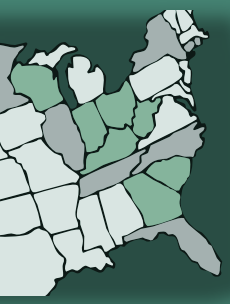
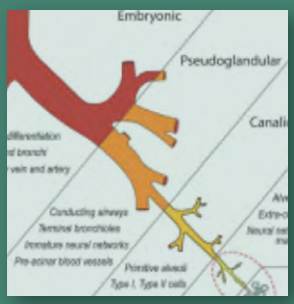
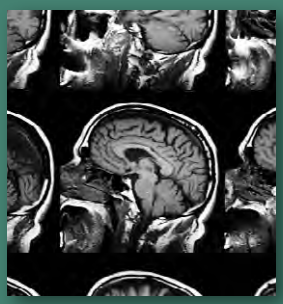
A Story of Health







ACKNOWLEDGEMENTS

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For more information:
Brian Tencza: bht1@cdc.gov
Maria Valenti: mvalenti@igc.org

Primary Authors/Development Team

Mark Miller MD MPH, Director, Western States Pediatric Environmental Health Specialty Unit at UCSF

Director, Children's Environmental Health Center, Office of Environmental Health Hazard Assessment, California EPA

Director, Community Outreach Translation Core, CIRCLE, UC Berkeley

Ted Schettler MD MPH, Science Director, Science and Environmental Health Network

Science Director, Commonweal

Brian Tencza MEd, Team Lead Education Services, Agency for Toxic Substances and Disease Registry (ATSDR)

Maria Valenti, Director, Health and Environment Literacy Project, Commonweal, www.commonweal.org.

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CONTRIBUTING AUTHORS

Christine Zachek, Victoria Leonard, Marya Zlatnik, Samuel M. Goldman, Sammy Almashat, Karin Russ

ART TEAM

Illustrations, eBook design, production
Stephen Burdick,
Stephen Burdick Design

Illustrations
Dan Higgins, Visual Information Specialist, Centers for Disease Control and Prevention

REVIEWERS

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Introduction and Asthma (Brett's Story): Polly Hoppin; Catherine Karr; Brian Linde; Maria Mirabelli; Madeleine Scammell, Rebecca Wolf

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OTHER CONTRIBUTORS

Agency for Toxic Substances and Disease Registry:

Online course development and video editing: Amanda Cadore

Copyright and Editing: Diana Cronin

Geographic Information Services Team: Charlton Coles; Stephanie Foster; Melissa M. Smith; Shannon Graham, Julia Bryant

Boston University Superfund Research Project: Ann Aschengrau, Wendy Heiger-Bernays, Jennifer Schlezinger, Veronica Vieira

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close window

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2. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the organizations listed (above) as funders.

3. The ATSDR, US EPA, NIEHS, and Cal EPA/ OEHHA do not endorse the purchase of any commercial products or services mentioned in this publication.

A Story of Health

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, prompt down-loads or navigate to a related page.)

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 the icons (above) 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

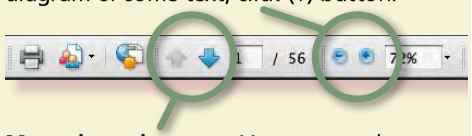
Our eBook Navigation: Click on selections in the bar at the top of each page to move between stories, navigate back to this 'Help Page', and to find out more in the References section.

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

Adobe Acrobat Tools

This interactive pdf document is best viewed on a laptop or desktop, down-loaded 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.



Move through pages - You can use the up and down arrows to move through pages.

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

Note: Navigation features may not work properly using other pdf reader platforms.

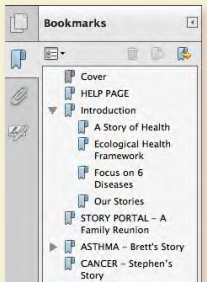


Table of Contents

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 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

skip this section

definition

Skip this section - If you wish to skip a technical section, choose the "Skip this section" arrow and you will jump to the page after the technical sections ends.

You can skip this section and continue to the Story of Health introduction.

INTRODUCTION

This is a story 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.

Our overall story is told through the personal stories of a number of fictional people of various ages attending a family reunion.

These individual stories highlight the many ways our health is influenced by the complex environments where we live, eat, work, play, volunteer, gather and socialize.

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.

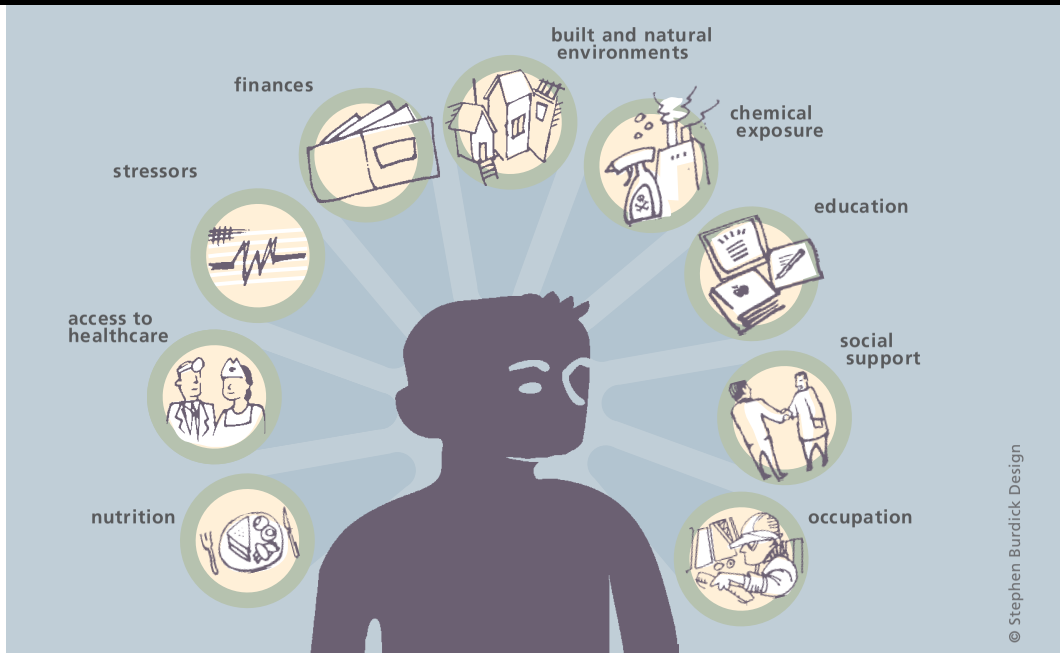
Important determinants of health come from the natural, built, chemical, food, economic, and social environments.

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.

Watch: Pediatrician Larry Rosen addresses the environment and family health. (2 min.)

Lawrence D. Rosen MD is an integrative pediatrician and founder of the Whole Child Center.



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

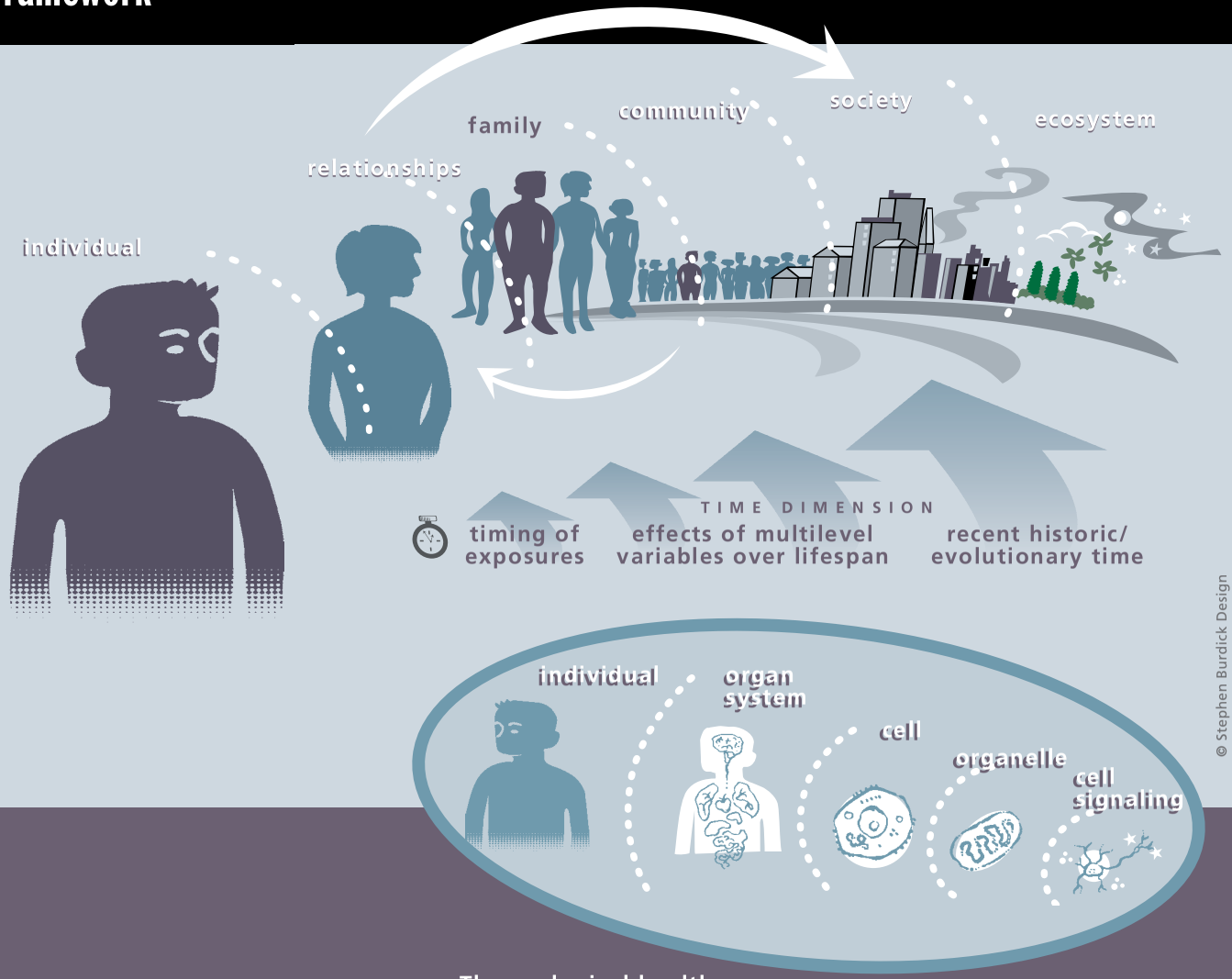
Rarely is one particular thing responsible for health or disease, so we refer to this as a multifactorial (or ecological) approach, the best way to promote health and prevent disease.

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 Focus on Six Diseases

Following are stories 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 we will explore include some of the most common and troubling diseases and disorders of our time.

They include:

- Asthma
- Cancer (childhood leukemia)
- Diabetes
- Infertility
- Learning and developmental disabilities
- Cognitive decline

INTRODUCTION Our Stories

These stories are not meant to be an exhaustive accounting of every variation of a disease or every possible cause.

Rather, we present current, authoritative scientific evidence to enable you to better understand environmental contributors and make more informed decisions and take action to help improve your health, and the health of your family, friends, community, and patients.

A FAMILY REUNION Six Stories

This page is your portal to six stories of health.

It is recommended that you read through the introduction first and then choose stories in the order you wish.

Health professionals can receive Continuing Education (CE) for completing *A Story of Health*. Click here for more details.

Choose stories in the order you wish. Select a disease term to highlight the affected person. Click the arrow button to read his or her fictional story of health.

Asthma | Cancer | Learning/ Developmental Disabilities | Diabetes | Infertility | Cognitive Decline

INTRODUCTION Free Continuing Education

Information on free Continuing Education offered from the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry

Each of the fictional stories in *A Story of Health* offers free Continuing Education (CE). On the "Final Thoughts" page of the last story of the entire eBook, or of each story (if you download them separately), you will be prompted to register for CE through a hyperlink.

This hyperlink links to the CDC/ ATSDR CE page where you can register and take the test for CE for each story. Before you begin each story, please review the learning objectives at right. These will help you focus as you read each story, and prepare you for each CE test.

Review these learning objectives for each story:

- Brett's Story (Asthma) >
- Stephen's Story (Cancer/Childhood Leukemia) >
- Amelia's Story (Developmental Disabilities) >
- Reiko & Toshio's Story (Infertility) >
- Sam's story (cognitive decline) >

FREE CONTINUING EDUCATION

Continuing education available by specialty

- Continuing Medical Education (CME) for Physicians

LEARNING OBJECTIVES

Sam's story (cognitive decline):

- Identify differences among cognitive decline associated with normal aging, MCI, and dementia.
- Identify two workplace risk factors for developing cognitive decline.
- Describe the importance of social interaction on the impact of Alzheimer's progression.
- Identify the association between pesticides and Parkinson's disease.
- Describe how alcohol consumption alters the risk for cognitive decline.
- Describe how traumatic brain injury (from sports, or accidents) may affect the development of Parkinson's disease.
- Identify socioeconomic factors that may contribute to cognitive decline.
- Identify three environmental factors that may contribute to chronic disease.

close window

CHILDHOOD LEUKEMIA 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 LEUKEMIA 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 LEUKEMIA 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,
reproduced with permission.

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

See this page for more information on the artist.

"Diagnosing the Leukaemic Cells"

A laboratory scene with staff using a blood cell analyser to carry out a full blood count. The machine transfers a measured small quantity of blood into a special fluid that is passed through the analyser, which counts the total number of each different blood cell type.

There are three main types of blood cells: white blood cells, red blood cells and platelets, some of which are illustrated at the top right of the analyser. In the majority of children with leukaemia there will be a higher total number of white blood cells in the blood due to leukaemic cells being present.

The analyser also estimates the amount of haemoglobin which carries oxygen and is contained in the red blood cells.

"A very busy machine with the staff moving from stage to stage in a trice- hence the figure is drawn 4 times in the one painting!"

On the left side of the painting the seated staff member is making a smear from a drop of blood to enable the cells to be studied under the microscope.

close window ⊗

CHILDHOOD LEUKEMIA 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**

Bone marrow is the soft tissue inside bones that helps form blood cells. It is found in the hollow part of most bones. Bone marrow aspiration is the removal of a small amount of this tissue in liquid form for examination.

close window ⊗

"Typing the Leukaemic Cells"
by Susan Macfarlane,
reproduced with permission.

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

See this page for more information on the artist.

"Typing the Leukaemic Cells"

"I am shown amazing colours and shapes under the microscope and must try to do them some justice."

To confirm that a child has leukaemia a bone marrow examination is essential. A Consultant Haematologist studies small samples of bone marrow smeared onto glass slides and then stained to assess the degree of marrow infiltration by leukaemic cells. The appearance down the microscope of a bone marrow infiltrated by acute lymphoblastic leukaemia, with the leukaemic cells stained blue, is shown in the painting at three different magnifications; low power top left, middle power bottom right and high power in the centre. One of the cells at 8 o'clock in the latter group is dividing, known as mitosis. The other member of the laboratory staff in the painting uses a flow cytometer which sorts the leukaemic cells according to any surface 'markers' present. The leukaemic cells have previously been reacted with a large series of fluorescent 'marker' proteins, or antibodies, which bind to any specific 'markers' present on the surface of the leukaemic cells. It is the identification of the specific 'markers' on the leukaemic cells which allows the leukaemia to be accurately typed.

close window ⊗

CHILDHOOD LEUKEMIA Stephen's Story

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

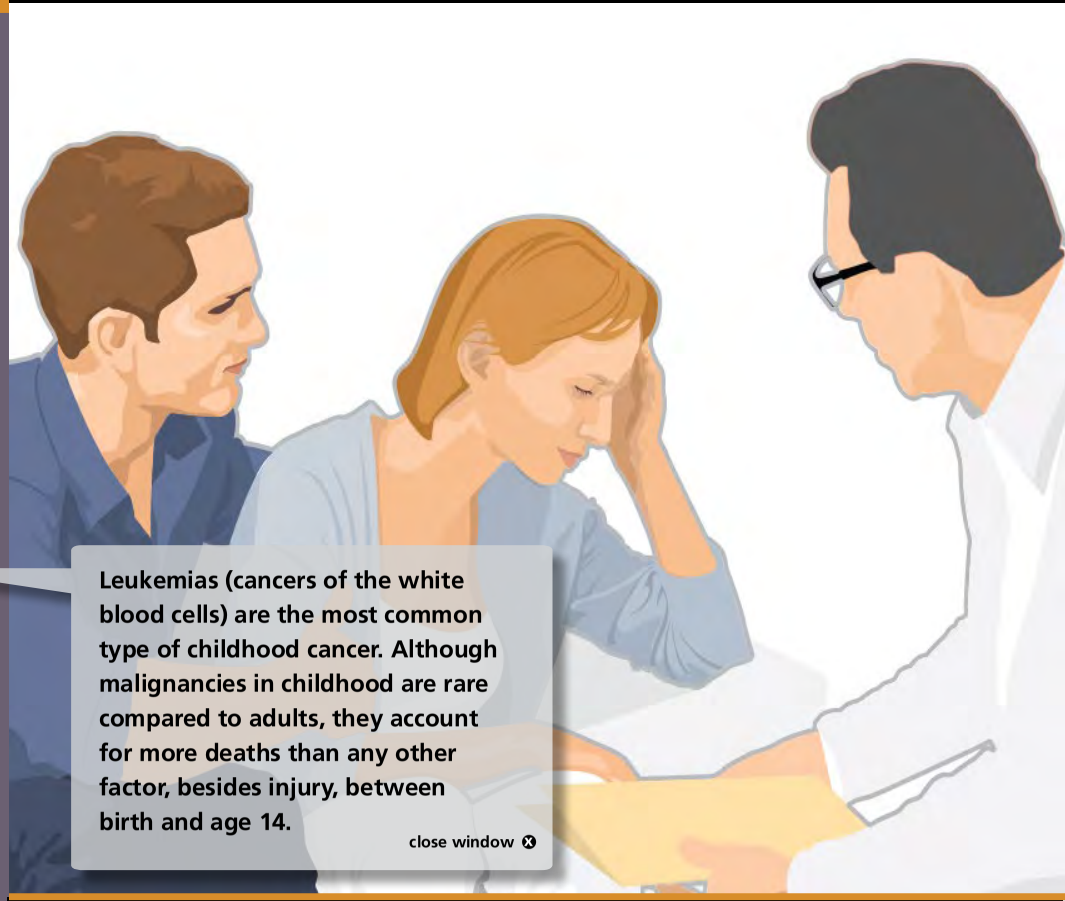
Dr. Baker explained the bone marrow procedure to Tricia and David and then performed the aspirate in a special room for procedures.

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 is Leukemia?



Leukemias (cancers of the white blood cells) are the most common type of childhood cancer. Although malignancies in childhood are rare compared to adults, they account for more deaths than any other factor, besides injury, between birth and age 14.

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

CHILDHOOD LEUKEMIA Stephen's Story

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 LEUKEMIA 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

In the 1960s, about 1 in 10 children with acute lymphoblastic leukemia lived for more than 5 years. For children diagnosed between 2003 and 2009, nearly 9 out of 10 lived for more than 5 years. (Ward et al., 2014)

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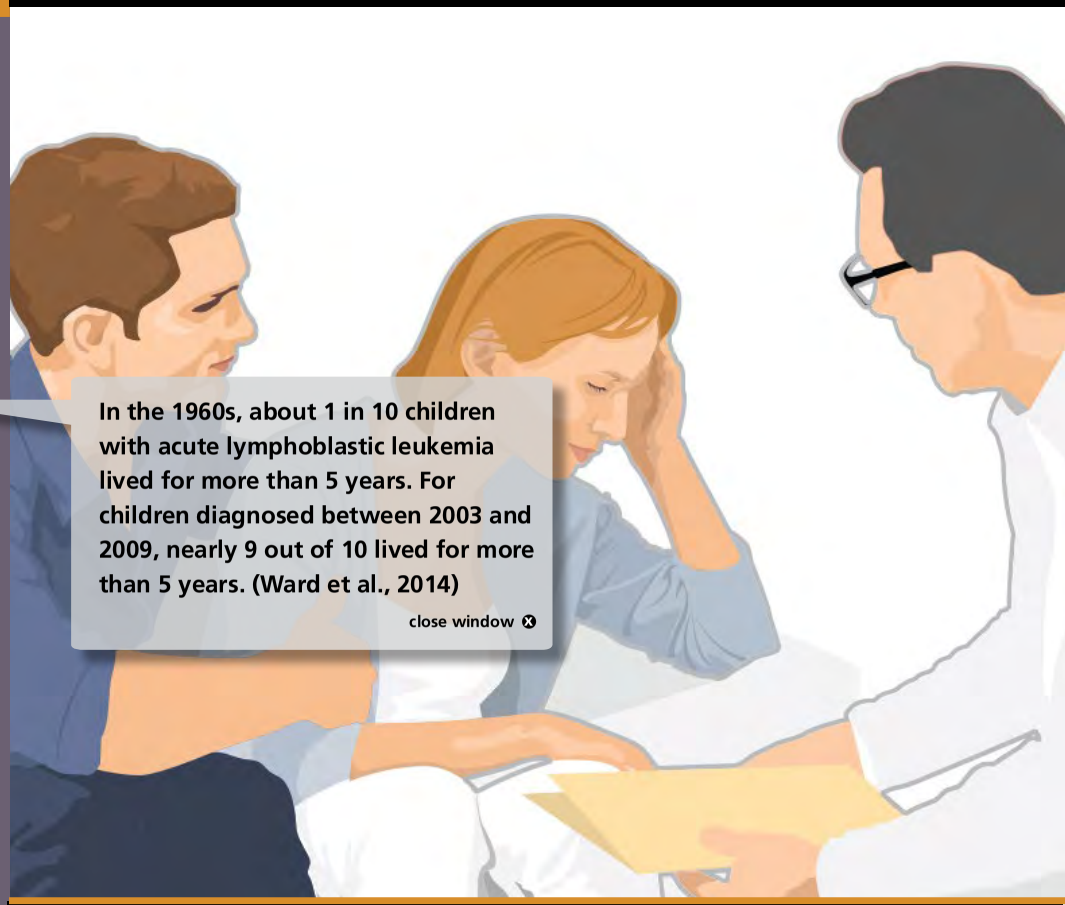
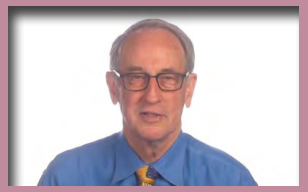


Watch: Dr. Gary Dahl discusses types of leukemia (4:13 mins.)



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

CHILDHOOD LEUKEMIA Stephen's Story

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.

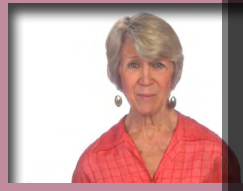
Factors such as age, initial white blood count at diagnosis, and cytogenetics (the specific differences or changes in DNA) of the leukemic cells at diagnosis are utilized to identify the most appropriate course of treatment.

Types of leukemia vary by age

Early life exposures are important: age-specific incidence chart

More Detail on ALL Subtypes

Watch: Dr. Patricia Buffler discusses leukemia classification (1:59 mins.)



Patricia Buffler PhD MPH, Professor of Epidemiology and Dean Emerita (deceased) of the School of Public Health, University of California-Berkeley

Types of leukemia vary by age

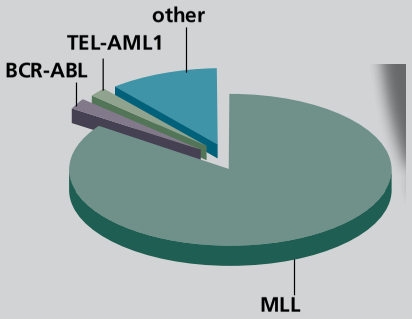
The two main types of leukemia based on cell histology are ALL and AML, but even within these groups, there are many different characteristics based on the presence of abnormalities of the chromosomes, whether the number of chromosomes is higher than expected (hyperdiploidy), or whether or not we see translocation or deletion in a specific chromosome.

These differences have practical implications: subgroups may have very specific risk factors. The leukemia subgroup also impacts treatment decisions.

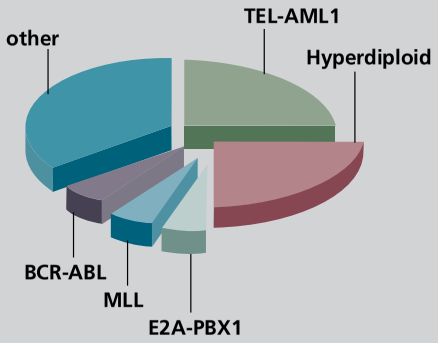
When grouped by underlying molecular markers, certain leukemias occur more frequently at different ages. MLL (mixed leukemia or Myeloid/lymphoid leukemia) is the predominant form in infants but relatively rare in older children. MLL is a particularly aggressive form of leukemia.

More details on translocations, hyperdiploidy, and other genetic changes in childhood leukemia are discussed later in this module.

INFANTS



CHILDREN



Types other than MLL are identified by various acronyms that refer to other subtypes of leukemia.

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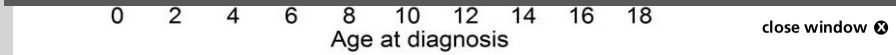

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CHILDHOOD LEUKEMIA Stephen's Story

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

This series of paintings by Susan Macfarlane captures the emotional, psychological, and physical toll imposed on children and families by childhood leukaemia. The paintings were commissioned by Dr. Geoffrey Farrer-Brown for the art exhibition "Living with Leukaemia" by the charity "A Picture of Health." We include these with our gratitude to Euan and Angus Mackay and Dr. Farrer-Brown for permission to reproduce them. The book, "Susan Macfarlane "1938-2002" contains a retrospective of the artist's work. For more information or to acquire a copy of the book, please contact Euan Mackay lafamillemackay@gmail.com

close window

click a preview image to view above

Paintings by Susan Macfarlane, reproduced with permission.

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CHILDHOOD LEUKEMIA 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.

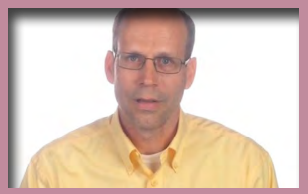
Childhood leukemia is difficult to study because it is relatively rare, which limits the design of studies intended to help clarify its etiology (cause). Nevertheless, substantial evidence identifying a number of risk factors has emerged over the past two decades. The etiology is likely to be attributable 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
- TEL-AML1 Gene Fusion
- ? Germ Cell Formation

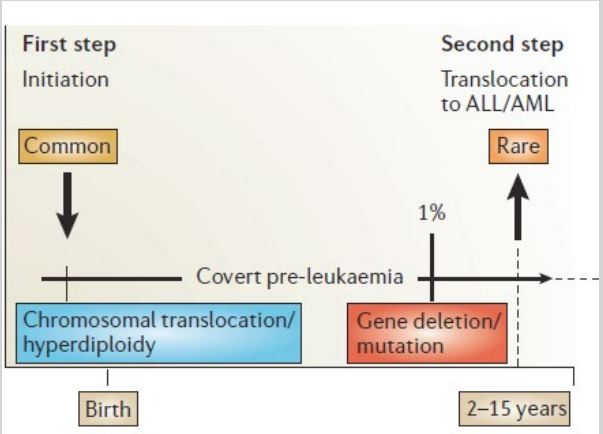
Watch: For clinicians: Dr. Joe Wiemels discusses timing of environmental exposures (2:23 mins.)



Joseph L. Wiemels PhD, Professor, Division of Cancer Epidemiology Leukemia & Lymphoma Society Scholar in Clinical Research, University of California-San Francisco School of Medicine

Childhood leukemia results from more than one insult to DNA

Researchers consider cancer to often be a result of more than one temporal event. For childhood ALL and AML, there are two exposure windows: one prenatal (before conception or in utero), when leukemia is commonly initiated through chromosomal rearrangements, and a second, postnatal window that is linked to the emergence of overt disease through secondary genetic changes.



This model is supported by evidence that the genetic changes are far more frequent than the actual disease. This suggests that initiation of leukemia may be a common event, but the second "hit" that transitions to ALL or AML is rare (Greaves, 2006).

Note: 1% refers to an estimated frequency of transition between covert pre-leukemia and overt clinical leukemia. Infant ALL and AML (<1 year of age) has a much-abbreviated natural history in which all the necessary genetic events are thought to occur prenatally.

Greaves, 2006, graphic used with permission.

close window

CHILDHOOD LEUKEMIA 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 red dots 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.

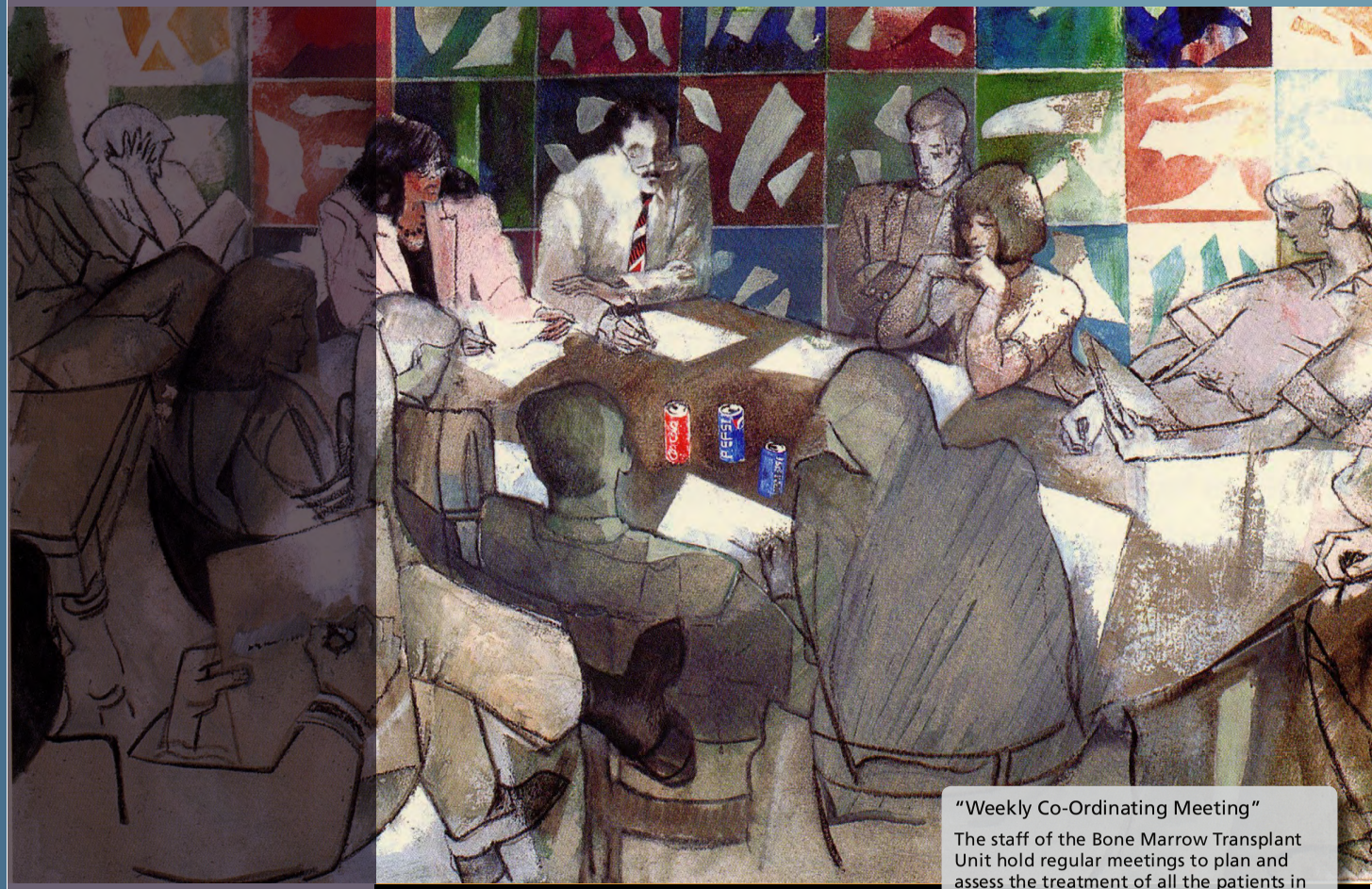
CHILDHOOD LEUKEMIA Stephen's Story

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.

*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"
by Susan Macfarlane,
reproduced with permission.

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

"Weekly Co-Ordinating Meeting"

The staff of the Bone Marrow Transplant Unit hold regular meetings to plan and assess the treatment of all the patients in their care. *"The body language of each and every member helped to make this an interesting design."*

close window ⊗

CHILDHOOD LEUKEMIA 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.

Key Concept: Causation vs. Association

Caesarian section and immune function

Birth characteristics

Fetal growth

Parental age

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

Mark Miller MD MPH, Director, 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

KEY CONCEPT:

Causation vs. Association

Epidemiologic studies identify

for evaluating intentional medical interventions, are typically not applicable or possible when studying the origins of environmentally-related diseases. A randomized controlled

Caesarian section and immune function

It is hypothesized that altered immune function plays a central role in the etiology of childhood leukemia. The priming of the immune-system starts immediately at birth when babies undergo different levels of "stress" and exposure to the maternal microbiota depending on the mode of delivery – vaginal versus Caesarian section (C-section). Two large studies (Marcotte et al., 2016; Wang et al., 2017) showed that planned C-section (likely to be the least stressful and most sterile mode of delivery) was associated with a higher risk of childhood leukemia compared to unplanned C-Section and vaginal delivery (likely to be the most stressful and least sterile mode of delivery), suggesting that the child's immune development at an early stage has a profound impact later in life. This finding is extremely important given the recent increases in planned C-sections in many countries. It is imperative that the clinical community continues efforts to reduce the rate of unnecessary C-sections.

close window

tal growth

cause childhood acute lymphoblastic ukemia usually develops at a young age to 5 years old), researchers have examined w fetal development may affect leukemia k. In a meta-analysis by Milne et al. (2013) at combined data from 12 case-control udies in the CLIC, leukemia patients were re likely than healthy controls to have en born with high birth weight for their stational age. This observation was later plicated by another consortium that oled data from six cohort studies (Paltiel al., 2015). These robust epidemiologic dings support the role of fetal growth the etiology of childhood leukemia. The derlying disease mechanisms are not fully aracterized, but insulin-like growth factors likely to be involved.

close window

Pesticides, solvents, air pollution, tobacco smoke

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 LEUKEMIA Stephen's Story

CHILDHOOD LEUKEMIA: US TRENDS

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

Childhood leukemia incidence has been increasing in the US (0.8% per year) during the last two decades.

In the US, between 1975 and 2010, the rate of leukemia among children 0-14 years increased 0.7% per year. This adds up to a 35% increase over 35 years.

Ethnic Trends

Genetic susceptibility to leukemia in Latinos

ETHNIC TRENDS:

Childhood leukemia is increasing more amongst certain ethnic groups such as Latinos

California with its large population and excellent data collection on cancer is the

non-Latino Black children, it is increasing at 1.7% per year amongst them. This is

Genetic susceptibility to leukemia in Latinos

Leukemia is more common among Latino Americans compared to other ethnicities. While the causes of this are still uncertain, what is now clear is that part of the answer is genetics. There are several rare genetic syndromes that predispose strongly for childhood leukemia, but account for only a few cases among any ethnic group. There are much more common genetic factors which contribute weakly to leukemia risk, but due to their high frequency they are responsible for a larger proportion of leukemia incidence. Interestingly, the proportion of these common genetic factors varies by ethnicity: the frequency of many genetic factors is higher in Native Americans and Latinos than in whites and blacks. These genetic polymorphisms in the genes, ARID5B, GATA3, PIP4K2A, and CEBPE, collectively account for a large proportion of the increased risk of leukemia in Latinos. There are also likely to be environmental risk factors that also contribute to the increased risk in Latinos including lifestyle and exposures from occupation, which are known to vary in frequency between ethnicities.

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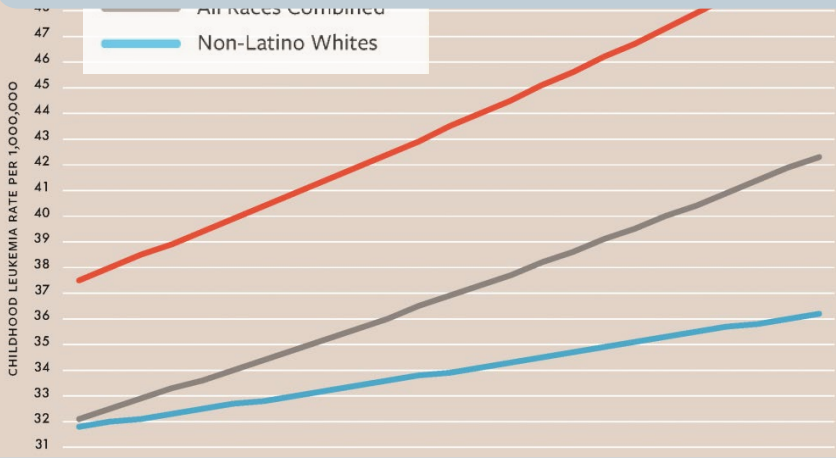

higher among Latino children than among non-Latino children and the gap is widening.

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Latino trend graphic used with permission from: Giddings BM, Whitehead TP, Metayer C, Mille M D. Childhood Leukemia Incidence in California: High and Rising in the Hispanic Population. Cancer. 2016 Sep 15; 122(18): 2867–2875.

PESTICIDES AND LEUKEMIA

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.

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

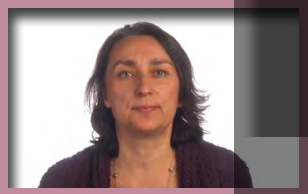
CHILDHOOD LEUKEMIA Stephen's Story

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.

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

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

Pesticide Regulation

Link to EPA website for more information on FIFRA

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

Residential Pesticide Exposures

Pesticide Regulation

EPA and each of the fifty states register or license pesticides for use in the US. EPA receives its authority to register pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). States are authorized to regulate pesticides under FIFRA and under state pesticide laws. States may place more restrictive requirements on pesticides than EPA. Pesticides must be registered both by EPA and the state before distribution.

Before registering a new pesticide or new use for a registered pesticide, EPA is supposed to ensure that the pesticide, when used according to label directions, can be used with a reasonable certainty of no harm to human health and without posing unreasonable risks to the environment. To do that, EPA is authorized to require various scientific studies and tests from applicants. Where pesticides may be used on food or feed crops, EPA also sets tolerances (maximum pesticide residue levels) for the amount of the pesticide that can legally remain in or on foods. Already-registered pesticides are supposed to undergo periodic tolerance reassessment and registration review.

A recent analysis of EPA practices, however, concluded that the government has allowed the majority of pesticides onto the market without a public and transparent process and in some cases, without a full set of toxicity tests, using a loophole called a conditional registration. In fact, as many as 65 percent of more than 16,000 pesticides were first approved for the market using this loophole (NRDC, 2013).

close window

The horizontal line is the study's confidence interval (a measure of how the results might vary due to chance).

The vertical line at 1 represents "no effect." If the confidence intervals for individual studies overlap with this line, it demonstrates that there is no statistically significant effect observed. The diamond represents the summary measure of all studies combined.

close window

lastic leukemia of 40 to
emia, the associations were
conception (OR=1.88) and
(OR=1.10).

CHILDHOOD LEUKEMIA Stephen's Story

OCCUPATIONAL EXPOSURES DURING PREGNANCY MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

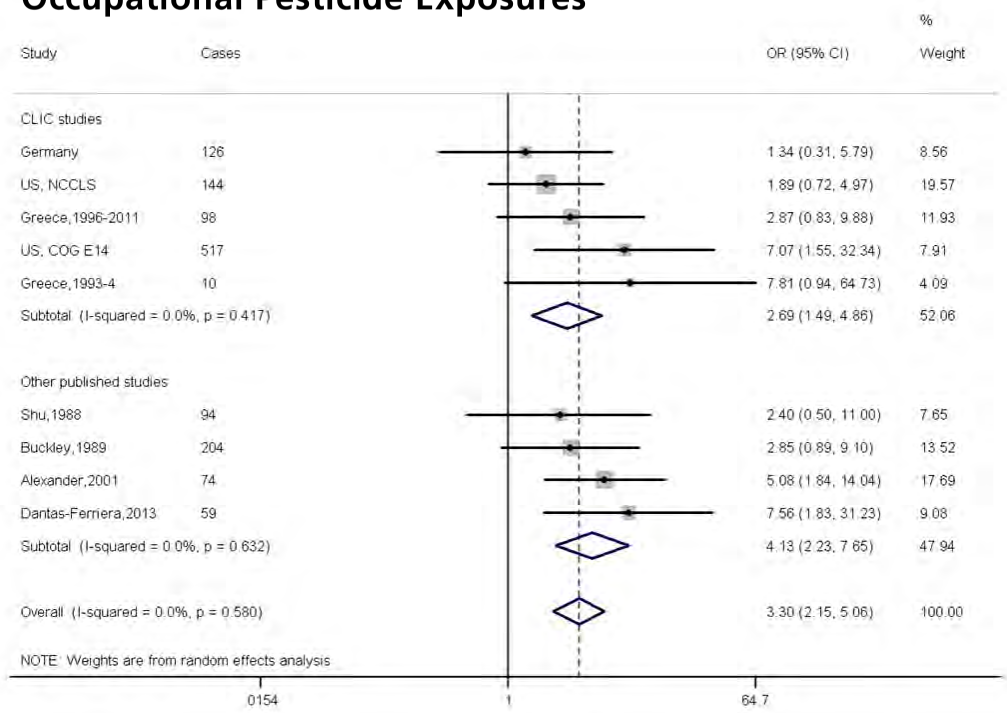
Dr. Baker asked a few more details about the garden center. Tricia said she worked in the back office while she was pregnant, up until a few months before Stephen was born.

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.

Sample prenatal environmental health history form for clinicians from the Consortium for Reproductive Environmental health in Minority Communities

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.

CHILDHOOD LEUKEMIA Stephen's Story

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 from the California EPA

KEY CONCEPT:

Take-Home Exposures

A "take-home" exposure refers to exposure of a child (or other household member) to chemicals, fibers, metals, or dusts brought home from a work site by a parent or from someone else. Examples of take home exposures have included solvents, heavy metals, and pesticides. These can be brought into the home on family members' or visitors' clothing or shoes. Workers might also bring home chemicals from work and use them around the house.

Take home exposures can be prevented by actions such as:

- Changing clothes at work
- Showering before leaving work
- Washing hands upon arrival at home
- Laundering work clothes separately
- Removing shoes before entering the home
- Not using chemicals at home that are meant to be used in the workplace

If hazardous substances are used by individuals working at home, care should be taken to keep the work and living areas separate – and hazardous materials should be stored and disposed of properly.

Similarly, hobbies such as painting, model building, furniture refinishing, and auto repair often involve using solvents. Children and pregnant or breastfeeding women should avoid these exposures.

close window

CHILDHOOD LEUKEMIA Stephen's Story

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 were 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).

continued

? Home remodeling and the risk of leukemia

Home remodeling and the risk of leukemia

Researchers from the California Childhood Leukemia Study examined the relationship between home remodeling and the risk of acute lymphoblastic leukemia (ALL) among 609 patients and 893 healthy controls. Participants were asked to describe construction activities carried out in the home between birth and diagnosis. Construction was associated with a significant increase in ALL risk (odds ratio: 1.52, 95% confidence interval: 1.14-2.02). The investigators concluded that remodeling activities were a non-specific proxy for exposure to toxic chemicals in building materials. Additional studies with more direct exposure assessment are warranted.

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CHILDHOOD LEUKEMIA Stephen's Story

EXPOSURES TO PAINTS AND SOLVENTS MAY INCREASE RISKS

continued from previous page

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.

*Statistically significant

? Home remodeling and the risk of leukemia

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Researchers from the California Childhood Leukemia Study examined the relationship between home remodeling and the risk of acute lymphoblastic leukemia (ALL) among 609 patients and 893 healthy controls. Participants were asked to describe construction activities carried out in the home between birth and diagnosis. Construction was associated with a significant increase in ALL risk (odds ratio: 1.52, 95% confidence interval: 1.14-2.02). The investigators concluded that remodeling activities were a non-specific proxy for exposure to toxic chemicals in building materials. Additional studies with more direct exposure assessment are warranted.

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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)

+ 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

PRECONCEPTION AND HEALTHY CHILD DEVELOPMENT

Preconception care for women and men is important for lifetime health as well as healthy child development.

Image source: Centers for Disease Control and Prevention, used with permission

All women and men can benefit from healthy habits throughout life, whether or not they plan to have a baby one day. These include eating healthy food, getting regular exercise, avoiding toxic substances, and reducing excessive stress.

Even prior to conception some specific actions are important for prospective parents to take because they can influence birth outcomes. Maternal exposures to toxic chemicals before or around the time of conception can adversely affect the quality of eggs (ova) and newly-conceived embryos. But these exposures can be harmful to men's reproductive health as well. For example, a father's occupational exposure to pesticides has been associated with increased risk of some childhood cancers and birth defects in his offspring. (Roberts et al., 2012). Parents can also take home from the workplace toxicants like lead and pesticides on their clothing, resulting in direct exposures to other family members. (Gerson et al., 1996; Fenske et al., 2013)

Nutritionally, a prospective father's diet that is deficient in folate (a "B" vitamin) increases the risk of birth defects in his offspring. (Lambrot et al., 2013). Similarly, maternal folate supplements in the periconceptual period (~ 6 weeks before and after conception) are associated with decreased risk of having a child with an autism spectrum disorder. (Lyall, 2014)

Of course optimal nutrition and appropriate vitamin and mineral supplements throughout pregnancy are also important to help promote optimal fetal development.

close window

used as flame retardants in foam and furniture), among others.

close window

CHILDHOOD LEUKEMIA Stephen's Story

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

CHILDHOOD LEUKEMIA Stephen's Story

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.

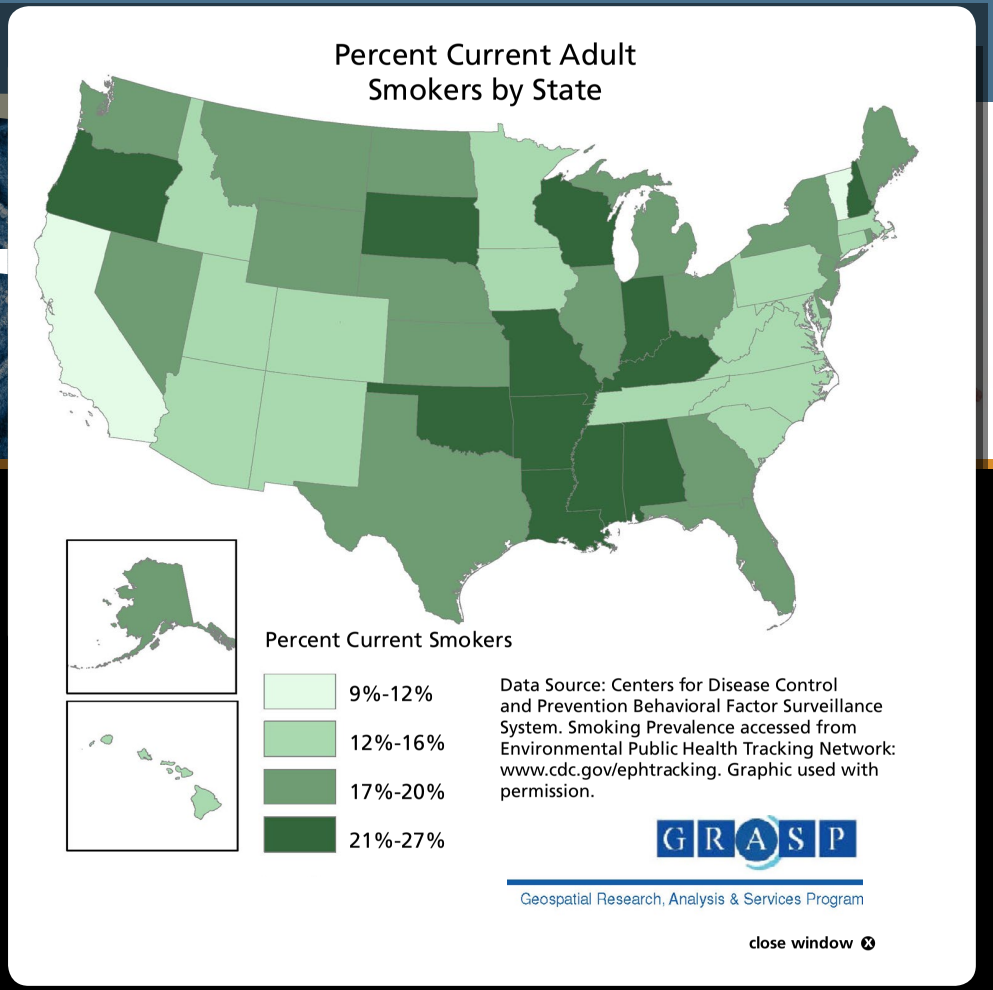
Key Concept: Windows of Vulnerability

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.)



CHILDHOOD LEUKEMIA Stephen's Story

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

Exposure to Tobacco Smoke Increases Risk of Childhood AML

Childhood AML is very difficult to study because it is a rare subtype and that means that there are fewer patients who might participate in observational studies. To deal with this practical limitation, investigators from the Childhood Leukemia International Consortium have pooled data from 12 studies conducted around the world to find risk factors for AML.

Overall, maternal smoking before, during, or after pregnancy was not associated with childhood AML; there was a suggestion, however, that smoking during pregnancy was associated with an increased risk among Latino children (but not other groups).

Paternal smoking was associated with an increased risk of AML in the pooled analysis (OR=1.34; 95% CI 1.11-1.62). Higher risks were reported for heavy smokers. Associations with paternal smoking varied by histological type.

Pooled Risk of Childhood Acute Myeloid Leukemia Associated With Paternal Smoking Across Time Periods, Childhood Leukemia International Consortium, 1974–2012

Window of Exposure	Total Controls, no.	Total Cases, no.	Exposed, %		OR [a]	95% CI
			Controls	Cases		
Ever-smoking	5,538	528	53	60	1.34	1.11, 1.62
Smoking during prenatal period	11,080	1,094	45	51	1.24	1.08, 1.42
Smoking during preconception period	7,699	860	46	50	1.18	1.01, 1.38
Smoking during pregnancy	7,337	810	44	48	1.24	1.06, 1.46
Smoking after birth	11,199	1,035	42	50	1.27	1.11, 1.45

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Odds ratios were adjusted for age, sex, ethnicity, highest parental education, and study center.

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of tobacco constituents in maternal

lymphoblastic leukemia: systematic review and meta-analysis. J Oncol. 2011;2011:854584.

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child was subsequently exposed to secondhand smoke after birth, there was a higher risk of childhood B-cell ALL characterized by a specific

their child's risk for ALL by choosing not to expose them to secondhand smoke after birth.

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acute myeloid leukemia in children: the Childhood Leukemia International Consortium. Am J Epidemiol. 2016 Aug 15;184(4):261-73.

CHILDHOOD LEUKEMIA Stephen's Story

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

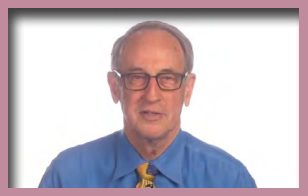
Toward the end of their clinic visit, Tricia and David were visibly distressed about all of the potential factors that could have contributed to their son's leukemia.

Dr. Baker told Tricia and David that they cannot blame themselves for their son's disease. He explained, 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.)



KEY CONCEPT:

Ecological Approach to Disease

Most complex diseases are not easily explained by a single variable. Rather, numerous interactions among many variables, across individual, community, and societal levels, over time, are more likely involved.

Ecological, multifactorial frameworks (or models) are best suited for understanding the origins of complex diseases as well as identifying opportunities to intervene to prevent or treat them. However, for historic and demanding practical reasons, epidemiologists have used simpler models, breaking this complexity into component parts, to enable identification of risk factors for a disease in a population.

Whereas that information is useful, this reductionist approach often cannot fully explain causal pathways to disease in groups of people and can only offer limited insight into the origins of a disease in a particular person. From a public health perspective, reassembling multi-level risk factors into a more complex model 1) acknowledges the systemic origins of disease patterns; 2) helps to make sense of the complexity; and 3) supports the development of new strategies to study and intervene.

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

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

"Playschool."

A child in the isolation unit is attending playschool. *"A captivating moment seen through the corridor window. A child, Stephanie, in 'isolation' happily paints stencils with the encouragement of her Nan and Sue the 'Playlady'. Much thought and care is given to help children remain creative and busy whenever possible."* Education of the child at whatever age is considered most important and is provided in the specialised treatment units.

close window

CHILDHOOD LEUKEMIA Stephen's Story

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

For all childhood cancers, including leukemia, first and second degree relatives of the diagnosed child may be at increased risk for developing cancer if there is already a family history of cancer. It is important to note that although the risk may be increased compared to the general public, since childhood cancer is very rare, the actual risk is still extremely small for siblings and other family members. A three-generation family history for cancer is indicated for all children diagnosed with cancer and should be regularly updated. If an increase in cancer is found, the family should be referred to medical genetics for evaluation. (Curtin et. al., 2013.)

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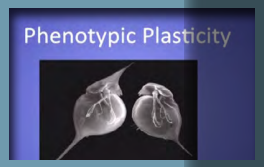
Key Concept: Epigenetics



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

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

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

Family History and Childhood Leukemia

KEY CONCEPT:
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.

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 environment, the body can adjust to retain more folate within our cells.

close window

Genetic conditions with increased incidence of ALL:

- Down syndrome
- Neurofibromatosis
- Shwachman syndrome
- Bloom syndrome
- Ataxia telangiectasia
- Inherited genetic polymorphisms

close window

CHILDHOOD LEUKEMIA Stephen's Story

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. 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.

PCBs and PBDEs in House Dust Linked to Leukemia Risk

Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are two classes of harmful chemicals that were routinely used as additives in certain consumer items and building materials. Due to their toxicity, both groups of chemicals were banned from U.S. production – first, PCBs in the 1970s and, more recently, PBDEs – but some contaminated items and materials that predate the bans likely remain in circulation. Plus, these chemicals do not readily breakdown in the environment and can persist in house dust for years.

The California Childhood Leukemia Study was the first to examine the role of PCBs and PBDEs in childhood leukemia. Exposure to dust contaminated by high levels of certain PCBs and PBDEs was associated with a doubling of ALL risk.

close window

…in contact with …t chemicals?

…ey off-gas …foam and …e into dust.

3) Dust is ingested through hand-to-mouth contact.

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

CHILDHOOD LEUKEMIA Stephen's Story

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
- Infection and leukemia risk
- Infection-related damage leading to leukemia
- Exposure to farm animals and pets

IMMUNE SYSTEM MODULATION:

Exposure to Common Childhood Infections May Modulate the Immune System and Reduce Leukemia Risk

One meta-analysis of 11 studies (shown below) indicates that day-care attendance is associated with a reduced risk of ALL (OR = 0.78) (Rudant et al., 2015). Day-care was used as a surrogate

used month of birth, timing of birth in relation to cold and flu season, and birth order as markers of exposure to infections. They found an increased risk of developing leukemia in children

Infection-related damage leading to leukemia

Exposure to a variety of infections

specific enzyme, APOBEC, which has a role in protecting our cells from viruses. APOBEC enzyme can attack and mutate invading viruses causing clusters of specific mutations in the viruses, but this activity can result in collateral damage to our own genetic code. Finding these mutation "signatures" in leukemia reveals a link between epidemiologic evidence that strong infections can trigger leukemia, and the mutations within leukemia cells themselves. We know that leukemia results from both prenatal and postnatal genetic events (the "two hit" hypothesis), and infection in this regard represents a cause for the second, postnatal hit. Prevention of this second "hit" by modifying our responses to infections may lead to prevention strategies for leukemia.

close window

Exposure to farm animals and pets

A pooled analysis that combined data from 13 studies in the Childhood Leukemia International Consortium showed that regular contact with animals in early childhood is associated with statistically significant reduced risks of childhood ALL (OR=0.65* for farm animals, 0.87* for cats and 0.92 for dogs*). Early childhood contact with farm animals and pets is hypothesized to be a surrogate marker for beneficial early-life immune stimulation.

Orsi L, Magnani C, Petridou ET, Dockerty JD, Metayer C, Milne E, Bailey HD, Dessypris N, Kang AY, Wesseling C, Infante-Rivard C, Wünsch-Filho V, Mora AM, Spector LG, Clavel J. Living on a farm, contact with farm animals and pets, and childhood acute lymphoblastic leukemia: pooled and meta-analyses from the Childhood Leukemia International Consortium. Cancer Med. 2018 Jun;7(6):2665-2681.

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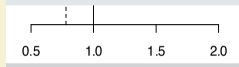

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Exposure to animals reference

Graphic 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.

CHILDHOOD LEUKEMIA Stephen's Story

CANCER CLUSTERS

One day while waiting in the hospital for Stephen's treatment, Tricia and David meet a military family who recently moved to the area. The family tells them about a study they learned of that showed a confirmed cluster of leukemia near a military base in Fallon, Nevada (see NCI cancer clusters fact sheet link at right).

A cancer cluster occurs when a greater than expected number of cancer cases arise among people in a defined geographic area over some 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 are very challenging.

Most investigations of a suspected possible cluster are not fruitful, meaning no cause is identified and the clustering of cases turns out to be random.

Find out more: Community Health Studies and Environmental Contamination

Read the Cancer Clusters Fact Sheet from the National Cancer Institute

Watch: View video of Steve Francis' presentation, "Could infection contribute to a possible leukemia cluster in Fallon?" (Long - 23:07 mins)

A cancer cluster occurs when a greater than expected number of cancer cases arise among people in a defined geographic area over time.

CHILDHOOD LEUKEMIA Stephen's Story

IONIZING RADIATION (INCLUDING X-RAY AND CT SCAN) EXPOSURE AND CHILDHOOD LEUKEMIA

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).

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 have not been extensively studied for links to leukemia, but their use has substantially increased in recent years and they often result in higher radiation exposures than X-rays (Linet et al., 2009). **More >**

- The Electromagnetic Spectrum
- Non-ionizing Radiation
- Childhood brain tumors
- National Cancer Institute - Radiation Risks and Pediatric Computed Tomography (CT)

Non-Ionizing Radiation

High frequency, ionizing radiation, including X-rays, is capable of breaking chemical bonds, creating highly reactive ions that can directly cause DNA mutations, thereby increasing cancer risk. Historically, lower frequency radiation, including microwaves, radiofrequency radiation (e.g., from cell phones), and extremely low-frequency magnetic fields (EMF; e.g., from electric power lines and electric appliances), has not been thought to increase cancer risk because of insufficient energy to break chemical bonds. Radiation from these sources is called non-ionizing. However, concerns about health effects of non-ionizing radiation began to grow when a 1979 study identified an increased risk of leukemia in children living near high-current-flow power lines (Wertheimer, 1979).

Since then many additional studies have examined this relationship using various measures of exposure, with inconsistent results. However, when studies are combined, they show a modera statistically significant increase in the r of leukemia only among children exposed to the highest level of EMF.

In 2011, the International Agency for Research on Cancer reviewed the available evidence. They concluded that radiofrequency electromagnetic fields are "possibly carcinogenic to humans" (2B classification) *...based primarily on the positive associations observed between exposure to radiation from wireless phones and the risk of brain tumors (glioma, acoustic neuroma).*

A recent pooled study has continued to raise the question of a small increased risk (Kheifets, 2010). Methodological issues have been identified as possibly contributing to the observed risk in some studies. Laboratory studies have identified several biologic mechanisms that could plausibly link EMF exposures

"Radiotherapy"

A child undergoing whole body irradiation, which, along with selected drugs, helps to destroy all the blood cells in the child's bone marrow and any other leukaemic cells in the body. This radiotherapy is in preparation for the child to receive an infusion of bone marrow.

"This little girl was suddenly on her own in a huge room while we were outside peering into screens in a darkened room." The mother watches through the glass of the control room, hand on mouth, as her child is carefully positioned for treatment. The painting depicts three other scenes showing the child being reassured and positioned.

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"Radiothe
by Susan
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About the painting with the words of the artist in *italics* >

Electromagnetic Spectrum reference: Wikipedia, Creative Commons license, use permission granted by author Victor Blacus.

CHILDHOOD LEUKEMIA Stephen's Story

IONIZING RADIATION (INCLUDING X-RAY AND CT SCAN) EXPOSURE AND CHILDHOOD LEUKEMIA

(continued)

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.

- The Electromagnetic Spectrum
- Non-ionizing Radiation
- Childhood brain tumors
- National Cancer Institute - Radiation Risks and Pediatric Computed Tomography (CT)

Childhood brain tumors

The second-most common childhood cancer and the cancer responsible for the most childhood deaths is brain cancer. Childhood brain tumors (CBT) are a collection of diseases with even more subtype heterogeneity than leukemia – from low-grade astrocytomas which have high survivability to higher-grade medulloblastomas and glioblastomas which have poorer prognoses.

CBTs share some common risk factors with leukemia including ionizing radiation and pesticides (Van Maele-Fabry et al., 2017), additional putative risk factors include hazardous air pollutants and dietary N-nitroso compounds (Johnson et al., 2014).

There are also strong genetic risk factors for CBT and children with congenital anomalies are particularly susceptible (Fisher et al., 2012).

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"Radiothe by Susan reproduce

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Electromagnetic Spectrum reference: Wikipedia, Creative Commons license, use permission granted by author Victor Blacus.

CHILDHOOD LEUKEMIA Stephen's Story

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.

- Hope Labs
- Commonweal Cancer Help Program
- Find out more about support groups, community links: CureSearch for Children's Cancer
  Cancer.Net
  The Leukemia & Lymphoma Society (LLS)

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

CHILDHOOD LEUKEMIA 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

Integrated Pest Management: Reducing Use of Pesticides in Homes, Schools and Other Buildings

Integrated pest management (IPM) is an approach to pest control that begins with avoiding the use of pesticides at all unless absolutely necessary. Many non- pesticide techniques can help to keep unwanted pests, like insects and rodents, from your home, lawn and garden, as well as public buildings and spaces.

If pesticides must be employed, preference is given to the least toxic alternatives. According to the EPA, IPM is "an effective and environmentally sensitive approach to pest management that relies on a combination of common-sense practices. IPM programs use current, comprehensive information on the life cycles of pests and their interaction with the environment. This information, in combination with available pest control methods, is used to manage pest damage by the most economical means, and with the least possible hazard to people, property, and the environment. The IPM approach can be applied to both agricultural and non- agricultural settings, such as the home, garden, and workplace."

close window

More Resources:

Pesticides: EPA - Integrated Pest Management

Bio-Integral Resource Center (BIRC)

Pesticide Action Network (PANNA)

University of California – Pesticide Application Equipment

IPM in Early Care and Education

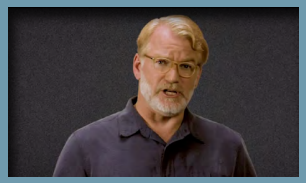
CHILDHOOD LEUKEMIA Stephen's Story

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, 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

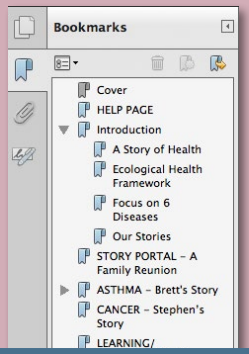
COMMON THEMES

Although the fictional narratives in *A Story of Health* describe the lives of children and adults with different conditions and diseases – infertility, asthma, developmental disabilities, childhood leukemia and cognitive decline - 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.

Resources

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 to help prevent disease and promote health:

Portal to Toxicant and Disease Database: A searchable database that summarizes links between chemical contaminants and approximately 180 human diseases or conditions.

Portal to Science Resources: Hundreds of additional resources on environmental health including organizations, publications, videos and more.

Pediatric Environmental Health Toolkit: application for mobile devices

Approaches to Healthy Living: A 4-page guide on how to avoid toxicants, eat healthier, reduce stress.

Healthy Aging: The Way Forward: An ecological approach to policy level interventions for healthy aging across the lifespan.

Continuing Education

Register for Continuing Education (CE) for *A Story of Health* for a variety of health professions. Free credits are offered by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry at this link.

Another free CE course on environmental health offered by the CDC/ATSDR is the **Pediatric Environmental Health Toolkit** online course.

REFERENCES: Childhood Leukemia

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Childhood Leukemia Case References and Resources by Topic

Note: there are many topic overlaps

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Flame retardants: Green Science Policy Institute

U.S. EPA. Polychlorinated biphenyls (PCBs): Basic Information

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