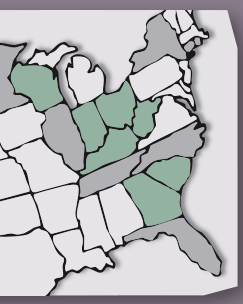
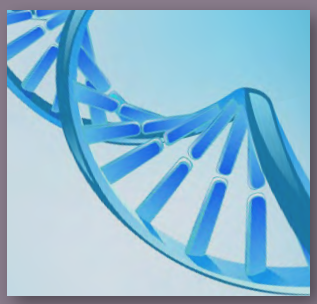
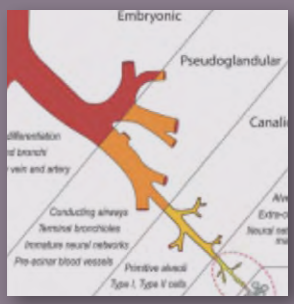
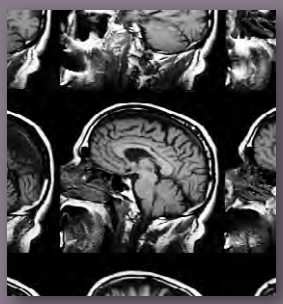
A Story of Health

Childhood Cancer: Stephen's Story









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The Center for Integrative Research on Childhood Leukemia and the Environment (CIRCLE) at the University of California, Berkeley, Commonweal, the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA), the Science and Environmental Health Network (SEHN), and the Western States Pediatric Environmental Health Specialty Unit (WSPEHSU) teamed up to leverage our combined resources to develop and produce *A Story of Health*.

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Any errors or misrepresentations that remain are entirely the responsibility of the authors.

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DISCLAIMERS:

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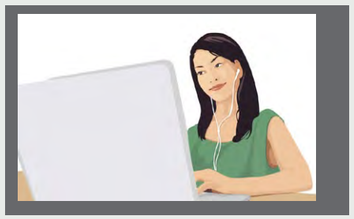
HELP PAGE How to Navigate Our eBook

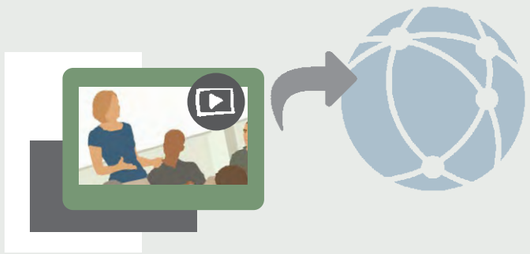
THE INDIVIDUAL STORIES OF HEALTH in this eBook are written to address many audiences. For example, some sections are more technical than others – you can skip sections if you wish.

(Note: underlined words or phrases link to online information that will open in a browser window, prompt downloads or navigate to a related page within the ebook.)



Each of the eBook stories is embedded with a wide range of resources. These help further explain possible environmental and/or genetic "risk factors" – (contributors to the development of a disease, or factors that might make a disease worse) – and how these factors interact.

We also provide links for additional resources, including actions you can take to prevent disease, and "tools you can use."



Resources include videos, slides with audio commentary, tables, charts, and graphics. Some 'pop-up' in the story, and some connect online. Through these links, you can choose to dig deeper and learn more. Refer to icons at right for guidance.

References and Citations: Certain references are cited in the text where we believe they are most warranted. Full references by topic can be found at the end of each story.

Getting Started

Our eBook Navigation: Click on selections in the page headers to navigate back to this **Help Page**, find out about **Continuing Education** opportunities and access further information in **References**.

If you lose your place, use the **Go Back** selection in the navigation bar to return to your previous screen.

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This interactive pdf document is best viewed on a laptop or desktop, downloaded and opened in a current version of Adobe Acrobat Reader. Refer to the top Adobe menu bar for features including:

Magnify - If you want to enlarge a diagram or some text, click (+) button.

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You can also move through pages using the scroll up and down feature to the right of your screen.

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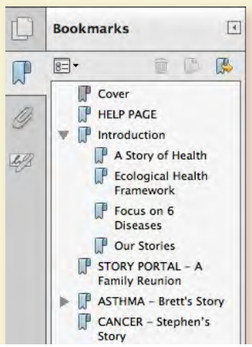


Table of Contents

Use the sidebar Bookmark Tools as a table of contents to skip to a section of interest, find your place, or return to this Help page.

Icons

Click on icons that may appear throughout the stories for pop-ups, videos, and links to more information as described.

key concept

watch a video

additional resources, tools

technical details for health professionals

definition

INTRODUCTION

This is one of a series of collected stories about health.

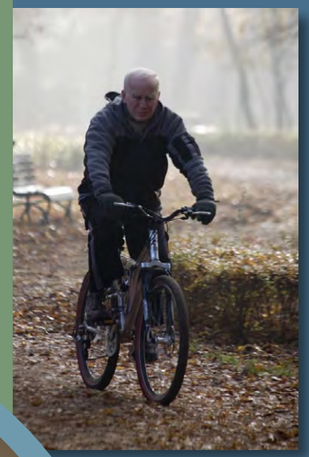
It is a story of how our own health is intimately connected with the health of our families, friends and communities.

It is a story about how human health is interdependent with our surroundings.

The collected stories include a number of fictional people and highlight the many ways our health is influenced by the complex environments where we live, eat, work, play, volunteer, gather and socialize.

Live

Volunteer



Play

Gather

Socialize

Eat

Work

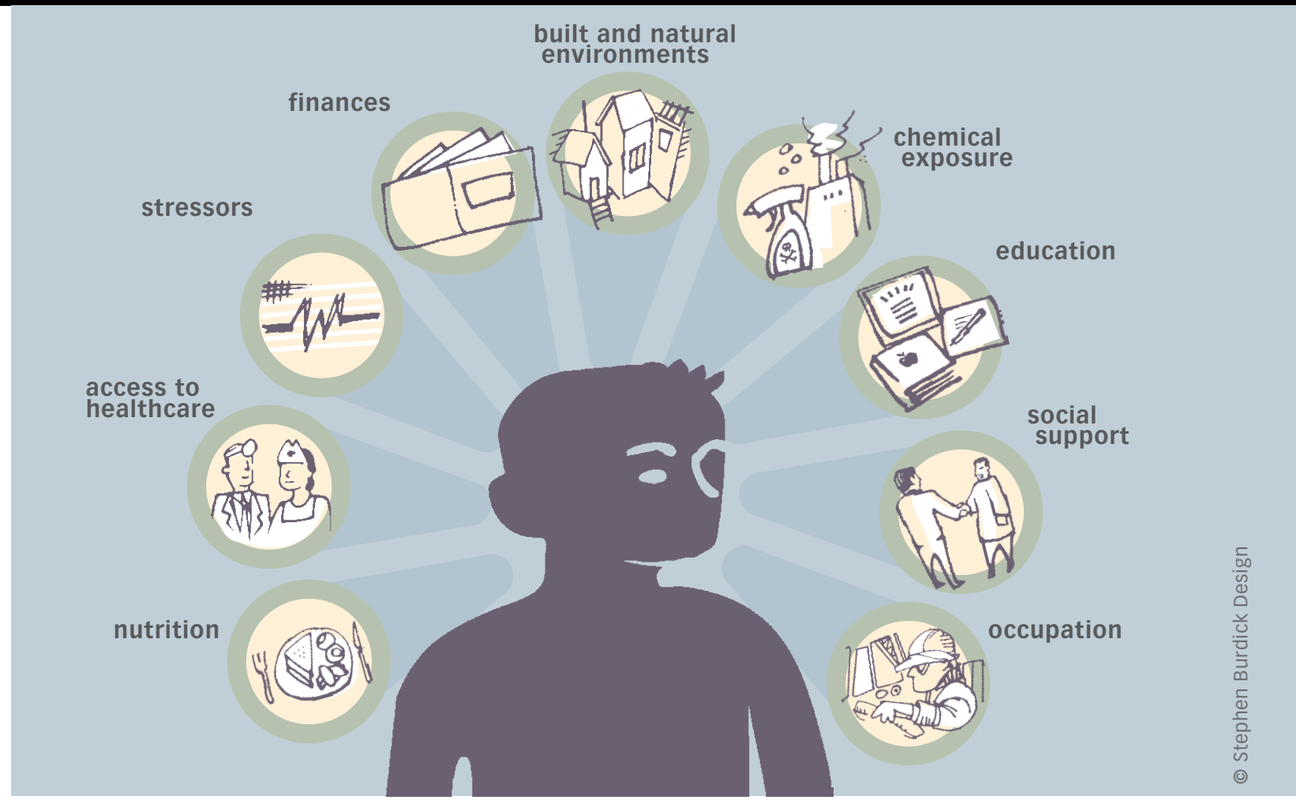
INTRODUCTION

Our stories explore how many aspects of our lives, and what we are exposed to in our environments, influence health across the lifespan—from the beginning of fetal development to elder years—and how they can promote health and resilience, or disease and disability.

Important determinants of health come from the natural, built, chemical, food, economic, and social environments.

These environments are further expressed through such things as education, housing, nutrition, access to health care, social supports and more.

Many of them interact to create the conditions for health and wellness, or vulnerability to disease.



Complex interactions occur among many variables and across individual, community, and societal levels.

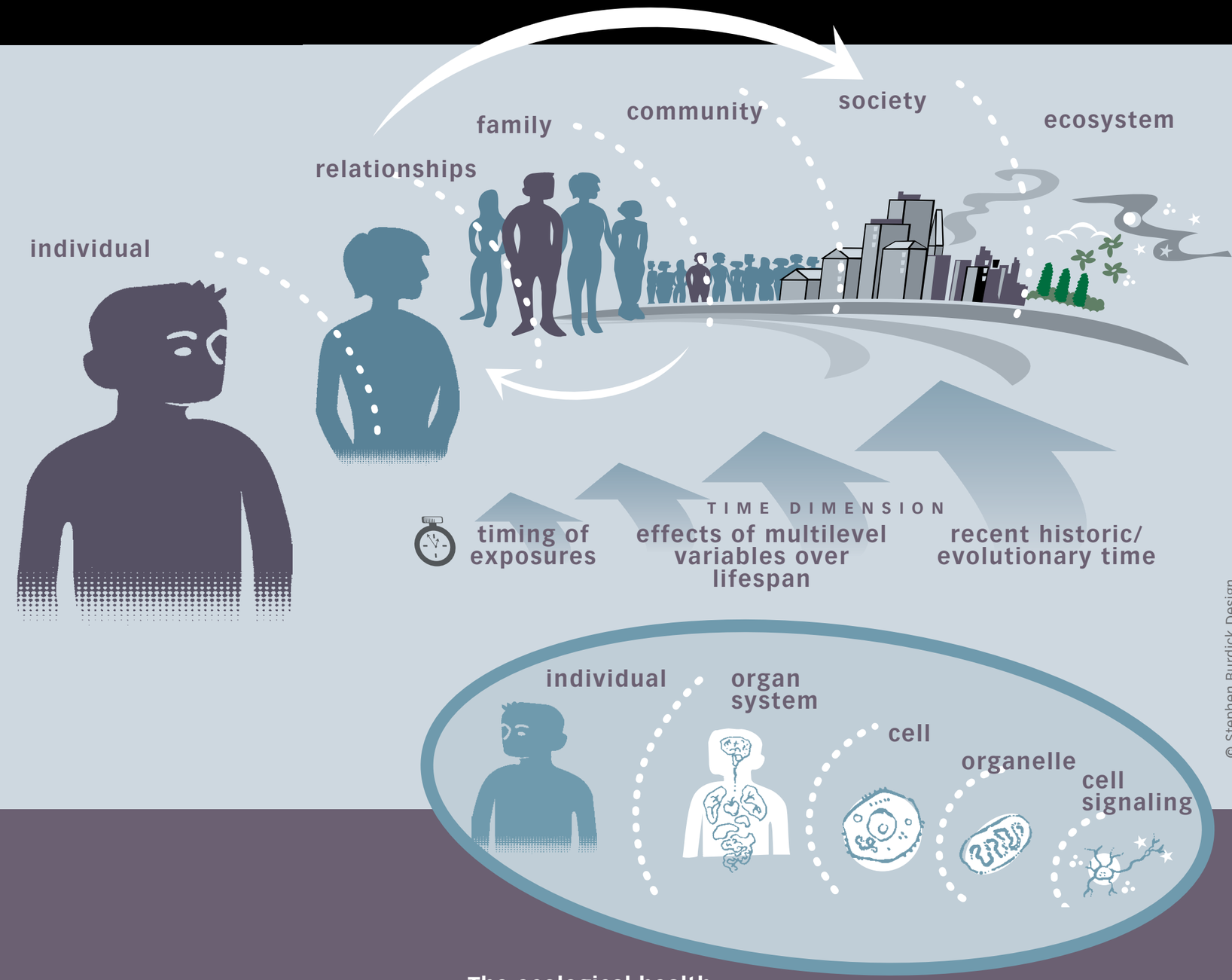
Rarely is one particular thing responsible for health or disease, so we refer to this as a multifactorial (or ecological) approach, the best way to promote health and prevent disease.

INTRODUCTION Ecological Health Framework

The ecological framework can include multiple levels from sub-cellular to societal.

It is not hierarchical in the sense that one level is more important than another, but rather in the sense that individual biology is progressively nested within the person, family, community, society and ecosystem.

The interactions and feedback loops within, across, and among these levels are complex and variable. They exert their influences on health across time.



The ecological health framework also extends to the sub-cellular level.

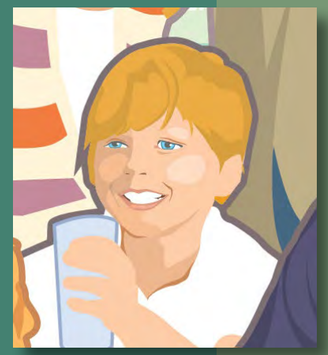
INTRODUCTION Six Different Stories

Following is a story of people like you and me, our partners, families and friends, our mothers and fathers, sisters and brothers, children, grandparents, cousins and aunts and uncles.

The personal health stories explored in this series include some of the most common and troubling diseases and exposures of our time. They include:

- Childhood cancer (this chapter)
- Asthma
- Wildfire health impacts
- Infertility
- Learning and developmental disabilities
- Cognitive decline

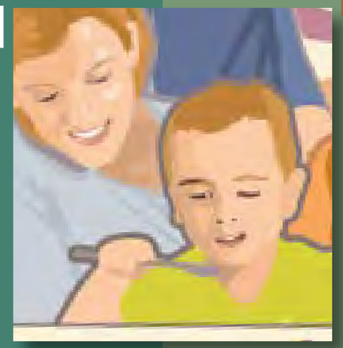
Download other *Story of Health* chapters here.



Asthma

Wildfire health impacts

Childhood cancer



Cognitive decline

Infertility

Learning and developmental disabilities

INTRODUCTION Free Continuing Education

Information on free Continuing Education offered from the Centers for Disease Control

This fictional *Story of Health* chapter offers free Continuing Education (CE).

To receive continuing education (CE) for SS4677-*A Story of Health – Childhood Cancers: Stephen's Story*, please visit CDC TRAIN and search for the course in the Course Catalog using SS4677.

Please review the learning objectives at right. These will help you focus as you read each story, and prepare you for each CE test.

Register for free CE here.

Free Continuing Education available by specialty:

- Continuing Medical Education (CME) for Physicians
- Continuing Nursing Education (CNE) for Nurses
- Continuing Education Units (CEU) for other professionals
- Continuing Education Contact Hours (CECH) for Certified Health Education Specialists (CHES)
- Continuing Education (CPH) for Certified Public Health Professionals

LEARNING OBJECTIVES

Stephen's Story (Childhood Cancer):

1. Describe the characteristics of childhood cancer.
2. Discuss trends associated with childhood cancer.
3. Discuss environmental risk factors for childhood cancer.
4. Discuss factors that reduce the risk of childhood leukemia.
5. Describe how to improve collaborative practice across the healthcare team regarding preventing risk factors for childhood cancer.

CHILDHOOD CANCER Stephen's Story*

Stephen is a 3-year-old boy who lives with his parents David and Tricia in a suburb in Connecticut.

He is an only child, and his parents spend as much time as they can with him even though they manage a successful plant nursery and garden center.

He spends four days a week at child care and is with his parents the other three days, sometimes at their house and sometimes at the garden center.

Stephen had been an active toddler, but during the past month, Tricia noticed that Stephen was not as lively and energetic as usual. His child care providers also mentioned this.

When he became listless and started to run a fever, Tricia became concerned. She took Stephen to see his pediatrician, Dr. Jones.

(*a fictional case)

CHILDHOOD CANCER Stephen's Story

After talking with Tricia and examining Stephen, Dr. Jones was also concerned. She confirmed that Stephen appeared ill, was very pale, and that the cause could be a number of things. She said she needed laboratory tests to make an accurate diagnosis.

Dr. Jones ordered blood tests that could be done at the local hospital and called to make an appointment for Stephen to get his blood drawn that same day.

Tricia was upset and called her husband David with the news. She started to ask a lot of questions. Dr. Jones tried to calm her and said she would call her as soon as she had the results.

Tricia brought Stephen to the hospital laboratory for the tests and went home very worried.

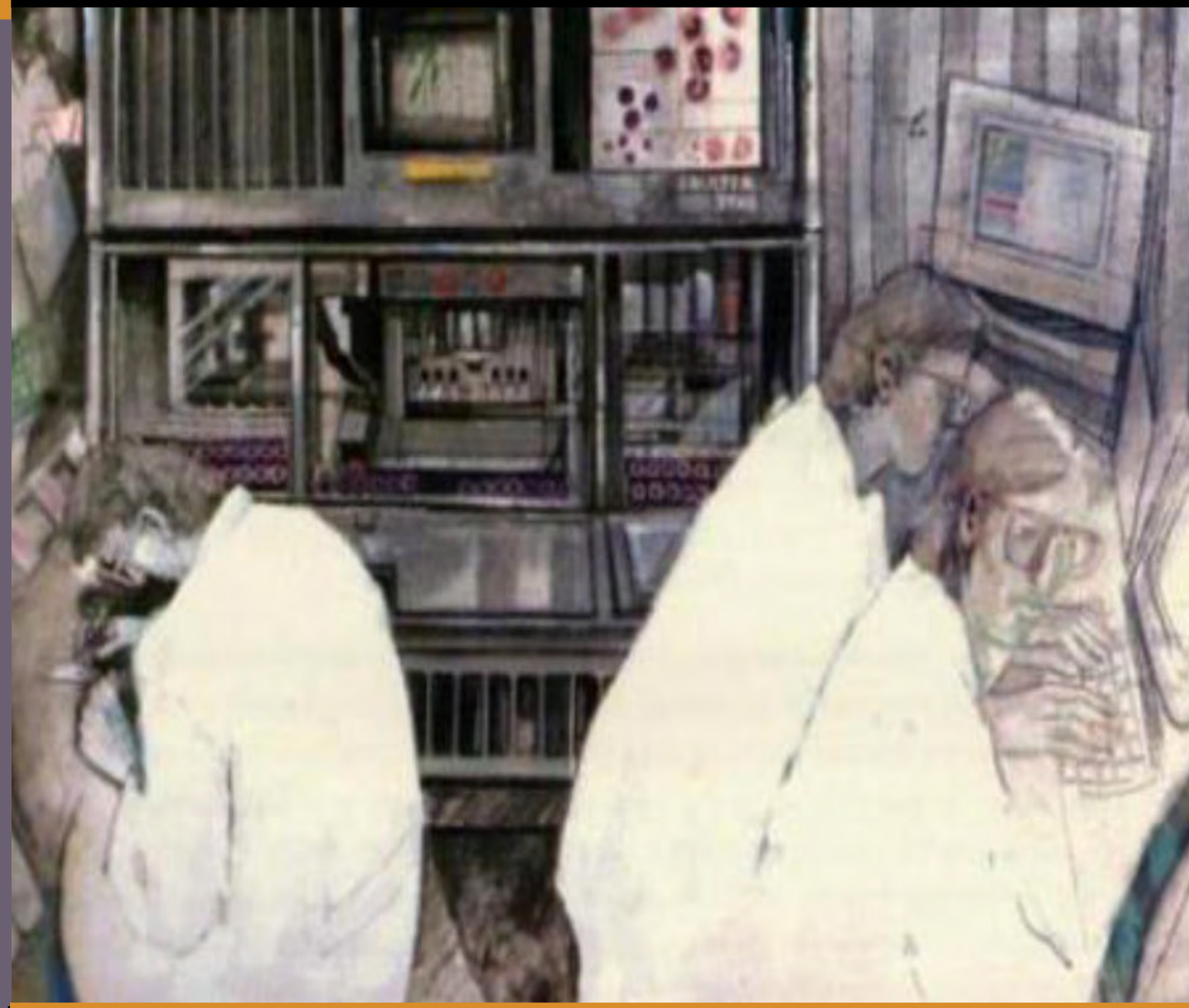
CHILDHOOD CANCER Stephen's Story

When Dr. Jones received the test results she called Tricia and David back into her office. She told them that the test results showed a very high white blood count and very low platelet count.

Dr. Jones said that Stephen would need to see a pediatric oncologist, Dr. Baker. She said she would arrange the appointment for Stephen at Dr. Baker's office next to the hospital and that he should go right over.

Tricia and David were shocked. They knew that oncologists dealt with cancer. Dr. Jones tried to reassure them and said they should wait to speak with Dr. Baker before drawing any conclusions.

They left Dr. Jones office still very worried.



"Diagnosing the Leukaemic Cells"
by Susan Macfarlane,
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About this painting, with words of the artist in *italics* >

See this page for more information on the artist.

CHILDHOOD CANCER Stephen's Story

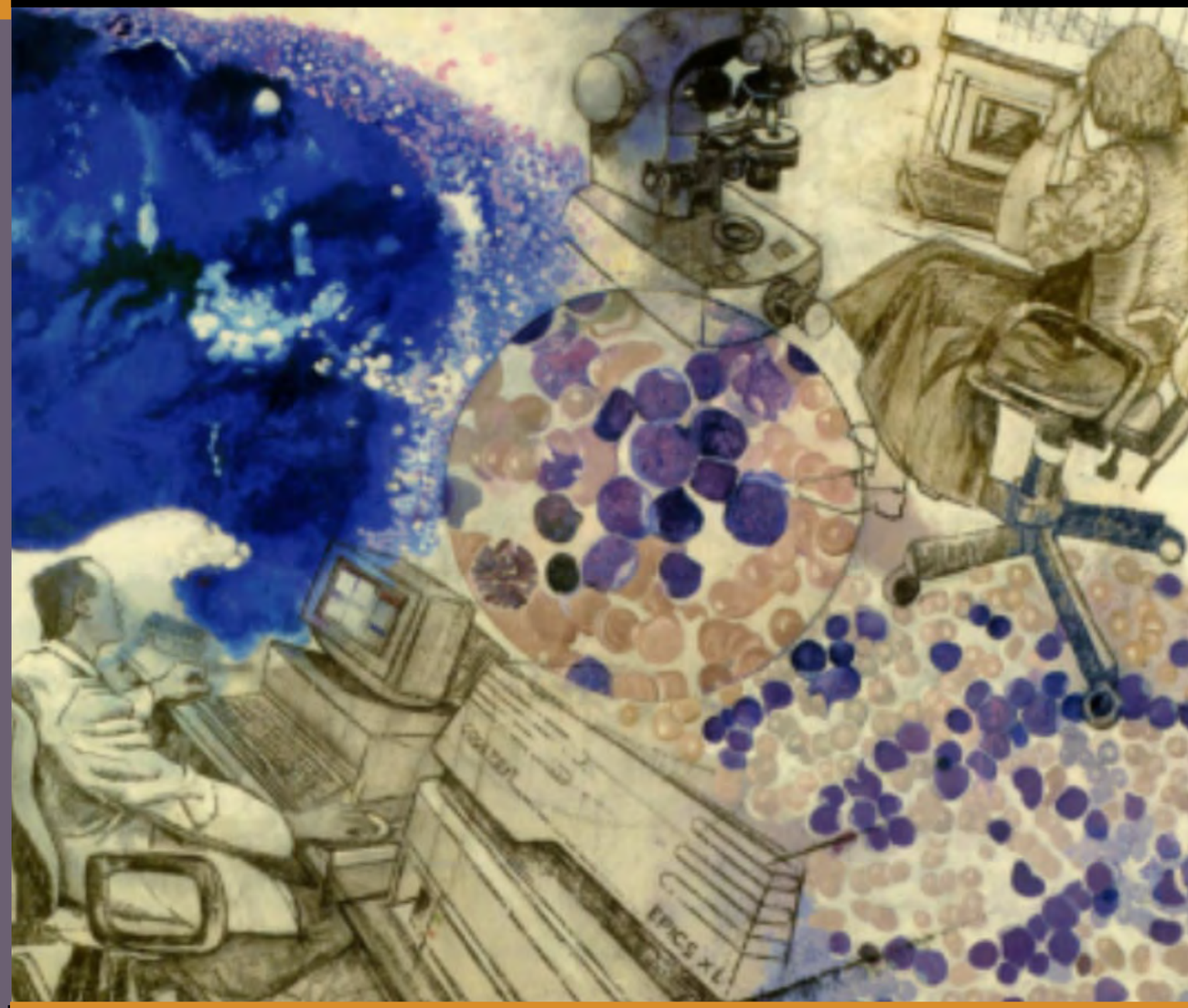
The pediatric oncologist, Dr. Baker, looked at Stephen's blood tests to confirm the findings from the laboratory.

After considering the differential diagnosis, Dr. Baker told Tricia and David that he was concerned that Stephen may have leukemia and needed to run more tests to confirm the diagnosis.

Since Stephen had a fever and suppressed immune system, Dr. Baker admitted Stephen to the hospital to start antibiotics and hydration therapy immediately.

Dr. Baker explained to Tricia and David that he would return in the morning to perform a bone marrow aspirate.

? **Bone marrow aspiration**



"Typing the Leukaemic Cells"
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CHILDHOOD CANCER Stephen's Story

The next day when Dr. Baker came to visit, Stephen looked well. He no longer had a fever and was playing.

Dr. Baker explained the bone marrow procedure to Tricia and David and then performed the aspirate in a special room for procedures.

When he returned to discuss the bone marrow test results, Dr. Baker tried to calm Tricia and David, but they were upset and imagined the worst.

Unfortunately, their fears were realized when Dr. Baker told them that Stephen's test results confirmed that he had leukemia. He said that further tests were being done to find out more about what type of leukemia he had. He said they should know the type of leukemia the following day, and then they can begin treatment.

They were devastated.

? What are children's cancers?

+ Find out more:
National Cancer Institute: Cancer in Children and Adolescents

Chart Source: California Cancer Registry, California Department of Public Health. Prepared by the California Department of Public Health, California Cancer Registry.

Dr. Baker discussed with them what the course of treatment should be, including intravenous (IV) hydration (liquids), and initiating a course of chemotherapy.

Stephen would need to be in the hospital for this, since the initial treatment is the riskiest time period.

Dr. Baker arranged for Stephen to continue his hospital stay and begin treatment immediately.

CHILDHOOD CANCER Stephen's Story

Later Dr. Baker explained that the type of leukemia Stephen had was called acute lymphoblastic leukemia (ALL). Dr. Baker told Stephen that he was sick, and that he would have to be in the hospital for a while so that the doctors can give him medicines to make him better.

Dr. Baker also explained to Tricia and David how the cure rate for children has improved dramatically over the past few decades.

? **Leukemia Survival Statistics**

Watch: Dr. Gary Dahl discusses types of leukemia (4:13 mins.)

Gary Dahl MD, Professor Emeritus of Pediatrics (Hematology/Oncology) at the Lucile Salter Packard Children's Hospital, Stanford School of Medicine

SEER relative survival rates table citation: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. Available here.

CHILDHOOD LEUKEMIA IS NOT A SINGLE DISEASE

Acute leukemias in childhood comprise a group of related but different diseases. In the United States they represent 31% of malignancies occurring among children under the age of 15.

Eighty percent of acute childhood leukemias, including Stephen's, are acute lymphoblastic leukemia (ALL). Approximately 17% are acute myeloblastic leukemia (AML).

It is important to identify characteristics of the leukemia at its presentation since this information helps to determine the course of treatment as well as prognosis. The types of cells involved in the leukemia (immunophenotype) are used to determine whether a person has ALL or AML.

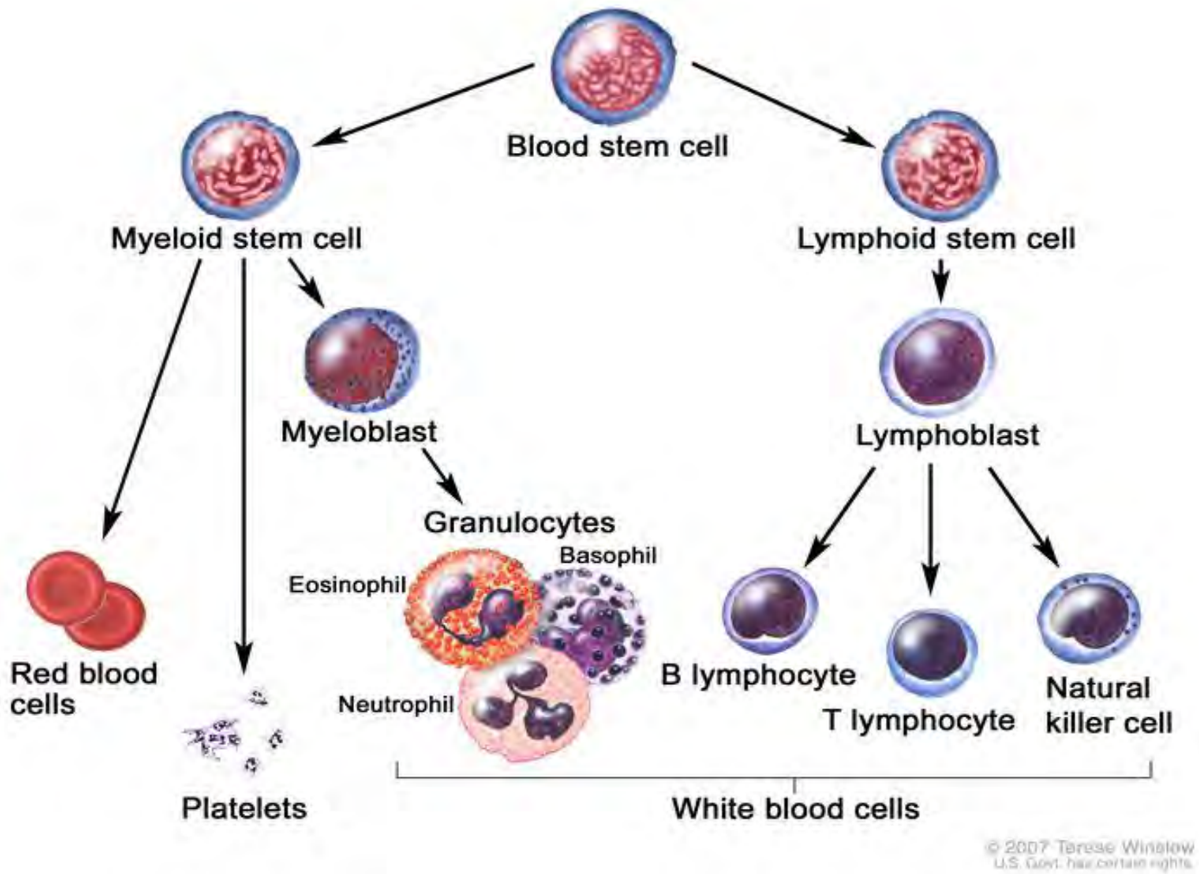
Factors such as age, initial white blood count at diagnosis, and cytogenetics (the specific differences or changes in DNA) of the leukemic cells at diagnosis are utilized to identify the most appropriate course of treatment.

Types of leukemia vary by age

Early life exposures are important: age-specific incidence chart

More Detail on ALL Subtypes

Leukemias originate in lymphoid and myeloid progenitor cells.



Graphic: Terese Winslow 2007.
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CHILDHOOD CANCER Stephen's Story

Stephen spent the first two weeks of his treatment in the hospital, then his protocol was continued on outpatient status. The treatment course would be up to three years with induction, consolidation, and maintenance therapy stages.

Dr. Baker warned Tricia and David that any time Stephen had a fever he would need to be evaluated, and if his white blood count was low he would need to be hospitalized.

Dr. Baker, along with the rest of the hospital team, carefully explained how the chemotherapy medications work and what side effects they might expect. Stephen's hospital stay was difficult for his parents. Stephen hated being away from home and the nausea and vomiting made him uncomfortable.

Treatment information for the general public

For clinicians

About the artist

"Initial Blood Test"

About this painting, with the words of artist Susan Macfarlane in *italics* >

click a preview image to view above

Paintings by Susan Macfarlane, reproduced with permission.

CHILDHOOD CANCER Stephen's Story

After the initial shock of the diagnosis and while dealing with Stephen's first chemotherapy course, Tricia and David began to ask Dr. Baker and others more questions about what might have been the cause of Stephen's disease.

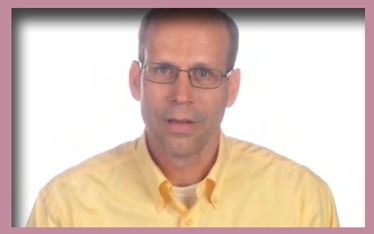
Childhood leukemia is difficult to study because it is relatively rare, which limits the design of studies intended to help clarify its etiology (cause). Nevertheless, substantial evidence identifying a number of risk factors has emerged over the past two decades. The etiology is likely to be attributable to a mixture of genetic and environmental factors and may vary by subtype or for ALL, immunophenotype.

Cancer is considered a multi-step process. It is thought that childhood leukemia is a result of distinct exposures during two or more developmental time periods including preconception, in utero, and postnatal.

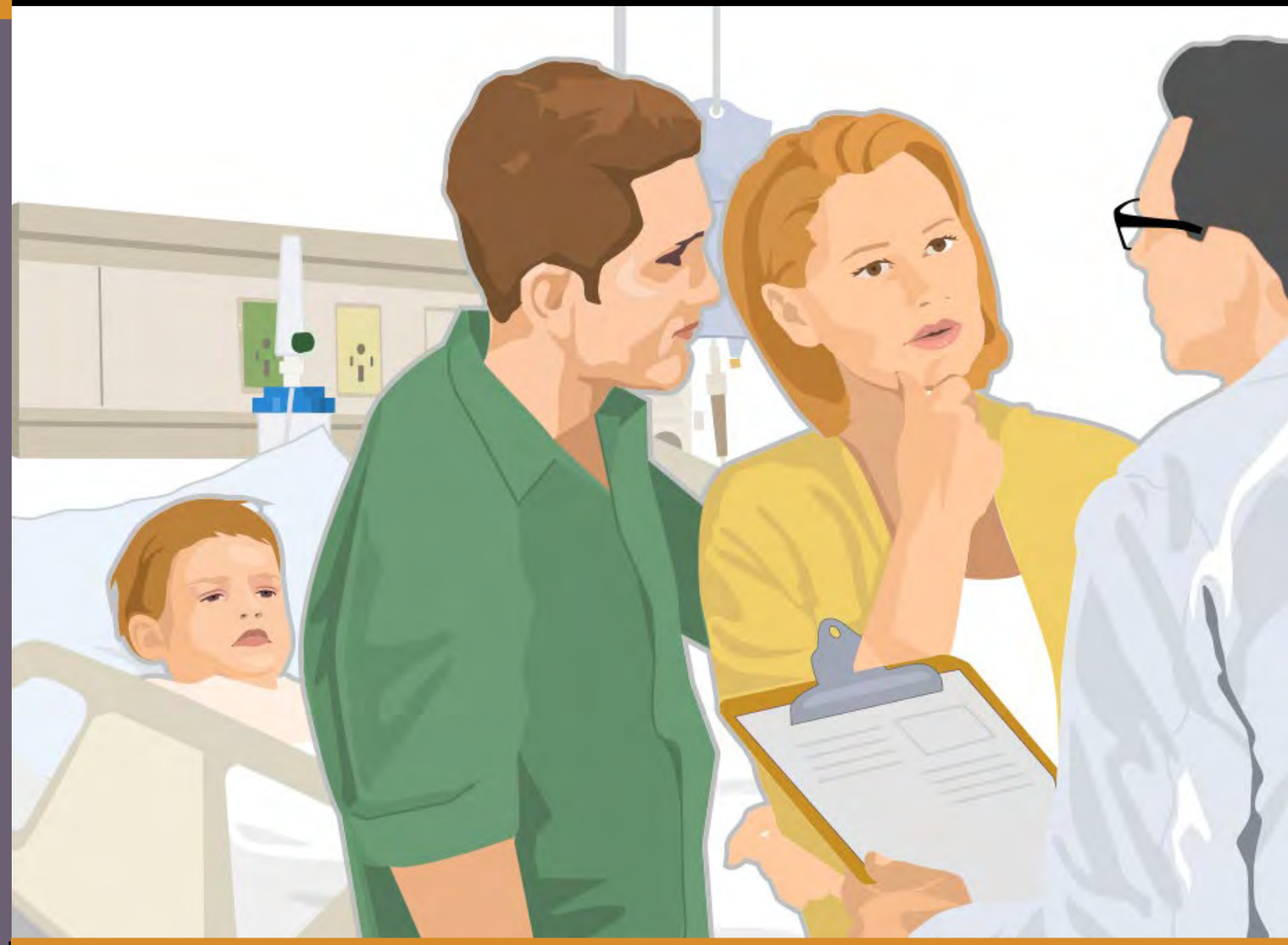
Changes to DNA that cause leukemia:

- **Changes to DNA that cause leukemia**
- **ETV6-RUNX1 Gene Fusion**
- **Germ Cell Formation**

Watch: For clinicians: Dr. Joe Wiemels discusses timing of environmental exposures (2:23 mins.)



Joseph L. Wiemels PhD, Professor, Center for Genetic Epidemiology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California



CHILDHOOD CANCER Stephen's Story

Since childhood leukemia is a rare disease and it takes many cases to identify environmental risk factors, the Childhood Leukemia International Consortium (CLIC) was established in 2007 (locations represented by the black icons on the map at right). CLIC develops and supports collaborations among member groups to identify factors that influence the risk of childhood leukemia through epidemiological studies and related research.

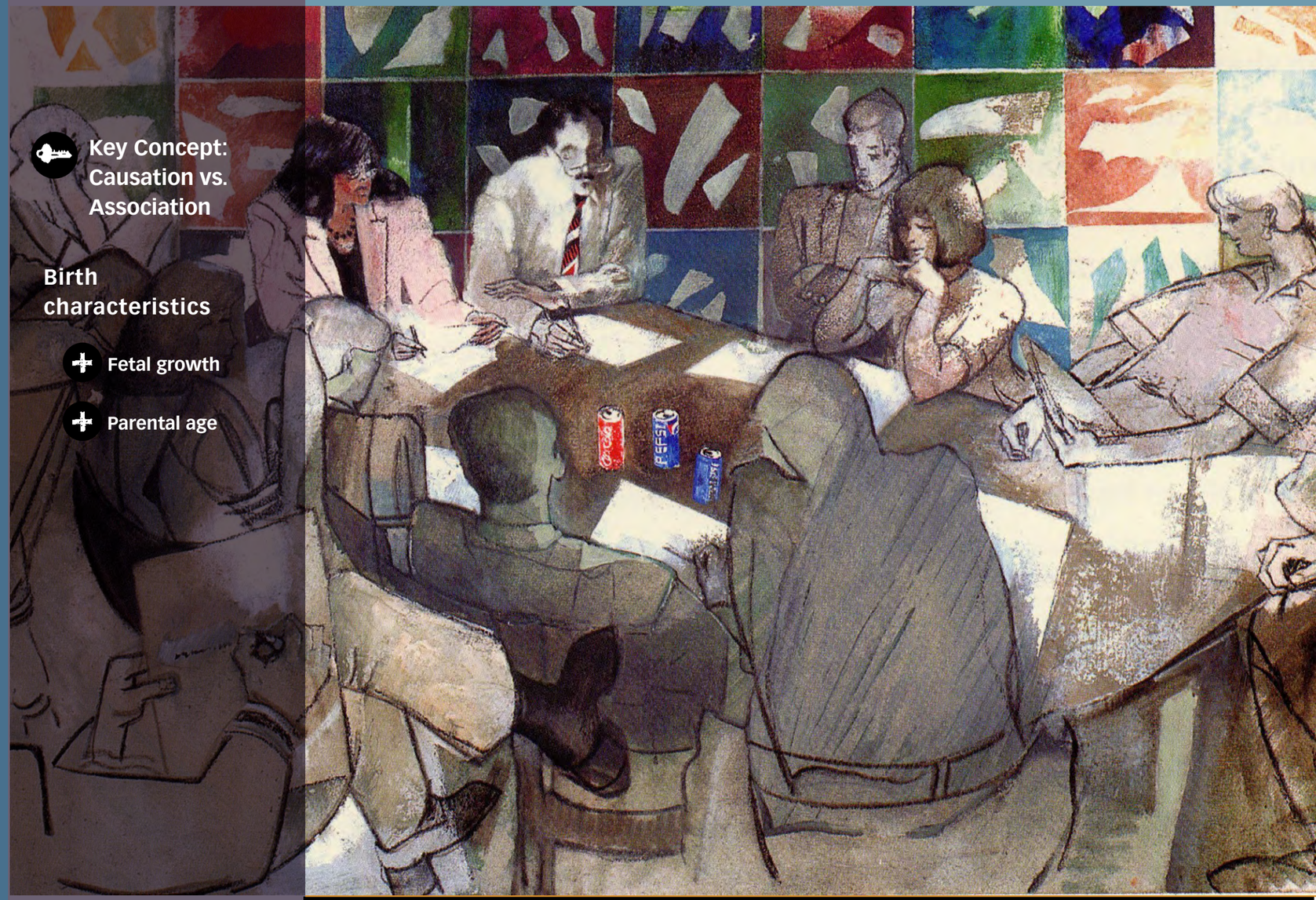
This consortium serves to strengthen the available data set regarding the role of environmental and genetic risk factors and critical windows of exposure, as well as to provide a more robust translation to clinical audiences worldwide.

FACTORS ASSOCIATED WITH RISK FOR CHILDHOOD LEUKEMIA

One of the hospital's pediatric residents asks Dr. Baker about the risk factors for childhood leukemia.* Dr. Baker mentions that this would be a great topic for everyone to hear at rounds and asked the resident to review the literature and develop a presentation.

The resident reported that there are many epidemiologic (human) studies that find exposures to certain groups of chemicals, air pollution, tobacco smoke, and radiation to be consistently associated with increased risk for a child developing leukemia. Additionally, some factors are associated with a protective effect such as early supplementation with folate. Along with environmental exposures and diet, studies show that inborn genetic factors play a role in risk, and may interact with environmental exposures.

*In the following pages of Stephen's story we describe environmental and genetic factors significantly associated with increased leukemia risk. Keep in mind, however, that childhood leukemia is a relatively uncommon disease. Thus, even if a person were exposed to something that doubled the risk of developing leukemia, the risk for that person would remain quite low.



"Weekly Co-Ordinating Meeting"
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About this painting, with words of the artist in *italics* >

CHILDHOOD CANCER Stephen's Story

FACTORS ASSOCIATED WITH RISK FOR CHILDHOOD LEUKEMIA

Dr. Baker is careful to note that, "Scientists and policy makers will continue to study and debate for years to come whether these associations are truly causal. And, there are also ethnic and demographic factors associated with leukemia risk. Interactions among risk factors and their common co-occurrence make it even more difficult to establish the cause of leukemia in a particular person or to identify the most important determinants of leukemia in a population. But, many environmental exposures associated with leukemia are also associated with other health problems, such as neurodevelopmental disabilities, asthma and other respiratory diseases, and reproductive disorders. For all these reasons, most people would want to avoid exposure as much as possible. The association with cancer is an additional reason."

He adds, "Some of these exposures simply cannot be reduced by individual action alone. Rather, in some instances, policy interventions that reduce exposures across the entire population will be necessary and more effective."

Childhood cancer risk also generally shares a number of common themes that we have seen in other disorders highlighted in *A Story of Health*, such as greater susceptibility during certain periods of development, underlying genetic risk factors, and gene-environment interactions.

+ Caesarian section and immune function

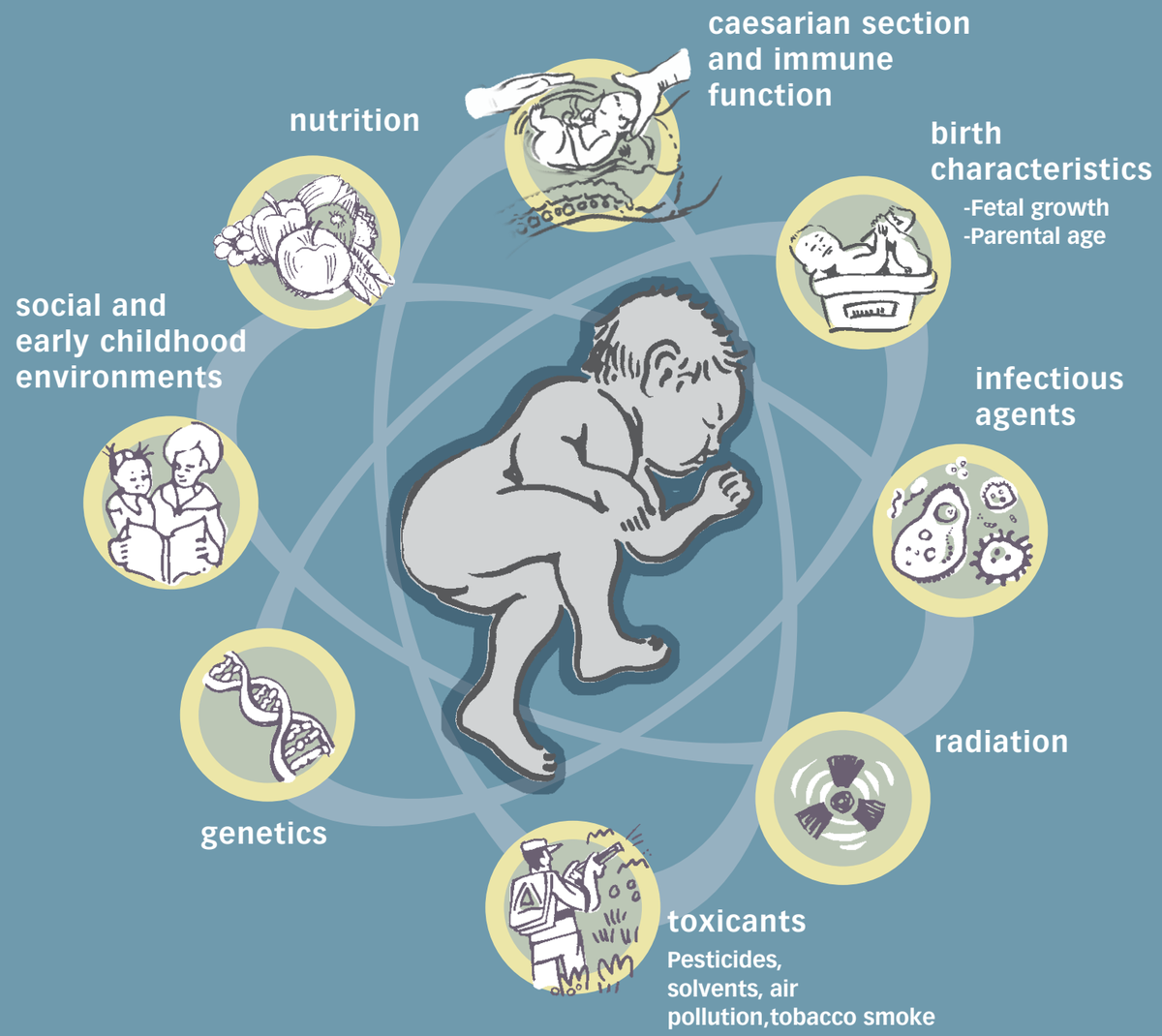
+ Causes and consequences of immune phenotypes that influence risk

+ Oil and gas proximity

Watch: Can we reduce exposure to risk factors associated with childhood leukemia and other cancers?

Mark Miller MD MPH, Director Emeritus, Western States Pediatric Environmental Health Specialty Unit at UCSF; Director, Children's Environmental Health Center, Office of Environmental Health Hazard Assessment, California EPA

Multiple Factors Associated with Risk to Childhood Leukemia



References, Birth Characteristics:

Milne E, et al. Fetal growth and childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium (CLIC). Int J Cancer. 2013 Dec 15;133(12):2968-79.

Paltiel O, et al. International Childhood Cancer Cohort Consortium. Birthweight and Childhood Cancer: Preliminary Findings from the International Childhood Cancer Cohort Consortium (I4C). Paediatr Perinat Epidemiol. 2015 Jul;29(4):335-45.

CHILDHOOD CANCER: US TRENDS

Although childhood leukemia is still rare, Stephen is one of a growing number of children with this cancer.

In the US, between 1975 and 2019, the rate of leukemia among children 0-14 years increased 0.7% per year. This adds up to a 36% increase over 44 years.

Leukemia

+ Genetic susceptibility to leukemia in Latinos

+ Leukemia Ethnic Trends

Other Childhood Cancer Trends:

+ Childhood Thyroid Cancer

+ Childhood Testis Cancer

Incidence of "all leukemias" in children under 15 years of age has consistently risen at 0.7% per year from 1975 through 2019. Overall this represents a 36% increase in risk over 44 years.

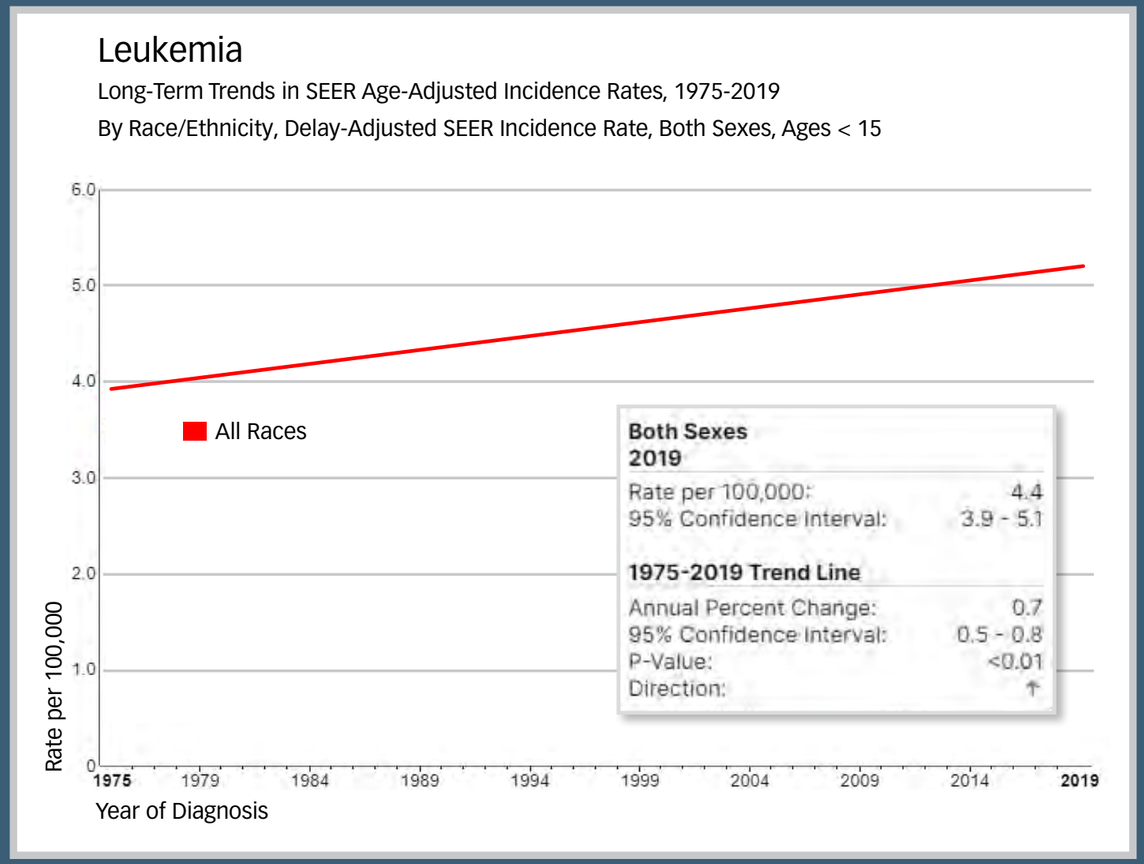


Chart citation: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. Available here.

SOURCES OF EXPOSURE TO PESTICIDES

At their next visit to Dr. Baker, Tricia mentions that she heard from a friend that pesticides might cause leukemia. This reminds Dr. Baker of the information on environmental exposures and childhood leukemia that the pediatric resident presented during rounds.

Dr. Baker asks if Stephen could have come into contact with any pesticides and specifically asks about pesticide use in the home and garden. Tricia says that they own a plant nursery and garden center, and they use some pesticides. Stephen sometimes visits the nursery after preschool and on weekends.

Residential exposures to pesticides (from indoor and outdoor personal use or living in proximity to agricultural areas) have also been consistently associated with childhood brain tumors and lymphomas that are the most common cancers in children and adolescents after leukemia.

Possible associations have also been reported for rarer childhood and adolescent cancers such as neuroblastoma, Wilms tumors, Ewing sarcoma, and testicular cancers.

Pesticide Exposure in Children: Policy Statement from the American Academy of Pediatrics

Link to EPA website for more information on FIFRA

Pesticide Regulation

Maternal pesticide exposure associated with increased risk of Wilms tumor

More Information:

- **American Cancer Society: Key Statistics for Wilm's Tumors**
- **National Cancer Institute: Wilms Tumor and Other Childhood Kidney Tumors Treatment**

PESTICIDES

Tricia mentions to Dr. Baker that other families in the neighborhood have regular pesticide applications to the perimeter of their house and some have lawn service, but they do not.

Tricia thought that Stephen's daycare might occasionally use pesticides to spray for ants and flying insects. Dr. Baker consulted the pediatrician at his regional Pediatric Environmental Health Specialty Unit, who confirmed that many studies from around the world have found statistically significant associations between pesticide exposure and childhood leukemia.

The consulting doctor suggested that Dr. Baker share with his team information about environmental exposures that may be risk factors for leukemia so they might be better prepared to answer families' common questions. Dr. Baker replied he agreed and that he also regularly asked pediatric residents to report to the team on potential environmental risk factors.

How to read and interpret the figure at right. What is a meta-analysis?

More information:

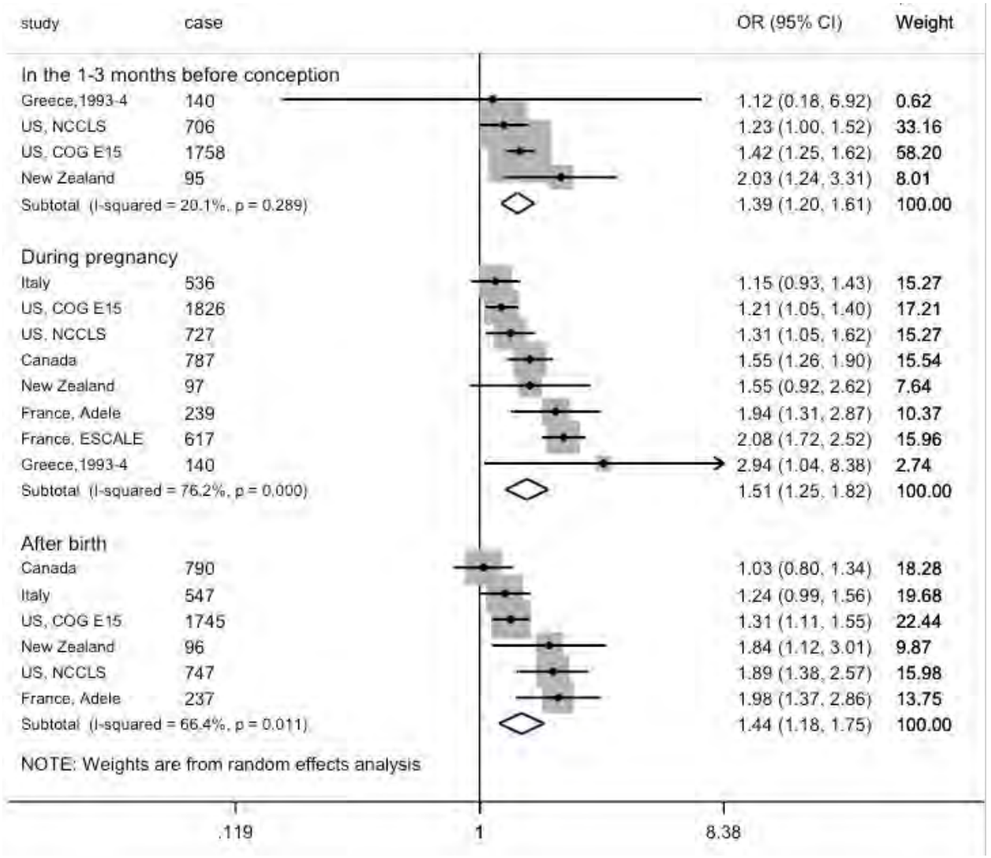
"5 Key Things to Know about a Meta-Analysis" *Scientific American* blog post

Find a local Pediatric Environmental Health Specialty Unit (PEHSU): A respected network of experts in children's environmental health.

Watch: Dr. Catherine Metayer discusses insecticides and herbicides (4:15 mins.)

Catherine Metayer MD PhD, Adjunct Professor, Epidemiology/ Biostatistics and Epidemiology, University of California-Berkeley, Principal Investigator, Center for Integrative Research on Childhood Leukemia and the Environment

Residential Pesticide Exposures



Forest plot showing individual and summary odds ratios for home pesticide exposures and the risk of childhood acute lymphoblastic leukemia, using random effects models.

In a meta-analysis by Bailey, et al. (2015) that combined data from 12 studies in the Childhood Leukemia International Consortium, residential insecticide use before conception, during pregnancy, or after birth was associated with increases in the risk of childhood acute lymphoblastic leukemia of 40 to 50% (OR*=1.39 to 1.51). For acute myeloid leukemia, the associations were somewhat similar for pesticide exposure before conception (OR=1.88) and during pregnancy (OR=1.60), but not after birth (OR=1.10).

Graphic used with permission from Bailey, et al. 2015, Supplementary Figure 1.

OCCUPATIONAL EXPOSURES DURING PREGNANCY MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

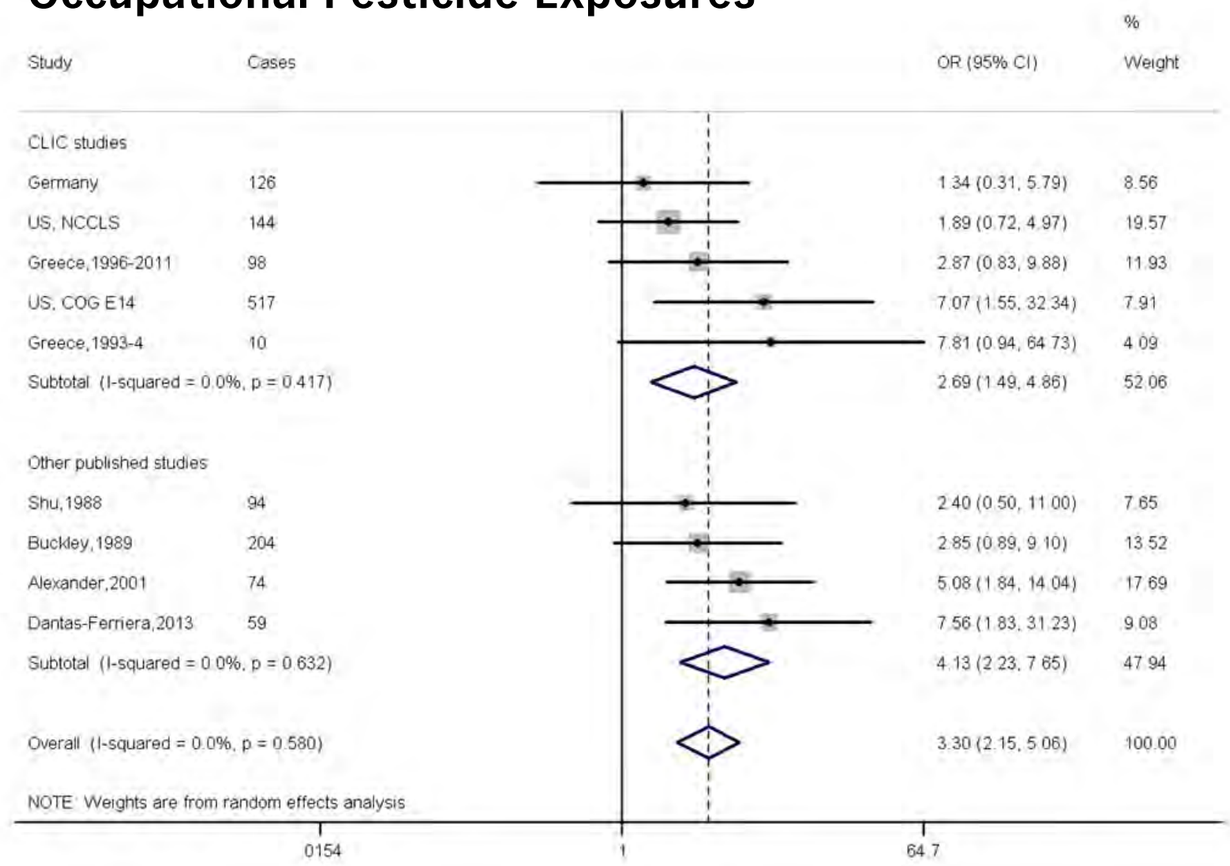
Dr. Baker asked a few more details about the garden center. Tricia said she worked in the back office while she was pregnant, up until a few months before Stephen was born.

Pesticides, solvents, and other chemicals may cause chromosomal alterations in parents' eggs and sperm cells that increase the risk of their children developing certain cancers, or maternal exposure may affect the child directly while in utero.

Studies have demonstrated a link between maternal occupational exposures to pesticides and childhood leukemia. Maternal use of pesticides at home has also been associated with AML risk. In case studies, maternal exposure to certain insecticides has been associated with translocations seen in children with AML.

Occupations and other cancers

Occupational Pesticide Exposures



The largest analysis combining original data from studies (1,329 cases) around the world found a near doubling of risk for AML if mothers were exposed occupationally to pesticides during pregnancy OR 1.94 (CI 1.19, 3.18).

No associations were found for childhood ALL. This forest plot of pooled data shows individual and summary odds ratios for maternal occupational pesticide exposure during pregnancy and the risk of AML in the offspring, using random effects model.

Source: Bailey, et al., 2014.
Reproduced with permission.

PATERNAL OCCUPATIONAL EXPOSURES AROUND TIME OF CONCEPTION MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

Analysis of data (pooled) from studies around the world, including over 8,000 cases of childhood leukemia showed a 20% increased risk of ALL associated with paternal occupational exposure to pesticides around the time of conception. The risk was about 40% increased in children whose diagnosis was at age 5 years or greater and in those with T cell ALL. This highlights the importance of considering both critical windows of exposure as well as the different sub-types of leukemia when possible.

Though "pesticides" includes a wide variety of different chemicals and these findings do not implicate specific agents, more than 20 pesticides have been classified as "possible" or "probable" human carcinogens by the International Agency for Research on Cancer (IARC).

Paternal exposures to solvents, paints, and employment in motor vehicle-related occupations have also been shown to be associated with childhood leukemia. Paternal exposures before conception could result in germ cell damage or changes in gene expression. Parental exposures after the child is born may result in exposure to the family by materials from work being brought home on clothing.

Key Concept:
Take-Home Exposures

More information:
Pesticide Safety Information for Farmworkers from the California EPA

EXPOSURES TO PAINTS AND SOLVENTS MAY INCREASE RISKS

David thought back to painting the nursery while Tricia was pregnant and wondered if using paint or paint thinners had exposed Stephen to substances linked to the development of leukemia.

In a pooled analysis that combined data from 8 studies in the Childhood Leukemia International Consortium (Bailey et al., 2015), home paint exposures before, during, and after birth were consistently associated with modest increases in the risk for childhood ALL; the risks were limited to children who were exposed to oil-based paints (~20% increase in risk). Although information about the scale of individual painting projects was not available, it can be assumed that professional painters tended to be hired for bigger jobs. As such, the observation that leukemia risk was highest when professional painting was reported (OR=1.53 before conception and OR=1.66 during pregnancy) can be interpreted as evidence of a dose-response relationship. Also, it appears that risks were higher for certain cytogenetic subtypes including translocation t(12;21) and MLL rearrangement, suggesting that etiologic pathways may be specific to childhood leukemia subtypes.

Use of solvents in the home was associated with a two-fold increase in AML risk (Scelo et al., 2009).

?

Home remodeling and the risk of leukemia

continued from left

In addition, a number of studies have reported elevated risks of childhood leukemia associated with complex mixtures of solvents such as those found in gasoline and traffic exhaust and from parental occupational exposures (see sections on occupational exposures and air pollution).

Many solvents are recognized carcinogens, with benzene being a well-established leukemogenic agent in adults. A meta-analysis of various sources of benzene (i.e., household use, occupations, and air pollution) showed associations with childhood ALL (OR=1.48) and AML (OR=2.07) (Carlos-Wallace et al., 2016). As evidence of a relationship between paint/solvent exposures and childhood leukemia risk continue to accumulate (Whitehead et al., 2016), parents may wish to avoid paint and solvent exposures (when feasible) during the immediate pre-conception period and pregnancy. This will also help lower the risk of other adverse health outcomes associated with the same agents.

TRAFFIC-RELATED AIR POLLUTION MAY INCREASE CHILDHOOD LEUKEMIA RISK

Living near major roadways results in exposure to many potential carcinogenic substances. Estimates place as much as 10% of the U.S. population and as many as 30-45% of urban residents living near major roadways.

Studies have suggested that chemicals and other components of air pollution may contribute to childhood leukemia. A recent meta-analysis of seven studies from Europe and the United States conducted by the CDC suggests that living near highly trafficked roadways after birth increases children's risk for leukemia by over 50% (OR 1.53; 95% CI 1.12, 2.10) (Boothe et al., 2014).

EARLY PRECONCEPTION AND PRENATAL INTRODUCTION OF VITAMINS AND FOLATE REDUCES RISK OF CHILDHOOD LEUKEMIA

At their next visit, Dr. Baker asks Tricia about her pregnancy with Stephen. Like many other women, she didn't think about taking vitamins before or during the first two months of the pregnancy, especially because she ate a nutritious diet. Otherwise she was very careful to live a healthy lifestyle while pregnant and did not smoke or drink. She started on prenatal vitamins with folate at her first prenatal visit at eight weeks gestation.

Folate supplementation has been associated with reductions in risk for childhood leukemia, at least for those at risk for lower folate consumption. Folate supplementation before conception and early in pregnancy not only appears to be protective in the case of leukemia risk, but also reduces neural tube and other birth defects, and may reduce the risk of developing autism. (Schmidt et al., 2012; Suren et al., 2012, Metayer et al., 2014.)

Preconception and Healthy Child Development

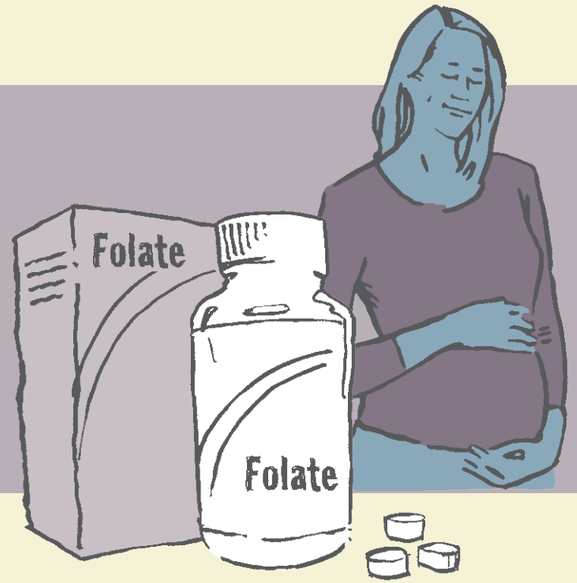
More information: CDC's Preconception care for women and men

Prenatal Care and Healthy Child Development

Folate and Leukemia, Folate Recommendations for Women

Developmental Origins of Health and Disease (DOHaD)

More information: Developmental Origins of Health and Disease (DOHaD)



More resources for prenatal care:

- CDC on pregnancy
- Royal Congress of OB/GYN:
  - Chemical Exposures During Pregnancy
- American Congress of Obstetrics and Gynecology (ACOG):
  - Good Health Before Pregnancy (pdf)
  - Environmental Chemicals
- UCSF: Program on Reproductive Health and the Environment

GENETICS AND EPIGENETICS

Cancer is an epigenetic disease as much as it is a genetic disease; fully 10% of the leukemia genome is epigenetically altered compared to normal blood cells. Some of these alterations may be a result of adaptations to our environment very early in our development. Such adaptations may be appropriate at the time, but have consequences later for disease risk. Such an idea was well explained in the Barker Hypothesis (developmental origins of health and disease), now known to have epigenetic mechanisms.

As the extent to which epigenetic mechanisms play a role in cancer become better understood, we will also better understand the influence of environmental variables on these mechanisms. This remains a highly active research field.

Watch: Dr. Mark Miller discusses the Barker hypothesis (1:40 min.)

Mark Miller MD MPH, Director Emeritus, Children's Environmental Health Program, Office of Environmental Health Hazard Assessment, California EPA; Director, UCSF Pediatric Environmental Health Specialty Unit

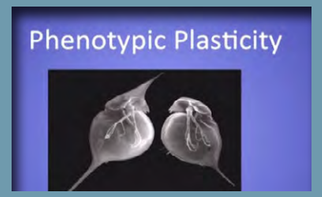
Familial Susceptibility

enlarge graphic

More information on cancer classifications:
International Classification of Childhood Cancer, Third ed.

Polygenic Risk Scores

Genetic conditions with increased incidence of ALL



Watch: Dr. Mark Miller discusses epigenetics (1:45 mins)

WHAT IS EPIGENETICS?

The genetic code, or DNA sequence, is exactly the same in each body cell. We need some way, however, to express our genes in a correct manner for each cell type, be it blood, bone, muscle, brain, etc. Early in development, our genes are encoded with a set of distinguishing marks on top of genes, or epigenetic marks, that influence gene expression. Epigenetic marks are important to all stages of all cell types, to keep each cell organized within our whole human organism.

Exposures to environmental chemicals, infections, and diet can result in the turning of genes on or off. For instance, in a high pollution environment, our bodies can turn on detoxification enzymes. In a low folic acid environ-ment, the body can adjust to retain more folate within our cells.

Polygenic graphic credit: Soyoung Jeon

Reference: Jeon S, de Smith AJ, Li S, Chen M, Chan TF, Muskens IS, Morimoto LM, DeWan AT, Mancuso N, Metayer C, Ma X, Wiemels JL, Chiang CWK. *Genome-wide trans-ethnic meta-analysis identifies novel susceptibility loci for childhood acute lymphoblastic leukemia*. Leukemia. 2022 Mar;36(3):865-868.

Increased burden of familial-associated early-onset cancer risk among minority Americans compared to non-Latino Whites. Feng Q, Nickels E, Muskens IS, de Smith AJ, Gauderman WJ, Yee AC, Ricker C, Mack T, Leavitt AD, Godley LA, Wiemels JL. Elife. 2021 Jun 22;10:e64793.

HEALTHY EATING PROMOTES HEALTH, PREVENTS DISEASE

Holistic nutritional assessments that accounted for both vitamin intake and diet have indicated that maternal prenatal vitamin supplementation – with folic acid or other B-vitamins – and healthy diet at the time of conception and during pregnancy significantly decreased the risk of having a child with leukemia.

Reduction in risk ranged from 10 to 60% depending on the type of data analyzed (B-vitamins or healthy diet index) and the type of leukemia (lymphoblastic or myeloid) (Singer et al, 2015a and 2015b). In contrast, heavy coffee consumption (but not tea) during pregnancy seems to be harmful, based on a pooled analysis from the Childhood Leukemia International Consortium (Milne et al., 2018).

Although findings linking maternal alcohol consumption to childhood leukemia are less consistent, it is prudent to refrain from drinking alcohol during pregnancy as well.

Breastfeeding reduces risk of leukemia

Breast milk contains antibodies and anti-inflammatory substances that have an overall beneficial impact on the infant and child later in life. Several pooled and meta-analyses have confirmed that breastfeeding 6 months and more reduces the risk of childhood leukemia by 15%. These findings provide additional rationale to promote breastfeeding.

FIND OUT MORE:

"Rosa and Carlos Plan a Family"

Raising a healthy child begins before pregnancy.
A CIRCLE microsite

CRITICAL WINDOWS OF EXPOSURE TO TOBACCO SMOKE

David smoked before Stephen was born but quit when his wife found out she was pregnant.

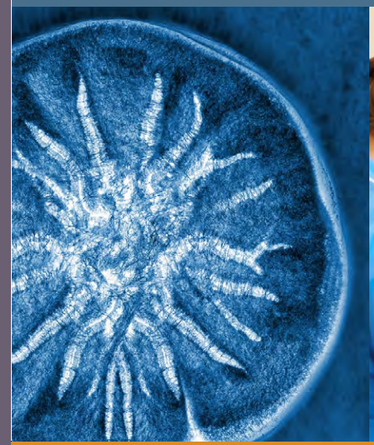
We know that tobacco smoke could be affecting the development of the fetus and the child during pregnancy and during the early years of life. We also know that tobacco smoke can affect the germ cells.

That means at the time of conception, or even before conception, tobacco smoke may have an effect. Exposures during multiple time periods may add additional risk.

- Key Concept: Windows of Vulnerability
- Map: Percent Current Adult Smokers by State

Smoking Cessation Resources:

- Free Help to Quit Smoking (Nat'l Cancer Institute)
- Getting Help to Quit Smoking (American Lung Assoc.)



PARENTAL SMOKING INCREASES RISK OF CHILDHOOD LEUKEMIA

At various times during a child's development, parental smoking – by either the mother and/or father – confers an increased risk of childhood leukemia.

Research from the Childhood Leukemia International Consortium (CLIC) has confirmed that paternal smoking before conception is linked to an increased risk of acute lymphoblastic leukemia (ALL) (Metayer, 2013 – see figure in the Paternal Smoking popup). The effect can be exacerbated if the child continues to be exposed to secondhand smoke after birth.

Interview-based studies of the relationship between maternal smoking during pregnancy and childhood leukemia were initially mostly negative; but recent advancements have pointed to specific at-risk populations. It also appears that certain subtypes of childhood leukemia are uniquely sensitive to maternal smoking. Modern techniques of assessing smoking habits during pregnancy may reveal more about the risks.

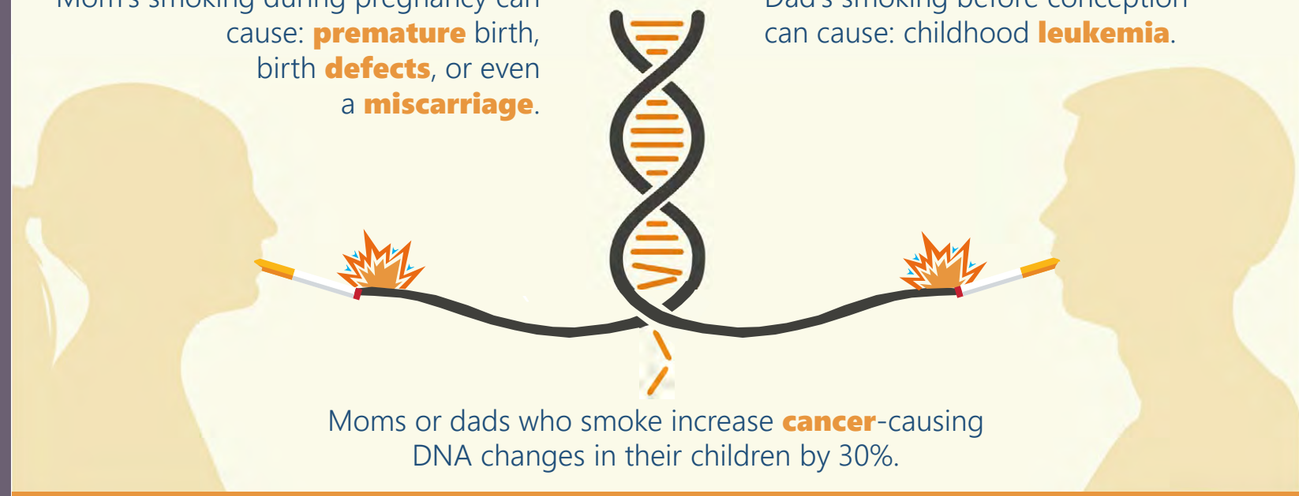
- **Paternal smoking associated with increased risk of specific leukemia subtype**
- **Tobacco Smoke and Childhood AML**
- **Molecular markers of past smoking**

Mom's Smoking During Pregnancy is Bad for Baby, but DID YOU KNOW?

Dad's Smoking *Before* Pregnancy Can Harm the Child, too.

Mom's smoking during pregnancy can cause: **premature** birth, birth **defects**, or even a **miscarriage**.

Dad's smoking before conception can cause: childhood **leukemia**.



Moms or dads who smoke increase **cancer**-causing DNA changes in their children by 30%.

Start Protecting Your Children's Health BEFORE They Are Conceived!

Graphic used in "Tobacco Smoke and Childhood AML" popup used with permission from Metayer C, Petridou E, Mejía Aranguré JM, Roman E. et al. Parental tobacco smoking and acute myeloid leukemia in children: the Childhood Leukemia International Consortium. Am J Epidemiol. 2016 Aug 15;184(4):261-73.

DOCTOR – IS ANY ONE RISK FACTOR THE IDENTIFIABLE CAUSE OF STEPHEN'S LEUKEMIA?

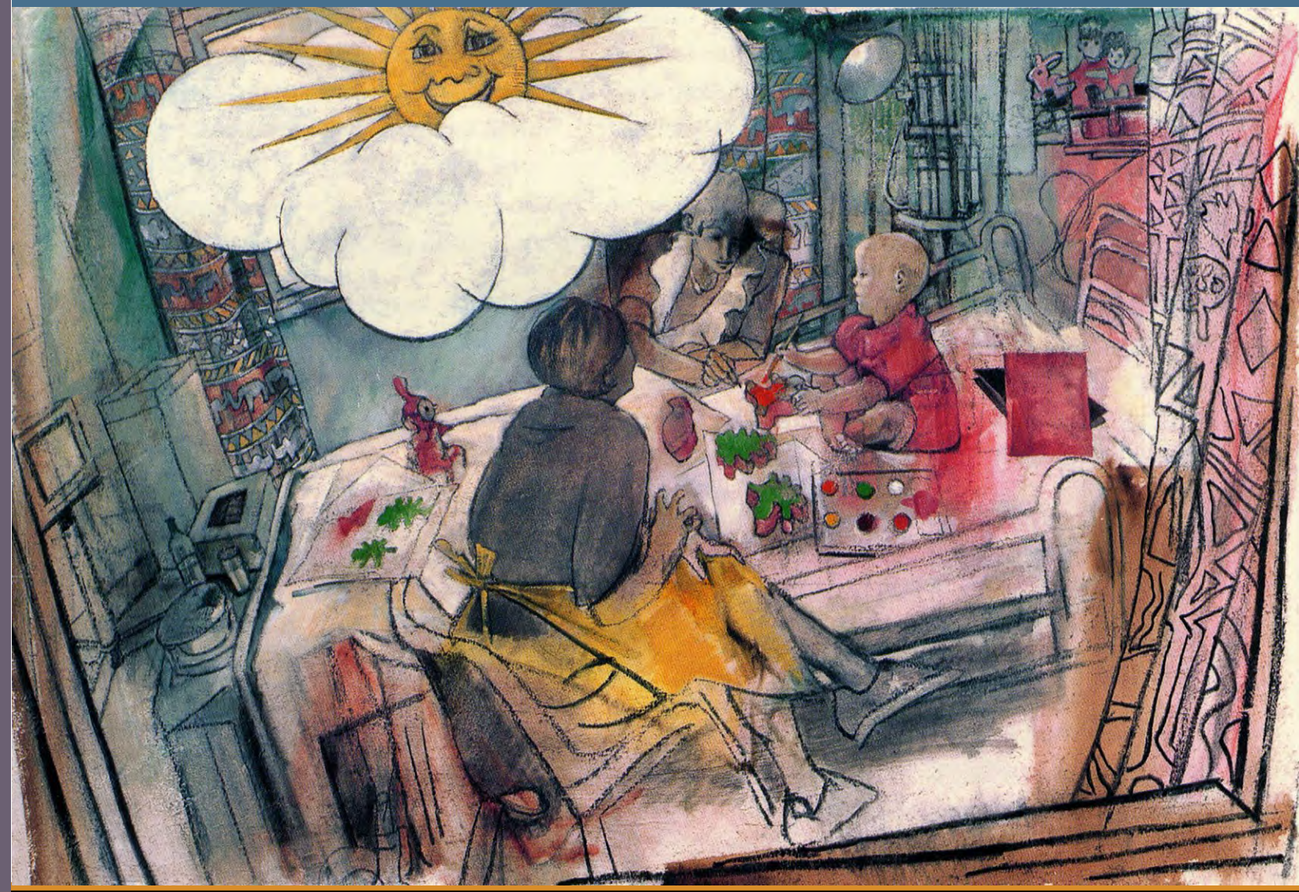
Toward the end of their clinic visit, Tricia and David were visibly distressed about all of the potential factors that could have contributed to their son's leukemia.

Dr. Baker told Tricia and David that they cannot blame themselves for their son's disease. Most complex diseases cannot be explained by a single variable. He said, for example, that studies examining the link between pesticide exposures and leukemia involve fairly large groups of people and cannot be used to establish the cause of disease in an individual. He pointed out that most children exposed to pesticides do not get leukemia and in most cases there is no clear explanation for the cause of a specific child's leukemia.

He added, that due to health concerns about exposures to environmental toxicants, it would be a good idea for everyone to minimize their exposures to them.

Ecological Approach to Disease

Watch: Dr. Gary Dahl discusses the clinic visit (3:08 mins.)



"Playschool."
by Susan Macfarlane,
reproduced with permission.

About this painting, with words of the artist in *italics* >

SOME CHILDREN ARE AT HIGHER RISK

A few months after Stephen began treatment, Tricia and David start chatting with a customer, Lynn, while she is purchasing plants at their garden center. Tricia recognizes Lynn's daughter Ava in the shopping cart because she used to be in Stephen's child care.

Ava has Down syndrome. Lynn asks about Stephen, who is napping nearby. Tricia explains about Stephen's illness. Lynn mentions that their pediatrician told her that kids with Down syndrome are at higher risk for leukemia (10-20-fold higher risk). Fortunately, fewer than one percent of children with Down syndrome get childhood leukemia.

? **Family History and Childhood Leukemia**

HOME EXPOSURES VIA DUST

After Stephen's diagnosis, his parents were approached by researchers and asked to participate in a study to analyze their household's dust. Stephen's parents wondered what could possibly be in the house dust that would give researchers clues as to what may cause childhood leukemia. The researchers were very clear that the study is designed to learn about the possible causes of leukemia and would not be able to pinpoint a specific cause of Stephen's leukemia.

The researchers explained that they were going to analyze the dust for polychlorinated biphenyls (PCBs) and structurally-similar polybrominated diphenyl ethers (PBDEs), classes of chemicals that can remain in the environment for long periods of time. A previous single study found that these two classes of chemicals in house dust were associated with an increased risk for childhood leukemia and they are trying to replicate the results (see pop up "PCBs, PBDEs in house dust"). PCBs had many industrial and commercial applications, including electrical equipment and building materials. PBDEs are used as flame retardants in plastics, textiles, and furniture.

These chemicals can migrate from consumer products and collect in house dust. Because children crawl on the floor and put their hands in their mouth, they may be exposed to higher amounts of chemicals commonly found in house dust than adults.

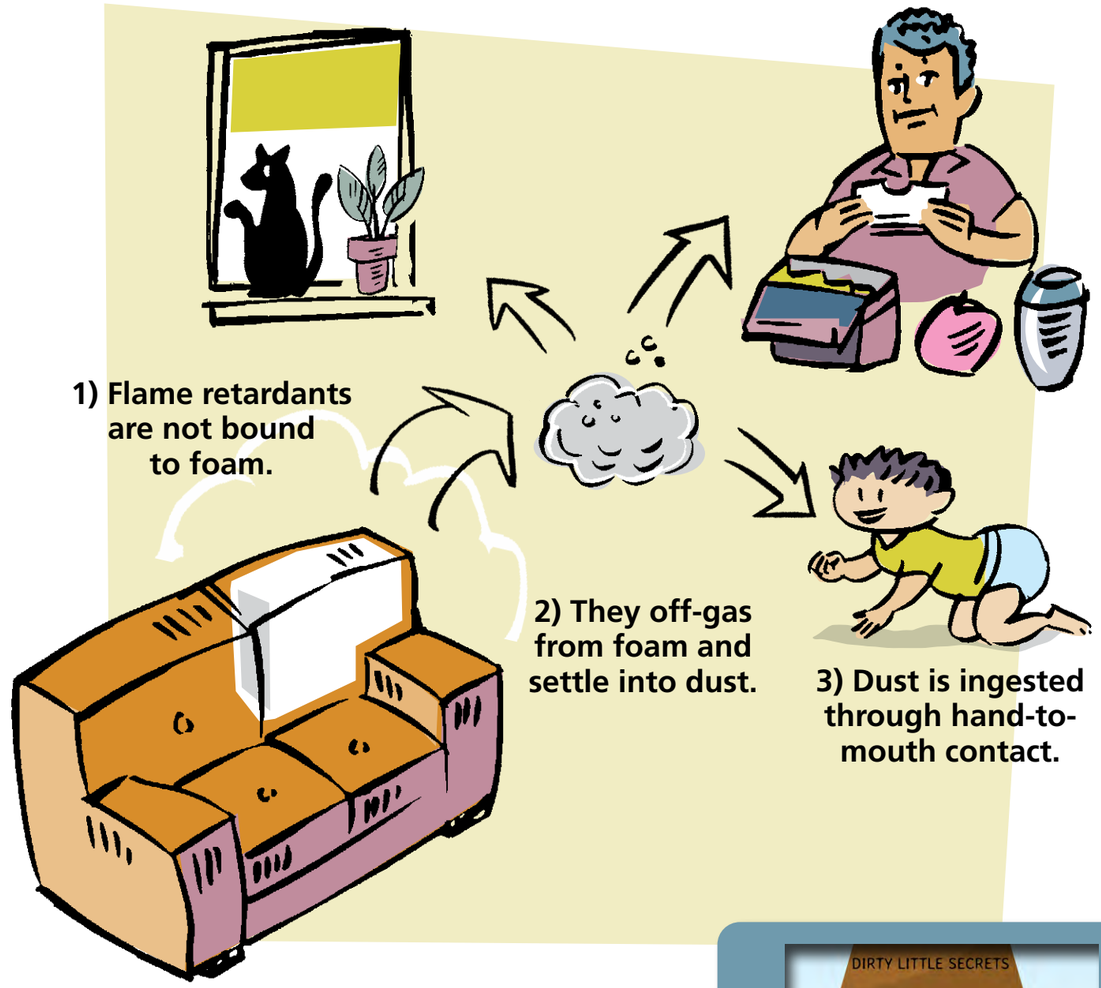
PCBs, PBDEs in house dust.

Watch: Dr. Todd Whitehead on chemical exposures from house dust (1:56 mins.)

Todd Whitehead PhD, Assistant Researcher, School of Public Health, University of California- Berkeley

Find out more: Tips to protect children from toxic house dust.

How do we come in contact with flame-retardant chemicals?



Find out more: Watch "Dirty Little Secrets About House Dust" Film

IMMUNE SYSTEM MODULATION AS A PROTECTIVE FACTOR

Stephen attended preschool before he started chemotherapy.

One day, Tricia and David ran into parents at the grocery store whose children also attended Stephen's preschool. They mentioned that their daughter had just gotten over a cold. Tricia thought it seemed like she was always hearing about someone getting sick in that school, but it was one of the larger preschools. She started to worry about whether something was going around at school that could have made Stephen sick.

Stephen got several serious infections as a young child and they emailed Dr. Baker about whether this could be related to their son's leukemia.

Dr. Baker responded that going to a large pre-school could actually be protective against childhood cancer, but that children with leukemia report more frequent severe infections throughout their childhood before diagnosis, perhaps indicating an altered or more severe immune system response to common infections.

Watch: Dr. Joe Wiemels discusses theories about infection and leukemia rates (3:55 mins.)

- Infection in the womb may be a primary cause of ALL
- Maternal infection
- Infection and leukemia risk
- Infection-related damage leading to leukemia
- Exposure to farm animals and pets

Exposure to animals reference

Graphic for Infection and leukemia risk used with permission.

Infections reference: Rudant J, et al. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium study. Am J Epidemiol. 2015 Apr 15;181(8):549-62.

CANCER CLUSTERS

One day while waiting in the hospital for Stephen's treatment, Tricia and David meet a family that looked familiar from the neighborhood. They realized that they were at the hospital for the same leukemia treatment. They wondered if other families in the neighborhood were facing the same thing, too. They asked their doctor to speak with local health officials to share this information and to see if other doctors might have reported seeing other cases of children with leukemia within the same neighborhood or community. The doctor agreed and told them about a study that showed a confirmed cluster of leukemia in Woburn, Massachusetts.

A cancer cluster occurs when a greater than expected number of cancer cases within a group of tumors or with similar risk factors arise among people in a defined geographic area during a specific time. Due to the nature of the disease and the time it takes for cancers to develop, investigations to determine if a cancer cluster exists and what might be the potential cause or contributing factors are very challenging. However, the Centers for Disease Control and Prevention encourages examinations of unusual patterns of cancer and environmental concerns when they appear through regular monitoring of disease rates or when concerns are brought to the attention of health officials (see CDC's About Unusual Patterns of Cancer).

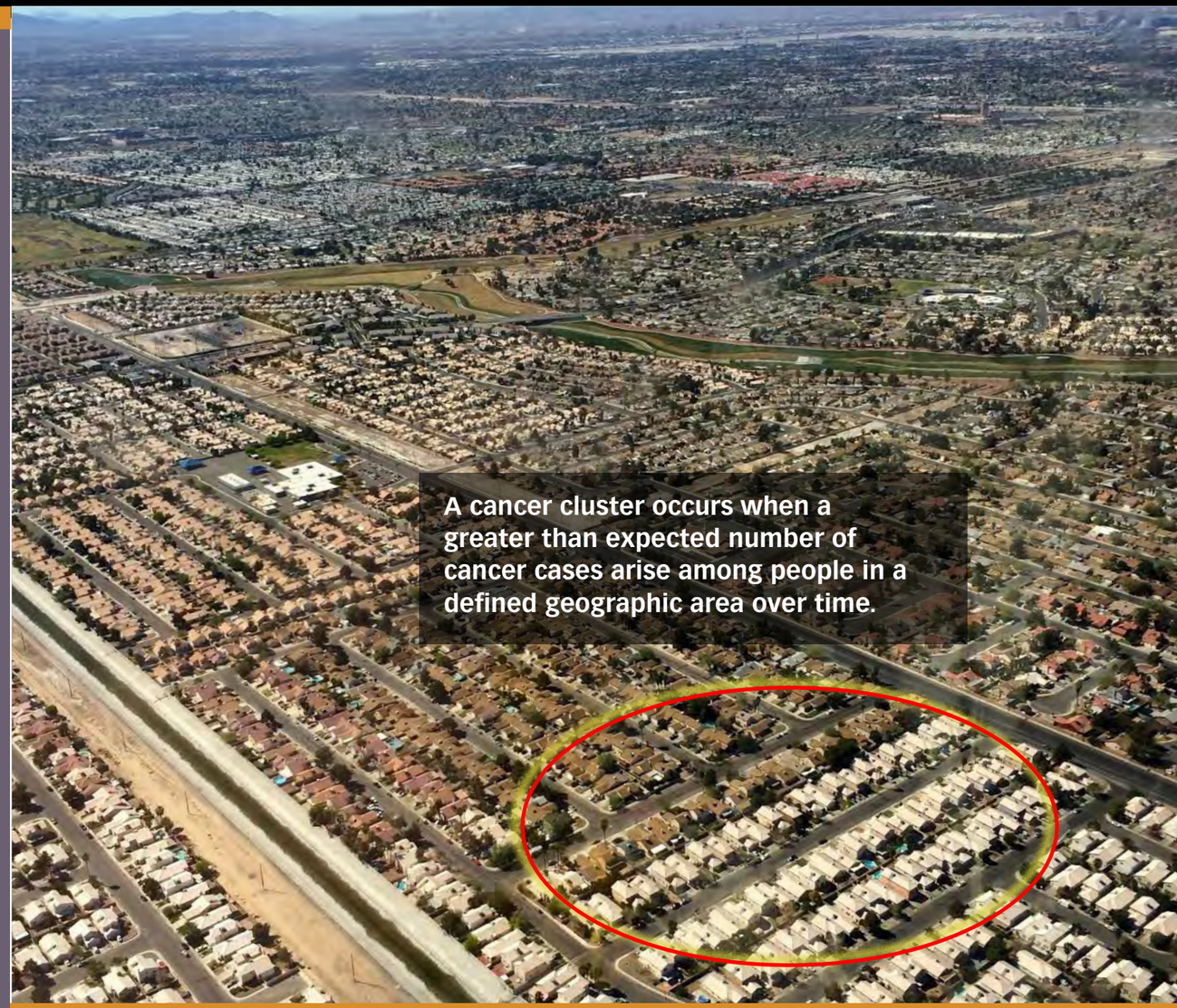
Although the causes of many cancers are unknown, some causal relationships have been shown between environmental exposures and development of cancer in specific organs (for example, exposure to asbestos and the development of mesothelioma. However, in most investigations of suspected cancer clusters, a cause is not identified.

What is a cancer cluster?

Find out more:

- Community Health Studies and Environmental Contamination
- About Unusual Patterns of Cancer NCEH | CDC
- Wilmington Childhood Cancer Study

Read the Cancer Clusters Fact Sheet from the National Cancer Institute



IONIZING RADIATION (including X-ray and CT scan) exposure and childhood cancer

Along with the few infections that Stephen had as a baby, he caught pneumonia when he was six months old. This required a trip to the doctor and a few chest x-rays.

Exposure to ionizing radiation from nuclear accidents, x-rays, or radiation therapy has been associated with increased risk of childhood leukemia. Multiple studies have consistently shown in utero exposures to ionizing radiation increase the risk of leukemia by approximately 40% (Buffler et al., 2005).

Due to high radioprotection standards for pregnant women, prenatal exposure to medical radiation is rare, yet child's exposure to medical imaging after birth remains common.

CT-scans are of particular concern for children because children are considerably more sensitive to radiation than adults, they have a longer life expectancy resulting in a larger window of opportunity for expressing radiation damage, and doses are cumulative over a lifetime. CT-scans use has substantially increased in the early 2000's and they often result in higher radiation exposures than X-rays (Linet et al., 2009).

Pooled analyses showed that diagnostic CT scans given at a young age augments the risk of developing both childhood leukemia and brain tumors (figures 4 and 5 in paper by Abalo et al., 2021), and that the risk increases with increasing levels of exposure (Pearce et al., 2012).

The Electromagnetic Spectrum

Non-ionizing Radiation

Cell Phone Radio Frequency Radiation

More information:
National Toxicology Program (NTP) Research Overview

Childhood brain tumors

National Cancer Institute: Radiation Risks and Pediatric Computed Tomography (CT)

In contrast, there is no definite evidence that X-rays increase the risk of those cancers (Abalo 2021).

However, if the imaging test is necessary and clinically justified, then the parents can be reassured that the benefits will outweigh the long-term cancer risks. In recent years, radiologists and technicians in many hospitals have undertaken steps to reduce the exposure from x-rays and CT scans while maintaining the necessary quality of the image (Lambert et al., 2014). Many clinicians are considering whether a patient evaluation involving radiation exposure is truly necessary, or if the information of interest can be acquired in some other way.

Another source of radiation exposure to the public is environmental background radon, which is an established lung carcinogen. However, studies on childhood leukemia have been inconclusive with both positive and negative results depending on the region/ country and study design (Lu et al., 2020).

Electromagnetic Spectrum graphic:
EPA: Radiation basics

"Radiotherapy"
by Susan Macfarlane,
reproduced with permission.

About the painting with the words of the artist in *italics*

SOCIAL SUPPORT

Dr. Baker emphasizes to Tricia and David the importance of Stephen continuing his chemotherapy medications throughout the duration of recommended treatment.

Stephen will undergo an intensive therapy period that ranges from 6-9 months, requiring frequent visits to Dr. Baker's office or the hospital. After this time, Stephen will receive maintenance chemotherapy where he visits the oncologist approximately once a month, but the frequency of these visits will depend on how well Stephen tolerates his medications.

A month into Stephen's therapy his parents joined a support group for parents of kids with leukemia and learned about different resources. Studies indicate that social support can improve the quality of life in pediatric cancer patients. These benefits can include reduced anxiety and post-traumatic stress among childhood cancer survivors. More adaptive coping strategies were also observed with family and social support.

Adolescent and Young Adult Cancer Programs

Commonweal Cancer Help Program

Find out more about support groups, community links:

National Cancer Institute:

- Adolescent and Young Adult Cancer Programs
- Emotional Support

CureSearch for Children's Cancer

Cancer.Net

The Leukemia & Lymphoma Society (LLS)

Watch: Dr. Gary Dahl on chemotherapy compliance (1:30 mins.)

CHILDHOOD CANCER Stephen's Story

After learning about the risks of chemical substances in the environment, Stephen's parents are taking steps to reduce exposures to their family and their community.

The nursery that they own will be transitioning to an all organic business model, and they are working with other local businesses like the town's golf course to partner together and use Integrated Pest Management (IPM). They have also become active in the local school board to help Stephen's preschool switch to IPM.

Tricia and David are considering having another child after Stephen completes chemotherapy and is in full remission. They are relieved that the risk of leukemia for siblings remains low

After researching the possible causes of Stephen's disease and becoming more knowledgeable about how many environmental factors impact health, they will take extra precautions to promote a healthy pregnancy. Tricia will be taking folate supplements before conception and during the pregnancy. She also plans to avoid the various environmental exposures that she has learned about to the extent possible.

Integrated Pest Management

More Resources:

Pesticides: Integrated Pest Management (IPM) Principles | US EPA

Bio-Integral Resource Center (BIRC)

Pesticide Action Network (PANNA)

UC Statewide Integrated Pest Management Program

IPM in Early Care and Education

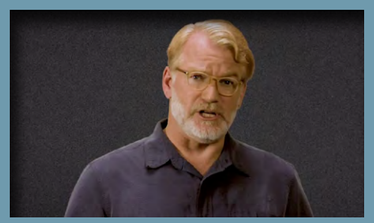
CHILDHOOD CANCER Stephen's Story

When Tricia, David, and Stephen joined the rest of the family at this year's reunion, they were cautiously optimistic about the future.

Stephen was responding well to chemotherapy and the family had found comfort in their local cancer support group and advocacy efforts to bring about change in their Connecticut town.

David tells the family about how far cancer treatments have progressed in recent years and that Stephen has approximately a 90% chance of being free of cancer in 5 years. They were all still concerned about the possibility of a relapse but have grown stronger as a family and as a community.

Watch: Cause or Cure?
Dr. Bruce P. Lanphear – Is the relentless pursuit of a cure hazardous to our health? (4:28 mins.)



Dr. Bruce P. Lanphear, MD MPH, Professor, Simon Fraser University

SUMMING UP

Several common themes arise in Stephen's story that are similar to others in *A Story of Health*. These include the importance of critical windows of susceptibility, the consideration of sub-groups within a disease, the multiple risk factors, and the interaction of underlying genetics with the chemical, social and other environments. We are also reminded that population studies can illuminate underlying risk factors of disease (and therefore possible preventive actions), but generally cannot answer the specific question, "what caused this illness in this child?"

Like other chronic diseases that have been increasing in recent years, childhood leukemia is complex. Although there is no consensus amongst experts about its causes, except in a small percentage of cases, evidence implicating a variety of risk factors continues to accumulate. For example, considerable evidence from multiple studies around the world implicates exposures to tobacco smoke, pesticides, radiation, and traffic-related air pollution. The evidence of protective effects of peri-conception folate supplementation, breastfeeding, and early exposures in daycare also has substantial support.

Other associations that we have discussed in Stephen's story (e.g., PCBs and PBDEs) have been examined in only one or two studies and highlight the need for further investigation.

Though it may seem daunting, viewing health and disease as a result of the complex ecology of modern life reveals many key leverage points in which preventive actions may reduce disease incidence and improve health. Several of these are merely reinforcing current recommendations from medical societies and other expert practice guidance.

Many of the risk factors associated with childhood leukemia are also risk factors for other diseases discussed in *A Story of Health*. People will benefit in a variety of ways from avoiding unnecessary exposures to tobacco smoke, pesticides, solvents and other environmental concerns.

Viewing health and disease as a result of the complex ecology of modern life reveals many key leverage points in which preventive actions may reduce disease incidence and improve health

Population studies can illuminate underlying risk factors of disease (and therefore possible preventive actions), but generally cannot answer the specific question, "what caused this illness in this child?"

SOME FINAL THOUGHTS

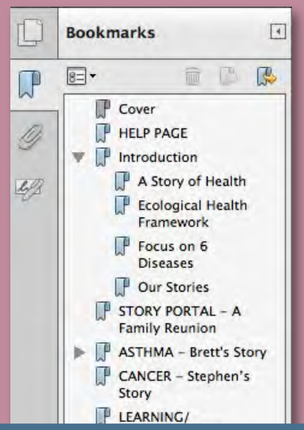
COMMON THEMES

Although the fictional narratives in *A Story of Health* describe the lives of children and adults with different conditions and diseases – childhood cancer, infertility, asthma, developmental disabilities, cognitive decline and health effects of wildfires, common themes resonate. They include:

- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly during critical windows of development, can have profound beneficial or detrimental lifelong effects, even into elder years.
- Healthy people and healthy communities are interdependent. All people do not have equal access to nutritious food, clean air and water, safe workplaces, healthy housing, green spaces, peaceful neighborhoods or quality health care.
- Preventing disease and promoting health require actions and commitments from the individual, family, community and society. Health promoting public policies are necessary to make healthy living available to all people.

Bookmarks

We have linked to many useful resources in each story relevant to a wide range of audiences, including clinicians. To quickly access resources on specific topics in each story, use the **Bookmarks** toolbar on the left (which you can open or close), or return to the **Help page** for more details on other eBook features.



Additional Resources

Pediatric Environmental Health Toolkit application for mobile devices

The Toolkit is an easy-to-use reference guide for health providers on preventing exposures to toxic chemicals and other substances that affect infant and child health. The new mobile device-ready online version of the PEHT includes links to many related online resources.

Continuing Education

To receive continuing education (CE) for SS4677- *A Story of Health – Childhood Cancers: Stephen's Story*, please visit CDC TRAIN and search for the course in the Course Catalog using SS4677.

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Childhood Cancer Case References and Resources by Topic

Note: there are many topic overlaps

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