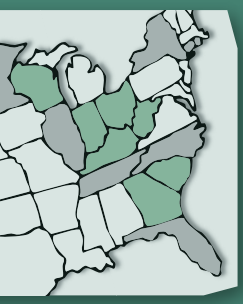
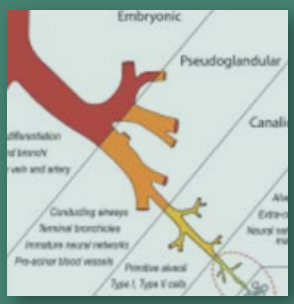
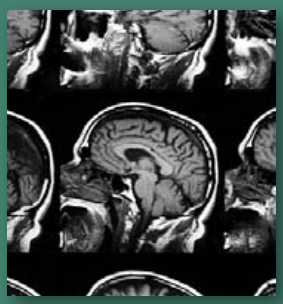
A Story of Health







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Dedication:

This eBook is dedicated to our designer Stephen Burdick for his extraordinary talent and vision.
- The authors.

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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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1. The UCSF Regional Pediatric Environmental Health Specialty Unit (PEHSU) prepared A Story of Health on behalf of the American College of Medical Toxicology (ACMT) and funded as part of the cooperative agreement award number 1U61TS000238-01from the Agency for Toxic Substances and Disease Registry (ATSDR).

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.

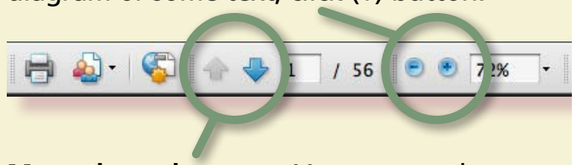
3. The ATSDR, US EPA, and Cal EPA/OEHHA do not endorse the purchase of any commercial products or services mentioned in this publication.

HELP PAGE How to Navigate Our eBook

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.

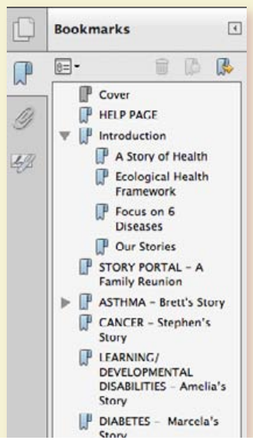


Table of Contents

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.

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."

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.

Icons

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

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.

key concept | **watch a video** | **additional resources, tools** | **technical details for health professionals** | **skip this section** | **definition**

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.

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.

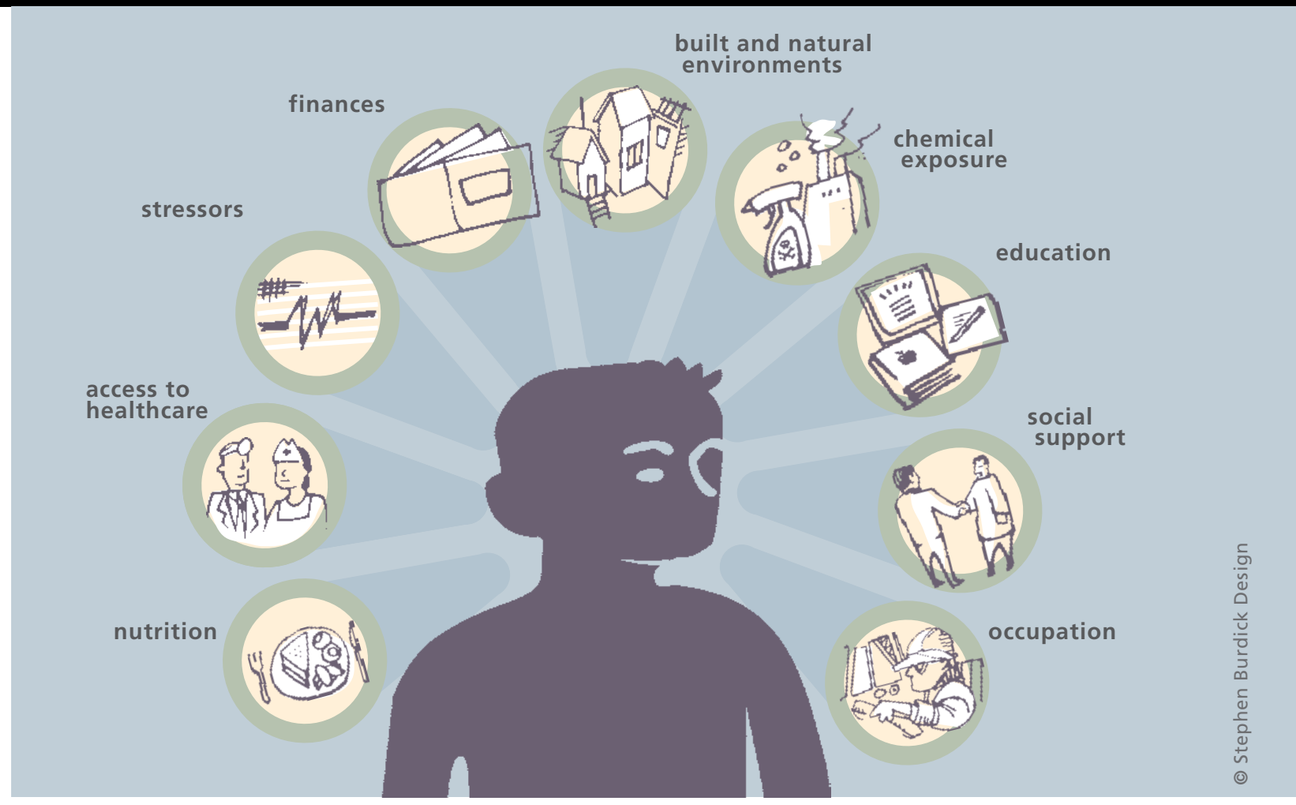
Important determinants of health come from the natural, built, chemical, food, economic, and social environments.

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. These aspects of our lives are not independent of one and other.

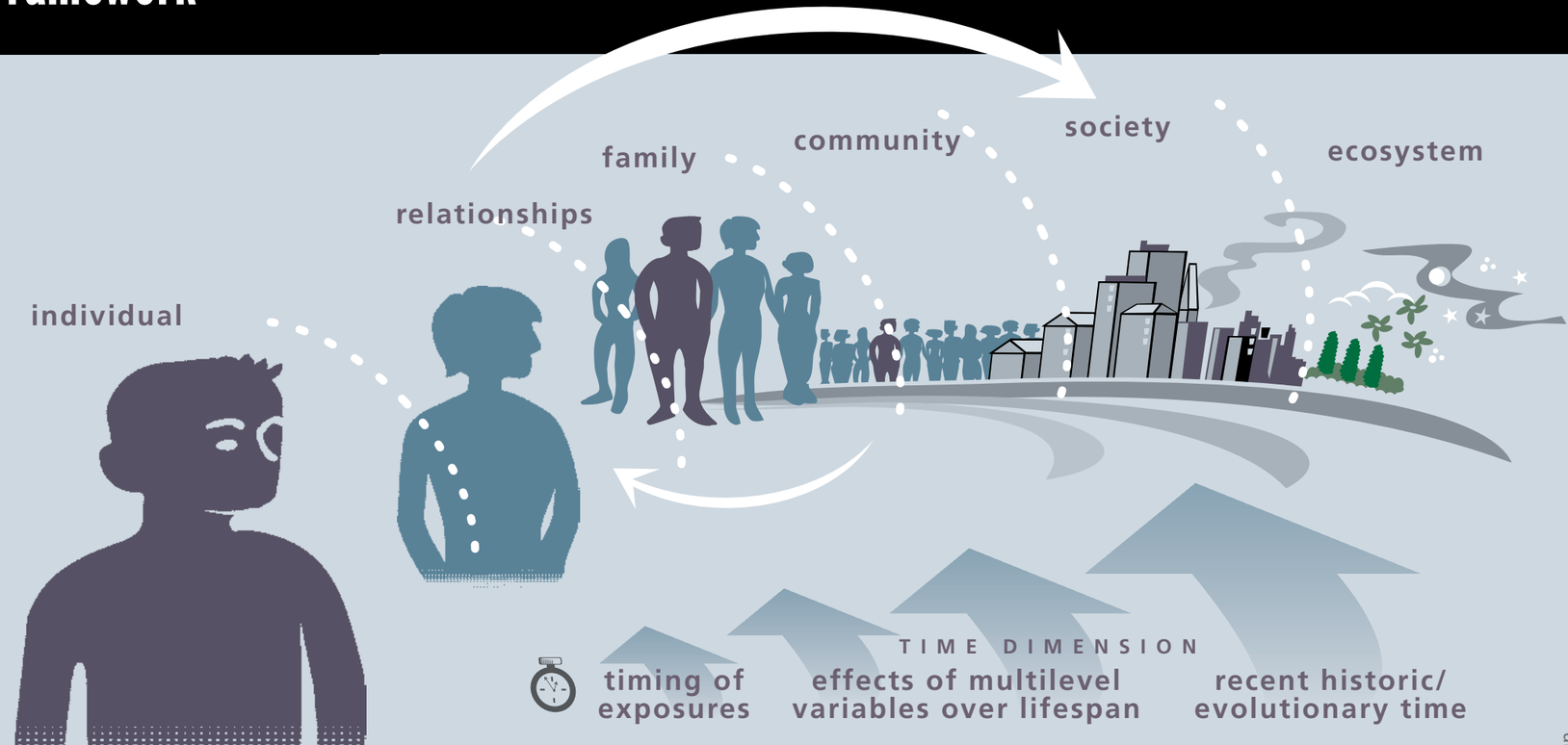
Rarely is one particular thing responsible for health or disease, so we refer to this as a multifactorial (or ecological) approach, the best way to promote health and prevent disease.

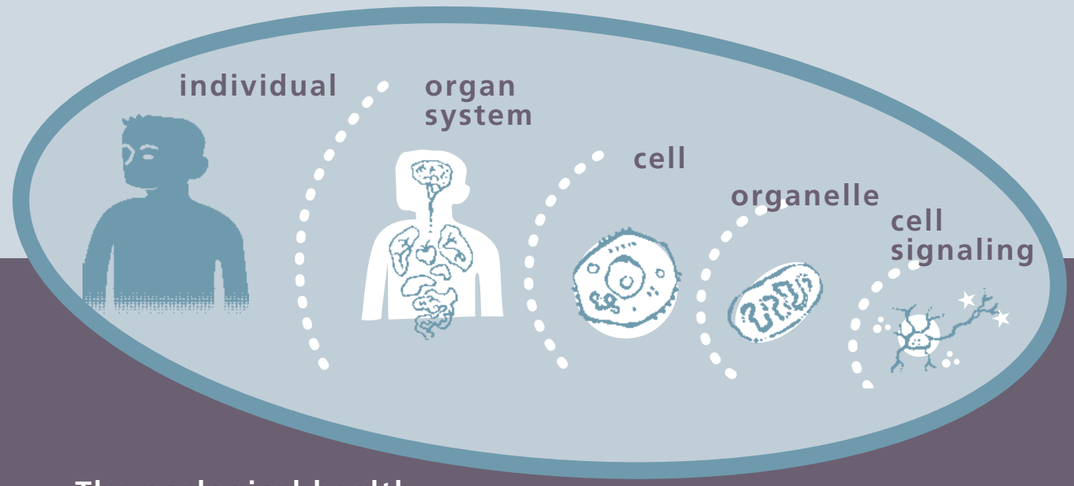
INTRODUCTION Ecological Health Framework

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.

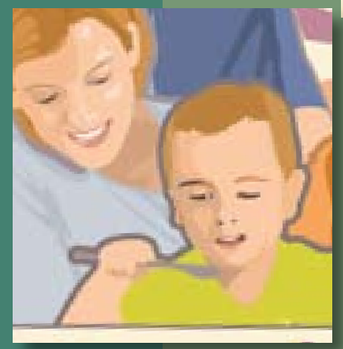
They include:

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

Asthma

Diabetes

Cancer



Cognitive decline

Infertility

Learning and developmental disabilities

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 CE credits 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 credits for each story (credits are offered by 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) >

FREE CONTINUING EDUCATION

Continuing education available by specialty

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

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 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.

CHILDHOOD LEUKEMIA Stephen's Story

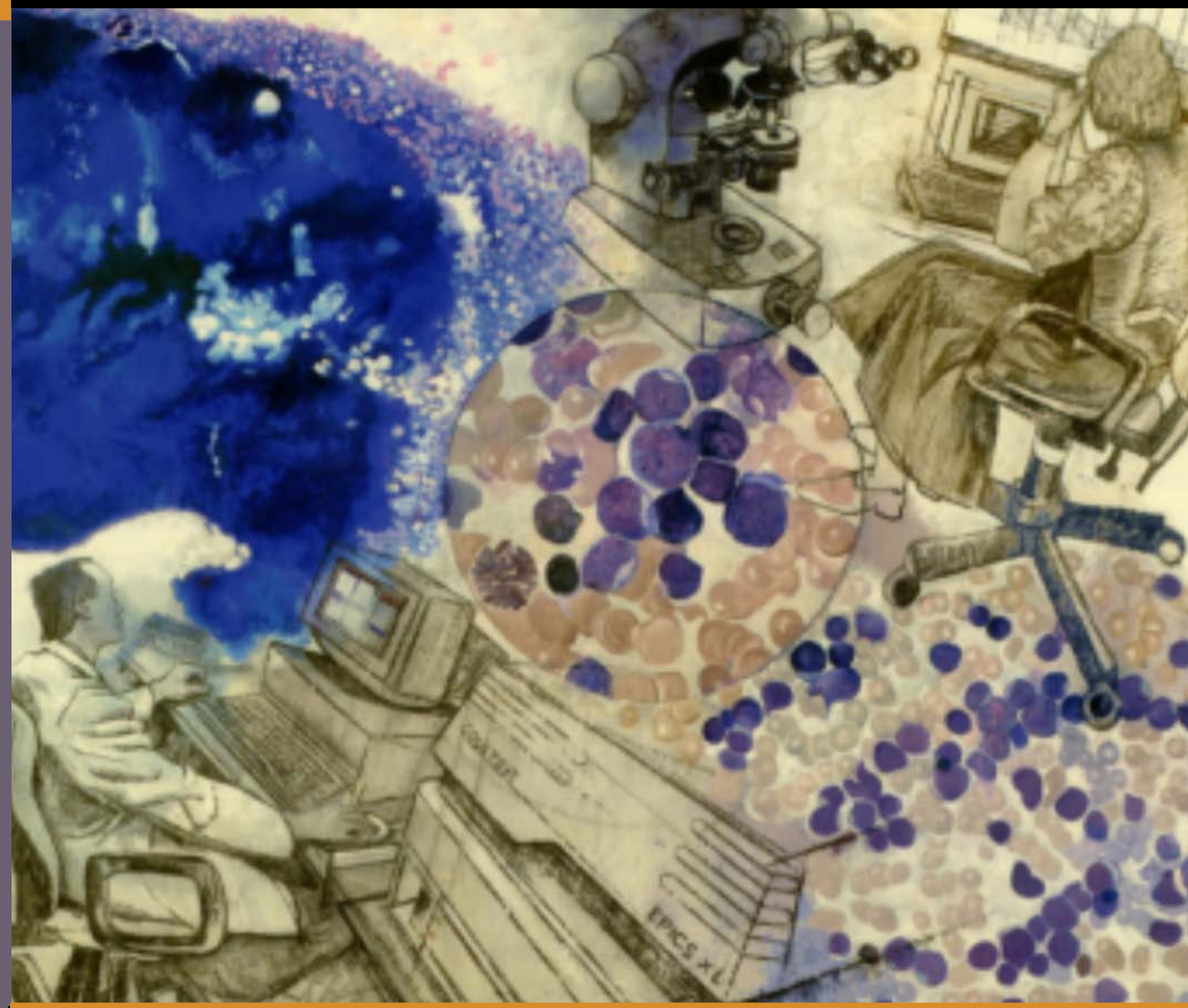
The pediatric oncologist, Dr. Baker, looked at Stephen's blood tests to confirm the findings from the laboratory.

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

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

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

? Bone marrow aspiration >



"Typing the Leukaemic Cells"
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.

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?

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

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

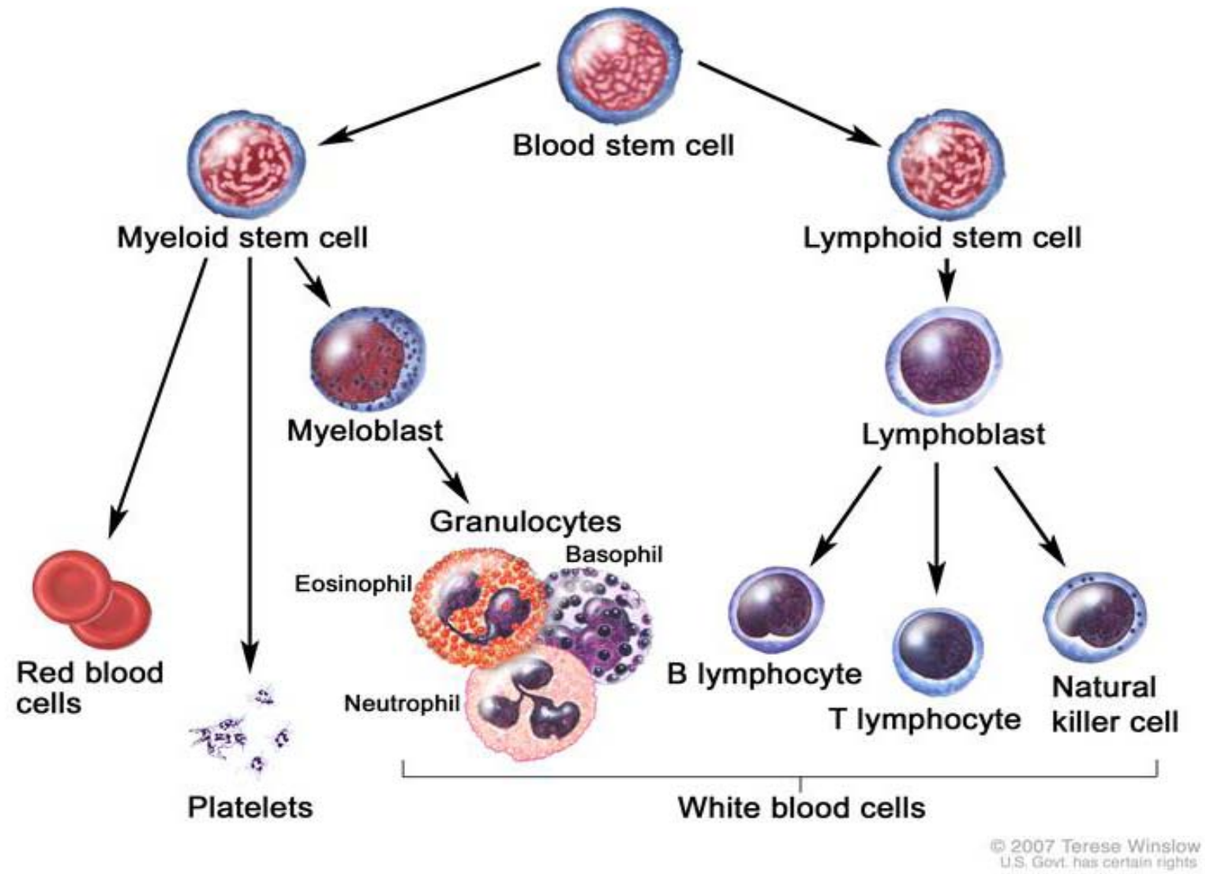
Early life exposures are important: age-specific incidence chart

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

Leukemias originate in B and T cells, which have important immune system functions.



Graphic: Terese Winslow 2007.
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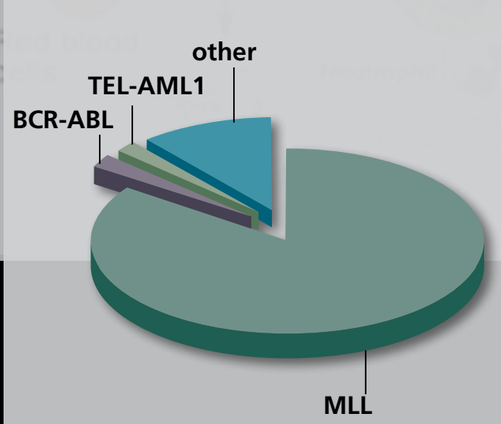
The two main types of leukemia based on cell histology are ALL and AML, but even within these groups, there are many different characteristics based on the presence of abnormalities of the chromosomes, whether the number of chromosomes is higher than expected (hyperdiploidy), or whether or not we see 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.

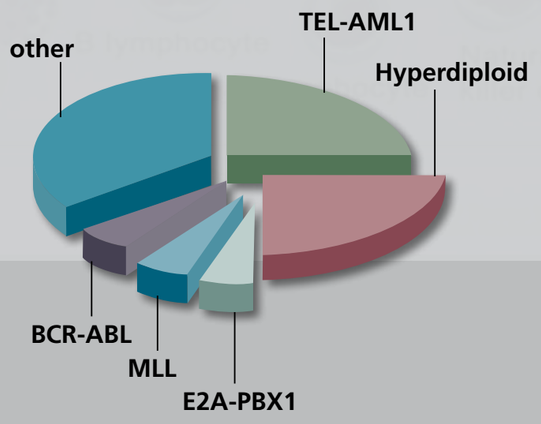
When grouped by underlying molecular markers, certain leukemias occur more frequently at different ages. MLL (mixed leukemia or Myeloid/ lymphoid leukemia) is the predominant form in infants but relatively rare in older children. MLL is a particularly aggressive form of leukemia.

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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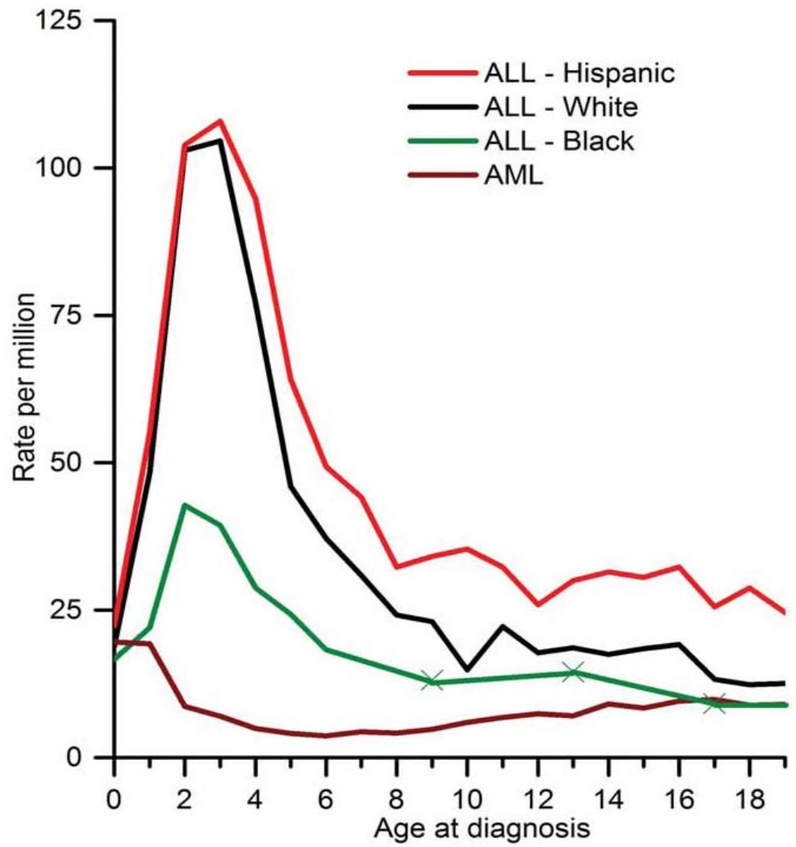
Early Life Exposures are Important

There is a peak of incidence of childhood ALL between the ages of two and five. This has led researchers to think that critical windows of vulnerability to environmental exposures are very important before conception, during pregnancy, and in the early years of life.

In contrast to ALL, the childhood AML rate seems to be more stable across ages, which implies different risk factors, windows of vulnerability, or mechanisms that may lead to AML in contrast to ALL.

Age-Specific Incidence Rates of Acute Lymphocytic Leukemia (ALL) by Race/ Ethnicity and Acute Myeloid Leukemia (AML) for All Races Combined



Rates are not shown when based on fewer than 25 cases. Data for whites and blacks exclude Hispanic ethnicity. Due to sparse data for ALL in blacks for some ages, data are shown for combined age groups: 7 to 10 years, 11 to 14 years, and 15 to 19 years as marked by asterisks. Source: Surveillance, Epidemiology, and End Results (SEER) program, 18 SEER Registries, National Cancer Institute.

Ward, et al., 2014. Used with permission.

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

"Initial Blood Test"

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

click a preview image to view above

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.

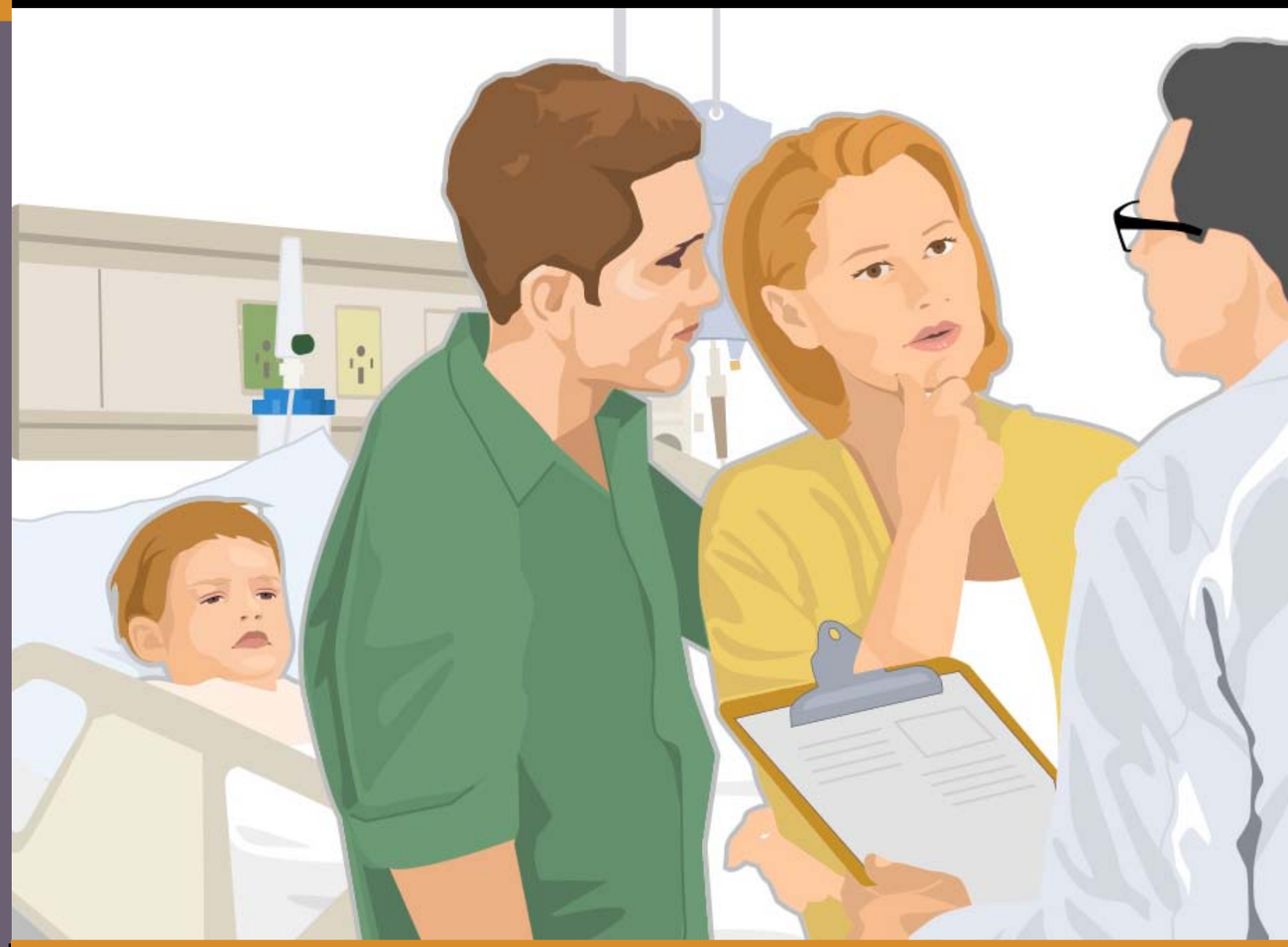
Childhood leukemia is difficult to study because it is relatively rare, which limits the design of studies intended to help clarify its etiology (cause). Nevertheless, substantial evidence identifying a number of risk factors has emerged over the past two decades. The etiology is likely to be attributable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

As with some cancers, it is thought that childhood leukemia is a result of distinct exposures during two time periods.

Changes to DNA that cause leukemia:

Two-Hit Model Hypothesis

TEL-AML1 Gene Fusion



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Two-Hit Model Hypothesis

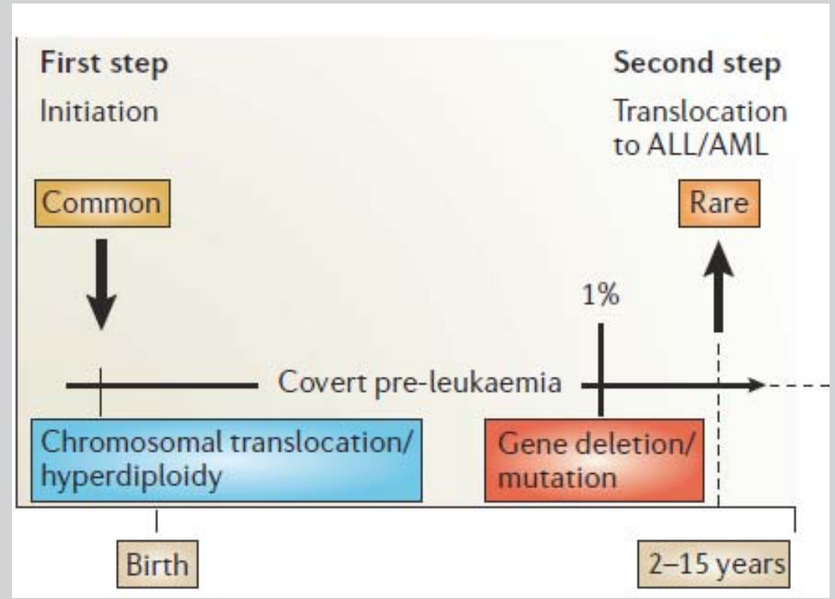
TEL-AML1 Gene Fusion

Changes to DNA that cause leukemia:

Two-Hit Model Hypothesis

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.

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.

As with some cancers, it is thought that childhood leukemia is a result of distinct exposures during two time periods.

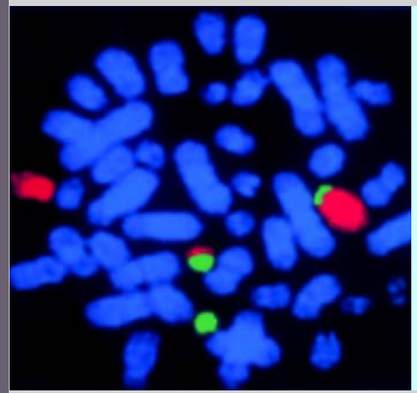
Changes to DNA that cause leukemia:

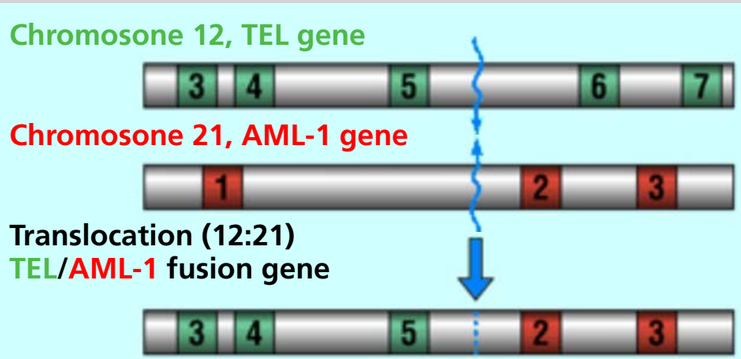
Two-Hit Model Hypothesis

TEL-AML1 Gene Fusion

Changes to DNA that cause leukemia:

Translocations Associated with ALL Occur In Utero: TEL-AML1 Gene Fusion





Results from FISH (fluorescent in-situ hybridization) study – Shows chromosomal fragments from 12 (green) and 21 (red) switched.

One of the common chromosomal abnormalities that has been identified is called the translocation TEL-AML, where there is a shift of genes between chromosome 12 and 21.

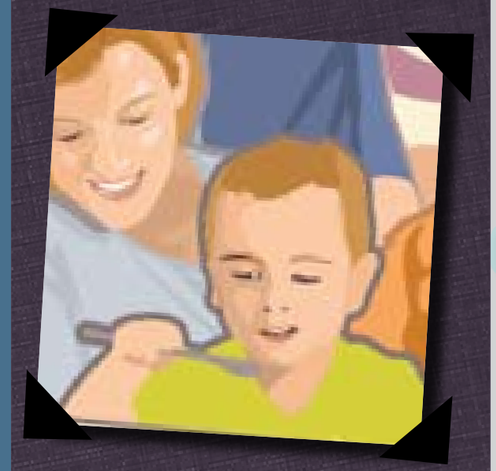
This translocation has been identified in blood specimens that are collected at birth. It indicates that there is an already ongoing process of DNA insult; however we know that not all of the children with this translocation at birth develop childhood leukemia.

Therefore, there may be another process after birth that is necessary to lead to a full-blown childhood leukemia disease.

- Occurs in approximately 20-25% of patients with pre B-cell ALL (the most common type of childhood ALL) with peak incidence between ages 2 – 5 years.
- Strong evidence that this occurs in utero.
- Frequency of this translocation at birth is 100-fold greater than the risk of developing the corresponding leukemia.

Graphics source: Greaves, 2000, used with permission.

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 white 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* >

CHILDHOOD LEUKEMIA Stephen's Story

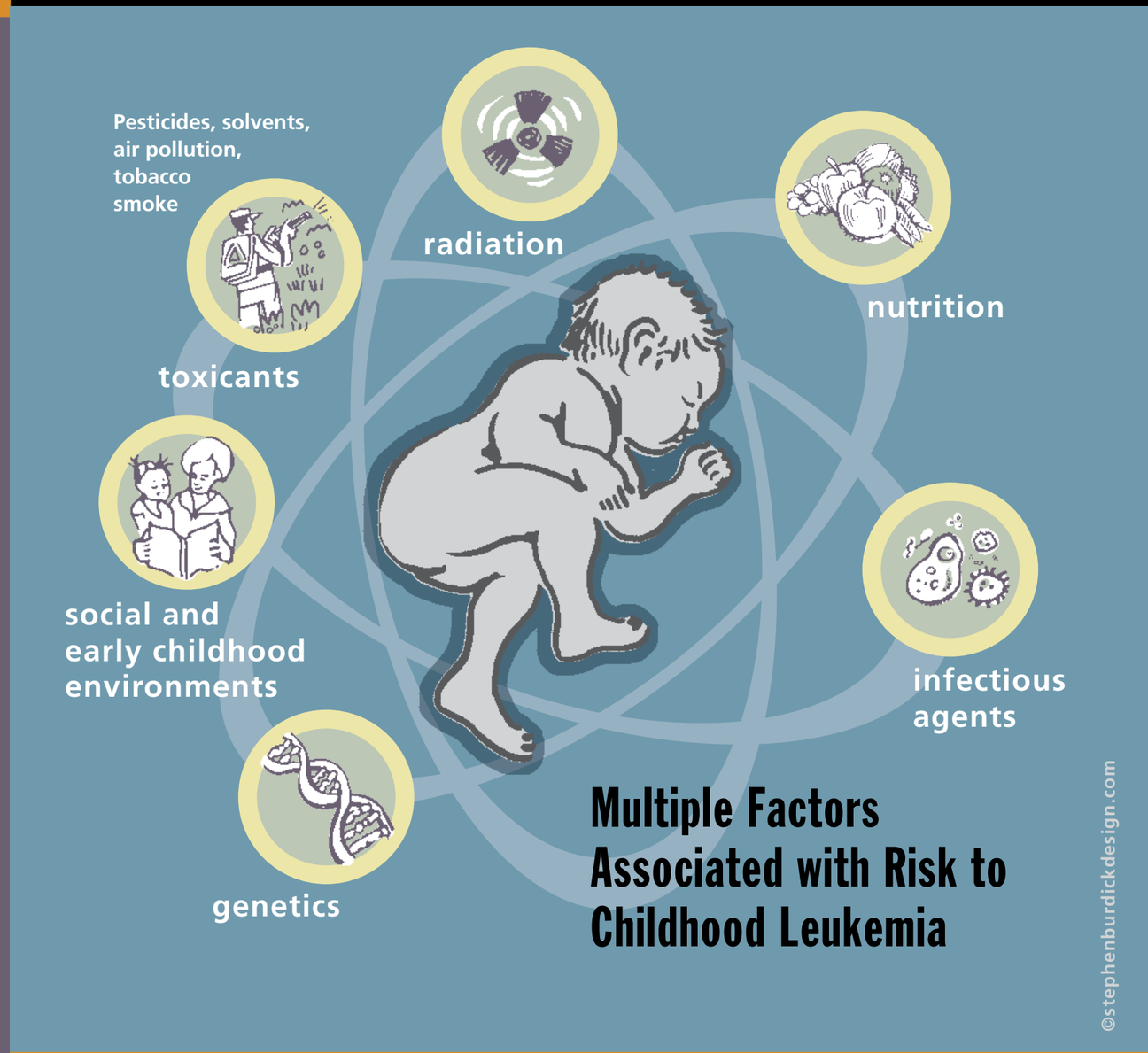
FACTORS ASSOCIATED WITH RISK FOR CHILDHOOD LEUKEMIA

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



CHILDHOOD LEUKEMIA Stephen's Story

CHILDHOOD LEUKEMIA: US TRENDS

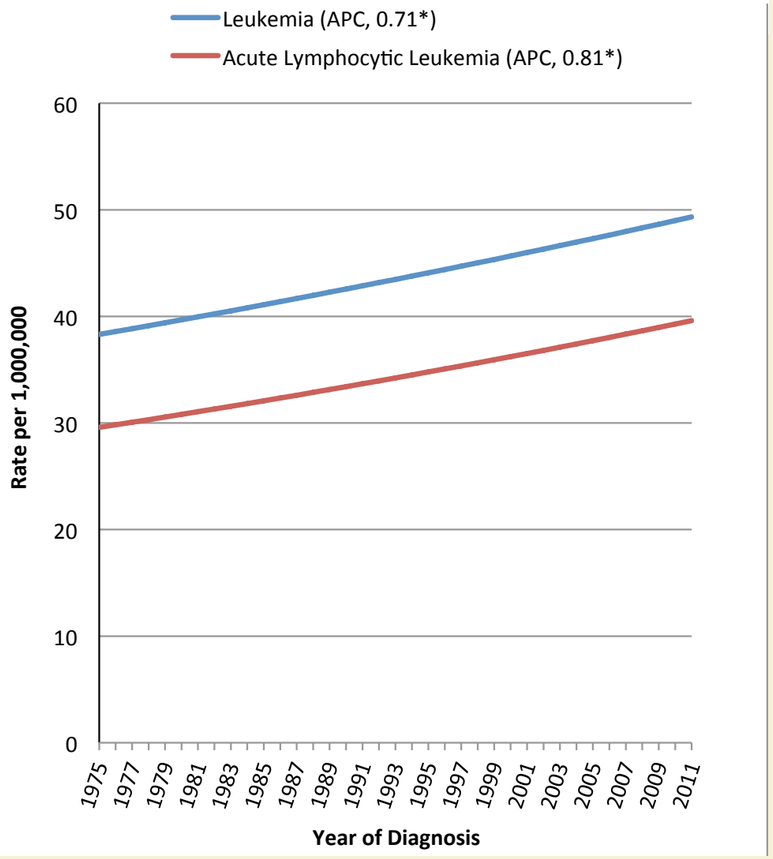
Although childhood leukemia is still rare, Stephen is one of a growing number of children with this cancer.

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 55% increase over 35 years.

- **Ethnic Trends**
- **Genetic susceptibility to leukemia in Hispanics**

Trends in the Age-Adjusted Incidence Rate of Childhood Leukemia and Acute Lymphocytic Leukemia, Ages 0-14, SEER 9, 1975-2011



***The Annual Percent Change (APC) is significantly different from zero at alpha=0.5**

Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment>

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ETHNIC TRENDS:

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

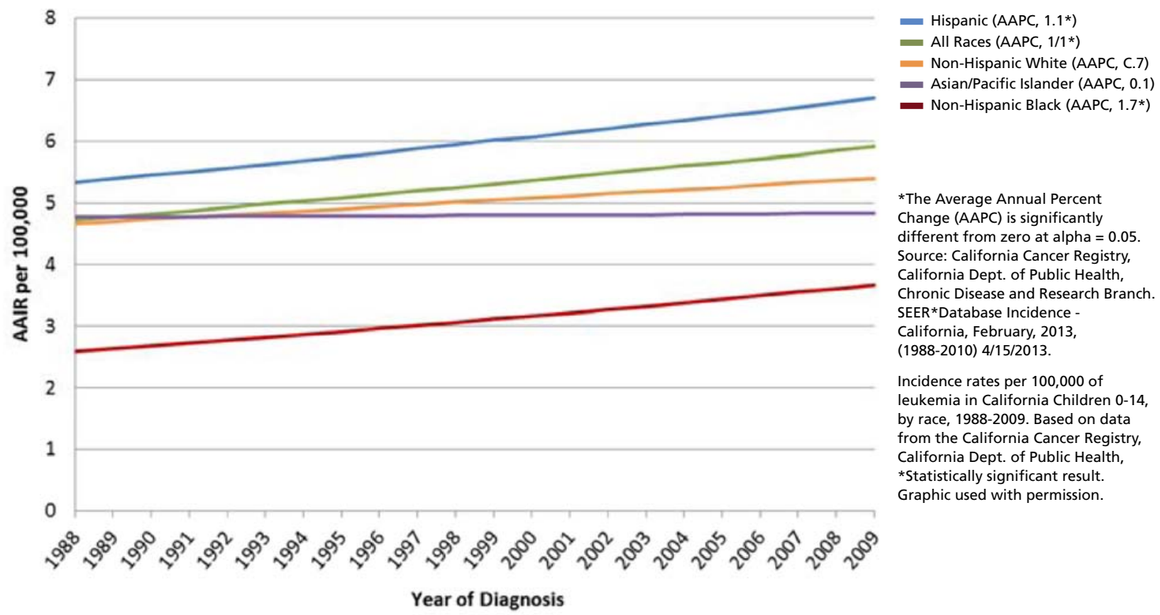
California with its large population and excellent data collection on cancer is the location of one of the largest studies designed to look at causes of childhood leukemia. Hispanic babies account for about half of all births in CA, making it a good place to examine possible genetic and environmental interactions that may underlie the recognized higher incidence of leukemia in children of Hispanic origin.

On average, childhood leukemia has been increasing 1.1% per year in Hispanics since 1988. Though much more rare in non-Hispanic Black children, it is increasing at 1.7% per year amongst them. This is compared with an increase of 0.7% in non-Hispanic White children. The rate seems to be stable among Asian/Pacific Islanders.

These trends may represent an interaction between predisposing genetics and environmental exposures.

Not only do Hispanic children have the highest incidence of leukemia but it is growing faster than in the non-Hispanic White population.

Trend in the Age-Adjusted Incidence Rate of Leukemia Among Children Aged 0-14 Years by Race/Ethnicity, CA, 1988-2009



*The Average Annual Percent Change (AAPC) is significantly different from zero at alpha = 0.05. Source: California Cancer Registry, California Dept. of Public Health, Chronic Disease and Research Branch. SEER*Database Incidence - California, February, 2013, (1988-2010) 4/15/2013.

Incidence rates per 100,000 of leukemia in California Children 0-14, by race, 1988-2009. Based on data from the California Cancer Registry, California Dept. of Public Health, *Statistically significant result. Graphic used with permission.

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Ethnic Trends

Genetic susceptibility to leukemia in Hispanics

Genetic susceptibility to leukemia in Hispanics

Leukemia is more common among Hispanic 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 Hispanics 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 Hispanics. There are also likely to be environmental risk factors that also contribute to the increased risk in Hispanics including lifestyle and exposures from occupation, which are known to vary in frequency between ethnicities.

CHILDHOOD LEUKEMIA Stephen's Story

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.

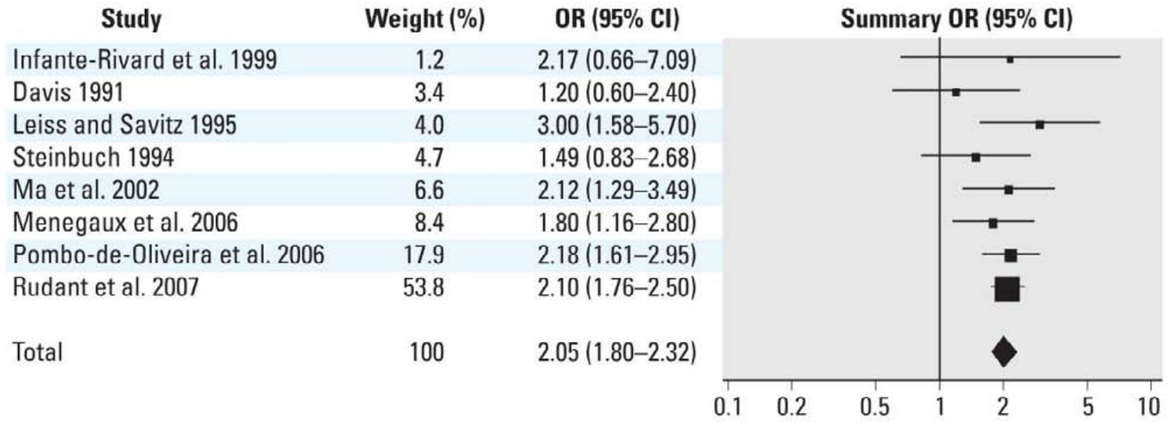
Tricia thought that Stephen's daycare might occasionally use pesticides to spray for ants and flying insects. Dr. Baker consulted the pediatrician at his regional Pediatric Environmental Health Specialty Unit, who confirmed that many studies from around the world have found statistically significant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

- **How to read and interpret the figure at right. What is a meta-analysis?**
- **Pesticide Regulation**
- **Find a local Pediatric Environmental Health Specialty Unit (PEHSU): A respected network of experts in children's environmental health.**

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

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

Residential Pesticide Exposures



In a meta-analysis by Turner et al. (2010), residential insecticide use during pregnancy was associated with a doubling of risk for childhood leukemia (OR*=2.05). The association was somewhat stronger for ALL than AML, and was found to be consistent over a variety of study designs.

Differences in leukemia risk associated with residential and occupational pesticide exposures may be due to differences in chemical doses and co-exposures.

*OR= Odds ratio

Turner, 2010. Graphic used with permission.

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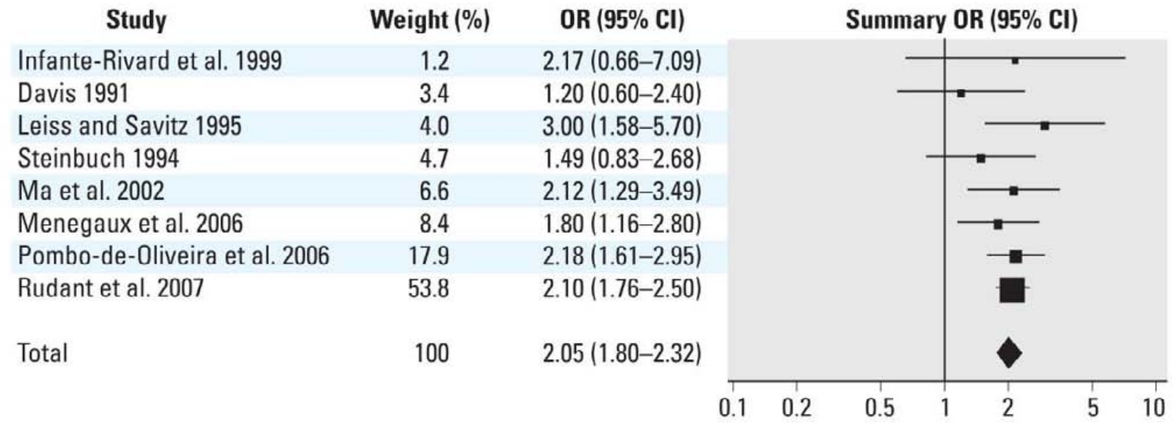

What is a meta-analysis?

A meta-analysis uses statistical methods to combine the results of different studies in order to identify an overall trend in the data. Generally, studies are grouped by a common measurement, and some studies are excluded on the basis of quality or study design.

Certain studies are given more weight in the meta-analysis. Weighting is usually related to the sample size in the individual studies.

This method can have some limitations. It usually relies on published studies, which may exclude studies that show negative or insufficient results that are less likely to be published. Additional bias can also skew the results if studies are cherry-picked using unsound methodology for selecting studies.

A graphic known as a Forest Plot (shown above) is often used to display the results of a meta-analysis. The size of the square is proportional to the weight assigned to the study.

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.

More information: "5 Key Things to Know about a Meta-Analysis" Scientific American blog post

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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).

- Link to EPA website for more information on FIFRA

OCCUPATIONAL EXPOSURES DURING PREGNANCY MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

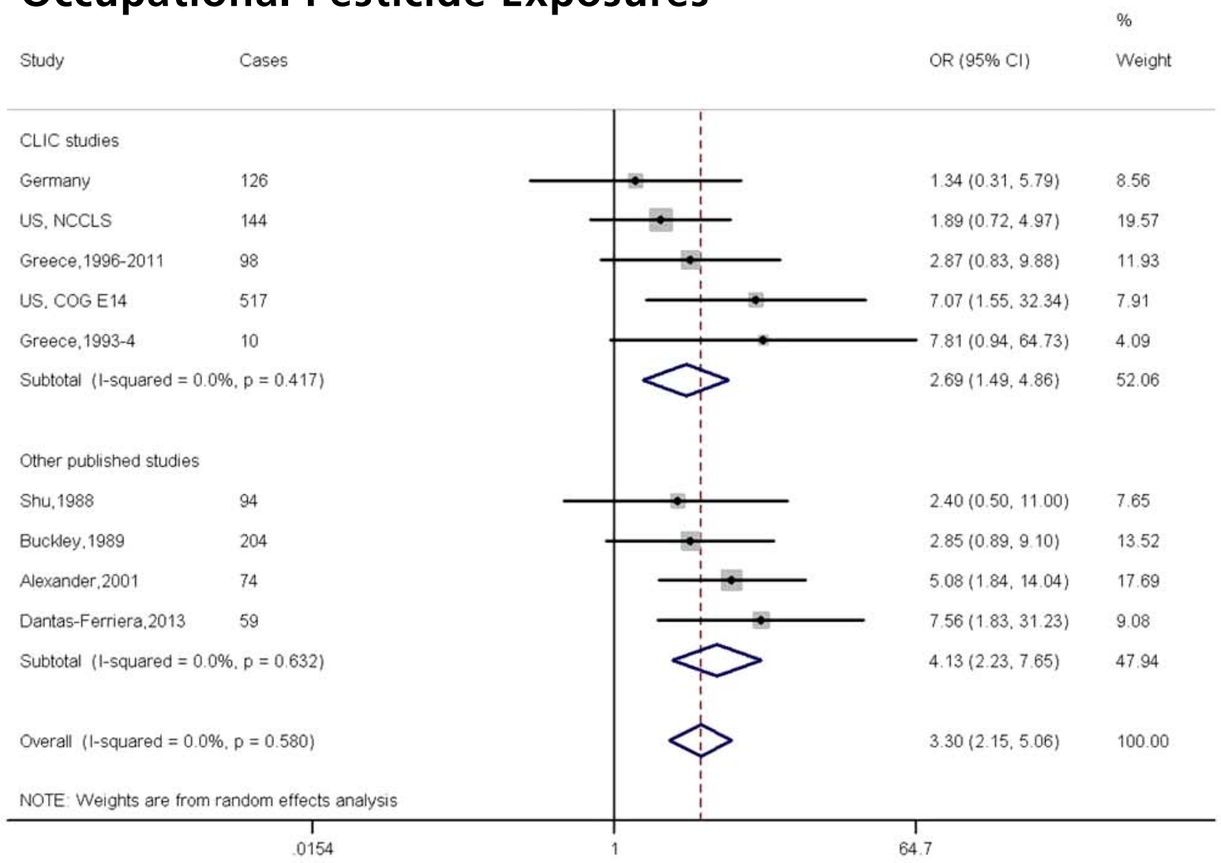
Dr. Baker asked a few more details about the garden center. Tricia said she worked in the back office while she was pregnant, up until a few months before Stephen was born.

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.

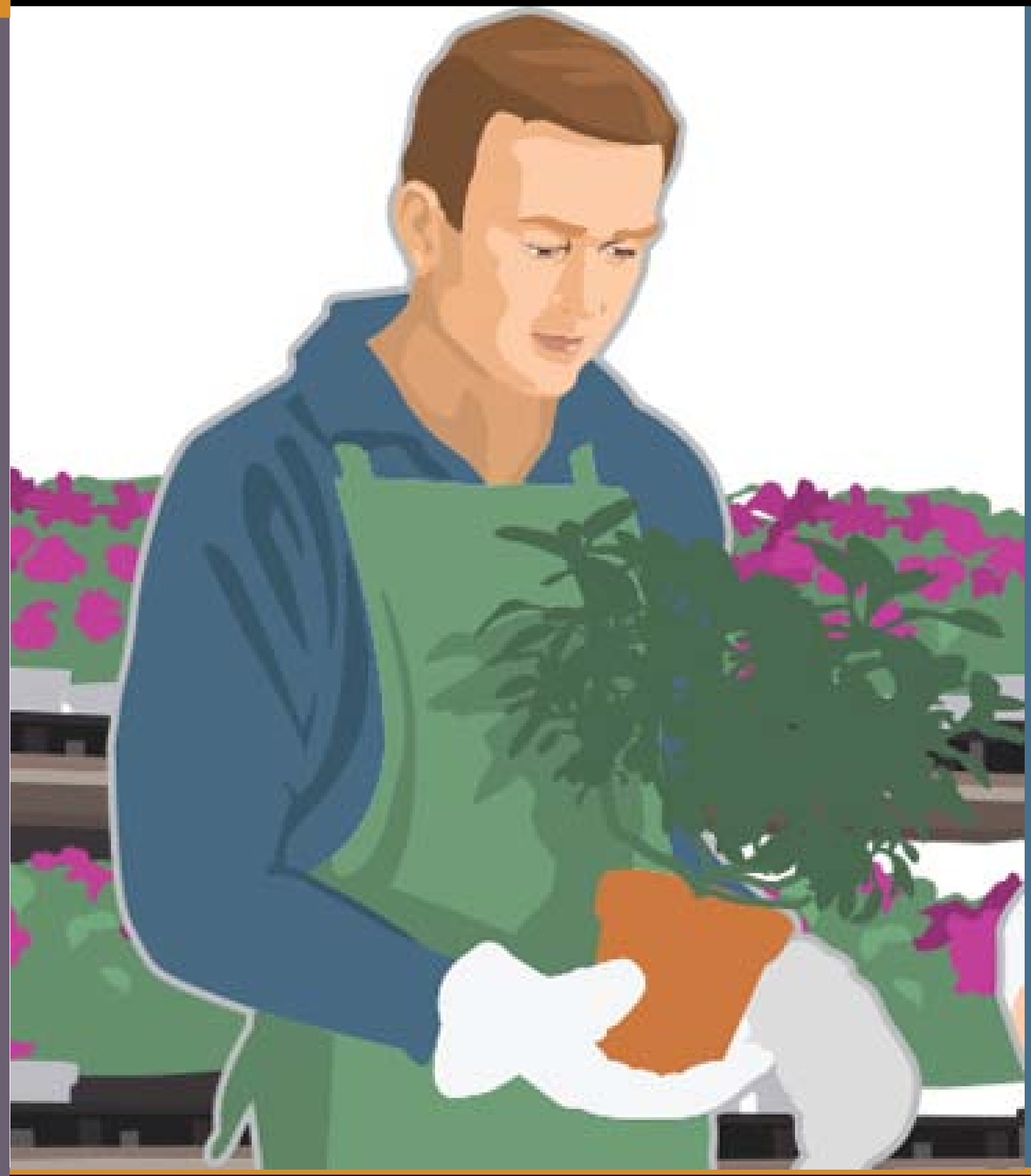
PATERNAL OCCUPATIONAL EXPOSURES AROUND TIME OF CONCEPTION MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

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



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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**
- **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 and children should avoid these exposures.

More information: Pesticide Safety Information from the California EPA

EXPOSURES TO PAINTS AND SOLVENTS MAY INCREASE RISKS

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

In one study of household use of paints and solvents, paint was associated with a 65% increase in ALL risk, and risk was higher with postnatal or frequent use.* When the analysis was restricted to the translocation (12;21) the risk increased four-fold.* Solvents were associated with a two-fold increased AML risk* (Scelo et al., 2009).

While some previous studies do not identify increased risks, other studies support these findings (Freedman et al., 2001; Bailey et al., 2010). In addition, a number of studies of exposure to gasoline and traffic exhaust find elevated risks. These complex exposures include a variety of solvents (see next section on traffic exposure). Many solvents are recognized carcinogens. While studies of the relationship between solvent exposure and childhood leukemia risk are not as extensive as those examining tobacco or pesticides, 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

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).

Studies examining exposure to benzene, one component of air pollution (for example, living near a gas station), have suggested an increase in risk for childhood leukemia. Benzene is recognized as a cause of leukemia in adults.

CHILDHOOD LEUKEMIA Stephen's Story

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

+ Prenatal Care and Healthy Child Development

? Folate supplementation recommendations for women

? Studies on Folate and Leukemia

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PRECONCEPTION AND HEALTHY CHILD DEVELOPMENT

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

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.

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

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

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PRENATAL CARE FOR HEALTHY DEVELOPMENT

The fetus can be harmed by environmental exposures including:

- Mom's smoking and second hand smoke,
- Mom's drinking alcohol and her exposure to other solvents like those in certain paints, and in products used in nail salons,
- Mom's exposure to lead, mercury (from some fish and other sources), pesticides, PCBs (banned in the US but still found in the environment) and certain polybrominated diphenyl ethers (PBDEs – a family of chemicals long-used as flame retardants in foam and furniture), among others.

Positive actions to protect the fetus:

- Avoid smoking or drinking,
- Maintain a healthy diet,
- Supplement with prenatal vitamins, including folic acid, iodine, and vitamin D if maternal serum levels are inadequate,
- Avoid toxicants.

More information:

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

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

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.

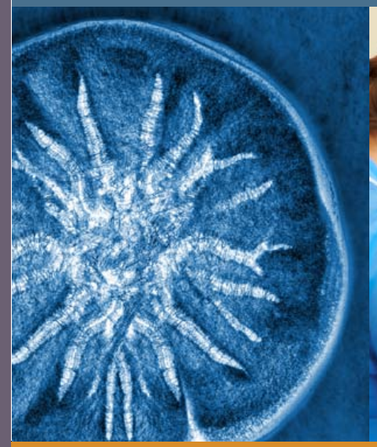
We know that tobacco smoke could be affecting the development of the fetus and the child during pregnancy and during the early years of life. We also know that tobacco smoke can affect the germ cells.

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.)



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KEY CONCEPT:

Windows of Vulnerability

A window of vulnerability is a time window(s) during pregnancy or child development when the fetus, infant, or child is especially susceptible to particular environmental exposures, general environmental deprivation, suboptimal nutrition, or psychosocial stress. Exposures during these time windows can disrupt important developmental processes, altering structural or functional development of various organs or physiologic systems, with potential lifelong consequences.

Time windows of vulnerability can be relatively long and extend throughout fetal and infant development, or they can be relatively short and precise. For example, thalidomide can cause severe limb abnormalities if exposure occurs in the fetus 20-36 days after conception. Alternatively, the manifestations of fetal alcohol exposure can vary considerably depending on the timing and extent of exposure throughout pregnancy.

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CHILDHOOD LEUKEMIA Stephen's Story

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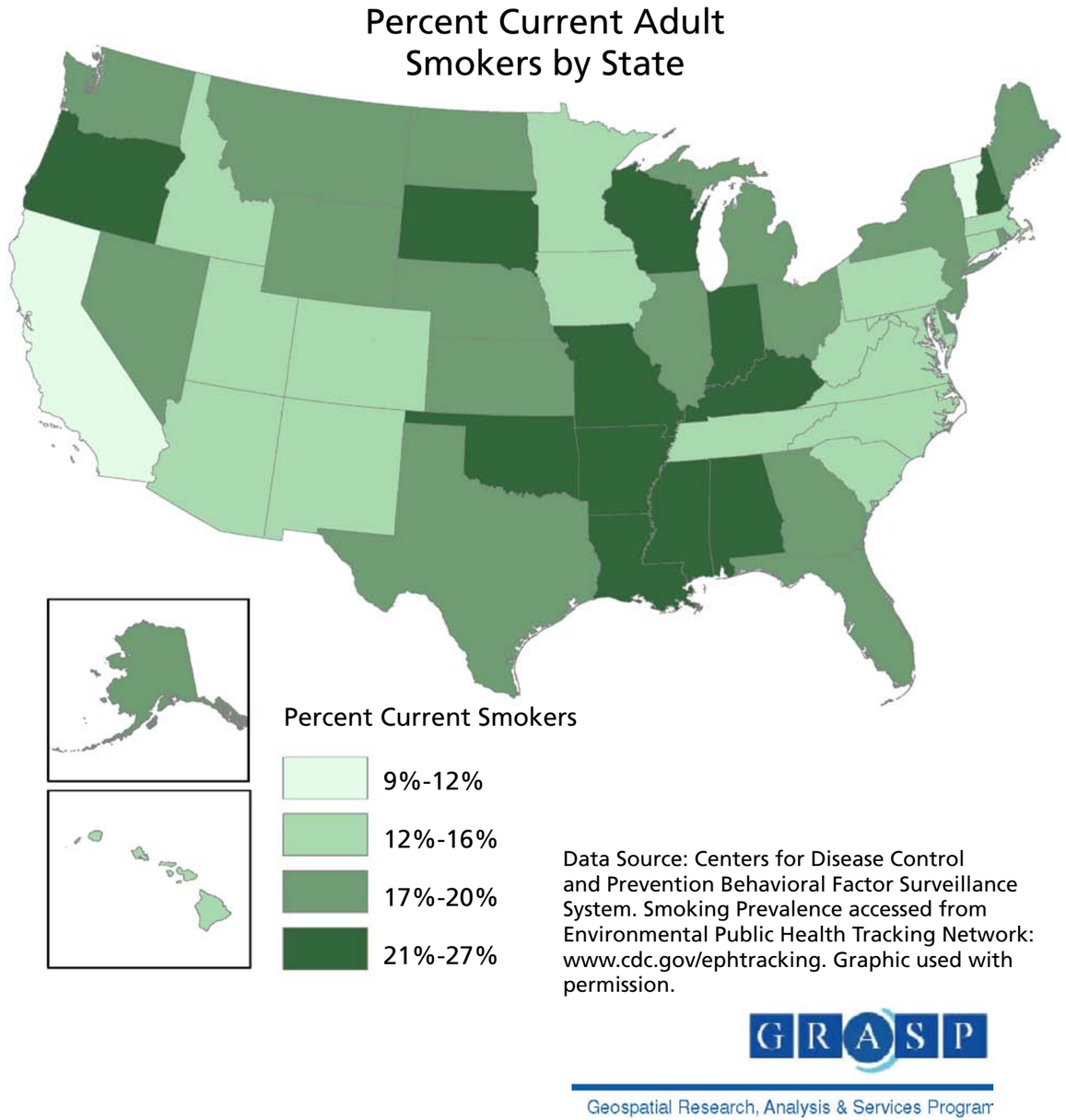

CHILDHOOD LEUKEMIA Stephen's Story

EXPOSURE TO FATHER SMOKING BEFORE BIRTH COMBINED WITH POSTNATAL EXPOSURE TO SECOND- HAND SMOKE RESULT IN INCREASED RISK FOR CHILDHOOD B-CELL ALL

Prenatal and postnatal exposures to environmental tobacco smoke are associated with increased childhood leukemia risk. Paternal smoking, in particular, prior to conception has also been linked to increased risk of childhood acute lymphoblastic leukemia (ALL). Father's smoking before birth combined with second-hand smoke, from any source, after birth increases risk for childhood leukemia. This seems to support the two-hit model previously discussed.

Studies of maternal smoking are inconsistent. There could be several reasons for negative findings including maternal under-reporting or fetal loss. Differences in how eggs and sperm are formed may also account for these differences.

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

Exposure to father smoking before birth combined with postnatal exposure to SHS result in increased risk for childhood B-cell ALL

FATHER smoked before birth	CHILD exposed to passive smoking	Number of cases (n=689)	Number of controls (n=975)	OR (95% CI)
No	No	444	670	Reference
No	Yes	90	127	0.94 (0.69-1.27)
Yes	No	44	74	0.90 (0.57-1.41)
Yes	**Yes**	**104**	**88**	**1.60 (1.07-2.38)***

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity, household income, and maternal smoking.
*p-value for interaction <0.05

Graphic: Based on Metayer et al., 2013, used with permission

CHILDHOOD LEUKEMIA Stephen's Story

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Joint Effect of Paternal Smoking and Early Childhood Exposure to Passive Smoking on Risk of Childhood B-cell ALL with Translocation

FATHER smoked before birth	CHILD exposed to passive smoking	Number of cases (n=130)	Number of controls (n=975)	OR (95% CI)
No	No	82	670	Reference
No	Yes	12	127	0.69 (0.36-1.32)
Yes	No	8	74	0.85 (0.35-2.03)
Yes	Yes	26	88	2.08 (1.04-4.16)*

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity, and household income.
*p-value for interaction =0.01

Graphic: Based on Metayer et al., 2013, used with permission

Paternal smoking associated with increased risk of specific leukemia subtype

This analysis separates the different time windows before and after birth.

Exposure to tobacco smoke was associated with an increased risk only of the translocation (12;21) but not the hyperdiploid subtype.

Excess risk of childhood B-cell ALL, with the specific translocation (12;21), is prominently identified when the father was smoking before birth (including preconception and prenatal exposure) and when the child was also exposed after birth. The identified risk is higher when restricted to this specific molecular subtype of leukemia.

Fathers who smoked pre-conceptionally can still impact their child's risk by not exposing them to passive smoke.

CHILDHOOD LEUKEMIA Stephen's Story

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Exposure to Tobacco Smoke Increases Risk of Childhood AML

Childhood AML is very difficult to study because it only makes up a fraction of all childhood leukemias. Tobacco smoke contains known carcinogens, and smoking is recognized to cause adult AML (IARC, 2002).

One recent study found that a child's passive exposure to tobacco smoke in the home is associated with a 40% higher risk of AML (OR = 1.41).

Although the numbers in this analysis are relatively small, this shows a similar pattern as ALL in that exposure in the home to tobacco smoke doubled the risk of getting AML for those subtypes that have structural abnormalities like translocation, deletion, or inversion (OR = 2.76;95% CI 1.01-7.58) (Metayer et al. 2013).

CHILDHOOD LEUKEMIA Stephen's Story

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

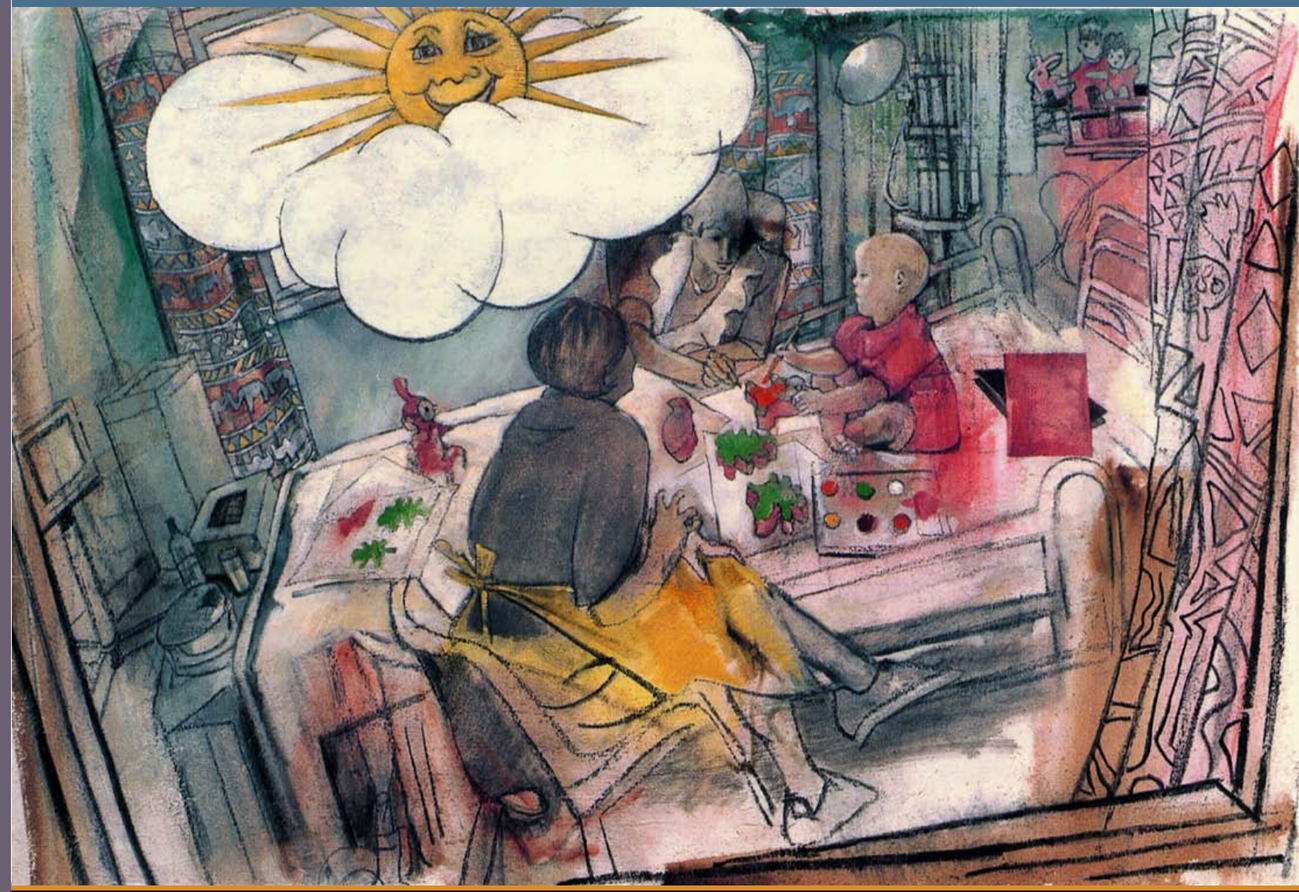
Toward the end of their clinic visit, Tricia and David were visibly distressed about all of the potential factors that could have contributed to their son's leukemia.

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.)



**"Playschool."
by Susan Macfarlane,
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About this painting, with words of the artist in *italics* >

CHILDHOOD LEUKEMIA Stephen's Story

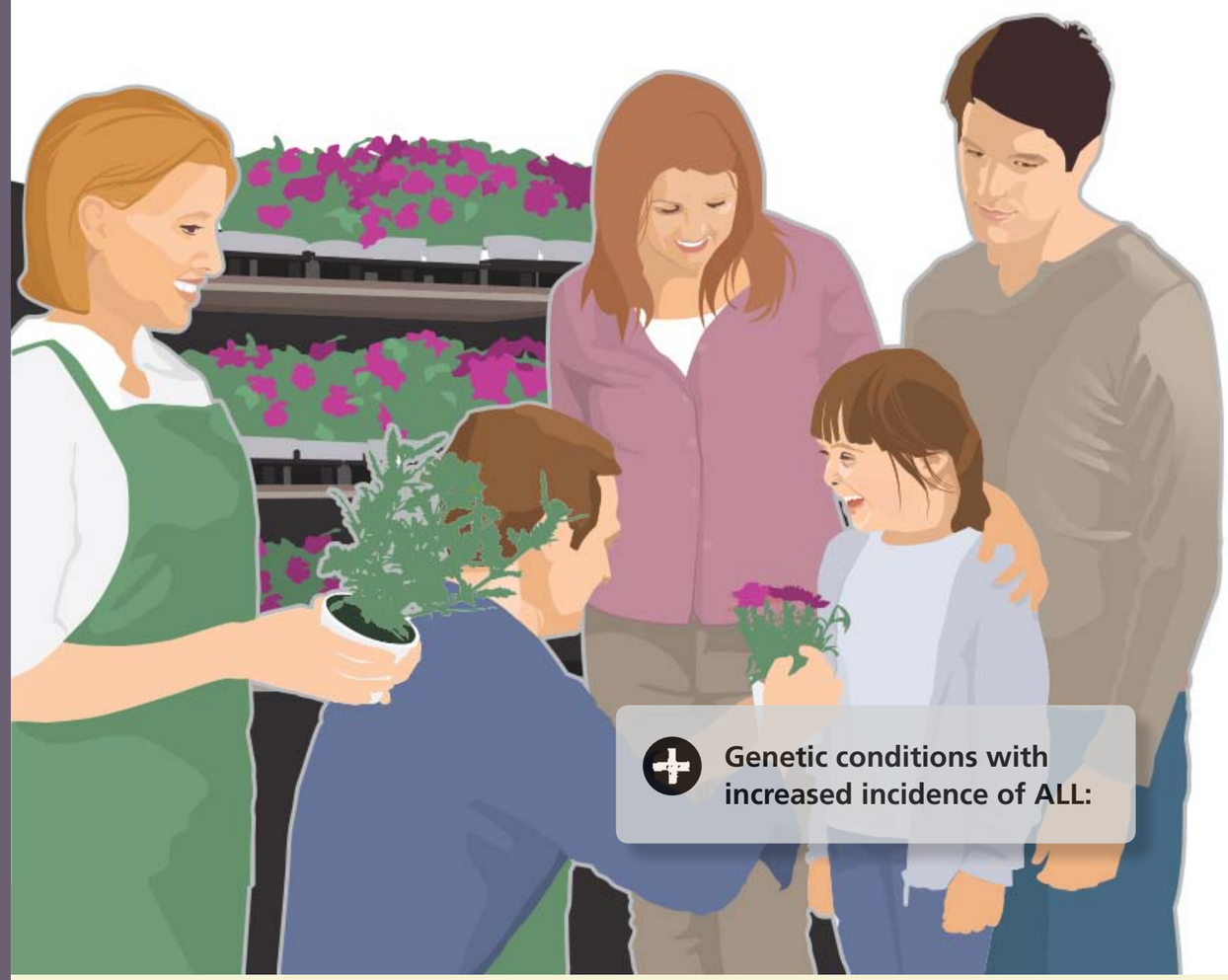
SOME CHILDREN ARE AT HIGHER RISK

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.

Key Concept: Epigenetics

? Family History and Childhood Leukemia



Genetic conditions with increased incidence of ALL:

CHILDHOOD LEUKEMIA Stephen's Story

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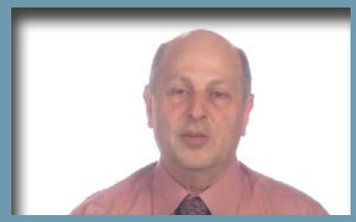
KEY CONCEPT:

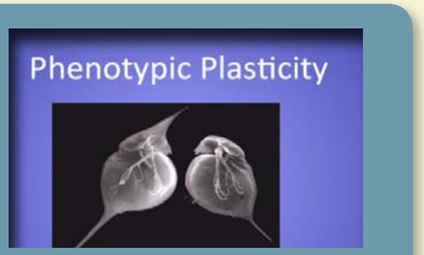
Epigenetics

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.



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

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



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

WHAT IS EPIGENETICS?

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

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

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

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.

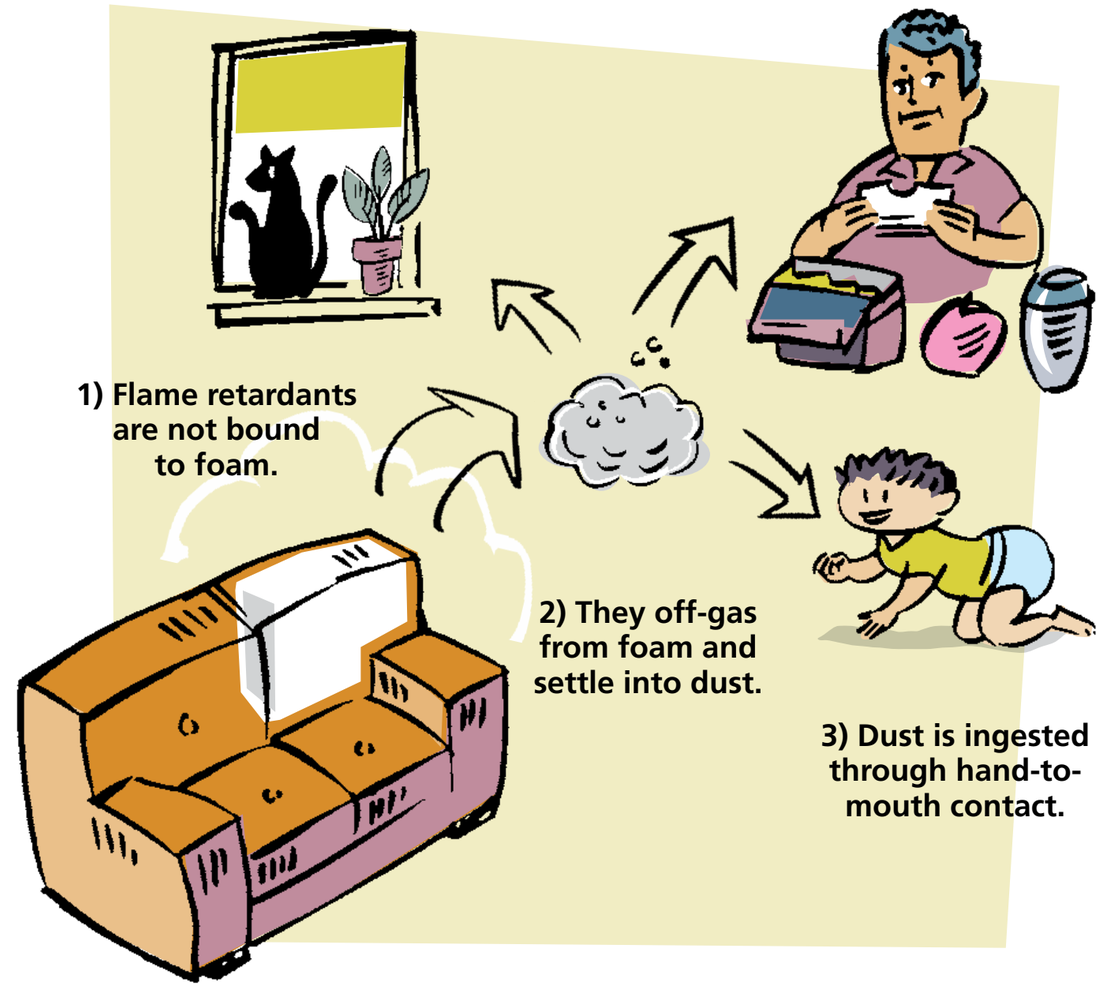
These chemicals can migrate from consumer products and collect in house dust. Because children crawl on the floor and put their hands in their mouth, they may be exposed to higher amounts of chemicals commonly found in house dust than adults.

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

Todd Whitehead PhD, post-doctoral fellow, School of Public Health, University of California-Berkeley

- **PCBs in house dust.**
- **PBDEs in house dust.**
- **Find out more: Green Science Policy Institute - California's policy and consumer resources**

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



CHILDHOOD LEUKEMIA Stephen's Story

INFECTIONS 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 and leukemia risk

Infection-related damage leading to leukemia

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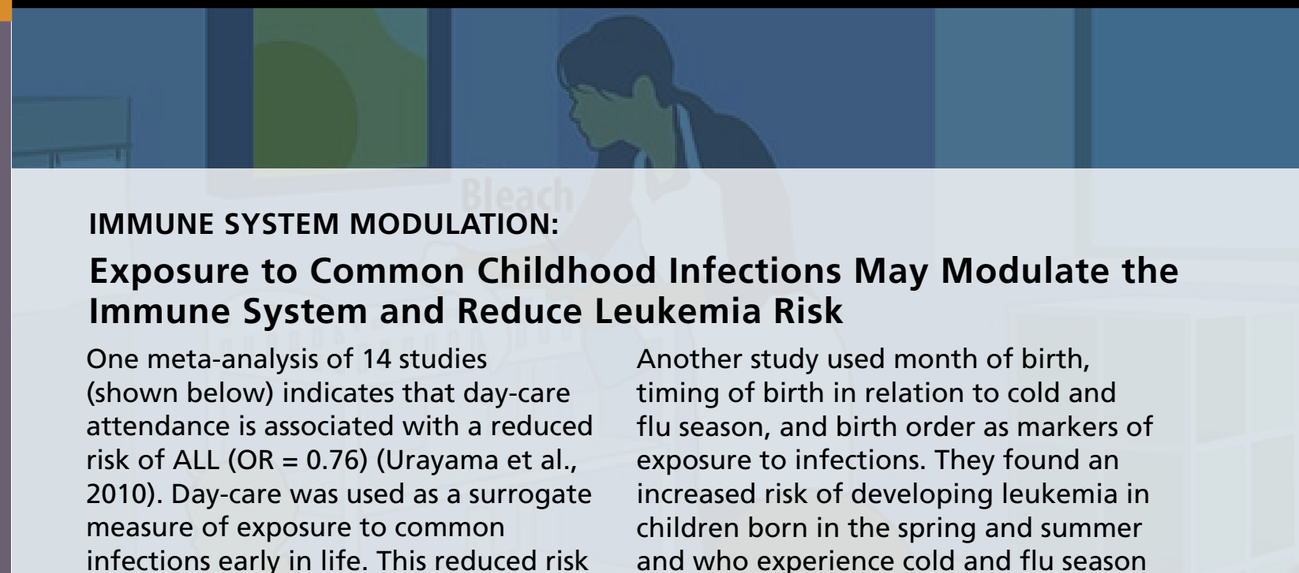
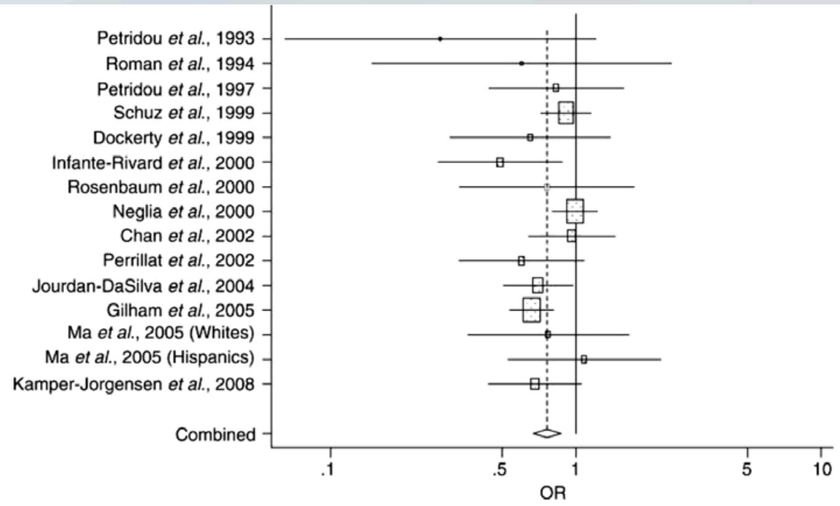


IMMUNE SYSTEM MODULATION:

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

One meta-analysis of 14 studies (shown below) indicates that day-care attendance is associated with a reduced risk of ALL (OR = 0.76) (Urayama et al., 2010). Day-care was used as a surrogate measure of exposure to common infections early in life. This reduced risk supports the hypothesis that common infections can be protective against exaggerated responses by the immune system that may be implicated in childhood leukemia.

Another study 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 born in the spring and summer and who experience cold and flu season at 9-12 months old (OR = 1.44) (Marcotte et al., 2014). This may indicate that early mild infections could be protective against leukemia.



Urayama et al, 2010.
Graphic used with permission.

CHILDHOOD LEUKEMIA Stephen's Story

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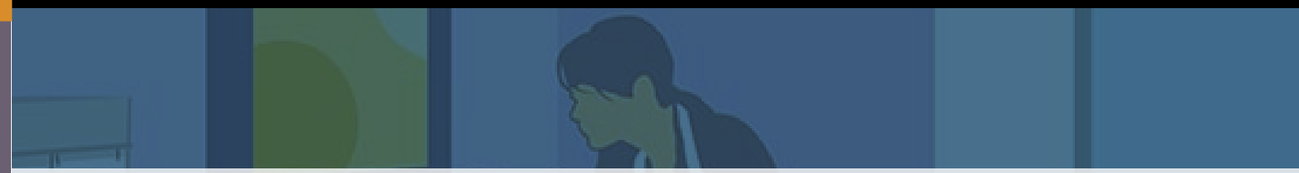


Infection-related damage leading to leukemia

Exposure to a variety of infections followed by an appropriate immune response is a healthy part of growing up, and seems to decrease leukemia risk. However, recent advances in DNA sequencing technology have revealed a mechanism by which strong immune response to infections may induce specific damage leading to leukemia. Researchers have now determined the detailed genetic code of the entire genome of cancer cells from many patients. Childhood leukemia cells have among the lowest level of mutations compared to all other cancer types, which is not surprising since there is very little time in a child's brief life prior to diagnosis to accumulate mutations. Interestingly, point mutations in leukemia cells appear to be predominantly produced by a 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.

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 possible clusters of leukemia near a military base in Fallon, Nevada.

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

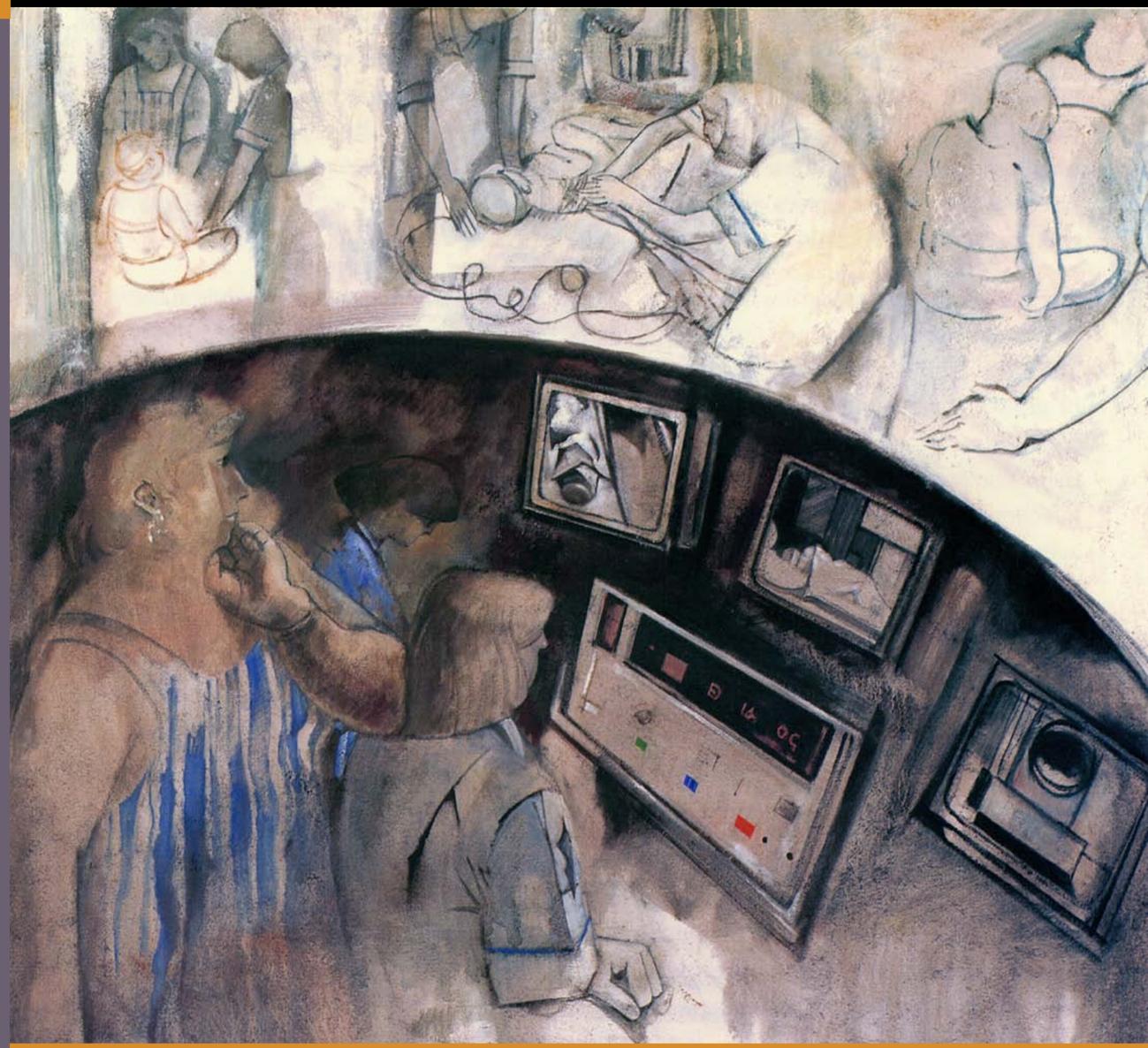
IONIZING RADIATION (INCLUDING X-RAY AND CT SCAN) EXPOSURE AND CHILDHOOD LEUKEMIA

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



"Radiotherapy"
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About the painting with the words of the artist in *italics* >

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

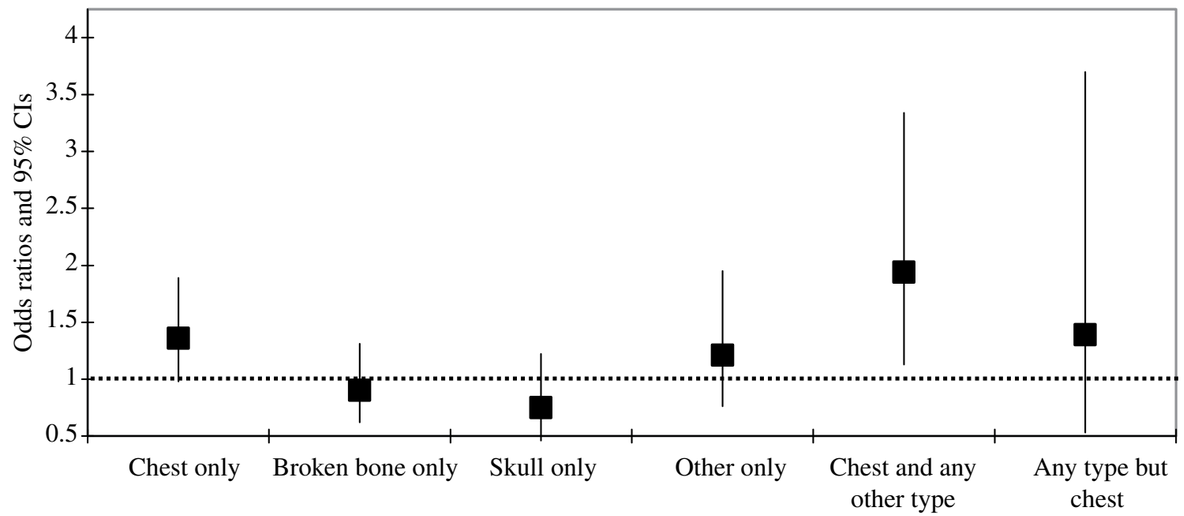
(continued)

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

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



One study's results suggest elevated risks of ALL associated with chest X-rays only (OR=1.36, 95% CI 0.99–1.89) and chest X-rays combined with other regions exposed (OR=1.94, 95% CI 1.13–3.34), indicating that risk of exposure may differ by region of body exposed.

Bartley et al, 2010. Graphic used with permission.

close window

"Radiotherapy"
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About the painting with the words of the artist in *italics* >

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

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."

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

Drawing courtesy of the Bio-Integral Resource Center. Artist Diane Kuhn.

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.

CHILDHOOD LEUKEMIA Stephen's Story

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 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.

Continue to Final Thoughts >

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 people with different diseases, common themes resonate. They include:

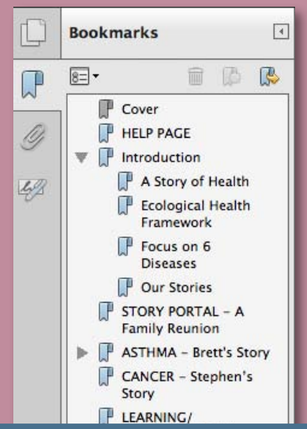
- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly during critical windows of development, can have profound beneficial or detrimental lifelong effects, even into elder years.
- Preventing disease and promoting health require actions and commitments from the individual, family, community and society, as they are all interconnected.

- **Common themes in stories**
- **Additional Resources**
- **Register for Continuing Education Credits**

We'd love to hear from you. Give us your feedback on *A Story of Health*. Click here!

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

Pediatric Environmental Health Toolkit: Materials for health care providers and patients in English and Spanish.

Out of Harm's Way: Preventing Toxic Threats to Child Development: Fact Sheets in English and Spanish.

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) credits 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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Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

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ASTHMA: Brett's Story (a fictional case)

Brett is a nine year old boy who lives with his mom, Karen in an urban area in southern California. They live in an apartment near a busy street, and Brett takes the bus to public school. He plays several sports including baseball, soccer, and basketball, and likes to go out with his friends. Unfortunately, today, many kids like Brett also have asthma.

Basic information: Click here to find out more about asthma.

Health professionals: Click here to read more about asthma.

Asthma resources and more information from the CDC .

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story *

Amelia is a 13-year-old who lives with her parents Darrell and Gloria in a small town in Louisiana.

She enjoys being with her friends, riding her bike, playing soccer, listening to music, and helping out at the restaurant where her mother is the bookkeeper.

Amelia likes school, although she has difficulty learning and is occasionally socially awkward.

Like one in six young people in America, Amelia has a developmental disability.

+ More information on learning and developmental disabilities definitions and US trends

(*a fictional case)

DIABETES Marcela's Story

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Basic information: (to come)

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STORY IN DEVELOPMENT

INFERTILITY Toshio & Reiko's Story

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COGNITIVE DECLINE Donald's Story

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References: (to come)

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