest match” (Tanner et al. 1975). Subjectivity of
measurement is obviously a disadvantage of this method; a specific radiograph will not, more than likely, exactly match one in the atlas series. Furthermore, the issue of whether to how to measure a radiograph which falls between two in the atlas is not addressed. Despite these limitations, the Greulich and Pyle method is used quite often to assess maturity through bone or skeletal age (Tanner et al. 1975).

Average bone or skeletal ages illustrate the maturation status in which normal children, male and female, attain an established chronological age (Jimenez-Castellanos et al. 1996). Similar to the growth of organs in the human body, bones of the skeleton progress through their morphological development at different age-specific rates in time. In the child, new (secondary) ossification centers appear over a span of time, and existing ones remodel their morphologies. Knowing initiation times and morphological changes on bones in the hand and wrist provide a means of relating skeletal age, or “developmental age” to chronological age, which is the person’s age in calendar years.

Hand-wrist radiographs are commonly used in the assessment of biological age because (1) the hand and wrist are reasonably accessible, (2) those vital organs particularly at risk to radiation damage are not in close proximity, and (3) there are numerous bones available by which developmental maturity may be measured. The standards used in this study to which hand-wrist
radiographs were compared were formulated by Greulich and Pyle in 1959, and are known as the GP2 standards.

The present study involved scoring the 108 hand-wrist films from 73 children (39 boys, 34 girls) who were treated for acute lymphoblastic leukemia at St. Jude Children’s Research Hospital, Memphis, TN. Mean chronological age at diagnosis was 4.54 years (sd = 2.81), with a range of 0.10 up to 11.02 years of age. The number of films per child was highly skewed, because most were taken soon after the diagnosis of ALL (and, thus, the onset of treatment). Of these 73 children, 53 had just one hand-wrist film.

How large are population differences in the tempos of HW maturation? In other words, can we anticipate that the GP2 standards—based on Ohio children growing up in the 1930s and 1940s—are broadly representative of white childrens’ growth? There have not been many published studies. Mappes et al. (1992) found no difference in rates of HW development between contemporary samples of young adolescents from Ohio and Tennessee (though dental ages differed significantly between the same groups). Loder et al. (1993) and Ontell et al. (1996) found only modest differences between blacks, whites, and Asian children growing up in Northern California, except that blacks showed a spurt in BA at adolescence. Van Rijn et al. (2001) found the GP2 standards to be appropriate for contemporary Dutch children. Mora et al. (2001) reported (A) that variability exceeds that of the GP2 standards and (B) that their white sample
from Southern California was delayed during the pubertal interval but then caught up with the GP2 standards.

Fry (1968) published an insightful comparison of the two commonly used HW bone age atlases, name the Tanner-Whitehouse norms based on British children (1959) and the GP2 standards based on mid-American children from Cleveland, Ohio (Greulich and Pyle 1959). Fry realized that the photographs of the HW bones at each stage in the GP2 atlas could be scored using the 20 bone RUS bone-specific method of Tanner and Whitehouse. Fry scored the skeletal ages of the 25 grades for boys (with CA of 1 through 17 years of age) and the 20 grades for girls (with CA of 1 through 15 years of age).

Data for the boys are plotted in Figure 22, where it is evident that the TW sample matures significantly faster than the GP2 sample. As shown in the top graph, the British children were appreciably more mature at most stages than the Ohio boys. The difference between groups (bottom graph) starts off fairly small but by stage 10 (3 years of age), the difference is about 1 ½ to 2 years throughout the rest of the graph. Use of the TW standards would, then substantially over-estimate the bone age of the ALL children in the present study and correspondingly under-estimate their amounts of potential growth ahead of them.

Comparable differences are obtained for the girls (Fig. 23). These comparisons show that the tempos of growth differ (A) by age (the lines are not
Fig. 22. Comparison of the Tanner-Whitehouse and Greulich-Pyle hand-wrist bone age standards for boys. See text for details.
Fig. 23. Comparison of the Tanner-Whitehouse and Greulich-Pyle hand-wrist bone age standards for girls. See text for details.
parallel even accounting for sample fluctuation) and (B) by sex.

Viewing the extent of differences between the TW and GP2 standards suggest that much smaller differences between the sample of children with ALL and the GP2 standards in the present study are easily attributable to population differences in the tempos of maturation.

Several studies utilized stature, as opposed to bone age, to assess “development” of children treated for ALL. Dalton et al. found a slight decrease in height in children who received cranial irradiation (2003). This decrease, however, was not statistically significant when these children were compared to nonradiated children. Additionally, the means for the $z$ scores at diagnosis for the sample were +0.22 for height and +0.11 for weight, revealing that, on average, the sample was slightly taller and heavier than expected according to United States growth data (Dalton et al. 2003).

Herber et al. (1985) evaluated growth in long term survivors of several childhood malignancies treated with cranial radiotherapy. Cranial irradiation “may cause growth hormone deficiency due to disruption of the hypothalamo-pituitary axis” (Herber et al. 1985:438). Since treatment of malignancies is not tumor specific and all dividing cells are affected, “there is no reason why the cells at the epiphyseal plate should be spared, which raises that possibility of growth retardation during treatment” (Herber et al. 1985:440). However, the mean of a smaller sample (5 treated with chemotherapy, 10 treated with spinal
irradiation, and 19 treated with cranial irradiation) was 12.12 (sd = 3.93) years as compared to the mean skeletal age overall at 12.02 (sd = 3.82) years. In addition, bone age was retarded by no more than 18 months in any patient. These results indicated that bone age was affected only slightly if at all. The majority of children in the study who received cranial irradiation had been diagnosed with acute lymphoblastic leukemia. Additionally, previous reports have suggested that children diagnosed with ALL are taller than average at diagnostic presentation (Griffin and Wadsworth 1980; Broomhall et al. 1983).

Kirk et al. (1987) reported high rates of diminished stature in children treated for ALL. However, overall growth retardation was not shown. Stature had decreased by more than one standard deviation in 32 percent of survivors at 4 years post-diagnosis and in 71 percent at 6 years post-diagnosis. Standard deviation scores were constructed as standard deviation scores from the population mean. Kirk et al. (1987) also mentioned growth of younger children and those children especially tall for their age at diagnosis were more susceptible to reductions in overall stature.

Birkebaek and Clausen (1998) evaluated height and weight patterns in children up to 20 years after treatment for ALL. Their results disclosed similar height deviation scores at diagnosis and at follow-up; however, there was a significant decrease in scores during treatment. As was similar to aforementioned studies, the sample of children with ALL evaluated was
significantly taller at the time of diagnosis when compared with the normal population. "Whether the coexistence of ALL and a high growth rate is incidental or the result of a common factor is not known" (Birkebaek and Clausen 1998:163).

Though several of the aforementioned studies noted an overall decrease in stature, bone age or the tempo of growth has not been shown to be adversely affected by chemotherapy and/or radiation. That is, chronological age (CA) in children treated for ALL was essentially equal to bone age (BA). This finding is optimistic in that it signifies that growth in children with ALL is not compromised, as one might assume. It is important to note that a long-term or permanent decrease in final adult stature was not seen unless (1) the patient sustained irreversible damage to the hypothalamic-pituitary axis, which in turn adversely affected the production and release of essential growth hormones and/or (2) the patient was so young that critical endocrinological changes were not expressed (Lawrence et al. 1971).

Statistical analysis revealed a desirable situation. We analyzed the data using analysis of variance, having partitioned the HW bone ages into intervals based on how long past the onset of treatment the examination was made, which is concomitantly, the age at diagnosis. The data for boys (Fig. 18) showed that the HW films taken within one year of diagnosis exhibited a developmental delay (mean BA-CA of -0.71 years), but the subsequent films showed a gradual
diminution in the size of BA-CA such that (1) only the first age interval showed a significant delay in HW bone age and (2) BA-CA improved over time. It seemed parsimonious to assume that the initial discrepancy (a 10% delay in BA compared to CA) because these children’s tempo of growth (irrespective of ALL) differed from the tempo of children used to develop the GP2 standards. Alternatively, it could be argued from these results that (1) in boys (but not in girls) ALL delays growth, so BA-CA is significant at the start of treatment and (2) the potent antimitotic drugs used to treat the disease is somehow protective such that BA-CA diminishes towards zero during and after treatment. This interpretation flies in the face of several known iatrogenic consequences of chemotherapeutic treatment, and this interpretation is not supported by the few other studies of HW bone age in children treated for ALL (Tamminga et al. 1993).

Moreover, the girls in the present sample show a simpler pattern (Fig. 19). Mean BA-CA is very close to zero at the start of treatment and remains there — there is no statistical evidence that treatment has any effect on BA-CA.

These data can be expressed in another fashion to affirm these earlier tests. Here we forego the categorization of cases into intervals after diagnosis and simply plot BA-CA against time in treatment (Fig. 24). The linear regression lines, calculated by sex, both begin slightly below zero but have positive slopes. For boys, the Y intercept, which is the status at diagnosis, shows that BA-CA starts off negative (intercept = -0.66; t = 3.3; P = 0.0018), but BA-CA diminishes
Fig. 24. Bivariate plot between time in treatment and BA-CA, by sex, using all 108 hand-wrist films. The lines are based on linear regression analysis.
insignificantly with time (b = +0.05; t = 1.0; P = 0.3062).

For girls, there is no evidence of the initial depression in BA seen for boys; the Y intercept is -0.08, which is not significantly different from zero (t = 0.3; P = 0.7979). The slope of the line fit to the data for girls is statistically indistinguishable from a horizontal line, meaning that there is no delay at diagnosis, nor does treatment have any discernible effect on the tempo of HW bone maturation. In sum, these results wholly duplicate those describe before, but use a different method of assessment to confirm the results.

It is simpler to invoke sampling fluctuation (i.e., a nonrepresentative sampling of boys early in treatment) to explain the observed BA-CA depression and/or a different tempo of growth in the GP2 standards than to accept that BA-CA depression is biologically important. These conjectures can be solved with replication of this study using different children who have been treated for ALL.
Acute Lymphoblastic Leukemia (ALL) constitutes the most common malignancy of childhood, consisting of 31 percent of all childhood malignancies. ALL primarily strikes children between primarily two and ten years of age, but may occur in adolescents and adults. Treatment strategies to target the disease include individual or combination therapy with chemotherapeutic agents, irradiation of the neck and/or spine, and, occasionally, bone marrow transplantation. The aggressive nature of anti-neoplastic therapies often results in numerous craniofacial and dental sequelae as well as additional iatrogenic effects on the entire body. Cranial irradiation may adversely affect the hypothalamic-pituitary axis, resulting in a decrease in growth hormone production. Children with ALL may experience a transient reduction in stature coincident with therapy, and the risk of permanent size diminution increases greatly if treatment includes cranial irradiation.

The present study used hand-wrist radiographs to determine the maturational status of children treated for ALL. We anticipated that anti-neoplastic therapies would influence a child’s bone development and thus children in our sample would show delayed bone development.
Hand-wrist (HW) radiographs of 73 children (39 boys, 34 girls) treated at St. Jude Children’s Research Hospital for ALL were evaluated to assess HW bone age. Mean chronological age at diagnosis was 4.54 years (sd = 2.81). Bone ages were scored using Greulich and Pyle’s 1959 atlas method.

We supposed that the combination of antimitotic drugs used to treat ALL would discernibly depress the childrens’ tempos of growth, so that BA-CA (bone age minus chronological age) would be negative. Instead, the data showed no evidence of any effect. In fact, since there was no depression of the rate of maturation during treatment, there was no need for a compensatory, or “catch-up,” phase. There is no evidence in this study that treatment for ALL has any effect on the progress of hand-wrist morphological bone age. Treatment for ALL spares the tempo of growth as assessed by HW bone age.

This finding is quite favorable from the standpoint of the child’s overall health, as well as for orthodontic treatment. Orthodontics frequently harnesses a child’s growth potential or “growth spurt” to improve the treatment outcome. Certain Class II or Class III malocclusions may be corrected in young children through orthodontic techniques that maximize the child’s growth potential. Such examples might include treating a Class II malocclusion with a facebow headgear to the maxillary molars. The headgear serves to constrain the maxilla, while allowing the mandible to grow forward. Knowing that the growth potential of children treated for ALL is not hindered or delayed ensures these
children may be treated orthodontically as normal individuals with normal growth spurts. Orthodontic treatment in these children, however, must always be in cooperation with and under the approval of the supervising oncologist or physician. Communication between the oncologist, dentist and orthodontist, as well as any additional physicians, may guarantee that the child’s overall health is best managed.
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APPENDIX
Appendix

Individual plots of hand-wrist bone age against chronological age for
the 73 children with ALL in this study
Fig. A-1. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1056). The square symbol denotes age at diagnosis of ALL.
Fig. A-2. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1036). The square symbol denotes age at diagnosis of ALL.
Fig. A-3. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1020). The square symbol denotes age at diagnosis of ALL.
Fig. A-4. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1039). The square symbol denotes age at diagnosis of ALL.
Fig. A-5. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1029). The square symbol denotes age at diagnosis of ALL.
Fig. A-6. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1059). The square symbol denotes age at diagnosis of ALL.
Fig. A-7. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1003). The square symbol denotes age at diagnosis of ALL.
Fig. A-8. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1030). The square symbol denotes age at diagnosis of ALL.
Fig. A-9. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1007). The square symbol denotes age at diagnosis of ALL.
Fig. A-10. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1052). The square symbol denotes age at diagnosis of ALL.
Fig. A-11. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1024). The square symbol denotes age at diagnosis of ALL.
Fig. A-12. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1047). The square symbol denotes age at diagnosis of ALL.
Fig. A-13. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1010). The square symbol denotes age at diagnosis of ALL.
Fig. A-14. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1025). The square symbol denotes age at diagnosis of ALL.
Fig. A-15. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1032). The square symbol denotes age at diagnosis of ALL.
Fig. A-16. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1013). The square symbol denotes age at diagnosis of ALL.
Fig. A-17. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1038). The square symbol denotes age at diagnosis of ALL.
Fig. A-18. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1040). The square symbol denotes age at diagnosis of ALL.
Fig. A-19. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1018). The square symbol denotes age at diagnosis of ALL.
Fig. A-20. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1055). The square symbol denotes age at diagnosis of ALL.
Fig. A-21. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1033). The square symbol denotes age at diagnosis of ALL.
Fig. A-22. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1065). The square symbol denotes age at diagnosis of ALL.
Fig. A-23. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1008). The square symbol denotes age at diagnosis of ALL.
Fig. A-24. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1058). The square symbol denotes age at diagnosis of ALL.
Fig. A-25. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1071). The square symbol denotes age at diagnosis of ALL.
Fig. A-26. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1041). The square symbol denotes age at diagnosis of ALL.
Fig. A-27. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1066). The square symbol denotes age at diagnosis of ALL.
Fig. A-28. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1012). The square symbol denotes age at diagnosis of ALL.
Fig. A-29. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1045). The square symbol denotes age at diagnosis of ALL.
Fig. A-30. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1063). The square symbol denotes age at diagnosis of ALL.
Fig. A-31. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1019). The square symbol denotes age at diagnosis of ALL.
Fig. A-32. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1022). The square symbol denotes age at diagnosis of ALL.
Fig. A-33. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1068). The square symbol denotes age at diagnosis of ALL.
Fig. A-34. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1061). The square symbol denotes age at diagnosis of ALL.
Fig. A-35. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1017). The square symbol denotes age at diagnosis of ALL.
Fig. A-36. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1043). The square symbol denotes age at diagnosis of ALL.
Fig. A-37. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1062). The square symbol denotes age at diagnosis of ALL.
Fig. A-38. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1054). The square symbol denotes age at diagnosis of ALL.
Fig. A-39. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1051). The square symbol denotes age at diagnosis of ALL.
Fig. A-40. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1031). The square symbol denotes age at diagnosis of ALL.
Fig. A-41. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1034). The square symbol denotes age at diagnosis of ALL.
Fig. A-42. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1069). The square symbol denotes age at diagnosis of ALL.
Fig. A-43. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1027). The square symbol denotes age at diagnosis of ALL.
Fig. A-44. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1006). The square symbol denotes age at diagnosis of ALL.
Fig. A-45. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1023). The square symbol denotes age at diagnosis of ALL.
Fig. A-46. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1057). The square symbol denotes age at diagnosis of ALL.
Fig. A-47. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1072). The square symbol denotes age at diagnosis of ALL.
Fig. A-48. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1028). The square symbol denotes age at diagnosis of ALL.
Fig. A-49. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1009). The square symbol denotes age at diagnosis of ALL.
Fig. A-50. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1064). The square symbol denotes age at diagnosis of ALL.
Fig. A-51. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1015). The square symbol denotes age at diagnosis of ALL.
Fig. A-52. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1050). The square symbol denotes age at diagnosis of ALL.
Fig. A-53. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1001). The square symbol denotes age at diagnosis of ALL.
Fig. A-54. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1021). The square symbol denotes age at diagnosis of ALL.
Fig. A-55. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1011). The square symbol denotes age at diagnosis of ALL.
Fig. A-56. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1067). The square symbol denotes age at diagnosis of ALL.
Fig. A-57. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1000). The square symbol denotes age at diagnosis of ALL.
Fig. A-58. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1016). The square symbol denotes age at diagnosis of ALL.
Fig. A-59. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1004). The square symbol denotes age at diagnosis of ALL.
Fig. A-60. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1026). The square symbol denotes age at diagnosis of ALL.
Fig. A-61. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1048). The square symbol denotes age at diagnosis of ALL.
Fig. A-62. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1042). The square symbol denotes age at diagnosis of ALL.
Fig. A-63. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1049). The square symbol denotes age at diagnosis of ALL.
Fig. A-64. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1044). The square symbol denotes age at diagnosis of ALL.
Fig. A-65. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1014). The square symbol denotes age at diagnosis of ALL.
Fig. A-66. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1046). The square symbol denotes age at diagnosis of ALL.
Fig. A-67. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1060). The square symbol denotes age at diagnosis of ALL.
Fig. A-68. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1070). The square symbol denotes age at diagnosis of ALL.
Fig. A-69. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1002). The square symbol denotes age at diagnosis of ALL.
Fig. A-70. Plot of chronological age against GP2 bone age (circle) for a boy (pseudo-record #1053). The square symbol denotes age at diagnosis of ALL.
Fig. A-71. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1037). The square symbol denotes age at diagnosis of ALL.
Fig. A-72. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1005). The square symbol denotes age at diagnosis of ALL.
Fig. A-73. Plot of chronological age against GP2 bone age (circle) for a girl (pseudo-record #1035). The square symbol denotes age at diagnosis of ALL.
Mary Elizabeth Martin was born in Norfolk, Virginia, on August 15, 1977 where her father, John Martin, was stationed with the United States Navy. Her family moved to Middle Tennessee when she was six months old and resided briefly with her paternal grandparents in Springfield, Tennessee. Her family eventually settled in Hendersonville, Tennessee where she graduated from Hendersonville High School in May of 1995. Mary Beth attended The University of Tennessee at Knoxville where she majored in Biology and received a Bachelor of Science degree in May of 1999. She received her dental training and a Doctor of Dental Surgery degree from The University of Tennessee at Memphis in May of 2003. In August of 2003, she entered The University of Tennessee’s Orthodontic program. She is expected to receive a Master of Dental Science degree in May 2006. Following graduation, Mary Beth will join her husband, David, to live in Jonesboro, Arkansas.