

Childhood Acute Leukemias in Hispanic Population: Differences by Age Peak and Immunophenotype

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1. Introduction

Childhood cancer represents 0.5–5.7% of all cancers (Birch & Blair, 1992; Smith & Gloecker, 2002). The most important kinds of cancer during childhood differ from those most frequently found in adulthood (Schellong, 1985). During infancy, the principal cancers are not epithelial, in contrast to those in the later stages of life (Miller, 1983). Therefore, it is possible that the risk factors for cancer are different during infancy than during adulthood; for children, risk factors may be present *in utero* or during the first months of the life (Draper, 1994).

The age peak of cancer during infancy, especially those for leukemias and lymphomas, varies among countries. Although the peak age for leukemias worldwide is principally between 2–5 years of age, a peak as late as 7–13 years of age was reported for Niger (William, 1975). In developed countries such as Germany or the United States of America (USA), the age peak for lymphomas is between 10–14 years of age, whereas in less developed countries, Mexico for example, the age peak is between 5–9 years of age (Fajardo-Gutiérrez et al., 1995; Kaatsch et al., 1995; Nully-Brown et al., 1989; Young et al., 1986).

Leukemia is the most common cancer in children under 15 years old, representing between 25–35% of all childhood cancers in most populations (Parkin et al., 1988, 1998). Leukemia is a heterogeneous group of hematopoietic malignancies, with several biologically distinct subgroups. The main subtypes of leukemia described by most cancer registries include acute lymphoblastic leukemia (ALL), representing about 80% of all leukemias; AML, with a frequency of 15%; and chronic myeloid leukemia (CML) with a frequency of 3–5% (Bathia, 2003). ALL is the most frequent leukemia in infancy (Mejía Aranguré et al., 2005a). The age

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peak at 2–5 years of age was reported for England after 1920, for the USA in 1940, and for Japan in 1960; during this time, this same peak was demonstrated for African-American with ALL in the USA (Greaves et al., 1993; Pratt et al., 1988; Ramot & Magrath, 1982).

We analyzed the immunophenotype of all cases of ALL registered in eight of the nine public hospitals, located in Mexico City, which attended children with ALL from January 2010 to May 2011. We showed that, for the 320 cases registered, the frequency of childhood ALL in Mexico City had two age peaks (Fig. 1), in agreement with data reported previously (Bernáldez et al., 2008; Mejía Arangure et al., 2005a). In Brazil, two peaks in ALL have also been reported (de Souza Reis et al., 2011).

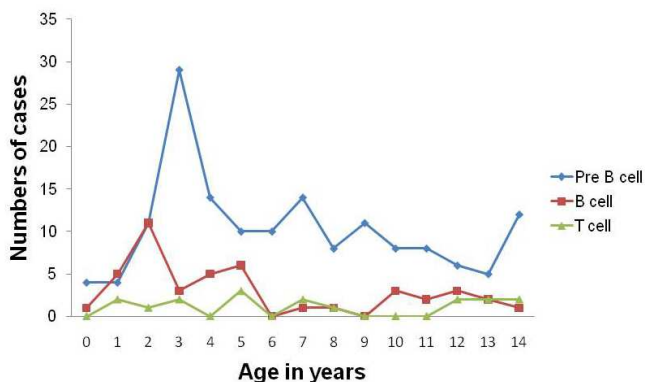


Fig. 1. Immunophenotypes in children from Mexico City during 2010–2011. The children with acute lymphoblastic leukemia have two age peaks, specially the children with Pre B cell immunophenotype.

The aim of this chapter is to present different hypotheses related to the age peak of the ALL in children. We briefly describe the ontology of B and T lymphocytes and discuss an apparent association between the genetic rearrangements involved and the age peak in leukemias. We also review data on the age peak of ALL in different countries. At the end of the chapter, we propose an hypothesis with respect to the age peak in Latin American populations and in general.

2. B- and T-cell development

After birth and throughout life, development and replenishment of lymphoid cells is a highly ordered process that starts in bone marrow (BM) with the differentiation of multipotential hematopoietic stem cells (HSC). In this multi-step process, multiple alternate lineage potentials are gradually lost and lineage commitment is coincident with gain of specialized functions. Over the last few years, remarkable advances have been made in characterizing the primitive progenitors that initiate the lymphoid program; the patterns of transcriptional activity that control decisions about the fate of early lineages and late maturation process; and the environmental signals that influence the differentiation pathway during normal hematopoiesis. Malignant early lymphoid development is currently under intense investigation, and the existence of leukemic stem cells is still a matter of debate. However, identification of cytogenetic abnormalities in cells lacking lineage markers

and the unsuspected genetic diversity within individuals strongly suggests the participation of primitive cells in this disease.

2.1 From stem cells to committed B-cell progenitors

Because mature blood cells have finite life spans, they are constantly replaced from a unique cell population of HSC that resides in specialized niches in the BM (Baba et al., 2004). Within the hematopoietic system, HSC are the only cells with the ability to extensively give rise to identical daughter stem cells (self-renewal) and to differentiate into all functional blood cells (multipotency) (Seita & Weissman, 2010). The hematopoietic system is organized as a hierarchy of cell types with differing capacities for self-renewal, proliferation, and differentiation. In the pathways of this system, developing lymphoid or myeloid cells progress through critical stages of differentiation of multipotential and self-renewing HSC to multipotential early progenitors, which give rise to oligopotent progenitors. Downstream, the production of lineage-committed precursors is crucial for maturation of blood cells (Fig. 2). The lymphoid lineage consists of B, T, and natural killer (NK) cells; the myeloid lineage includes granulocytes, monocytes, macrophages, erythrocytes, megakaryocytes, and mast cells. Dendritic cells (DCs) are generated starting from the pathways of lymphoid or myeloid differentiation.

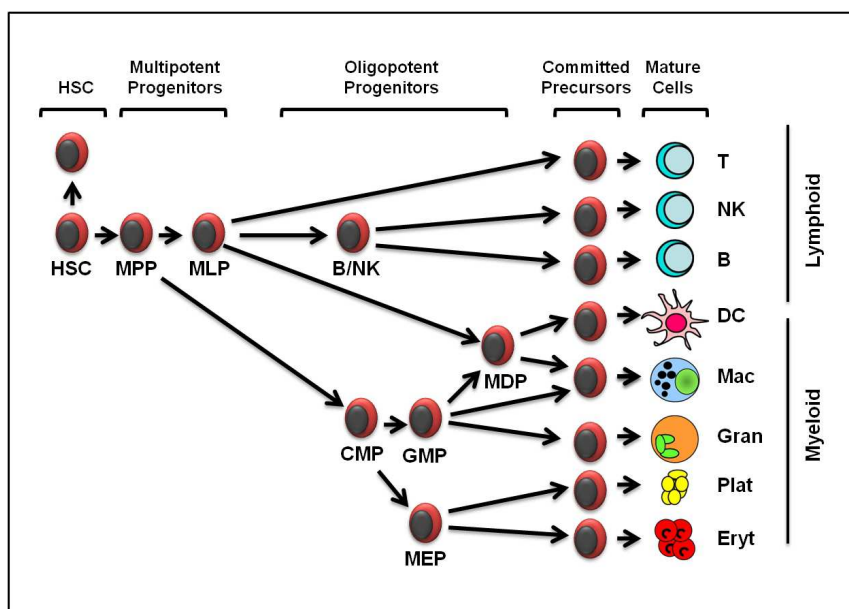


Fig. 2. Hematopoietic development in humans. The self-renewing hematopoietic stem cell (HSC) gives rise to multipotent progenitors (MPP), which have the ability to differentiate into common myeloid progenitors (CMP), and into multi-lymphoid progenitors (MLP). Mature blood cells are produced from lineage-committed precursors. The hierarchical structure of the hematopoietic system is shown. GMP, granulocyte and monocyte progenitors; MEP, megakaryocyte and erythrocyte progenitors; MDP, monocyte and dendritic cell progenitors; NK, natural killer cells; DC, dendritic cell; Mac, macrophage; Gran, granulocyte; Plat, platelets; Eryt, erythrocyte.

Current knowledge about the development of the lymphoid system is based, in great part, on the work done in mouse models, which has demonstrated that this differentiation program begins in BM in the fractions of lymphoid-primed multipotent progenitors (LMPP) and early lymphoid progenitors (ELP) capable of differentiating into T, B, NK, and conventional dendritic cells (Pelayo et al., 2005a, 2006a; Welner et al., 2008b). ELP also produce plasmacytoid dendritic cells (pDC), and interferon-producing killer dendritic cells (IKDC), both of which are key components of the innate immune response to infections (Pelayo et al., 2005b; Welner et al., 2007). The more differentiated common lymphoid progenitors (CLP) have substantially lost the possibility of differentiating into multiple lineages and efficiently generate B- and NK-cell precursors. Interestingly, HSC and early progenitors proliferate in response to systemic infection and replenish innate immune cells by using mechanisms that apparently involve interferons, tumor necrosis factor- α , and Toll-like receptors (TLR)—these last recognize viral/bacterial components. Thus, plasticity in primitive progenitor cells is sensitive to extrinsic agents that can modify differentiation fates during infection, thus supporting the idea that the stages of restriction of hematopoietic lineages are less abrupt than previously thought (Baldrige et al., 2011; Welner et al., 2008a). In humans, the early hematopoietic progenitors are confined in the BM to a cellular compartment that expresses CD34 (Bloom & Spits, 2006). This fraction of multipotent stem cells is characterized by the phenotype Lin-CD34⁺CD38^{-/lo}CD10⁻CD45RA⁻, whereas that of the earliest lymphoid progenitors is characterized by the phenotype Lin-CD34⁺CD38^{-/lo}CD45RA⁺CD10⁺ and has been recently designated as multi-lymphoid progenitor (MLP) (Doulatov et al., 2010). While a description that fully matches the definition of mouse ELP is still missing, Lin-CD34⁺CD38⁺CD45RA⁺CD10⁺ cells, which differentiate principally into B and NK cells, are considered the counterparts of mouse CLP (Fig. 2). Downstream, the sequential differentiation of lineage-restricted precursors generates Pro-B, Pre-B, and immature-B cells that eventually are exported to the peripheral lymphoid tissues. As in mice, human lymphopoiesis can undergo adjustments in cell-fate decisions under inflammatory conditions or during infections (Baldrige et al., 2011; Kim et al., 2005).

2.1.1 Biological differences between early hematopoiesis in neonatal and in adult

Some properties in hematopoietic development, including cell-cycle progression, transcription-factor networks, and growth-factor production, show substantial differences between newborns and adults (Mayani, 2010; Nguyen et al., 2010; Pelayo et al., 2006b).

During fetal and neonatal development, the hematopoietic system faces a complex set of demands, including rapid population turnover, protection against infection, and avoidance of harmful inflammatory immune responses (Levy, 2007; Pelayo et al., 2006b). After birth, there is an age-dependent maturation of the immune response; apparently, prenatal and postnatal exposure to microbial components or products may accelerate this maturation process (Levy, 2007). In response to TLR agonists, production of cytokines and chemokines is poor in early life but increases with age, though it is still limited in one-year-old infants, suggesting that the first year of life represents a critical period for the acquisition of competence by developing hematopoietic cells (Nguyen et al., 2010).

Moreover, hematopoietic stem and progenitor cells must divide extensively to generate the billions of new blood cells needed each day. Yet, little is known about the period when the expansion takes place or about the mechanisms responsible for the biological differences between fetal and adult primitive cells. However, it is widely recognized that fetal- and

neonatal-derived HSC and lymphoid progenitors possess higher proliferation and expansion potentials. Furthermore, during rebound from chemotherapy, adult progenitors acquire some, but not all, of the characteristics of fetal cells (Mayani, 2010; Pelayo et al., 2006b). Telomere dynamics, key cell-cycle mediators, and differential gene expression may account for the fetal/adult disparity. Whether the potential for high proliferation during early life makes hematopoietic precursor cells more vulnerable to gene mutations is not as yet clear, but its implication in the onset of neoplastic hematological diseases in neonates might be decisive.

2.1.2 Early steps in malignant lymphoid development

ALL is characterized by the monoclonal/oligoclonal proliferation of hematopoietic precursor cells of the lymphoid series within the BM. Although in recent years studies have reported important advances in the investigation of genetic, molecular, karyotypic, and phenotypic abnormalities that are prevalent in this disorder, the understanding of the mechanisms that damage the earliest program of lymphoid development remains poor. Results from cell cultures for early hematopoiesis, detection of specific leukemic karyotypes in primitive CD34+ cells, and data showing that cells with immature phenotypes are capable of engrafting and reconstituting leukemia in immunodeficient mice suggest that infant B cell-leukemia initiating cells have primitive characteristics (Cobaleda et al., 2000; Cox et al., 2004, 2009; Espinoza-Hernández et al., 2001) and are subject to intrinsic and extrinsic stimuli that could trigger lineage instability. On the other hand, leukemic blasts can also completely re-establish leukemic phenotypes *in vivo*, conferring them with stem-cell properties (Heidenreich & Vormoor, 2009). These conflicting results reveal that key questions regarding leukemic stem cells and lymphoid development in ALL remain unsolved. Recently, the combination of clonal studies, alterations in genetic copies, and xenotransplantation models have shown unsuspected genetic diversity, supporting the idea of multi-clonal evolution of leukemogenesis, rather than that of lineal succession (Dick, 2008). Future progress in this area will ultimately lead to an understanding of the biology of leukemia, as well as behavior and prognosis among individual groups.

2.2 Murine B-cell maturation in bone marrow

The first cells that exhibit commitment to the B-cell lineage in mice (the model in which this process is currently better understood) are B220+, CD19+, and CD43+ pro-B cells (Allman et al., 1999). During B-cell development, the main goal is to generate functional cell populations that are capable of expressing a diverse repertoire of B-cell antigen receptors (BCR), with each clone having specificity to recognize and counteract a new or recurrent pathogen. Antigen recognition is mediated by a heterodimer of immunoglobulin (Ig) heavy chains and light chains and signaling for an antigen-induced B-cell response is mediated by the molecules Ig α (CD79a) and Ig β (CD79b). Ig α and Ig β exist as a disulfide-coupled heterodimer in non-covalent association with the Ig antigen-recognition element. Ig α /Ig β signaling is dependent upon distinct motifs localized in the cytoplasmic tails of these proteins, the immunoreceptor tyrosine-based activation motifs (ITAM) (Cambier, 1995; Fuentes-Pananá et al., 2004b). The BCR can generate signals that lead to a variety of outcomes, depending upon the developmental stage of the B cell and the degree and persistence of receptor aggregation. Although the mature form of the BCR is present only in immature and mature B cells, genetic and biochemical studies have shown that various

forms of the BCR are expressed at defined stages of B-cell development that are required for progression of B cells through several defined developmental checkpoints (Fuentes-Pananá & Monroe 2001; Fuentes-Pananá et al., 2004a).

In the pro-B stage in which the heavy chain is in the process of recombination, the signaling proteins Ig α and Ig β are expressed on the cell surface and are associated with the protein calnexin, and perhaps other as yet unknown proteins, forming the so-called "pro-BCR" (Nagata et al., 1997). Pro-B cells that successfully produce an Ig heavy-chain protein transport it to the surface in association with Ig α /Ig β and with the surrogate light-chain complex that is composed of $\lambda 5$ and V pre-B (the pre-BCR receptor) (Karasuyama et al., 1996; Melchers et al., 1993). Surface expression of this receptor marks the transition to the pre-B stage, a step that is marked by loss of CD43 and gain of CD22 expression, by allelic exclusion of the un-recombined heavy-chain allele, and by the opening and initiation of recombination at the λ Ig light chain loci (Rolink & Melchers, 1993). A similar mechanism operates in the pre-B stage in which the successful recombination of light chain and its pairing with the Ig heavy chain and Ig α and Ig β allows the assembly of the mature form of the BCR and marks the transition to the immature stage. Intimate contact between the immature-B cell and the stromal cells of the BM allows those receptors capable of recognizing self-antigens to be identified and eliminated through a variety of mechanisms collectively termed "tolerance". Non-self-reactive B cells exit to the periphery and reach the spleen where they are again tested for reactivity against self-antigens before they transition to the mature stage (von Boehmer & Melcher, 2010).

2.2.1 Heavy and light chain VDJ recombination and positive selection in BM

The main goal during the pro-B and pre-B stages is to generate a signaling-competent antigen receptor, with the progression of development conditioned by the signaling capacity of the receptor complex. The BCR Ig heavy and light chain genes are composed of constant and variable domains, the recombination of which makes BCR clonal diversity possible. The variable domain is formed by a series of segments termed variable (V), diversity (D), and joining (J) (Fig. 3A), which are brought together by a site-specific recombination process termed VDJ recombination. This is a highly ordered process during which the D and J fragments are rearranged and the V segment is then joined to the DJ fragment; these steps occur first in the heavy and then in the light chain loci (Fig. 3B) (Fuentes-Pananá et al., 2004b; Thomas et al., 2009). This process is essential for the adaptive immune function of the lymphocyte. As mentioned above, the pro-B stage is characterized by rearrangement of the Ig heavy chain and it is further divided according to the status of the rearrangement; in mice, Marshall named these sub-stages proB-A (during which the heavy chain is in the germ-line state), proB-B (during which D and J are recombined), and proB-C (during which V-DJ is recombined) (Hardy et al., 1991). In the pre-B stage, the light chain V and J fragments are recombined, first in the λ and then in the κ loci (Fig. 3A).

Unsuccessful recombination (e.g., heavy chain VDJ fragments that are not in a proper reading frame) or unsuccessful pairing of the pre-BCR components results in pro-B cells that are unable to proceed to the pre-B stage, thus leading the developing pro-B cell to apoptosis. This observation supports the concept of an active signaling role for the pre-BCR in generating the permissive signal that allows differentiation through the pre-B stage (Bannish et al., 2001; Mandal et al., 2009; Yasuda et al., 2008). A similar mechanism is thought to operate for the transition from pre-B to immature cells, which requires expression of the

mature form of the BCR (Bannish et al., 2001; Mandal et al., 2009; Yasuda et al., 2008). In addition to their VDJ recombination status, all pro-B and pre-B stages can be recognized by their patterns of surface-marker expression (Hardy et al., 1991).

2.3 T-cell development

T-cell development occurs in the thymus through equivalent processes of VDJ recombination, selection against self-reactive clones, and maturation into fully functional clones (Figure 3B). Expression of the T-cell antigen receptor (TCR) on the surface of the T cell marks the transition through all developmental stages. The TCR is a complex of proteins that may be functionally divided into the antigen-binding unit formed by the β and α chains (also in a smaller fraction of T cells, the γ and δ chains) and the signaling unit formed by the CD3 chains. The β and α (and γ/δ) chains consist of constant and variable regions, with VDJ recombination taking place in the latter. There are different types of CD3 chains and each mature TCR is associated with six of them: two CD3 ϵ , two CD3 ζ , one CD3 γ , and one CD3 δ . The stages of T-cell development are known as the following: pro-T (CD3^{pos}CD44^{pos}CD4^{neg}CD8^{neg}; the TCR β chain is rearranged); pre-T (CD3^{pos}CD44^{pos}CD25^{pos}CD4^{neg}CD8^{neg}; the TCR α chain is rearranged); CD4 and CD8 double-positive T cells [CD3^{pos}CD4^{pos}CD8^{pos}; equivalent to immature/transitional B cells (the stage in which tolerance mechanisms are applied to the developing T cell)]; and CD4 or CD8 single-positive cells (mature helper or cytotoxic T cells). Pro-T and pre-T cells are further subdivided according to the status of the β and α chains rearrangements: DN1 (β chain is in germ-line configuration); DN2 (D and J rearrangement of the β chain); DN3 (V joins to DJ of the β chain); and DN4 (V and J rearrangement of the α chain). DN1, DN2, and DN3 are pro-T stage; DN4 is a pre-T stage. The progression of recombination-associated development is illustrated in Fig. 3B. Expression of pro-TCR, pre-TCR, and mature-TCR receptors mark the progression through T-cell developmental checkpoints, homologous to the positive- and negative-selection mechanisms for B cells (Love et al., 2010; Wiest, 1994, 1995).

2.4 Human B- and T-cell development

Selection processes operating on developing B and T cells of all mammals are the same; thus, B- and T-cell development in human is also mainly divided by the process of VDJ recombination and expression of antigen-recognition complexes on the cell surface and by the proliferative expansion of clones that have successfully completed the rearrangement of their receptors (Blom & Spits, 2006). However, for the human, all these processes are less well understood than are their counterparts in the murine model. Importantly in human lymphocyte development, the pro-B and pre-B sub-stages are the ones generally found to be compromised in human pediatric B-cell ALL. B-cell ALL is characterized by cells unable to progress along the differentiation pathway. The stages more often compromised are: proB-A (before heavy-chain recombination), proB-C (after heavy-chain recombination), and large pre-B stage (before light-chain rearrangement) (Fig. 3B) (Hardy et al., 1991; Rolink et al., 1991). These stages are better known in humans as early proB or pre-proB (A); proB (B); preB1 (C) (proB stage); and preB2 (large preB stage) (Fig. 3B). All these stages in human B and T cells can also be recognized by the expression of specific surface markers, a characteristic that has helped to classify the different types of pediatric ALL. In humans, B cells are recognized by the expression of CD19 and CD10; T cells by CD2, CD3, CD5, and

CD7; and, for the proliferating immature-B cells, pre-proB cells by CD34⁺CD19⁺CD10⁺; preB1 by CD34⁺CD19⁺CD10⁺; and preB2 by CD34⁺CD19⁺CD10⁺. Immature T cells are mainly recognized by the lack of expression of CD4 and CD8 and expression of T-cell markers.

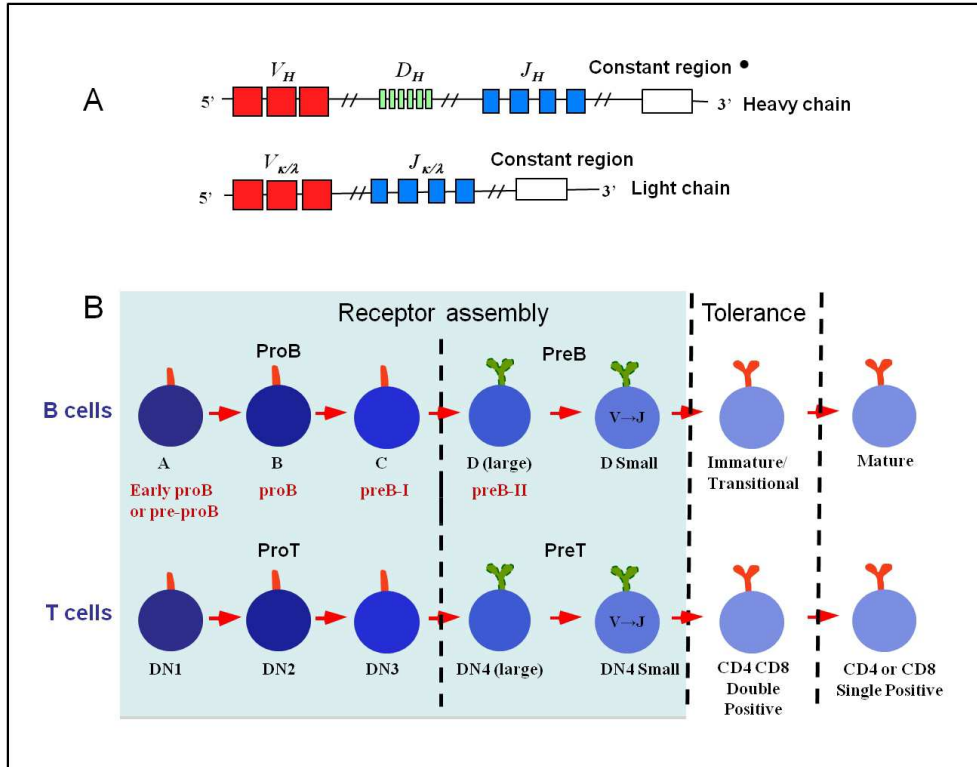


Fig. 3. B- and T-cell development. A) The Ig heavy and light chain genes are comprised of constant and variable domains; the variable domain is formed by an n number of segments termed variable (V), diversity (D), and joining (J) in the heavy chain and by segments V and J in the light chain. These segments are brought together by a site-specific recombination process, termed VDJ recombination, which is responsible for the extensive repertoire of BCR specificities. There are two loci for light chain, κ and λ . Here, all the loci are shown in germline configuration, prior to the process of VDJ recombination. B) All B- and T-cell stages can be divided according to the main processes guiding development: receptor assembly, tolerance, and activation. Receptor assembly stages (light blue box) in B and T cells are differentiated by the process of VDJ recombination in the heavy (IGH) and light (IGL) chains, which are recombined in the pro-B and pre-B stages, respectively (β and α rearrangement in pro-T and pre-T cells). The nomenclature of each sub-stage in the mouse model is shown in black letters, A-D (Marshall's) for B cells and DN1–4 for T cells; the most common human nomenclature is shown in red letters. The dashed lines separating all stages indicate checkpoints at which signaling from the preBCR and BCR is required for positive selection and progression along the B-cell maturation pathway. The proBCR, proTCR, preBCR, preTCR, and mature receptors are also illustrated in their respective stages.

3. Incidence peak of acute leukemia with specific cytogenetic aberrations in childhood

ALL is a clonal disease driven by mutations. The incidence of leukemia among children varies considerably with age. Age at diagnosis has played a relevant role in the epidemiology of these diseases and in the determination of risk groups and treatment stratification (Smith et al., 1997). The age-related incidence pattern of ALL has been established by the demonstration of the clone-specific 11q23-, t(12;21)-, as determined by blood testing (Guthrie cards), and hyperdiploidy (Gale et al., 1997; Wiemels et al., 2002).

The majority of childhood ALL cases show the emergence *in utero* of pre-leukemic cells and, postnatally, rare interactions between the immune system and childhood infections (Greaves, 2002).

The incidence rates of childhood ALL vary from country to country; in Europe and the USA, 85–90% of the cases have a B-cell-precursor phenotype (pre-B) with an incidence peak in the 2–7 years age group. For childhood T-cell ALL, lower incidence peaks have been reported (Hjalgrim et al., 2003). Most cases of pre-B ALL carry either a high hyperdiploid karyotype or the chromosomal translocation t(12;21) (p13;q22). A high hyperdiploid karyotype, which is present in 30% of pediatric patients, shows a modal chromosome number above 50, which involve trisomies of chromosomes X, 4, 6, 10, 14, 17, 18, and 21 and which, in most cases, arise by simultaneous chromosomal gain in a single abnormal mitosis (Paulsson et al., 2005). The chromosomal translocation t(12;21) (p13;q22) is found in 20–25% of cases and involves the gene *RUNX1* in chromosome region 21q22 and the gene *ETV6* in chromosome region 12p13. Both encode transcriptional factors that are essential for normal fetal hematopoiesis (Romana et al., 1995). High-hyperdiploid leukemic clones are sometimes missed by standard G-band karyotyping due to poor metaphase quality. The detection rates can be raised by extended fluorescence in situ hybridization (FISH) analyses, flow cytometry, DNA-index analyses, high-resolution comparative genomic hybridization (CGH), and comparative genomic array CHG (Kristensen et al., 2003; Nyggard et al., 2006). Translocation t(12;21) is cryptic by standard G-band karyotyping; its diagnosis is based on FISH analyses and reverse transcriptase-polymerase chain reaction (RT-PCR) (Nordgren, 2003).

Recent studies from twins with concordant leukemia suggest that a genetic event is involved in these acute leukemias: chromosomal translocations can have a prenatal origin (Ford, 1993, 1997, 1998; Gill et al., 1994; Wiemels et al., 1999a, 1999b). There is also indirect support that the prenatal origin of leukemic clones is derived from the presence of clonotypic rearrangements at the IGH and TCR loci in Guthrie spots (Fasching et al., 2000; Yagi et al., 2000). Because most of the studies have included a limited subset of leukemias, primarily those of lymphoid phenotypes, it remains an open question as to whether the prenatal origin of childhood leukemia is a possible, or a common, occurrence in other subgroups.

The most frequent translocation both in children (1–20 years of age) and in adults (older than 20 years) is t(8;21) AML1-ETO, which results in a fusion protein that disrupts the normal function of the transcription factors AML1 and ETO (Finnette et al., 1996). The incidence of leukemia with the t(8;21) AML1-ETO translocation increases slowly during childhood and is constant thereafter (Downing, 1999).

MLL/11q23 translocations are known to be involved in the leukemia of infancy, but they can also be found in older children and sometimes in the elderly (Johansson et al., 1998). MLL/11q23 translocations, of which t(11;19)(q23;p13) and t(4;11)(q21;23) are the most

common, have an incident peak during first year of life; 11q23-aberrant leukemias are the second most common malignancy. When these leukemias appear in very early infancy, their prenatal origin is proven; in monozygous twins (with identical MLL-rearrangements), the concordance rate is almost 100%. This suggests that, when these mutations are present at birth, they invariably lead to overt leukemia (Greaves et al., 2003). It is not known when MLL/11q23 translocations occur in adults.

Childhood acute leukemias are clinically related, but cytogenetically different, diseases; therefore, cytogenetic subgrouping is important to understand the diversity in their etiology, natural history, and epidemiology. An understanding of the epidemiology of childhood acute leukemia is relevant in order to clarify the cytogenetic backbone of etiologic research.

4. Infectious etiology of childhood leukemia

The hypothesis concerning an infectious etiology of childhood leukemia was first raised several decades ago (Cooke, 1942). Although, to date, it has not been possible to demonstrate the involvement of one or more particular infectious agent(s), different hypotheses are still in force based on epidemiological and demographic studies that have yielded evidence about the possible participation of infectious agents in childhood leukemogenesis. Independently, Greaves (1988), Kinlen (1988), and Smith (1997) have suggested different mechanisms by which certain events of infection may explain at least some cases of childhood leukemia.

4.1 Greaves' hypothesis

More than 20 years ago, Greaves (1988) proposed the involvement of infectious agents in the etiology of childhood leukemia. In the most recent version, his hypothesis includes a model of the natural history of ALL with a minimum of two oncogenic hits (Greaves, 2002), whereby a first hit occurs *in utero* and forms a pre-leukemic clone that requires at least one secondary, postnatal carcinogenic hit to unleash the malignant transformation. According to this hypothesis of "delayed infection", the second oncogenic event could be indirectly promoted by delayed exposure to an infectious agent that causes an uncontrolled immune response and promotes the malignant, abnormal proliferation of the pre-leukemic clone.

A number of studies have shown that first-born children have a higher risk of developing leukemia. Only children and those children who do not attend daycare have been assumed to be evidence of the hypothesis, in that, by having less contact with other children and potentially less frequency of exposure to infectious agents, the probability of developing the disease increased, when compared to children outside these groups (Dockerty et al., 2001; Infante-Rivard et al., 2000; Jourdan-Da Silva et al., 2004; Perrillat, et al., 2002; Petridou et al., 1993),

Nevertheless, some research has not provided absolute support for Greaves' hypothesis: data from the Northern California study group (Ma et al., 2005) indicated that daycare attendance and ear infections during infancy are associated with a lower risk of ALL; however, this was true only for non-Hispanic children.

It should be noted that Greaves' hypothesis concerns the common form of ALL (B-cell precursor). This form comprises most of the ALL cases that peak at 2–5 years of age and that are seen in developed countries or in affluent communities that have improved their living

standards and have become "more hygienic". Therefore, any relevant infection should occur in the first two years of life. Through comparison of international reports, variations in the peaks of childhood ALL have been identified. The aforementioned peak at 2–5 years of age is reduced, or even absent, for Black Africans and for other developing communities (Court & Doll, 1961; Hewitt, 1955; Ramot & Magrath, 1982, as cited in Chan et al., 2002). In Mexico, for example, two peaks have been reported; the first occurring at 2–3 years of age and the second at 6–9 (Bernaldez-Rios et al., 2008). A recent epidemiological study done in Mexico City showed that severe infections, occurring in the first year of life and requiring hospitalization, were associated with a higher risk of developing leukemia for children with Down syndrome (Flores-Lujano et al., 2009).

A possible interpretation of these results showing that infections in the first year of life represent risk factors (Cardwell et al., 2008; Roman et al., 2007) is that such infections could play a role as promoters, not as protectors, in the genesis of leukemia. In principle, this could mean that, for these groups, the infectious etiology of leukemia might be different than that proposed by Greaves.

4.2 Kinlen's hypothesis

When clusters of childhood leukemia and non-Hodgkin lymphoma were observed in the early 1980's near nuclear plants in Cumbria, England (Black, 1984), and at Dounreay, Scotland (Heasman et al., 1986), it was thought that such increase could have been a consequence of radioactive contamination by the nuclear plants, which might have caused somatic or germinal line mutations that produce cancer. However, there was no evidence of radioactive leaks (Committee on Medical Aspects of Radiation in the Environment [COMARE], 1986) or of epidemiological associations that showed greater occupational exposures of the parents (Gardner et al., 1990).

Kinlen proposed that the observed clusters of leukemia could have resulted from the unusual population mixing that occurred due to migration of workers and their families, who had travelled to work in the nuclear plants; he also hypothesized that a common, but unidentified, infectious agent could have been involved (Kinlen, 1988, 1995a). According to his proposal, cases of childhood leukemia would be a rare response from the isolated, uninfected individuals who were, therefore, susceptible to a putative infectious agent carried by these newcomers.

By extrapolating from animal leukemias caused by virus, a subtype of leukemia in adults, and by considering that childhood leukemia is not a contagious disease, Kinlen proposed that the agent involved could be a common virus causing a non-common response (Kinlen, 2011).

To date, Kinlen's working group has directed several studies, mainly in England and Scotland, and has observed a significant increase in cases of childhood leukemia where large-scale mixing between rural and urban populations occurred with unusual patterns of contact in the different communities (Kinlen et al., 1990, 1993, 1995b; Kinlen & Balkwill, 2001; Kinlen & Hudson, 1991; Kinlen & John, 1994).

Kinlen first proved his population-mixing hypothesis in the infectious etiology of childhood leukemia in Scotland, in a rural area that had received large influxes of people: the results showed a significant increase in the leukemia cases in children under five years of age (Kinlen, 1988). Another of his studies showed that excess of leukemia was higher in the 0–4 years age range; it was predominantly higher for children younger than 1 year, suggesting

an infection during pregnancy (Kinlen & Hudson, 1991). From his observations, Kinlen proposed that, during population influx, adults are the main transmitters of an infectious agent and that a rare response was more likely to be made by a naive immune system; thus, in the foregoing case, population mixing could be responsible for the leukemia cases seen, even in the first year of life. Nonetheless, the author did not associate the leukemia clusters with a particular subtype of disease and interpreted that any type of childhood and infant leukemia might have a common cause.

4.3 Smith's hypothesis

A third hypothesis regarding the infectious etiology of childhood leukemia was proposed by Smith (1997). He hypothesized that some cases of ALL observed in the 2–5 years age group (B-cell precursor) could be the result of an infection that occurred during pregnancy and that was transmitted from mother to fetus.

Unlike Greaves, who postulated that infections are secondary etiological factors acting indirectly, Smith suggested that infection is one of the first hits in leukemogenesis and that a related infectious agent acts directly, i.e., the agent is able to infect the immature-B cell and to promote genomic instability, thereby leading to the transforming process. According to his model, the agent involved must be able to cross the placenta and infect the fetus without causing serious abnormalities, have limited oncogenic capacity, and produce minimal primary symptoms (Smith, 1997).

Studies that have shown that maternal infections are associated with an increased risk of ALL support this model. Lehtinen et al. (2003) showed that maternal infection with Epstein-Barr Virus (EBV) was associated with a significantly increased risk of ALL. Naumberg's work group found a similar association when the mother had lower genital tract infections (Naumberg, 2002). However, other studies have shown little or no association between infections, either by varicella or influenza during pregnancy (Little, 1999, as cited in McNally 2004), by unspecified infection in pregnancy (McKinney et al., 1999), or by recurrent maternal infections (Infante-Rivard et al., 2000), and subsequent childhood leukemia in their offspring.

Molecular screening for viruses in leukemic cells has been used as a distinct approach to explore possible mechanism(s) of direct transformation occurring *in utero* or during infancy. Smith postulated that JC polyomavirus (polyomavirus are named from the initials of the patients from whom the first isolates were made) would be a good candidate, because it met all the conditions for his model. However, to date, viral sequences from the polyomaviruses, JC or BK (a closely related virus), have not been found in leukemic cells (MacKenzie, 1999). A number of viruses have been analyzed by different researchers. When blood or BM samples from patients diagnosed with childhood ALL were screened for members of the human herpesvirus family (HHV4, HHV6, HHV7, and HHV8), no evidence of the presence of these viruses in leukemic cells was found (MacKenzie, et al., 2001). Screenings for bovine leukemia virus (BLV) and transfusion-transmitted virus (TTV) have also been negative (Bender et al., 1988; Shiramizu et al., 2002). However, as the list of candidates has not been exhausted, massive sequencing to analyze non-human genomic components from leukemic cells, even those not previously identified, is an attractive approach.

There is evidence supporting each of the hypotheses presented here. Although the postulated mechanisms differ from each other, such hypotheses are not mutually exclusive. Because the notion of a unique carcinogenic factor is a biologically absurd assumption, the

various cases of leukemia in Mexico and around the world must be triggered by a variety of agents. Given the evidence of an infectious etiology involved in childhood leukemia, the identification of this agent, or agents, remains a scientific challenge.

5. Age peak of ALL in the world: epidemiologic aspects

Industrialization, urbanization, economic growth, and technological development have brought benefits to people, making everyday tasks easier and offering accessibility to services. However, modernization and industrialization have also led to changes in the environment and in lifestyle, which have changed the pattern of diseases in adults and children over the last century. Children now face predominantly chronic and disabling diseases such as obesity, diabetes, asthma, learning disabilities, birth defects, and cancer (Suk et al., 2003).

Internationally, published studies have reported lower incidence rates of ALL in Africa, Asia, and Vietnam, with the high rates found for Hong Kong, United Kingdom (UK), USA, and Japan, thus suggesting a correlation between the reported variations in incidence of ALL and socio-economic status (Parkin, et al., 1988, 1998; Stiller, 2004). However, the highest incidence rates of ALL have been reported for Costa Rica, Mexico City, and the Hispanic populations of Los Angeles, California and of Florida in the USA. (American Cancer Society, Surveillance Research [ACSSR], 2009; Glazer et al., 1999; Mejía-Aranguré et al., 2005b; Monge et al., 2002; Surveillance Epidemiology and End Results [SEER], 2008; Wilkinson et al., 2001). Of all cases diagnosed with ALL in the 2–7 years age group in Europe and the USA, approximately 85–90% had a precursor-B (pre-B) cell immunophenotype; the remainder were classified as having either T-cell or B-cell immunophenotype (14% or 2%, respectively (Pui, 1997). Reports from the USA indicate that African-American children have half the risk of developing ALL than do White children, with a peak age of presentation of ALL between 2–6 years old (median 4 years old) and with ALL predominating in males (male:female ratio of 1.2: 1) (Eden, 2010).

Reports regarding the incidence and trend for ALL from the Surveillance Epidemiology and End Results (SEER) in the USA and the Manchester Children's Tumor Registry (MCTR) in the UK indicate that the rates have increased annually by 0.6% and 1.1%, respectively. However, recent reports indicate a modest increase of 0.4% annually for the USA (Linabery & Ross 2008) and 1–4% for Europe (McNally et al., 2001) in the group of 1–4 years old.

Of particular note in reports of cancer registries are the high incidences of ALL in Costa Rica, Mexico City, and the Hispanic populations of the USA (Table 1). For the last case, it has been suggested that, because this population tends to live in more crowded conditions and poverty that does the White population, thereby exposing this population to infectious agents that have not as yet been identified but which may promote the development of acute leukemia (Yaris et al., 2004). There are marked variations in the incidence of ALL among populations worldwide; these variations can provide valuable clues to help understand the etiology of ALL.

A review of the latest articles published about the incidence of ALL in countries around the world (Table 2), some studies reported only the incidence of acute leukemia; nevertheless we included these studies because, as 80% of leukemias are ALL, the incidence rates reported provide very important information. We considered only those works that reported incidence rate, age group, and when done, immunophenotype. In these studies, the

results were generally reported by age groups: <1 year; 1–4 years; 0–4 years; 5–9 years; 10+ years; or 0–14 years. Some studies did not estimate the overall incidence rate and reported only by sex. Few studies had a graphic concerning the incidence of ALL and age, which would have better illustrated the peak incidence. Most published studies are from the Americas or Europe; few studies determined the immunophenotype of acute leukemia.

Report	Period	Age group (years)	Incidence rate per 10 ⁶ children
United States SEER ¹ (Howlander et al., 2010)	2007	0–14	35.0
CDC (NPCR) ² (USCS ³ Working Group, 2010)	2003–2007	0–19	46.0
ACSSR ⁴ (American Cancer Society, 2009)	2002–2006	0–14	46.7
Florida (Wilkinson et al., 2001)	1985–1997	0–14	49.7
California (Glazer et al., 1999)	1988–1994	0–14	44.0
Mexico City IMSS ⁵ (Mejía-Aranguré et al., 2005b)	2006–2007	0–14	57.6
Costa Rica (Monge et al., 2002)	1981–1996	0–14	43.1

¹ Surveillance, Epidemiology and End Results Program in United States of America.

² Center for Disease Control, Division of Cancer Prevention and Control, National Program of Cancer Registries (NPCR).

³ United States Cancer Statistics

⁴ American Cancer Society, Surveillance Research.

⁵ Instituto Mexicano del Seguro Social

Table 1. Incidence rates of lymphoid leukemias per million Mexican and Costa Rican children from cancer registries.

For the Americas, a highest incidence rate of ALL, 73.2 per 10⁶ children in the 1–4 years age group, was reported for the USA for the period 1992–2004 (Linabery & Ross, 2008); the lowest incidence rate of ALL (35.5 per 10⁶ children) was in Uruguay (Castillo et al., 2001), this latter report covered a different period and did not report incidence rates for different age groups. It is very important to note that, for both Brazil (de Souza Reis R et al., 2011) and Mexico City (Bernáldez-Ríos et al., 2008), the highest peak incidence of ALL was reported for the same age groups, with high (albeit distinct) incidence rates in both countries. From these data, one can speculate that these two countries share certain genetic or environmental characteristics. Although in a report from Puerto Rico (Pérez-Perdomo & Rodríguez-Figueroa, 2000), there are data only for individuals <20 years, these data were included here to provide information, not for comparative purposes. For countries in Europe, the highest incidence rate was reported for Italy (95.6 per 10⁶) (Magnani et al., 2003) and Greece (82.5 per 10⁶) (Petridou et al., 2008), for different periods and immunophenotypes, but for the same age group. The lowest incidence rate (35.7 per 10⁶) was reported for Ireland (Stack et al., 2007).

The differences in trends across demographic subgroups provide starting points for the etiological investigation of ALL. Such research should generate testable hypotheses that include factors such as the child's birth characteristics and environmental exposures and topics such as the creation of cancer registries.

Location	Period	Type of cancer	Immuno-phenotype	Age group	Incidence rate ¹
The Americas					
North America					
USA					
SEER (Linabery & Ross, 2008)	1992-2004	ALL ²	ND ³	1-4	73.2
Hispanic children (Glazer et al., 1999)	1988-1994	ALL	ND	0-4	66.0
Hawaii, USA (Goodman et al., 1989)	1960-1984	ALL	ND	0-4	49.6 (M) 44.8 (F)
Mexico City (Bernáldez-Ríos et al.,	1996-2006	ALL	B-cell Precursor	3 6	65.0 50.0
Mexico City (Mejía-Aranguré et al., 2005b)	1996-2000	ALL	ND	1-4	64.6
Ontario, Canada (Agha et al., 2006)	1986 2001	AL ⁴	ND	0-14	52.8 44.4
Puerto Rico					
(Pérez-Perdomo & Rodríguez-Figueroa et al., 2000)	1980-1991	AL	ND	<20	35.7
Central America					
Costa Rica					
(Monge et al., 2002)	1981-1996	ALL	ND	1-4	68.5
El Salvador					
(Mejía-Aranguré et al., 2005b)	1996-2000	ALL	ND	1-4	48.4
South America					
Brazil					
(de Souza Reis et al., 2011)	1997-2004	ALL	ND	3 6	72.8 40.0
Trinidad and Tobago					
(Bodkyn & Lalchandani, 2010)	2001-2006	AL	ND	0-4	49.0 (M) 27.0 (F)
Uruguay					
(Castillo et al., 2001)	1992-1994	ALL	ND	0-14	35.5
Asia					
Iran					
(Mousavi et al., 2010)	2003-2007	AL	ND	0-14	15.9 (M) 14.1 (F)

Europe					
North Europe					
Nordic Countries (Hjalgrim et al., 2003)	1998–2001	ALL	B-cell precursor	0–14	35.9
West Europe					
Ireland (Stack et al., 2007)	1994–2000	ALL	ND	0–14	35.7
Northwest England (McNally et al., 2001)	1954–1998	ALL	ND	1–4	51.2
Northwest England (McNally et al., 2000)	1995–1998	ALL	B-cell precursor	1–4	54.0
Southwest England (McKinney et al., 1993)	1984–1988	ALL	Pre-B	1–4	50.0 (M) 54.0 (F)
Yorkshire, UK (Feltbower et al., 2001)	1995–1997	ALL	B-cell precursor	1–4	46.6
Central Europe					
Eastern Germany (Spix et al., 2008)	1991–2004	ALL	ND	0–14	44.0
Germany (Kaatsch, 2010)	1988–1997	AL	ND	0–14	44.0
South Europe					
Castilla and León, Spain (González García et al., 2010)	2003–2007	AL	ND	0–4	47.6
Greece (Petridou et al., 2008)	1996–2006	ALL	B-cell precursor	1–4	82.5
Northwest Italy (Magnani et al., 2003)	1995–1998	ALL	Common Pre-B	1–4	95.6
Spain (Peris-Bonet et al., 2010)	1983–2002	AL	ND	0–14	45.9
Oceania					
Australia (Baade et al., 2010)	1997–2006	ALL	ND	0–4	84.6

¹per 10⁶ million children

²Acute lymphoblastic leukemia

³No data

⁴Acute leukemia

Table 2. The incidence of AL and ALL and the peak age in different continents expressed in cases by million.

6. Conclusions

The ontology of B and T lymphocytes demonstrates that different factors may be involved at the moment when the cell is most vulnerable to undergo an alteration that promotes the development of ALL. An important factor may be an infectious agent(s). For children with

ALL, both the presence of MLL/AF4, principally during the first year of life, and the presence of ETV6/RUNX1 in 2-6 year olds are considered causes of ALL. MLL/AF4 is sufficient to promote the development of ALL and that children born with this genetic rearrangement will always develop ALL. However, in the case of children born with the rearrangement ETV6/RUNX1, one or more additional risk factors (e.g., an exaggerated response to late common infections) would be needed to initiate leukemogenesis.

It is possible that the age peak of ALL reflects a higher degree of susceptibility with which a child is born, such as is the case with both bilateral retinoblastoma and bilateral Wilm's tumor: an earlier age peak is found in the bilateral forms of these diseases than when the retinoblastoma or Wilm's tumor is unilateral (National Wilm's Tumor Study Committee, 1999; Pastore et al., 1988; Sanders et al., 1988; Teppo et al., 1975). Thus, children with the highest susceptibility at birth should show an early age peak for ALL (say, during the first year of life), whereas children born with the lowest susceptibility will evidence an age peak of ALL in later years. For those children for whom it is not possible to determine their susceptibility to ALL at birth, it may be that many environmental factors are involved when the child develops ALL during the first year of life. That is to say, in order for a child to develop ALL, both risk factors (susceptibility at birth or degree of exposure) must be present and at least one of the two risk factors must be high. Thus, to develop ALL, a child born with a high susceptibility for developing the disease may need only a low degree of exposure to environmental factor(s), whereas a child born with low susceptibility for developing ALL will need a higher degree of exposure to environmental factor(s) (Figure 4).

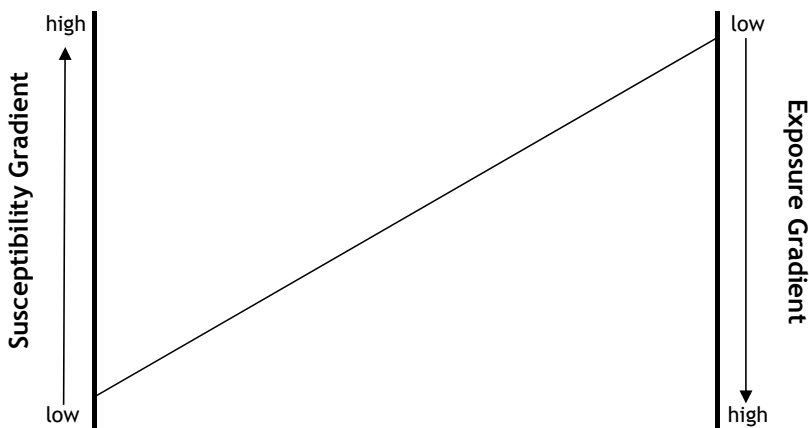


Fig. 4. Interaction between a gradient of susceptibility and a gradient of exposure to carcinogenic environmental factors. From this, to develop acute leukemia, an individual with a higher susceptibility, as determined by the interplay of genetic factors, would need a lower exposure, as determined by the interplay (unknown, possibly synergistic) of the characteristics of the exposure. Conversely, the higher the exposure, the lower the susceptibility needed to result in developing the disease.

It is possible that the two age peaks for ALL reported for children from Brazil and Mexico City reflect different etiologies, or are a result of each child's having a different etiology. It is probable that there is no one genetic rearrangement that determines susceptibility to ALL, nor one environmental factor associated with ALL. However, if the effect(s) of exposure to

environmental factor(s) is(are) cumulative and if the degree of exposure to environmental factor(s) perfectly complements the degree of susceptibility with which the child was born, then the child develops ALL. The age peak of ALL permits the prediction of the degree of susceptibility with which the child was born and/or the degree of exposure to environmental factor(s) experienced by the child during the first years of life.

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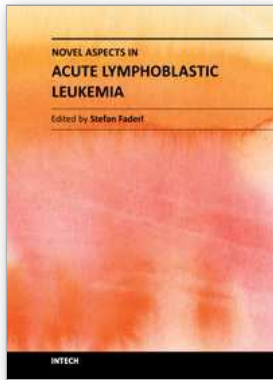
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Novel Aspects in Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to overcome this discrepancy and improve the prognosis of adult patients as well. This exemplary progress in ALL therapy has been possible by the combination of an increasingly better understanding of the biology of the disease, availability of a range of effective drugs, and astute designs and relentless executions of many clinical trials. ALL is a complex disease requiring complex therapy. Whereas this book cannot provide a comprehensive review of every one of its many facets, the chapters from many investigators from around the world nevertheless cover a number of relevant topics: aspects of the epidemiology of ALL in Hispanics, ophthalmologic manifestations of ALL, overviews of current therapy and drug-resistance mechanisms, novel biological pathways and targets, new drugs in development, and long-term consequences of CNS prophylaxis and therapy. The publishers and editor therefore hope that the prospective readers will find enough insight and information for their own endeavors.

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