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AN EPIDEMIOLOGICAL CRITIQUE OF TWO CHILDHOOD LEUKEMIA CLUSTER STUDIES: WOBURN, MASSACHUSETTS AND WEST CENTRAL PHOENIX, ARIZONA

By

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ABSTRACT

AN EPIDEMIOLOGICAL CRITIQUE OF TWO CHILDHOOD LEUKEMIA CLUSTER STUDIES: WOBURN, MASSACHUSETTS AND WEST CENTRAL PHOENIX, ARIZONA

By

Allen William Stout

This paper was undertaken to critically review and analyze the childhood leukemia studies conducted in West Central Phoenix, AZ and Woburn, MA in light of Leo Kinlen and Melvin Greaves' infectious etiology hypotheses, and to provide a general epidemiologic critique of the studies. The focus is on Acute Lymphocytic Leukemia (ALL) (ICD-9 code 204.00 and 204.01), as the infectious etiology hypothesis pertains to this type of leukemia. The studies are critiqued according to an epidemiologic investigation checklist (e.g. potential biases, confounders, descriptive and analytic methods, validity of statistical interpretation, etc.) to determine if the ALL cases fit a model that is consistent with an infectious disease etiology. The findings of this paper indicate that there is some evidence to support the infectious etiology hypothesis for ALL and study methodology recommendations are made for future research in this area.

Dedicated to my mother who has always encouraged me to excel.

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LIST OF ABBREVIATIONS

Acute Lymphocytic Leukemia	ALL
Acute Myelogenous Leukemia	AML
Aberrant Response Model	ARM
Arizona Department of Health Services	ADHS
Common Acute Lymphocytic Leukemia	cALL
Centers for Disease Control	CDC
Chronic Lymphocytic Leukemia	CLL
Chronic Myelogenous Leukemia	CML
Department of Environmental Quality Engineering	DEQE
Electro Magnetic Field	EMF
Massachusetts Department of Public Health	MDPH
Massachusetts Health Research Institute	MHRI
National Institute for Occupational Safety and Health	NIOSH
Surveillance, Epidemiology and End Results	SEER
Trichlorethylene	TCE
West Central Phoenix	WCP
Woburn Environment and Birth Study	WEBS

INTRODUCTION

Cancer is a major concern in the United States and many other regions of the world. This concern is heightened when cancer occurs among children. A notable form of childhood cancer that has received much attention in the past is childhood leukemia. Childhood leukemia is still a fairly rare occurrence. Acute lymphocytic leukemia (ALL) is the most common leukemia in young people (0-19), and it has an incidence rate of only 3.1 per 100,000. The next most common childhood leukemia is acute myelogenous leukemia (AML), and it only has an incidence rate of 0.6 per 100,000 (Wang & Haines, 1995). In spite of the small numbers of childhood leukemia cases and the improvements in treatment, childhood leukemia is still viewed as a serious problem. Concerns about childhood leukemia are heightened even more when a cluster of cases is observed.

Cancer clusters are the occurrence of a greater than expected number of cases of a particular type of cancer within a group of people, a geographic area, or a period of time. Cancer clusters capture public attention and therefore must be investigated, however they are extremely difficult to evaluate and to conclusively link to a putative agent. In fact, from 1961 to 1982, the Centers for Disease Control (CDC) investigated 108 reported cancer clusters in 29 states and 5 foreign countries and all had negative results. The types of cancer clusters studied were leukemia (38%), leukemia and lymphoma (30%), leukemia and other cancer combinations (13%), and all other cancer or combinations (19%). Although 14 different categories of associations were reported, no clear cause

was found for any cluster. (Caldwell, 1990) Also, Freda Alexander recently noted that "no causal factor has been identified which can explain a single cluster of childhood leukemia" (Alexander, 1999).

Childhood leukemia clusters in Woburn, Massachusetts and West Central Phoenix (WCP), Arizona are prime examples of the difficult nature of cluster analysis. After careful consideration, the studies of these two clusters were chosen for critique in this paper. The clusters at Woburn and WCP were identified as key clusters in the United States, and they also demonstrated stark contrasts in their features and the way in which they were studied. Woburn, a small community in existence for over 300 years, is located in the Northeastern United States and has a long industrial history. West Central Phoenix is a much newer Southwestern United States community inside the larger City of Phoenix. These two communities also differ widely environmentally, climatically, and on residential, commuting, and migration patterns. Additionally, Woburn experienced its most significant population growth between 1940 and 1960, while WCP grew more substantially in the 1970's and 1980's.

Woburn is the largest childhood leukemia cluster that has been investigated by the CDC. The leukemia cluster led to thirteen environmental and environmental health studies being conducted in Woburn from 1979 to 1997 by the CDC, the Massachusetts Department of Public Health (MDPH) and Department of Environmental Quality Engineering (DEQE). After nearly two decades of cluster investigation, the Woburn researchers were only able to provide a weak association between the excess of leukemia and the suspected

putative agent, contaminated well water exposure. The childhood leukemia cluster in WCP, one of the largest in the western United States, was also exhaustively studied over the period 1983 to 1997. Unlike Woburn, the most significant excess of childhood leukemia was of the acute myelogenous type rather than the acute lymphocytic type. The lengthy and costly effort by the Arizona Department of Health Services (ADHS), in investigating this excess of leukemia, yielded only weak associations between childhood leukemia and several potential putative agents out of the dozens that were evaluated. However the final conclusion of the ADHS was that no specific putative agent was ever identified that accounted for the cluster of childhood leukemia.

In Woburn, researchers quickly focused on environmental exposures from contaminated water supplies, largely because of a publicly perceived connection between the water and leukemia. Conversely, investigators in WCP explored virtually every possible risk factor for childhood leukemia, largely because of the public expectation for the identification of a putative agent. Both the Woburn and WCP clusters were highly publicized, with the Woburn story being made into a book and feature film, "A Civil Action", and the WCP story being made into a televised documentary. Thus, these studies demonstrate both the sociological factors and political pressures that can influence the investigation of a cluster of childhood leukemia and drive methodological decision making.

Due to the significance and contrasts of these clusters, the numerous studies of these two large and notable childhood leukemia clusters were chosen for careful review in this paper. My intention is to demonstrate the flaws in the

science and epidemiology of the cluster investigation efforts in Woburn and WCP, and to advance potential solutions to the inherent problems of childhood leukemia cluster analysis. I will also evaluate the studies for evidence that supports an infectious etiology. And in this context, I will make recommendations on how to advance research in the elucidation of an infectious etiology of childhood leukemia.

Before examining the nature of the infectious etiology hypothesis one must first understand the basic background of childhood leukemia. The identification of the malignant hematopoietic disorders, collectively referred to as leukemia, occurred in the early nineteenth century. The earliest observations of patients who had marked elevation of their white blood cells was by European pathologists who assigned the term "Weisses blut" or "white blood" as a designation for the disorder. The pathologist Velpeau was likely the first to clinically describe leukemia in 1827, but Virchow was the individual who assigned the disease name in 1847. The term "leukemia," which is derived from the Greek words "leukos" meaning "white" and "haima" meaning "blood," was used to indicate the disease. Leukemia was differentiated into two subgroups, acute and chronic, as early as 1889. Naegeli subdivided acute leukemia into the myelocytic and lymphocytic categories, subsequent to his description of the myeloblast cell in 1900. The chronic subgroup was later differentiated in the same fashion as acute leukemia. (Linet, 1985)

The modern classification for leukemia has changed little since the initial discoveries. The major forms of leukemia are divided into four categories. The

terms myelogenous or lymphocytic denote the cell type involved. Myelogenous (also called nonlymphocytic, granuleocytic, myelomonocytic, myelosclerotic, myelosis, myeloid, myelocytic, or myeloblastic) and lymphocytic (also called lymphoid, lymphatic, lymphogenous or lymphoblastic) leukemia have an acute or chronic form. Thus, the four major types of leukemia are as follows: acute lymphocytic leukemia (ALL), ICD-9 codes 204.00 and 204.01; chronic lymphocytic leukemia (CLL), ICD-9 codes 204.10 and 204.11; acute myelogenous leukemia (AML), ICD-9 codes 205.00 and 205.01; and chronic myelogenous leukemia (CML) ICD-9 codes 205.10 and 205.11. (Note: ICD-9 code extensions .00 & .01 indicate no mention of remission and .01 & .11 indicate leukemia in remission) The differentiation of the types of leukemia has been a problem in the past with regards to epidemiological research. Many epidemiologic studies have failed in this differentiation either because of lack of recognition of epidemiologic differences or because of the rarity of leukemia. The fact that leukemia is not very prevalent has made it difficult to obtain adequate sample sizes for studies. For this reason, sampling is problematic when all types of leukemia are combined and even more so when separated. (Linet, 1985)

In spite of the difficulties in obtaining samples for leukemia research, it is critical that studies focus on individual types. Each of these main types of leukemia has unique features, and more importantly, unique etiologies. The basic pathophysiology and epidemiology of the four categories of leukemia will be further discussed, but the emphasis will be placed upon those types most

commonly experienced by children, and specifically on ALL. The term childhood leukemia is a general term encompassing the leukemias which afflict children, and the acute leukemias are those most likely to be found in child populations, while the chronic forms are rarely, if ever, observed in children. Therefore, studies on childhood leukemia typically involve ALL and AML, but ALL is more common and is responsible for the majority of childhood leukemia morbidity. Additionally, due to potentially age-dependent causal pathways, cases of ALL in people age 0 to 19 likely have a distinct etiological pathway as compared to adult cases of ALL (Gilman, McNally and Cartwright, 1999). Therefore childhood ALL (age 0 to 19) must be examined separately from other leukemias.

It is childhood leukemia of the ALL type to which the infectious etiology hypothesis applies. The infectious etiology hypothesis has taken more than one form, and the first was advanced by Leo Kinlen in 1988. Kinlen stated that in the United Kingdom massive migration into previously remote and unpopulated areas led to clusters of childhood leukemia. Kinlen asserted that:

1) The influx of individuals into an isolated community produces conditions in which leukemia is more likely to occur.

2) Isolated communities (susceptible individuals) newly exposed to migrants (infected individuals) from elsewhere could experience an unusual exposure to some hypothetical infectious agent or to otherwise common infections for which no immunity happens to exist.

3) This exposure, in turn, increases the risk of childhood leukemia.

4) Consequently, isolated communities may experience "mini-epidemics" because they are too small to maintain common infections in endemic form, which could lead to a cluster of ALL (Kinlen, 1988).

Melvin Greaves' infectious etiology hypothesis takes a slightly different form. Greaves hypothesized that ALL, which is almost exclusively responsible for the childhood peak (3-5 years of age), may be due to two separate genetic events:

1) spontaneous mutation of a pre-B-cell *in utero*

2) proliferation of the mutated pre-B-cell when exposed to a later antigenic challenge (i.e. an infectious agent)

Greaves stated that the early in utero and later childhood (age 2-3 being the crucial period of cell promotion) mutagenic events lead to acute lymphocytic leukemia. Older children who have delayed exposures to specific agents may experience more vigorous B-cell proliferation, resulting in the second genetic event leading to leukemia. (Greaves, 1988)

Freda Alexander provides an Aberrant Response Model (ARM) that unifies the Kinlen and Greaves models. The ARM states that a substantial portion of ALL cases arise as a rare host response to certain patterns of exposure to common infectious agents. This is at the core of the various infectious etiology hypotheses. (Alexander, 1993) Therefore the infectious etiology hypothesis could possibly follow either the Kinlen or Greaves model or some combination thereof. There also is the possibility that Kinlen's model may occur in the reverse order with susceptible individuals moving from rural areas

and mixing with infected individuals in more urban areas. This could very well be the case in most industrialized countries, such as the United States. Also Greaves' model could possibly be varied to state that an *in utero* antigenic challenge is the event which causes mutated pre-B cell proliferation. Thus, this paper will explore the evidence in the literature and the studies at Woburn and WCP to identify evidence that would support some facet of the infectious etiology hypotheses.

Objectives:

1) To critically review and analyze the childhood leukemia studies conducted in West Central Phoenix, Arizona and Woburn, Massachusetts and identify the flaws in the scientific and epidemiological methods and study results. The studies will be critiqued according to an epidemiologic investigation checklist (e.g. potential biases, confounders, descriptive and analytic methods, validity of statistical interpretation, etc.).

2) To examine the literature and the studies in West Central Phoenix, Arizona and Woburn, Massachusetts to elucidate evidence for the Leo Kinlen and Melvin Greaves infectious etiology hypotheses (Kinlen, 1988) (Greaves, 1988). This will be done to determine if the studies' childhood leukemia cases fit a model (see objectives below) that is consistent with an infectious disease etiology.

2.1) Evaluate if Woburn and West Central Phoenix were relatively isolated from newcomers and did not experience a great deal of population mixing prior to the ALL epidemic.

2.2) Evaluate if Woburn and West Central Phoenix experienced (a) an influx of newcomers and (b) increased incidence of ALL in children (age 0 to 19) following an influx of newcomers.

2.3) Evaluate if Woburn and West Central Phoenix experienced significant mixing of newcomer and indigenous populations prior to and during the elevated incidence of ALL in children (age 0 to 19).

2.4) Evaluate if the cases of ALL occurred primarily in children (age 0 to 19) born in Woburn and West Central Phoenix and whose parents were indigenous to the community (susceptibles) or vice versa in the case of susceptibles moving into an infected population (urban to rural or rural to urban).

2.5) Evaluate if the increased incidence of ALL in children (age 0 to 19) Woburn and West Central Phoenix was a result of an aberrant response to an infectious agent(s) (*in utero* or *in vivo*) introduced by the newcomers.

2.6) Evaluate if susceptible indigenous children exposed to the infectious agent(s) at the ages of 3-4 were more likely to develop ALL according to the typical peak in ALL incidence at that age.

3) To advance recommendations on how to better evaluate childhood leukemia clusters and how to better study the childhood ALL infectious etiology hypothesis.

Chapter 1

BIOLOGICAL ASPECTS OF LEUKEMIA

Human leukemia is a heterogeneous group of disorders characterized by disruption of normal blood cell production. The normal process of blood cell development, called hematopoiesis, occurs in the spongy bone marrow. A small group of cells, the pluripotent bone marrow stem cells, are responsible for making all the blood cells in the marrow. The stem cells eventually transform into the specific blood cells by a process of differentiation and proliferation. The process begins with the differentiation of the self-renewable pluripotent stem cells into multipotent stem cells, myeloid or lymphoid, followed by differentiation into the committed stem cells. The proliferating and differentiating cell process then continues until functioning blood cells are produced. The cells produced include: erythrocytes, platelets, neutrophils, eosinophils, basophils, monocytes, and T and B lymphocytes. When these cells are fully formed and able to function, they leave the marrow and enter the bloodstream.

The leukemia disorders cause blood cell dysfunction through malignant expansion of aberrant blood cells. The malignant transformation can occur at any level of the proliferating stem cell process. The subsequent representation of transformed cells depends entirely on which level of precursor cell is involved in the malignant transformation. Thus, depending on which stem cell is involved, different blood cells will be effected and rendered dysfunctional. This variability accounts for the different categories of leukemia, which are identifiable by the

presence of specific transformed blood cells. If the pluripotent stem cells are the source of the malignancy, a mixed lineage form of leukemia will be observed. The rapid production of the abnormal blood cells causes the pluripotent stem cells to limit their expression of differentiation to the particular cell lineage. Thus, abnormal cells proliferate and few healthy cells are produced. This reduction of normal circulating blood cells precipitates the clinical consequences of the various types of leukemia. Acute leukemia is a rapidly progressing disease that affects mostly cells that are not yet fully developed or differentiated. These immature cells cannot carry out their normal functions, which readily debilitates an individual. Chronic leukemia progresses slowly and permits the growth of greater numbers of more developed cells than does acute leukemia. These more mature cells can carry out some of their normal functions, lessening the impact on the leukemia patient (Mauer, 1990).

The acute leukemias are characterized by the presence of malignant blast cells. The term "blasts" refers to the earliest marrow cells identified by the light microscope. Blasts represent approximately 1 percent of normally developing bone marrow cells. The majority of blast cells are myeloblasts, which are cells that develop into neutrophils. The remaining blast cells are lymphoblasts, which are cells that are part of lymphocyte development. In the acute leukemias, malignant blast cells, similar in appearance to normal blast cells, accumulate in huge quantities of as much as 80 percent of all marrow cells. Abnormal myeloblasts accumulate in AML, and abnormal lymphoblasts accumulate in ALL. The leukemic blast cells fail to function as normal blood cells and act as a

blockade to the production of normal marrow cells, leading to a deficiency of erythrocytes (anemia), platelets (thrombocytopenia), and normal white cells (especially neutrophils, i.e., neutropenia) in the blood.

Within the individual acute leukemia categories, there exist several subtypes. The size and appearance of the leukemia cells are the criteria utilized in the subtype differentiation. Additionally, the leukemic cells are classified by their morphological similarity to normal B or T lymphocytes. There are three principal subtypes of ALL which can be distinguished microscopically, and they have been labeled L1 (small), L2 (large), or L3 (large with other phenotypic features). Approximately 85% of the ALL cases in children present small malignant cells that are related to the B lymphocytes and are of the L1 subtype. In adult cases of ALL the B lymphocyte cells are typically of the L2 subtype. The L3 type is very rare and accounts for only 3% or less of ALL cases in both children and adults. ALL cases of T cell lineage are more commonly found in adolescent and adult populations. There are seven principal sub-classifications of AML, which include the following: M1 (myeloblastic, without maturation), M2 (myeloblastic with maturation), M3 (promyelocytic), M4 (myelomonocytic), M5 (monocytic), M6 (erythroleukemic), and M7 (megakaryocytic). This sub-classification system is based upon the dominant leukemic cells in the marrow at the time of diagnosis of the leukemia. These sub-classifications of ALL and AML are not necessarily a major concern from an epidemiologic perspective, but they do bear noting as they have unique diagnostic and prognostic implications.

Distinguishing between ALL and AML is quite obviously a necessity. Not only do ALL and AML have distinctive etiologies, but they also present different clinical features, as do their subtypes. ALL is frequently associated with central nervous system degradation and dysfunction while AML is not. Also, ALL has a higher recovery, and consequently lower mortality, than that of AML. The individual sub-classifications are significant as well. The L1 morphologic type of ALL has a better outcome than the cases involving the L2 subtype. The subtypes of AML also demonstrate different prognostic and clinical features. The M3 cell type has been associated with the longest duration of remission among the AML subtypes. The M4 morphologic type is associated with a higher incidence of central nervous system leukemia, presenting with isolated tumors. Hyperplasia and skin nodules are more common in the M5 subtype of AML, and simultaneous or subsequent development of meningeal leukemia is more likely to occur with this cell type. The white blood cell counts in AML patients have been found to be higher in both the M4 and M5 cell types than in M2 or M3. There is also evidence to indicate that there is a higher incidence of the M6 subtype in secondary leukemias associated with radiation or chemotherapy exposure. The M7 cell type appears to have the poorest prognosis as it has a low rate of remission followed by rapid relapse and typically a fatal outcome (Mauer, 1990). The variations in clinical presentation and prognosis among the various sub-classifications of ALL and AML may provide clues to subtle etiological differences, but achieving any significant results from epidemiological research in this area is very difficult. The rarity of ALL and AML collectively makes research

problematic, but the successful study of subtype etiologies can be affected through large population-based case-control studies that look at large regions or nations rather than focusing on small clusters of disease.

Chapter 2

ETIOLOGY OF ACUTE LYMPHOCYTIC LEUKEMIA

A. Descriptive Epidemiology of Acute Childhood Leukemia

The acute leukemias, ALL and AML, are not only pathophysiologically distinctive diseases, but they are also distinctive in their epidemiology. This fact is demonstrated by a population study conducted in the Province of Saskatchewan in Canada. The objective was to describe and analyze the incidence and survival data, on the childhood and adolescent leukemias, available from the Cancer Registry of the Saskatchewan Cancer Foundation. The provincial population is small, but the findings of the study are among the most reliable estimates of childhood leukemia time, cohort, and survival trends that were available at the time. The Cancer Registry utilized is believed to be the oldest, continuously collected cancer data source for a geographically defined population. The data utilized included all incident leukemia cases, ages 0-19, which occurred over a sixty year period from 1932-1991. Through review of incidence trends and univariate and multivariate survival analysis, it was observed that age-adjusted incidence of ALL is 3.1 per 100,000 while for AML (ANLL) it is only 0.6 per 100,000. The findings of the study also revealed that the incidence of ALL had been steadily rising over the sixty-year period, but it was acknowledged that previous studies did not necessarily support this conclusion. Hence a certain amount of controversy exists on the issue.

The demographic features of the Saskatchewan leukemia study population are congruent with previous research. The occurrence of ALL in these children was very significant with 46% of the cases occurring in children before age five and 74% occurring before age nine. Additionally, incidence of ALL has remained consistently higher in male children, and this is evidenced among varied racial and geographic boundaries. The results of the AML data analysis identified two key differences between ALL and AML. First of all, the AML data did not demonstrate any statistically significant increasing time trends, and the risk by age was considerably different. Compared with the ALL figures, AML risk was as high or higher for ages 10-19 as for ages 0-4. Also, ages 5-9 had the lowest risk of all the age groups. Considering that the risk rates for ALL decrease from age 0-19, AML and ALL are certainly unique. Another observation in the data seems to indicate that while AML incidence in male children is still higher than in females, the slightly increasing incidence in females appears to be converging with the steadily decreasing incidence in males. A dramatic increase in survival rates was also observed, especially in ALL. Period effects likely account for the higher mortality in the earlier portion of the sixty year interval, due to less efficacious therapeutic interventions being available. It was also determined that, in ALL cases, children under five have a much better survival outlook than do older children and adolescents. The inverse of this is true for AML. (Wang and Haines, 1995)

The incidence, incidence trends, mortality and survival rates provided in the Saskatchewan study are further supported by the statistics provided from the

Surveillance, Epidemiology, and End Results (SEER) nine standard cancer registries in the United States. The data collected from SEER is representative of the child population of the United States (ages 0-14), and is inclusive from 1973 to 1995. The SEER incidence information on ALL (see Table 1) indicates that the annual incidence rate of males has been consistently higher, with few exceptions, than females in each of the three age brackets, over the 23 year period. The average annual incidence from 1991 to 1995 (see Table 2) also shows the higher burden of ALL in male children versus female children. The stark gender differences with ALL are not nearly so pronounced in AML. The SEER data (see Table 3-4) indicate a quite different trend in AML. It appears that AML annual incidence is actually higher in females age 0-4 and slightly lower in the age 5-9 and age 10-14 categories. Overall, it appears that gender differences are gradually disappearing in AML incidence rates.

Table 1:

Annual Incidence of ALL in the U.S. based on 9 Standard SEER Registries

	Male			Female		
Year	**Age 0-4**	**Age 5-9**	**Age 10-14**	**Age 0-4**	**Age 5-9**	**Age 10-14**
1995	6.79	3.59	1.76	5.01	2.17	1.39
1994	5.98	2.22	1.44	4.84	2.09	1.40
1993	4.49	2.25	1.79	5.15	3.65	1.17
1992	5.79	3.17	2.05	4.19	1.66	1.92
1991	7.34	2.94	1.63	5.46	2.73	1.47
1990	5.06	4.09	1.44	5.53	2.98	1.51
1989	6.28	3.54	2.97	5.54	3.95	1.43
1988	6.52	4.15	1.01	5.89	1.93	0.53
1987	5.79	2.57	2.44	5.35	2.33	2.02
1986	6.50	3.81	1.54	4.90	1.87	1.21
1985	6.07	3.29	2.11	5.39	2.42	1.69
1984	4.14	3.49	2.54	6.87	2.35	1.77
1983	4.74	3.06	2.35	4.96	2.14	0.61
1982	5.64	2.07	2.31	3.81	2.70	1.69
1981	4.54	2.45	1.70	5.75	3.90	1.30
1980	6.51	2.25	1.59	4.63	2.75	0.83
1979	4.68	2.69	1.68	4.63	1.79	1.17
1978	4.79	2.99	1.86	5.70	2.24	0.80
1977	5.79	2.59	1.80	4.95	2.21	1.21
1976	5.53	3.25	0.82	4.26	2.54	1.60
1975	5.11	1.98	0.99	3.34	1.33	0.72
1974	6.08	3.23	2.33	3.95	2.32	1.43
1973	5.05	2.33	1.43	4.02	1.28	0.74

Table 2:

Average Annual Incidence of ALL in the United States from 1991 to 1995

Sex	**Age 0-4**	**Age 5-9**	**Age 10-14**
Male	6.07	2.84	1.73
Female	4.93	2.46	1.47

Note: The crude/age-specific incidence rates are based on a standard population of 100,000.

Table 3:

Annual Incidence of AML in the U.S. based on 9 Standard SEER Registries

	Male			Female		
Year	**Age 0-4**	**Age 5-9**	**Age 10-14**	**Age 0-4**	**Age 5-9**	**Age 10-14**
1995	0.64	0.00	0.66	0.78	0.11	0.46
1994	0.52	0.22	0.33	0.44	0.23	0.35
1993	0.73	0.67	0.45	1.21	0.35	0.12
1992	0.21	0.57	0.80	0.66	0.36	0.36
1991	0.32	0.68	0.23	1.34	0.47	0.61
1990	0.75	0.45	0.12	0.68	0.36	0.63
1989	0.44	0.23	0.37	0.69	0.60	0.39
1988	0.22	0.23	0.38	0.59	0.36	0.13
1987	0.45	0.23	0.39	0.36	0.73	0.27
1986	0.68	0.24	0.51	0.24	0.25	0.27
1985	0.57	0.85	0.87	0.36	0.26	0.78
1984	0.23	0.12	0.12	0.60	0.13	0.63
1983	0.58	0.13	0.35	0.73	0.67	0.12
1982	0.12	0.00	0.81	0.49	0.27	0.48
1981	0.36	0.26	0.57	0.37	0.00	0.36
1980	0.49	0.25	0.91	0.64	0.39	0.47
1979	0.38	0.61	0.56	0.53	0.77	0.70
1978	0.65	0.36	0.33	0.81	0.12	0.23
1977	0.39	0.35	0.21	0.41	0.49	0.33
1976	0.13	0.46	0.51	0.55	0.36	0.53
1975	0.89	0.35	0.40	0.67	0.24	0.52
1974	0.81	0.75	0.64	0.56	0.90	0.55
1973	0.59	0.55	0.48	1.39	0.28	0.87

Table 4:

Average Annual Incidence of AML in the United States from 1991 to 1995

Sex	**Age 0-4**	**Age 5-9**	**Age 10-14**
Male	0.48	0.42	0.50
Female	0.88	0.30	0.38

Note: The crude/age-specific incidence rates are based on a standard population of 100,000.

The SEER incidence rates show the gender differences in both ALL and AML from 1973 to 1995, and the data also demonstrate time trends in incidence similar to those observed in the 1995 Wang and Haines childhood leukemia study. The SEER ALL incidence trends (see Table 5) show an increase in males and a significant increase in females from 1973 to 1995, but the incidence for both genders has declined somewhat since 1991. The SEER numbers for AML are much more encouraging (see Table 6). From 1973 to 1995 a remarkable decline in overall AML incidence was observed in all children. The bulk of the decline appears to have occurred in the past decade.

Table 5:

SEER Incidence Trends of ALL (Age 0-14) in the United States: % Change

From-To	Male	Female
1973-1995	+5.66	+22.78
1991-1995	-5.21	-3.59

Table 6:

SEER Incidence Trends of AML (Age 0-14) in the United States: % Change

From-To	Male	Female
1973-1995	-38.40	-48.49
1991-1995	-18.75	-37.09

Note: The incidence trends could be slightly misleading as the leukemia immunophenotyping methods have improved since 1973, thereby reducing misclassification errors.

The SEER mortality trend data provide an encouraging prognosis for the newly incident ALL and AML cases. ALL has experienced greater than a 60% decline in mortality from 1973 to 1995, and the percent change from 1991 to 1995 indicates a continuation of this trend (see Table 7). The percent change in

mortality for AML is not quite so profound, but AML mortality has declined approximately 35% over the 23-year span (see Table 8). The concern with AML is with the recent change in mortality in female children from 1991 to 1995. Mortality has increased nearly 2% (though this slight change could be due to improved diagnostic methods rather than an actual increase) in this time period, while male children's mortality declined nearly 4%.

Table 7:

SEER Mortality Trends of ALL (Age 0-14) in the United States: % Change

From-To	Male	Female
1973-1995	-64.62	-60.39
1991-1995	-7.96	-10.73

Table 8:

SEER Mortality Trends of AML (Age 0-14) in the United States: % Change

From-To	Male	Female
1973-1995	-35.31	-34.69
1991-1995	-3.80	+1.84

Note: The mortality trends could be slightly misleading as the leukemia immunophenotyping methods have improved since 1973, thereby reducing misclassification errors.

The SEER relative survival rate information echoes the observations from the mortality trends for the acute leukemias (see Table 9-10). ALL 1-year and 5-year survival rates are greatly improved in the 1989-1994 time frame as opposed to survival rates in 1975. The 1975 survival rates were not available for AML, but considering the decline in AML mortality over the respective time period, it is likely that survival rates for AML have followed the same trend as that seen in ALL. Comparison of the most recent survival rate data for ALL and AML

indicates that AML is significantly more lethal than ALL, as the survival rates for ALL are nearly 30% greater than for AML. This could be a result of the greater prevalence of ALL in children and the subsequent increased focus on treatment and prevention for ALL, from a public health standpoint.

Table 9:

SEER Relative Survival Rates of ALL (Age 0-14) in the U.S.: Percentage

Year	Male 1 Year	Male 5 Year	Male 20 Year	Female 1 Year	Female 5 Year	Female 20 Year
1989-1994	95.58	79.93	59	95.59	80.48	64
1975	88.18	40.43	28.53	88.17	59.64	45.36

Table 10:

SEER Relative Survival Rates of AML (Age 0-14) in the U.S.: Percentage

Year	Male 1 Year	Male 5 Year	Male 20 Year	Female 1 Year	Female 5 Year	Female 20 Year
1989-1994	69.67	50.44	N/A	68.43	37.99	N/A
1975	N/A	N/A	N/A	N/A	N/A	N/A

The incidence information regarding ALL and AML, seen in the data from the Saskatchewan study and the SEER, is fairly consistent globally. The following table (see Table 11) was excerpted from the British Journal of Cancer and demonstrates the global similarities in childhood leukemia incidence. The incidence rates are not broken down by acute leukemia sub-type, but they show how the leukemic disorders afflict children nearly identically in the different geographical regions. The ALL/AML ratio provided in the table also reinforces the much greater prevalence of ALL throughout the world.

Table 11:

Comparison of Reports on Childhood Leukemia in Europe, NA & Australia

Country	Period	Incidence Age 0-4	Incidence Age 5-9	Incidence Age 10-14	Adjusted Age 0-14	ALL/ AML Ratio
Sask,Can	1976-90	6.9	3.9	2.3	4.4	6.7
US/SEER	1973-82	6.8	3.5	2.3	4.4	5.4
Fla,US	1981-86	7.0	3.5	2.6	4.4	5.2
Australia	1977-82	7.4	3.6	2.2	4.6	5.3
Torino,It	1967-86	7.7	4.2	2.6	4.8	5.1
Finland	1971-82	5.4	3.0	2.7	3.9	5.0
GB(male)	1974-76	7.0	3.7	2.3	-	-
W.Germ	1980-86	6.5	3.5	2.2	4.4	6.6
Denmark	1980-84	5.7	2.7	2.8	3.9	5.3
Manch,UK	1971-83	5.7	3.2	2.2	3.8	5.7
LRF-UK	1984-86	6.4	3.0	1.7	3.9	5.1
The Neth.	1973-86	6.1	3.1	1.9	3.9	8.3

Note: The incidence rates are based on a standard population of 100,000.
Source: British Journal of Cancer 1989: 59: 100-105

While macro geography demonstrates tremendous similarities in childhood leukemia incidence across the globe, there are indications that the place where childhood leukemia occurs may actually contribute to the leukemogenesis. There has been substantial evidence accumulated that clustering of childhood leukemia cases occurs within geographical areas, and many hypotheses have been advanced to explain this phenomena.

B. Potential Causal Factors of Acute Childhood Leukemia

1. Environmental Factors

Numerous physical and chemical agents have been implicated in the epidemiological origin of childhood leukemia. Benzene has been identified as a potential causal factor in childhood AML but not ALL (Alexander, Leon and

Cartwright, 1996). An ecological study was conducted in the municipalities of Sweden, over an 11-year period from 1975-1985, to determine if environmental exposure to gasoline was associated with leukemia incidence in children and young adults (ages 0-24). Leukemia incidence rates were obtained from the National Swedish Cancer Register and compared to the number of cars per area. As expected, an association between car volume and AML incidence was found, but no association was found for ALL. The incidence of AML in municipalities with more than 20 cars per km^2 was 5.5 (95% CI 4.4-6.8) per 1 million person-years as compared to 3.4 (95% CI 1.9-5.7) in municipalities with less than 5 cars per km^2. This association between childhood AML and car density is likely attributable to benzene exposure from gasoline vapors and exhaust gases (Nordlinder and Jarvholm, 1997). Another potential environmental contributor to the onset of childhood leukemia is radon. Radon exposure was significantly correlated with AML in a study conducted in Great Britain. The study analysis concluded that 6-12% of the AML incident cases in the UK could be attributed to radon and between 13-25% of world cases may be caused by radon (Henshaw, Eatough and Richardson, 1990). Radium-226 contaminated drinking water in the region of Ellweiler, Rheinland-Pfalz, Germany has also been implicated in leukemogenesis. It is believed that prenatal exposure and dose accumulation of the Radium-226 was the cause of the excess childhood leukemia cases in the Ellweiler region (Hoffman, Kranefeld and Schmitz-Feuerhake, 1993).

Another environmental exposure, that may put children at risk for leukemia, is the presence of pesticides in the home and at large. A case-control

study of children, under the age of 15, was undertaken in the Denver area between 1976 and 1983 to determine if an association existed between home pesticide use and childhood cancer. 252 cases (70.8% of eligible cases) and 222 control subjects (79.9% of eligible controls) were obtained for the study in which the cases had home pesticide use and the controls had no home pesticide use. Regarding leukemia, the study results indicated a significant risk in the homes which used pest strips (OR from 1.7 to 3.0) and elevated risk in homes which had home exterminations or yard treatments (OR from 0.3 to 1.1). The varying odds ratios arise from consideration of differing exposure periods (prenatal, less than 2 years, and greater than 2 years of age) but are inclusive of all of the data collected. Although the exposure measures were rather crude, this study does indicate an association between home pesticide use and leukemogenesis (Leiss and Savitz, 1995). A critical review of 31 previous residential or occupational pesticide exposure epidemiologic studies published between 1970 and 1996 reported that relative risks to pesticide exposure and development of childhood cancers were modest. The review found that childhood leukemia was more strongly associated with home pesticide use than with professional pesticide use or yard treatments (Daniels, Olshan and Savitz, 1997). A recent large case-control study in Germany evaluated 1,184 cases of childhood leukemia and 234 with non-Hodgkin's lymphoma, and the data provided some evidence for an increased leukemia risk for children living on farms who are exposed to agricultural pesticides (OR 1.5, 95% CI: 1.0, 2.2). Also a significant trend ($p = 0.02$) was identified between frequency of parental

use of household insecticides and risk of childhood leukemia. (Meinert et al., 2000)

The exposure to pesticides prenatally and early in childhood seems to be associated with onset of leukemia, and studies indicate a similar association in children who were exposed to alcohol *in utero* or cigarette smoke *in vivo*. A case-control study of childhood AML was formulated, from data obtained from 187 matched pairs, and was examined for evidence of associations between parental cigarette smoking and alcohol consumption and subsequent onset of AML. Alcohol consumption during pregnancy appears to associated with increased risk of AML in children less than 2 years of age (OR 3.00; 95% CI 1.23 to 8.35), but little evidence was found to associate cigarette smoking and AML (Severson et al., 1993). A similar study was conducted utilizing 302 cases matched to 558 controls, and parental alcohol consumption and cigarette smoking were again the subject of interest. The study found slight associations between maternal alcohol consumption during pregnancy and elevated risk of ALL and AML, but maternal prenatal cigarette smoking was actually found to be negatively associated with infant leukemia risk. However, a significant association was found between maternal prenatal alcohol consumption and AML of the M1 or M2 morphology (OR 7.62; 95% CI 2.03-28.64). Thus, in utero alcohol exposure appears to contribute to the leukemogenesis of certain AML subtypes (Shu et al., 1996). Prenatal exposure to Phenobarbital and other drugs is also suspected of contributing to leukemogenesis, but there is little evidence to support a strong association or causal relationship. Association between

childhood leukemia and administration of intramuscular vitamin K to newborns, to prevent hemorrhaging, is also controversial, but some evidence from the UK supports the hypothesis. Two studies on the subject found no association; however, one study found "borderline significance" while another in northern England revealed a 2-fold risk of ALL in children age 1-6 who received the intramuscular vitamin K at birth (Voelker, 1998).

One more environmental exposure that has generated controversy is the association between childhood leukemia and exposure to electromagnetic fields (EMF). EMF exposure can occur as a result proximity to power lines, certain household wiring codes, and other magnetic field producing electrical items within the home or in a child's overall environment. Numerous studies have been undertaken on the subject, but the recent studies appear to be the most relevant. The landmark case-control study conducted by Linet et al. (1997), in the United States, enrolled 638 children with ALL and 620 controls. Data were amassed through exhaustive measurement of magnetic fields in the previous and current homes of the children, by blinded collectors, and a computer algorithm was utilized to assign wire-code categories. The findings of the study revealed an odds ratio for ALL of 1.24 (95% CI 0.86-1.79). Therefore, the results provide little if any evidence that ALL is associated with EMF exposure (Linet et al., 1997). A study of proximity to power lines in relation to childhood leukemia was undertaken in Greece in 1993-1994, and its findings were in concordance with Linet et al. (1997) (Petridou et al., 1997). Many have seen the Linet et al. (1997) study as the conclusive debunking of the EMF hypothesis, but the hypothesis

should not be ruled out altogether. Less elaborate but more recent studies have indicated that an association may still exist. The risk of childhood leukemia and proximity to high-voltage transmission lines in three urban districts of Taiwan was examined. Data from 1987 to 1992 showed a standardized incidence ratio of 2.69 (95% CI 1.08-5.55) of childhood leukemia in children living within 100 meters of the power lines compared to the total child population of Taiwan (Li, Lee and Lin, 1998). EMF measurements were taken from 1992 to 1996 in two population-based case-control studies on childhood leukemia in the northwestern part of Germany and in Berlin. A total of 176 case subjects were utilized and matched to 414 controls to determine if an association existed between EMF exposure and childhood leukemia. The results were not statistically significant, but they did reveal a trend that seemed to support the EMF hypothesis of association to childhood leukemia (Michaelis et al., 1998). Two detailed EMF studies conducted in 2000 revealed that distance from power lines, exposure index, peak exposure, threshold values, measures of short-term variability, and spot measurements demonstrated little or no association with risk of childhood ALL (Kleinerman et al., 2000) (Auvinen et al., 2000).

2. Genetics

There is little evidence to show an association between heredity and childhood leukemia, but heredity remains an interest in leukemogenesis epidemiology. The impetus for researching genetic factors arises from the observed examples of familial aggregation. A twin study undertaken in the UK examined the various determinants of concordant childhood leukemia in

monozygotic twins. The results of the analysis indicated that the genetic determinants of childhood leukemia operate before the time of cleavage, but the study cautioned that these determinants alone were insufficient for childhood leukemia to ensue (Knox, Marshall and Barling, 1984). An earlier twin study found that the childhood leukemia concordance rate among monozygotic twins was approximately 25% (Jackson, Norris and Klauber, 1969). Certain genetic defects that cause some cancers are inherited and therefore are associated with familial predisposition to cancer. However, research indicates that the genetic defects, such as observed chromosomal abnormalities, that increase the likelihood of leukemia are actually acquired rather than inherited (Cline, 1994).

A recent population-based cohort study was undertaken in Denmark to assess the role of birth characteristics and sibling patterns in the development of childhood leukemia. The study established a cohort of children whose mothers had been born between April 1935 and March 1978, and children who developed ALL or AML between April 1968 and December 1992. The cohort included approximately 2.0 million children from which the childhood leukemia cases were identified. The results of the birth order analysis were not significant for ALL and only slightly significant for AML, but the birth weight findings were substantial. The overall risk of ALL increased by a factor of 1.46 (95% CI 1.18-1.81; P=.0005) for each kilogram of increase in birth weight, and the overall risk of AML increased by a factor of 2.14 (95% CI 1.19-3.85; P=.009) for each kilogram of increase in birth weight. The possible explanation for this effect was that with increasing birth weight there is greater cell proliferation, which places a larger

number of precursors at risk for malignant transformation (Westergaard et al., 1997). The evidence in the literature regarding heredity and familial aggregation, as well as the confounding effects of siblings sharing common environments, makes it is difficult to implicate heredity as a contributing factor in childhood leukemia etiology. However, the possibility of hereditary involvement should not be dismissed, as it could play even a small role in the epidemiology of the disease state of childhood leukemia.

3. Radiation

There has been substantial evidence accumulated that clustering of childhood leukemia cases occurs within geographical areas (Laurier and Bard, 1999), and many hypotheses have been advanced to explain this phenomena. Clustering of childhood leukemia has been observed in various areas, but the clustering around nuclear facilities has probably generated the most research. A metanalysis of investigations into the occurrence of childhood leukemia near nuclear facilities in the United Kingdom identified space-time clustering in the vicinity. Following an initial report of childhood leukemia clustering near one nuclear plant in northern England, numerous subsequent investigations were undertaken. The investigations revealed that there is a consistent pattern of a slightly elevated risk of leukemia for children living near nuclear establishments. However, the author acknowledges that these findings do not imply any causal relationship, and the presence of the nuclear plants may be nothing more than a convenient etiological scapegoat (Beral, 1990). A study conducted in northern Germany identified a cluster of six cases of childhood leukemia, between

February 1990 and December 1995, among the residents of the small rural community of Elbmarsch. Five of the cases occurred in only a 16 month period between February 1990 and May 1991. All of the cases lived within 4.5 km of Germany's largest capacity nuclear boiling-water reactor. The study was only able to identify the cluster and did not attempt to rule out other potential risk factors (Hoffmann et al., 1997). Clustering of childhood leukemia, within a ten-mile radius of the U.S. nuclear plant at Three Mile Island, was observed over the period of 1975 to 1985. The cases identified had been or were suspected to have been exposed to varying levels of background gamma radiation from the nuclear facility. The study found an elevated odds ratio (OR=2.4) among incident cases of leukemia for children under age 15 who had exposure, but the association was not statistically significant. Also, the data on childhood leukemia mortality showed little or no association to background gamma radiation exposure (Hatch and Susser, 1990).

Another area of concern in childhood leukemogenesis lies in paternal preconceptional exposure to radiation. Kinlen undertook a matched case-control study in Scotland to determine if paternal preconceptional radiation exposure in the nuclear industry was at all related to childhood leukemia and non-Hodgkin's lymphoma. The findings of the study found no statistically significant excess of either disease at any level of paternal radiation exposure (Kinlen, Clarke and Balkwill, 1993). A more recent case-control study, of cancer incidence in the offspring of radiation workers in Great Britain, confirmed the findings of Kinlen et

al. (1993). The results are not conclusive though, as the numbers were too small to generate reliable estimates of elevated risk (Draper et al., 1997).

Between 1951 and 1958, twenty-six nuclear tests were conducted in southwestern Utah. A retrospective cohort study was undertaken twenty years later to determine if radiation from nuclear fallout was associated with increased incidence of childhood leukemia in the effected areas. Mortality records for children under 15 years of age were evaluated and the subjects were assigned to either a low exposure or high exposure cohort. For some unknown reason, the low exposure cohort in the high-fallout areas actually had a leukemia mortality rate that was half that of the rest of Utah and the United States. The mortality in the high exposure cohort increases by 2.44 times (95% CI 1.18 to 5.02) to just slightly higher than that of the United States (Lyon et al., 1979). A more recent case-control study evaluated the same Utah population utilizing estimates of dose to bone marrow computed from fallout deposition rates and the residence locations of the subjects. Using 1,170 leukemia deaths as cases and 5,330 controls who died from other causes, only a weak non-significant association was found between bone marrow dose and all types of leukemia. However, trend analysis revealed a statistically significant ($p<0.05$) excess risk in the individuals of the high-dose group, with ALL and AML, who were under 20 years of age and died before 1964 (Stevens et al., 1990). While these Utah studies do not provide strong evidence for the role of radiation as a risk factor in childhood leukemia, an analysis of the data collected through the Leukaemia Registries in Hiroshima and Nagasaki Japan provides stronger evidence. Following the dropping of atomic

bombs on these two cities, tremendous increases of both the acute and chronic leukemias occurred in the surviving population. The acute leukemias witnessed the greatest increase, especially in children less than age 15 at the time of the bombing who experienced at least a 100 rad total air dose. From 1950 to 1955 the annual incidence rate of acute leukemia in this group soared to over 90 per 100,000. From 1955 to 1960 the rate fell off to approximately 50 per 100,000. Similar trends were observed in the other age groups and in the chronic types (Greaves and Chan, 1984). The gross excess of childhood leukemia and other leukemias, as a result of the radiation exposure, certainly implicates radiation as a potential inductive agent even if it is not at the etiological core.

4. Infectious Etiology

The presence of these various clusters of childhood leukemia around nuclear sites would seem to implicate the nuclear facilities in the etiology, but this is likely not the case. There could quite possibly be other underlying factors that lead to the presence of the clusters as childhood leukemia clusters are observed in numerous locations that are completely isolated from nuclear radiation exposure. This fact led to Kinlen's population mixing (infective) hypothesis, which proposes that "the bringing together of rural and urban groups, or different socioeconomic groups, can increase the frequency of childhood leukemia through increased contact between susceptible and infected individuals. Geographical isolation, high social class, and frequent population turnover all promote susceptibility" (Kinlen, 1997). Kinlen's hypothesis was first brought forth in 1988 and 1990 in two separate studies. In Kinlen's 1988 paper he challenged

the unfounded accusations that the childhood leukemia clusters around Sellafield and Dounreay were a result of proximity to the only British nuclear power stations that also reprocessed spent nuclear fuel. Kinlen hypothesized that the clusters near Dounreay and Sellafield had nothing to do with radiation and were a result of the same causes that explained clusters elsewhere. The three key elements of Kinlen's hypothesis in this study were as follows: (1) that influxes of population into rural and isolated areas are conducive to epidemics of certain infections, (2) that Sellafield and Dounreay are extreme examples of isolation and population influx, and (3) that childhood leukemia is an aberrant response to some infectious agent(s). Kinlen tested his hypothesis by examining the mortality records of the New Town of Glenrothes, Scotland, which was identified as the only other rural area that received a large influx at the same time as Sellafield and Dounreay. The results of the study revealed that a significant increase of leukemia below age 25 was found, with 10 cases observed compared to the expected 3.6 cases. The greatest excess was found in children below the age of 5, with 7 cases observed compared to the expected 1.5 cases (Kinlen, 1988). Kinlen's 1990 study found further evidence to support his hypothesis. Kinlen et al. examined the mortality data for childhood leukemia in rural and urban overspill areas, where immigration into the towns was rapid and on a large scale, in Great Britain from 1946 to 1985. The data indicated that the hypothesis was not limited to a particular cell type of leukemia, and that the distribution seemed to follow the same increased social contact pattern as in feline leukemia in house cats (which is the result of a leukemogenic virus). It was also noted that due to the lack of

appreciable space-time clustering, if childhood leukemia is of an infective origin then the spread of infection is primarily done by trivially infected subjects rather than by leukemia subjects (Kinlen, Clarke and Hudson, 1990).

A study of leukemia clusters in Great Britain supported the Kinlen hypothesis in its findings. The study focused on the space-time interactions and geographical concentrations of childhood leukemia in England, Wales, and Scotland. The data examined included all registered cases of leukemia and lymphoma between 1966 and 1983 in children aged 0-14. Statistically significant excesses of case pairs occurred jointly within 0.5 km of each other, and these clusters were observed mainly in the more rural northern England and Scotland. The study concluded that the occurrence of childhood leukemia in the recognized clusters followed a common epidemic process, and that the distributions almost certainly reflect some sort of biological process that is likely communicable (Knox and Gilman, 1992).

The infectious etiology hypothesis is multifaceted. In addition to Kinlen, others have advanced slightly different yet epidemiologically coherent hypotheses. For comparison let us first consider the essential nature of the Kinlen hypothesis: "Massive migration into previously remote and unpopulated areas led to clusters of childhood leukemia. The influx of individuals into an isolated community produces conditions in which leukemia is more likely to occur. Isolated communities newly exposed to migrants from elsewhere could experience an unusual exposure to some hypothetical infectious agent or to otherwise common infections for which no immunity happens to exist. Perhaps

this exposure, in turn, increases the risk of childhood leukemia. Isolated communities may experience "mini-epidemics" because they are too small to maintain common infections in endemic form (Kinlen, 1988)." The Greaves hypothesis, in contrast, takes a somewhat different approach: "cALL (common form of ALL), which is almost exclusively responsible for the childhood peak (3-5 years of age), may be due to two separate genetic events: 1) spontaneous mutation of a pre-B-cell in utero 2) proliferation of the mutated pre-B-cell when exposed to a later antigenic challenge (i.e. an infectious agent). The early in utero and later childhood (age 2-3 being the crucial period of cell promotion) mutagenic events lead to leukemia. Older children who have delayed exposures to specific agents may experience more vigorous B-cell proliferation, resulting in a second genetic event leading to leukemia (Greaves, 1988)." Freda Alexander provides an Aberrant Response Model (ARM) that unifies the Kinlen and Greaves models. The ARM states that a substantial portion of ALL cases arise as a rare host response to certain patterns of exposure to common infectious agents. This is at the core of the various infectious etiology hypotheses (Alexander, 1993).

Support for an infectious etiology hypothesis in the occurrence of childhood leukemia has been provided by numerous studies which have demonstrated the patterns of population mixing and clustering in the epidemiology of the disease. The first investigation of an association between population mixing and childhood leukemia in Asia was conducted in Hong Kong, where the study analyzed the childhood leukemia incidence data from 1984 to

1990 for evidence of variation between small areas. The results showed that ALL incidence was similar to that in Caucasian populations, but the peak age was somewhat older and broader in Hong Kong. Also the typical male predominance in ALL was observed with an overall male-female ratio of 1.4:1.0. More importantly though, the Potthoff-Whittinghill test was implemented and found evidence of overall spatial clustering for ALL in the 0-4 age group which includes the peak age group. Less statistically significant but similar spatial clustering results were obtained for total childhood leukemia in all age groups. The results yield strong evidence of ALL clustering concentrated in the areas where population mixing was most likely, and the data on T-cell ALL supports the hypothesis linking common ALL to exposures to common infection microepidemics (Alexander et al., 1997).

Kinlen led another investigation in 1995 in which the WHO database was utilized to evaluate the childhood leukemia mortality records of 33 countries from 1958 to 1987 with an emphasis on the late 1950s and early 1960s. The countries chosen were primarily rural and experienced major rural-urban migrations; and, consequently, population mixing occurred. The study revealed that the two countries with the greatest amount of rural population movement, Greece and Italy, also experienced abnormally high mortality rates from childhood leukemia. In fact, Greece, which was more rural than Italy and therefore more greatly impacted by the mixing, had the highest mortality from childhood leukemia from 1958 to 1972. The high childhood leukemia mortality in Greece, where extensive rural migration took place, during the 1960s is

apparently the highest ever recorded in any country. With the relative rarity of childhood leukemia, it is very doubtful that the disease would have been over diagnosed in Greece, and it would actually be more likely overlooked (Kinlen and Petridou, 1995).

Kinlen and Hudson conducted an ecological mortality study of the impact of servicemen being stationed in rural areas on the burden of childhood leukemia from 1950 to 1963. The study aggregated rural counties and urban counties and determined proportions of servicemen to indigenous populations. The rural counties with the highest proportion of servicemen had the greatest excess of childhood leukemia, and the distribution of leukemia reflected the spread of poliomyelitis at the time (Kinlen and Hudson, 1991). Another study on the effect of population mixing identified a significantly increased risk of childhood leukemia mortality in children (age 0-14) in areas which experienced more than a 50% increase in population over a ten year period (Langford, 1991). Three additional studies by Freda Alexander support these findings. The studies implemented cluster analysis of childhood leukemia clusters in England, and they indicated that either persistent infection in utero or horizontal transmission models could account for the density and proximity of cases (Alexander et al., 1990) (Alexander et al., 1992) (Alexander, 1992).

Another interesting observation about the role of population mixing was made by Kinlen. Kinlen identified increased childhood leukemia trends in cities within the UK that had greater commuting levels. From this data he was able to advance the plausibility that children in families with high levels of personal

contacts (of which the age and background may be significant factors) may be at greater risk of manifesting childhood leukemia (Kinlen et al., 1991) (Kinlen, 1993). Several other investigations of possible leukemia clusters have found that cases have occurred predominantly in Catholic families and members of the same parish or church (Heath, 1974). The isolation of populations and subsequent clustering of childhood leukemia, due to an infective etiology, was again supported by a study of the relationship between car ownership and small area variation in ALL incidence in children. The study found that ALL and car ownership were inversely associated, which indicates that isolated groups may be more susceptible to the hypothesized infectious agent(s) (Alexander, Leon and Cartwright, 1996). Alexander also identified that an excess risk of childhood ALL was associated with ecologically defined areas farthest from large urban centers (Alexander et al., 1990). Similar findings were observed in Sweden (Hjalmars and Gustafsson, 1998).

Recent evidence has also supported the infectious etiology through examination of space-time clustering and population density. In 1999, a European population density study was conducted that included 13,551 cases of childhood leukemia diagnosed between 1980 and 1989 in 17 different countries or regions. The investigators found that there was statistically significant evidence of extra-Poisson variation of case counts in intermediate density areas (specifically, those with a density of 250-499 persons/km2, $p < 0.001$ for childhood leukemia). The evidence suggests that childhood leukemia epidemics arise regularly in moderately densely populated areas and also sporadically in

areas which are somewhat less densely populated. This provides strong support for an infectious putative agent in childhood ALL, in that susceptibles would be most likely to be exposed in intermediate areas as they move into them and occasionally in the more rural areas when a unique infection is introduced (Alexander et al., 1999). Also, in a more recent study in the United Kingdom similar infectious etiology supporting evidence was found. Utilizing Knox tests for analysis of space-time interactions between cases of childhood leukemia, researchers revealed that there was highly significant evidence of space-time clustering based on place of birth and time of diagnosis, particularly for ALL cases age 0-4 years. The researchers concluded that their findings were consistent with an infectious hypothesis (Birch et al., 2000). Both of these studies demonstrate the potential role of a putative infectious agent through population mixing, as evidenced by density, and susceptibility, as evidenced by temporal and spatial characteristics at birth.

The potential infectious etiology of childhood leukemia is additionally supported by observations of birth order. Regarding childhood leukemia there appears to be a birth order effect in which the first-born children are at greater risk of leukemia than their siblings. This could be the result of the older sib bringing home infections to the younger sibs and thereby conferring immunity and reduced risk of leukemia to younger sibs (James, 1990). While the older sibling risk has been identified, no association with breastfeeding and onset of ALL has been identified (Shu et al., 1995). The lack of protective effect from breastfeeding could be viewed as negative evidence for the infectious

hypothesis, but it is not necessarily so and further research in this area is indicated. Another interesting finding, from a large Danish cohort study, that may support the role of an infectious agent in childhood ALL is the weak association found between parental autoimmune disease and hematopoietic malignancies in their offspring during childhood. Results were not statistically significant but did show an elevation in malignancies among children with parents having autoimmune disease (Meelemkjaer, Alexander and Olsen, 2000).

The role of viral agents in the development of other human cancers also supports the notion that childhood leukemia may have an infectious origin. The Human T-cell leukemia virus (HTLV-1) has been identified by serological and molecular analyses as the causal factor of adult T-cell leukemia. The chronic immunosuppression caused by the human immunodeficiency virus (HIV) has been linked to the increased incidence of some tumors in infected individuals. HIV infected individuals have also manifested Epstein-Barr virus (EBV) related immunoblastic lymphomas, Kaposi's sarcoma, and human papillomavirus (HPV) related anogenital cancers such as cervical and anal cancer. At least 40% of Hodgkin's disease tumors carry genetic traces of EBV. Also, hepatitis B virus (HBV) has been found to increase the lifetime risk of hepatocellular carcinoma by a factor of 30-100 (Morris, Eddleston and Crook, 1995) (Toren et al., 1996). Research has indicated that as many as 15 percent of all cancers worldwide may be caused by viruses (McCool, 1996).

Malcolm Smith proposes that the JC virus is possibly the infective agent that leads to ALL (Smith et al., 1997). The JC virus is a polyoma virus with a B-

cell predilection. Approximately 50% of all pregnant women are seropositive for the virus, and infection with the virus tends to occur earlier in developing countries and in the lower socioeconomic stratum. Primary infection with the JC virus is generally subclinical. Smith et al. (1997) did not identify the seroprevalence in ALL cases, but previous studies indicate that this prevalent JC virus is oncogenic in animal models (Davies and Ross, 1997). The hypothesis that the JC virus is leukemogenic in ALL cases will require substantial further research, but it does add to the growing body of information implicating an infectious origin for childhood leukemia.

A growing body of evidence is also developing around the possibility of in utero infectious origin. Greaves and colleagues (1997) have recently shown that three children diagnosed with ALL at 5 months, 6 months, and 24 months each had an abnormal "fusion gene" at birth. This MLL-AF4 gene is the product of a translocation between two chromosomes and is commonly found in very young children with ALL. They also found a pair of identical twins diagnosed with ALL at age 3 and 4 years (within peak age range) who had a translocation between two genes known as TEL and AML1. Both genetic abnormalities are not hereditary and could have arisen as a result of an insult from an infectious agent and/or the subsequent promotional event, necessary for development of clinical leukemia, could be in response to an antigenic challenge (Greaves et al., 1997) (Felix, 1999) (Wiemels et al., 1999). It was also recently concluded that the frequency, age, distribution and clinical features of the TEL-AML1 fusion gene-positive ALL cases in Brazil were similar in the diverse ethnic backgrounds of the

Brazilian children to those in other countries with predominantly white Caucasian or oriental ethnicity (Magalhaes et al., 2000). Fetal infection models have also been elucidated and are plausible (Knox et al., 1983). General horizontal infectious models have also been substantiated by the sharp peak in incidence of ALL at ages 2-5. Due to the potential for *in utero* antigenic challenge followed by the 2 to 5 year latent period that precedes onset of ALL, the sharp peak in incidence strongly suggests the effect of an infectious agent (MacMahon, 1992) (Greaves and Alexander, 1993).

Animal models also provide coherence for the infective origin hypothesis. Retroviruses have been determined to be the causative agents of leukemogenesis in numerous animal species including: chickens, rats, mice, guinea pigs, cats, cattle, and gibbon apes. Given that the morphology and clinical features of animal leukemias and lymphomas closely resemble those in man, the possibility that such viruses are involved in the induction of human leukemias and lymphomas is quite high (Goldman and Jarrett, 1984).

The following critical analysis will elucidate some of the evidence that lends support to the infectious etiology hypothesis through application of hypothetical modeling of the study results.

Chapter 3

WOBURN, MASSACHUSETTS CHILDHOOD LEUKEMIA STUDIES

Introduction

Woburn, Massachusetts, is a community of approximately 35,000 people, located 13 miles northwest of Boston. It has an extensive industrial history spanning over 130 years, which included greenhouse operations, leather manufacturing and chemical manufacturing. Products manufactured included arsenic compounds used in pesticides, textiles, paper, TNT, and animal glues. The deposition of hazardous material and waste products from these industries was a serious point of environmental concern for citizens and government officials, and led to the execution of several studies.

Thirteen environmental and environmental health studies have been conducted in Woburn, Massachusetts by the Massachusetts Department of Public Health (MDPH) and Department of Environmental Quality Engineering (DEQE) since 1979. In 1979, environmental concerns were brought to the forefront of public attention when excavation of a former industrial site unearthed significant amounts of industrial waste that were laden with high levels of lead, arsenic, and heavy metals. It was subsequently learned that two municipal drinking water wells (Wells G & H), which had been installed near this site, were contaminated with trichlorethylene (TCE), perchloroethylene, chloroform and other organic compounds. These wells supplied public water primarily to the eastern portion of Woburn between 1964 and 1979.

Woburn residents were concerned regarding health effects that may have resulted from consumption of the contaminated water from wells G & H. Between January 1969 and December 1979, twelve cases of childhood leukemia had been diagnosed in Woburn. Six of these cases resided in a six-block area, which was served directly by the contaminated wells. Identification of these cases, and the potential link to the wells, prompted the Massachusetts Department of Public Health (MDPH) and the Centers for Disease Control (CDC) to begin a formal investigation of the health status of Woburn residents.

In January 1981 a case-control investigation was conducted by MDPH to evaluate the situation in Woburn. The investigation concluded: (1) the incidence of childhood leukemia was significantly elevated in Woburn (12 observed cases vs. 5.3 expected cases between 1969 and 1979); (2) the majority of the excess cases were males; and (3) six of the cases were diagnosed while residing in a single census tract in east Woburn. At the time, the cases in this census tract represented half the identified childhood leukemias, a number disproportionate to the geographic distribution of the population in the community. In 1984, an additional seven cases were identified that had been diagnosed through 1983. This demonstrated a continued excess in the incidence of childhood leukemia (19 observed cases vs. 6.1 expected).

By the middle of 1986, a total of 21 childhood leukemia cases had been diagnosed in Woburn. Cases diagnosed after 1979 had birth residences which were more evenly distributed throughout Woburn than the original 12 cases. As a result of the continued elevated incidence and the change in the geographic

distribution of the cases, MDPH conducted the Childhood Leukemia Follow-Up Study, the results of which are detailed later in this chapter.

The following describes each of the Woburn studies and summarizes their findings: (note: each bold heading represents an individual publication by the same name) (See Appendix A & B for maps indicating the location of Woburn and Wells G & H)

Woburn Health Data Analysis 1969 - 1978 (Kotelchuck and Parker, 1979)

The first study conducted in Woburn was the Woburn Health Data Analysis 1969 - 1978, which was presented December 21, 1979. The MDPH ascertained that Woburn's cancer death rate was higher than what should be expected considering the age and sex characteristics of its residents. The MDPH also determined that although the mortality rates were elevated, they did not represent an epidemic situation.

Based upon the statewide experience with cancer mortality from 1969 - 1978 for all causes (International Classification of Diseases categories 140 - 199, Malignant neoplasms), the expected cancer mortality for Woburn was 503.5 deaths but 569 cancer deaths were observed. Woburn's cancer mortality was 13.7% greater than expected. Cancer mortality in Woburn was found to be on the increase, but only during the last five-year period was the observed number of deaths significantly higher than expected. During 1974 - 1978, 307 cancer deaths were observed in Woburn with 248 expected. In the earlier 5-year period, 1969 - 1974, 262 cancer deaths were observed with 255.5 expected. From 1974 - 1978, Woburn had the highest rate of cancer out of the 70 largest

Massachusetts communities (defined as having a population greater than 20,000). Woburn had significantly elevated cancer mortality rates for only a limited number of cancer types. In the period 1974 -1978, Woburn had elevated mortality rates for bronchus/lung, breast, prostate, kidney, and liver cancers. Childhood and young adult leukemia mortality was elevated but not significantly elevated in Woburn during the 10 year study period. During the 1969 - 1973 period there was a statistically significant elevation of leukemias in Woburn (18 leukemia deaths observed with 10.9 expected), but there was no statistically significant elevation for 1974 - 1978. The study also examined three specific types of cancers in Woburn for clustering: liver, kidney, and childhood leukemia. No strong pattern of clustering of deaths was found. Additionally, no increase in infant mortality, low-birthweight infants, or congenital malformation was found. (Kotelchuck and Parker, 1979)

Woburn: Cancer Incidence and Environmental Hazards 1969 - 1978 (Parker and Rosen, 1981)

This study dealt primarily with questions concerning childhood leukemia, renal cancer, and liver cancer. Cases with these cancers were investigated by means of an interview study. An investigation into the incidence of bladder cancer was also made. A case was defined as a person with confirmed childhood leukemia, renal cancer, liver cancer, or bladder cancer, who was diagnosed with the disease between 1969 and 1978 (1969-1979 for the leukemia cases) and who was a resident of Woburn at the time of diagnosis. The study questionnaire was developed, pretested, and revised by the MDPH and CDC.

The topics investigated included demographic information, disease processes, past medical history, smoking, residence, schooling, occupational histories, and environmental exposures. Trained interviewers from the CDC and NIOSH conducted the majority of the interviews. Two age- and sex-matched controls were interviewed for each of the twelve leukemia cases. One control was a person of the same age and sex who lived close to the case. The other age and sex-matched control lived in a distant part of Woburn. Interviews were conducted with one or both parents of the leukemia cases and controls.

The investigation confirmed that there was a significantly elevated incidence of childhood leukemia in Woburn for the period 1969-1979, with 12 cases observed and 5.3 expected. The excess observed was largely among males, with 9 cases observed and 3.1 cases expected. Analysis of residence at the time of diagnosis revealed a significant concentration of cases in the eastern part of Woburn, where the incidence of the disease was at least seven times greater than expected. For males, the incidence of childhood leukemia in this area was over 12 times that expected. The incidence of childhood leukemia for the rest of Woburn was not significantly elevated compared to national rates.

The investigation established that the overall incidence of childhood leukemia was significantly elevated in Woburn and that there was a significant concentration of cases in one particular area of east Woburn. No evidence was ascertained that indicated that the increase in leukemia incidence was associated with environmental hazards in Woburn, and specifically with the contamination of drinking water supplies. (Parker and Rosen, 1981)

Retrospective Study of Woburn 1949 - 1968 (Rowe, 1981)

This study was undertaken to analyze cancer mortality in Woburn from 1949-1968. The main impetus was to evaluate the pattern of childhood leukemia. Since the survival from childhood leukemia was 5% in 1950, mortality rates closely reflected the actual incidence figures for that time. Thus, this study relied on mortality records as a proxy for childhood leukemia incidence. Every death certificate that mentioned cancer was abstracted. Childhood leukemia cases were included if it was noted as an immediate cause of death and if the individual was 19 years of age or under at death. Analysis of the SMRs for leukemia showed a gradual increase from 76 to 123 in the period 1949-1968. The increase in childhood leukemia mortality was greater than adult leukemia mortality. Investigators concluded that "If one suspects an environmental toxin such as the contaminated drinking water to have been a factor in the occurrence of childhood leukemias, then there must have been a sufficient latent period such that they didn't show up until the late 1970's. At the present time there is no evidence to support an environmental toxin in the etiology of the cases of leukemia in Woburn." (Rowe, 1981)

CDC: Cancer in Woburn (CDC, 1981)

In 1980 the Massachusetts Department of Public Health and the Centers for Disease Control undertook a case-control study to investigate possible associations between environmental hazards and the incidence of childhood leukemia plus three other types of cancer (kidney, urinary bladder, and liver) in Woburn residents for the period 1969-1978. This investigation confirmed that the

increase in incidence of childhood leukemia, concentrated in eastern Woburn, was statistically significant when compared with nationwide rates. Because of limited environmental data, the investigation did not establish an association between known environmental hazards in Woburn and the elevated childhood leukemia incidence. Also, kidney cancer incidence was slightly significantly elevated, and rates for liver and bladder cancer were not significantly elevated.

Childhood leukemia cases were defined as Woburn residents under 19 years of age, whose cancer was diagnosed between 1969 and 1979. Trained interviewers from CDC and NIOSH conducted interviews with one or both parents of the 12 childhood leukemia cases. For each leukemia patient, two age- and sex-matched controls were interviewed (one control resided near the case).

Twelve cases of childhood leukemia occurred in Woburn from 1969-1979. Nine (75%) of the children had acute lymphocytic leukemia, and all cases were diagnosed before the patients reached 15 years of age. Childhood leukemia incidence in Woburn in this period was significantly higher than expected with 12 observed and 5.3 expected ($p=0.0058$). Boys had an elevated incidence rate ($p=0.00380$), and girls did not. However, all of the girls' cases were all diagnosed when they were between ages 10 and 14, which was a significant elevation for that age group ($p=0.008$).

At the time of diagnosis, the leukemia cases were concentrated in the eastern part of Woburn, just north of Walker Pond. Six patients lived within or on the border of census tract 3334, in an area approximately ½ mile in radius. There was a significant concentration of cases in this census tract. The binomial

distribution probability that 6 or more of the 12 cases would occur in this area, which contains only 17% of the town's population in the 1 to 14 year age group, was less than 0.01. The six cases in this census tract were 7.5 times (p=0.00018) higher than the expected 0.8 cases. Childhood leukemia for the rest of Woburn was not significantly elevated (p=0.297).

There were no significant differences between case and control groups with respect to medical histories, parents' occupations, or environmental exposures. Interestingly, four of the ALL cases were born in a 6-month period, indicating a potential *in utero* exposure. (CDC, 1981)

Cancer Mortality in Woburn: A Three Decade Study 1949-1978 (Telles, 1981)

This study utilized a systematic search through all death certificates at the Woburn City Hall for the period 1949-1968. Every certificate that mentioned cancer was abstracted and the data were analyzed according to the site of cancer, year of death, age of death and sex. These observed deaths were compared to the expected number of deaths, by computing standardized mortality ratios. During the period 1949-1978 there were fourteen deaths due to childhood leukemia (cases 19 years and younger).

One objective of this study was to test further whether there was an association between the use of water from Wells G and H and the occurrence of leukemia. These additional data weakened the association, in that the number of childhood leukemia deaths began to rise from 1959-1963 (SMR = 120), before the wells were drilled, and continued to rise in the period in which the wells were drilled 1964-1968 (SMR = 169). Given an average latent period of two to five

years, childhood leukemia associated with Wells G and H should not have started to increase until 1969-1973, when in fact, the rate was lower than expected (SMR = 50). However, from 1974-1978 the rate increased substantially (SMR = 357).

Additionally, childhood leukemia mortality was not elevated during the period 1949-1958, but childhood leukemia mortality began to rise in 1959-1963. No unusual geographic distribution of childhood leukemia mortality occurred during the period 1949-1968. The investigators concluded that these data were consistent with the possibility that, excluding a chance occurrence, the elevated incidence of leukemia and the concentration of cases in eastern Woburn during 1969-1978 must have been due to some newly introduced factor which became present and active during the late 1950's. (Telles, 1981)

Childhood Leukemia, Woburn, MA: An Update (Cutler, 1984)

This study evaluated the 28 cases to date in Woburn. The important findings were for the period 1980 – 1983, in which there were 7 new incident cases of childhood leukemia. The cases occurred in a scattered geographic pattern, although 1 of the cases was in the Walker Pond area. All of the cases white; 5 of 7 were male, the age range was 22 months to 14 years; all had ALL, with unambiguous clinical and histological diagnoses.

Investigators also calculated expected and observed leukemia cases for Woburn for the period 1969-1983. Although all the leukemias were ALL, because 3 of 12 cases before 1980 were other leukemias, expected cases were calculated for leukemia, all types, age 0-14. Male - 3.99 expected and 14

observed (ratio 3.00, 95% CI 1.55, 5.25); Female – 2.02 expected and 5 observed (ratio 1.98, 95% CI 0.54, 5.07); Both – 6.01 expected and 19 observed (ratio 3.16, 95% CI 1.90, 4.93).

Geographical clustering was observed in east Woburn around Walker Pond (census tract 3334) with 7 cases observed and 0.92 expected. The number of cases was significantly elevated in tracts 3331 (4 observed/ 1.08 expected) and 3335 (6 observed/ 1.46 expected) as well.

When soil samples were analyzed from the vicinity of Walker Pond, no single compound or group of compounds was found to be associated with the cases of leukemia. In addition, air samples were found to be normal. The investigators concluded that "The problem of excess leukemia in Woburn children continues, and there is no explanation." (Cutler, 1984)

Final Report of the Woburn Advisory Panel to the Massachusetts Department of Public Health (MDPH, 1985)

This paper did not report any study findings, rather it was a list of recommendations on how to proceed with future studies in Woburn. The advisory panel advanced recommendations on epidemiological studies of the cluster of childhood leukemia, etiological studies, environmental studies, as well as health surveillance in Woburn. (MDPH, 1985)

Health Assessment Wells G&H, Woburn (MDPH, 1989)

The suspected leukemogenic contaminated wells in Woburn, Wells G & H, were located about 10 miles north of Boston, Massachusetts. Woburn Municipal Wells G and H were used from 1964 to 1979 to supplement Woburn drinking

water supplies. The ground water extracted from Wells G and H was found to be contaminated with volatile organic compounds in 1979. The predominant ground water contaminants were trichloroethylene, tetrachloroethylene, trans-1,2-dichloroethylene and 1,1,1-trichloroethane. Five contaminated properties located near the wells were known contributors to the ground water contamination. Ground water and both surface and subsurface soil contamination on-site at the facilities was extensive and resulted from liquid-waste spills on the ground, sludge disposal, buried and surface disposal of 55-gallon drums, and leaking tanks. Based on a 30-day aquifer test, Municipal Wells G and H were found to intercept, either entirely or partially, ground water from beneath these five contaminated properties. Wells G and H have not been used since 1979. As residences and industries were located both on-site and nearby, there was a potential for human exposure to contaminants by: (1) inhalation of dusts and vapors from surface soils, industrial use of contaminated well water, and migration of vapors from contaminated shallow ground water to the inside of buildings; 2) skin contact with contaminated surface soils at Wildwood Conservation Corporation, New England Plastics Corporation, and Olympia Nominee Trust Corporation, sludge at Wildwood Conservation Corporation, and contaminated industrial well water at New England Plastics Corporation and John J. Riley Tannery; and 3) ingestion of dusts, surface soils, and, possibly, contaminated fish and contaminated industrial well water. (MDPH, 1989)

Exposure to Wells G&H in Woburn Massachusetts (Murphy, 1990)

This report attempted to quantify the exposure of Woburn citizens to drinking water from Wells G and H. The calculation of exposure was a function of both the approximately 50 hydraulically distinct neighborhoods within Woburn and of the 114 months of Wells' G and H operation.

The method used to calculate this exposure to water from the wells begins with a computer model of the water distribution system that was developed by the investigators under a previous contract with the Massachusetts Department of Environmental Quality Engineering (DEQE). This Woburn water distribution model was applied to the various pumping and water use configurations that occurred during each month that Wells G and H were in operation. The results of these calculations were then individually analyzed with a hydraulic mixing model to calculate the mixture of water supplied to each neighborhood, the monthly average exposure index for each neighborhood, and the cumulative exposure.

The levels of exposure to water from Wells G and H were found to vary widely. Typically, the neighborhoods south and west of the center of the city received no or very little water from Wells G and H. The neighborhoods of east Woburn received water mostly from Wells G and H whenever those wells were pumping. The mixture zone between the two water sources ran along, or just to the east of Main Street (the center of the city). (Murphy, 1990)

Final Report of the Woburn Environment and Birth Study (MDPH, CDC and MHRI, 1994)

The Woburn Environment and Birth Study (WEBS) was implemented to determine if adverse reproductive outcome rates in Woburn (such as specific

birth defects and stillbirths) differed from rates in other communities, and also to determine if the opportunity for exposure to contaminated drinking water from Woburn municipal Wells G & H was related to a higher rate of any of these outcomes. The study population consisted of all live-births and stillbirths that occurred among Woburn residents between January 1969 and March 1991 (more than 11,500). Rates of adverse reproductive outcomes occurring in Woburn live-births and stillbirths were compared to corresponding rates in other local and regional populations to determine if the Woburn rates were elevated.

WEBS included a 20-year (1969 - 1988) retrospective cohort study (N = 10,383) to evaluate the overall reproductive health of Woburn residents relative to several referent populations and relative to exposure to the contaminated water and a 27-month (1/l/l989 - 3/31/1991) prospective surveillance study (N = 1,227) to evaluate the more recent reproductive health of Woburn residents relative to the referent communities. Maternal exposure to contaminated water was assessed on the basis of an estimate of the proportion of contaminated water that reached each birth residence location during pregnancy.

Comparison with the referent populations indicated no differences in the prevalence of most outcomes for Woburn births. Over both the retrospective and prospective surveillance study periods, there was a trend over time for a greater prevalence of male fetal deaths in Woburn, but this trend was significant only during the prospective surveillance period (after closure of the contaminated water wells). During the retrospective study period, there were both significantly

higher and lower rates of particular organ groupings and specific birth defects relative to two referent birth defects registries.

Analysis of the effects of exposure to contaminated water, revealed a trend for a lower prevalence of the birthweight, pre-term and infant death outcomes for exposed groups than for unexposed groups. Conversely, the trend was for a somewhat higher prevalence of the small-for-gestational-age and fetal death outcomes for exposed groups, but in most instances the differences were not significant. There were too few cases of birth defects by diagnostic category to make reliable comparisons between the exposure categories, although in the few instances in which there were sufficient numbers, no significant association with exposure to contaminated water was observed.

Investigators concluded that the WEBS results provided little support for the hypothesis that environmental contaminants in the public water supply had an adverse effect on the reproductive health of exposed subgroups of Woburn residents or of Woburn residents as a whole. (MDPH, CDC and MHRI, 1994)

Health Assessment - Industriplex Site in Woburn (MDPH, 1995)

This study evaluated the 244-acre Industriplex site located in Woburn, Massachusetts. This was previously the location of various chemical manufacturing plants, and most recently a hide glue manufacturing plant. The U.S. Environmental Protection Agency designated the site in the Woburn study area as a Superfund site. Various chemicals were detected on-site and off-site in the surrounding study area. Arsenic, chromium, lead, benzene, and toluene are the primary contaminants on-site and were generally detected at elevated

concentrations in soils and sediments. Volatile organic compounds (VOCs), semi-volatile organic compounds (semi-VOCs), polynuclear aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and other metals were also detected on-site and in the study area.

Populations with the greatest potential for historical exposures to contaminants originating from the site were on-site workers, unauthorized individuals who accessed the site, and workers and residents in the site vicinity. The only chemical present at concentrations at which adverse human health effects are known to occur was arsenic. Individuals who may have accessed the site in the past would have been at the greatest risk of exposure due to contamination of the soil (0-12 inch depth), subsurface soil, and sediment through ingestion of these contaminated media.

The health effects which are expected to occur as a result of exposure to site-related contaminants were primarily associated with exposure to contaminants in on and off-site soil 0-12" in depth. Ingestion of arsenic contaminated soil may have resulted in abdominal pain, diarrhea, and sore throat. Skin exposure to chromium in this media could have enhanced already existing dermatitis, and ingestion of lead contaminated soil may have caused mild hematological effects by disrupting enzyme activity. All these effects are reversible and would have been effectively halted with the termination of exposure. No linkage to childhood leukemia has been identified for any of these exposures. (MDPH, 1995)

Health Assessment Addendum - Wells G&H, Woburn (MDPH, 1995)

The Wells G and H site encompassed two municipal wells located in Woburn, Massachusetts that were used as a municipal water supply for the city of Woburn from 1964 to 1979. The initial health assessment was completed in 1989, and this addendum was published to address the indoor air monitoring studies conducted at the Wells G and H site following the initial assessment. Three nearby residences and a local day care center were sampled to determine the extent of indoor air contamination due to volatilization of contaminants from the groundwater plume into the basements of the residences and the day care center. The primary contaminants detected in indoor air were carbon tetrachloride, benzene, 1,2-dichloroethane, trichloroethylene, 1,1-dichloroethylene, methylene chloride, and chloroform.

Populations potentially exposed to the inhalation of indoor air contaminants from the study area included residents and workers in the general area and workers and children at the day care center. Adverse health effects from exposure were determined to be unlikely due to the low concentrations detected.

Investigators determined that the chemicals detected during these sampling investigations were not likely related to the Well G & H sites. The concentrations measured were typical of concentrations seen in many studies of ambient or indoor air. The majority of the samples taken at three Woburn residences and the day care center resulted in either non-detectable levels of contaminants or low levels of contaminants. The highest levels were detected consistently at one of the residences, which stored a considerable amount of

household products containing a variety of the compounds of concern associated with this investigation (suggesting another potential source of contamination other than groundwater). The proximity of various industrial companies, including a printing press, may have been a source of contamination for the indoor air of the day care center. Thus, it was concluded that identifying the contaminated groundwater as the only source contributing to air concentrations in the basements, could not be made with any certainty; and the indoor air in the site vicinity represented no apparent public health hazard. (MDPH, 1995)

Woburn Childhood Leukemia Follow-Up Study (MDPH, 1997)

This was the final study conducted by MDPH and they do not wish to analyze the situation at Woburn any further. Consequently, they refused to give the author of this critique access to any of the original data that was utilized for this or any other childhood leukemia study conducted in Woburn.

Study Methods:

The study was a matched case-control design with two controls selected for each case. All cases were residents of Woburn who were 0 to 19 years of age at time of diagnosis and were diagnosed with leukemia between 1969 and 1989. Controls were selected randomly from Woburn school records and matched to cases based on date of birth (plus or minus 3 months), sex and race. Controls must have been Woburn residents at the time of diagnosis of the matched case. Residential, occupational and health history data were collected during the interview for the etiologic period for each case and its matched controls. The etiologic period was defined as the period of time from two years

before conception to the case's leukemia diagnosis and was sub-divided for analysis into three time segments: two years before conception to conception, during pregnancy, and from birth to case diagnosis.

Study Results:

Univariate Analyses – Detailed analyses of data collected at interview revealed five variables for which 10 or more total positive responses were identified and that demonstrated odds ratios greater than or equal to 1.50 in relation to the childhood leukemia incidence. Maternal alcohol consumption during pregnancy (OR = 1.50, C.I. = 0.54, 4.20), diagnosis of paternal grandfather with cancer (OR = 2.01, C.I. = 0.73, 5.58), having a father who worked for industries considered high risk for occupational exposures (OR = 2.50, C.I. = 0.78, 8.30), and the subject's consumption of public water as their primary beverage (OR = 3.03, C.I. = 0.82, 11.28) were all variables which showed non-significant but positive associations with childhood leukemia incidence. A statistically significant association was identified between developing childhood leukemia and being breast-fed as a child (OR = 10.17, C.I. = 1.22, 84.58).

Multivariate Analyses and Exposure to Wells G and H - Multivariate analyses of the relationship between childhood leukemia and exposure to water from Wells G and H revealed that although five variables discussed above showed elevated odds ratios as univariates in relation to the leukemia, they did not significantly affect odds ratios specific to water exposure. Adjusted odds ratios were calculated controlling for socioeconomic status, maternal smoking

during pregnancy, maternal age at birth of the child, and maternal alcohol consumption during pregnancy. Of these variables, only maternal alcohol consumption during pregnancy demonstrated a slightly elevated odds ratio in univariate analysis.

Adjusted odds ratios describing the effects of Wells G and H water on leukemia incidence showed a non-significant elevation for the overall etiologic period (OR = 2.39, C.I. = 0.54, 10.59) and each time period subcategory. The strongest relationship between exposure and leukemia among time period subcategories was during pregnancy (OR = 8.33, C.I. = 0.73, 94.67), the second was in the two years before conception (OR = 2.61, C.I. = 0.47, 14.37) and the time period between the birth of the case and the diagnosis of leukemia (OR = 1.18, C.I. = 0.28, 5.05).

Sub-stratification of the pregnancy time period to assess specific effects of water exposure by trimester revealed high correlation coefficients between trimester exposure values. Thus, independent effects of water exposure by trimester on leukemia incidence could not be distinguished.

Analyses to assess potential dose response relationships were completed using a trichotomous parameterization of the actual study subject exposure values by time period. Results demonstrated elevated odds ratios between dose categories for the preconception and pregnancy periods. A significant trend across exposure categories was also identified for the period during pregnancy ($P < 0.05$) suggesting a dose-response relationship for subjects whose mothers drank Wells G and H water during pregnancy. Tests for trend for the etiologic

period overall and for each of the other time period subcategories were not significant (P>0.05).

Study Discussion and Conclusions:

The investigators concluded that the results suggested the relative risk of developing childhood leukemia was greater for those children whose mothers were likely to have consumed water from Wells G and H during pregnancy. This conclusion was based on the association of the relationship to the amount of water households received (dose-response). However, there appeared to be no associations between the development of childhood leukemia and consumption of water from Wells G and H by the children prior to their diagnosis.

Relatively few positive associations were identified between childhood leukemia incidence and residential parental occupation, and medical history related risk factors, and none were statistically significant with the exception of the breast-feeding finding.

Investigators noted that TCE, one chemical detected in the well water, is known to have weak hematologic effects in mammals. No studies have shown this effect in humans, although effects on the developing human fetus are unclear. They also noted that the nature and extent of historical contamination of Wells G and H is not known.

Investigators also acknowledged that the small number of study subjects leads to imprecise estimates of risk. As a result, the exact magnitude of the association between exposure to water from Wells G and H and risk of childhood leukemia could not be stated. However, results suggested a dose-response

relationship and demonstrated a decrease in effect after the elimination of the potential for exposure. The study authors concluded that the incidence of childhood leukemia in Woburn between 1969 and 1989 was associated with mothers' potential for exposure to contaminated water from Wells G and H, particularly for exposure during pregnancy. (MDPH, 1997)

Chapter 4

WEST CENTRAL PHOENIX, ARIZONA CHILDHOOD LEUKEMIA STUDIES

Introduction

In 1982 a parent first identified an elevated number of children with leukemia attending a school in West Central Phoenix. Subsequently, the principal of St. Vincent de Paul School, a parochial school in West Central Phoenix (WCP), reported to the Arizona Department of Health Services (ADHS) that seven students had died of leukemia between 1961 and 1982. The ADHS computed the leukemia mortality rate in the city of Phoenix and in the school catchment area for children age 5 through 14 for the years 1970 through 1981. The number of leukemia deaths in the catchment area of school during the twelve-year period was thirteen, about seven more cases than would have been expected in comparison to the leukemia rate in the remainder of the city. A 1983 evaluation by the ADHS did not reveal any unusual environmental factors. Public concerns resurfaced in 1987, leading to two ADHS studies that addressed overall death rates and childhood cancer incidence rates in Maricopa county and West Central Phoenix (WCP), defined here as the 50 square mile area from 27th Avenue to 83rd Avenue, and Camelback Road to Southern Avenue. The ADHS reported the results of those two studies in 1988 and 1990. The incidence study showed an elevation of the rate of leukemia in WCP among children 0-19 years of age (29 cases expected between 1965 and 1986, with 49 observed in that time period). The only leukemia subtype that was significantly elevated in WCP

was acute myeloid leukemia (AML), an uncommon subtype in children. These studies were followed by a comprehensive case-control study and an updated incidence study.

The following describes each of the West Central Phoenix studies and summarizes their findings: (note: each bold heading represents an individual publication by the same name) (See Appendix A & C for maps indicating the location of West Central Phoenix)

Report on Mortality in Maricopa County 1966-1986 (Flood and Chapin, 1988)

This study was conducted to investigate the cluster of childhood leukemia in WCP. This was a retrospective study of mortality in Maricopa county for the years 1966 through 1986 that aimed to quantitatively confirm the 1982 observations, determine leukemia mortality rates in previous and subsequent time rates, and to examine total cancer mortality within four suspect areas and the remainder of Maricopa county.

This study confirmed the previous finding of a higher rate of childhood leukemia deaths in West Central Phoenix and in east central Phoenix between 1970 and 1981. During 1966-1969, the leukemia rates were not significantly elevated in these areas. During 1982-1986, leukemia deaths only in WCP were significantly elevated, with eight deaths observed and 3.8 expected. The finding of an elevated leukemia rate in WCP during 1982-1986 was found to be accurate and not biased by a sampling problem that occurred during 1970-1981. These findings corroborated by an another group that assessed the spatial occurrence

of childhood leukemia mortality in WCP using standardized rate ratios with a simple linear Poisson model (Aickin et al., 1992).

When compared to U.S. rates, total cancer rates in east central Phoenix were significantly elevated in children between 1970-1981 and in middle-aged adults (45-64) between both 1970-1981 and 1982-1986. During this latter period, the total cancer rate among elderly (65+) was found to be significantly elevated in West Central Phoenix. Total cancer mortality rates in all adult age groups and during all three time periods in the non-suspect area of Maricopa county areas were all significantly lower than U.S. rates. (Flood and Chapin, 1988)

Incidence Study of Childhood Cancer in Maricopa County: 1965-1986 (Flood et al., 1990)

This incidence study was conducted to determine whether there was an elevated incidence of childhood leukemia among children residing in WCP, to explore the data for factors that could guide the search for causes of the apparent cluster of leukemia, and to examine the rates of other childhood cancers within Maricopa county.

For this study, a case was defined as a malignancy diagnosed from 1965 to 1986 in a person age 0-19, who was a resident of Maricopa county at the time of diagnosis. All leukemias were aggregated together.

The analysis showed an elevated childhood leukemia incidence rate in WCP in both the overall period, 1965-1986, and in the latter period, 1982-1986; but there was no elevation in the other 3 suspect census tract areas where cases had been identified. The magnitude of the elevation, as reflected in the

standardized incidence ratio, was relatively small, 1.67 and 1.91 respectively, and not statistically significant. The analysis also showed that there was no elevation in WCP in the rate of all childhood cancers combined, only the leukemia rate was elevated. Rates of cancer and leukemia in the entire county were comparable to the rates reported by other geographic areas of the national SEER program.

Researchers reported that the analysis of the leukemia rates within WCP revealed no obvious geographic clustering of cases within the area, nor was there an elevation in the rates that was specific to gender, age-group, or time-period. Analysis of leukemia rates failed to demonstrate an association with three potential risk factors: proximity to wells which pumped TCE-contaminated water, the catchment area of St. Vincent de Paul school, and proximity to the gasoline tank farms. (Flood et al., 1990)

Follow-Up of Childhood Leukemia Incidence Rate in Maricopa County Standardized Incidence Ratio of Area F to Area R for 1987-1990 (ADHS, 1993)

The purpose of this study was to calculate new incidence rates for childhood leukemia (ages 0-19 years) in a previously defined combined census tract area that comprises WCP (Area F) in Maricopa county. The comparison standard area (Area R) was comprised of all of Maricopa County, excluding the 4 suspect areas (including WCP). This study compared childhood leukemia in area F with area R for the years 1987-1990.

During the period of 1987-1990, childhood leukemia incidence was found to be no higher in area F than the standard area R. The standardized rate ratio (SRR) for area F standardized to area R for 1987-1990 was calculated to be 0.8547 (95% CI 0.4758, 1.5354). The observed number of cases for area F was 9 during this time period and 10.53 were expected. The data indicated that the incidence of childhood leukemia in WCP from 1987-1990 was much improved with an inclination toward lower rates. (ADHS, 1993)

Case-Referent Study of Childhood Leukemia in Maricopa County, Arizona, 1965-1990 (Flood et al., 1997)

This final study, a case-referent (case-control) study, was undertaken to evaluate children diagnosed with leukemia between 1965 and 1990 in Maricopa County, Arizona. The Arizona Department of Health Services administered the study and selected participants from West Central Phoenix and all of Maricopa County.

The purpose of this case-control study was to investigate possible risk factors for childhood leukemia in Maricopa County with a primary focus on the factors that might have produced the elevated childhood leukemia rate in WCP. The lack of known causes of leukemia presented fundamental difficulties for the study. The investigators looked broadly for possible risk factors because of the numerous competing etiologic hypotheses for childhood leukemia. The primary of objectives of this study were to (1) characterize the association of residence in WCP with the occurrence of childhood leukemia; (2) to assess whether the residence of cases tended to cluster around local sources of environmental

exposure; and (3) to determine if the risk for childhood leukemia was associated with exposure to pesticides, solvents, and petroleum products. The secondary objective was to determine if there was an association of childhood leukemia with other known or suspected risk factors, such as ionizing radiation, genetic and familial factors, traffic volume, cigarette smoke, drugs, electromagnetic fields (EMF), and migration patterns.

Study Methods:

Investigators collected information from questionnaires administered over the telephone to the parents of cases and referents. In addition, parents were asked to provide complete residential histories, and to document the characteristics of the homes in which they had lived. Also, in a limited number of homes, investigators collected samples of indoor air, soil, and household dust, and measured the strength of electromagnetic fields.

A case was defined as a child, age 0-19, who resided in Maricopa county when diagnosed with leukemia during the period 1965-1990, and was identified from the Arizona Cancer Registry.

Of 413 eligible cases of leukemia there were 274 for whom investigators located at least one parent and requested their participation. Of these, the parents of 222 cases (81% of the 274 locatable; 54% of the 413 eligible) actually participated in the study. These 222 participating cases were compared to 219 age and gender matched referents, that were selected by using random digit dialing of telephone numbers in Maricopa county.

The participation rate of case families living in WCP when diagnosed with leukemia was lower than the rate of participation for all cases. Of 58 eligible cases registered from WCP, there were 36 families located. Of these, the parents of 23 cases (64% of the 36 locatable; 40% of the 58 eligible) participated.

The general characteristics of the cases and referents (more precisely, their parents) were very similar with respect to race and ethnicity, income, education level, and the participation by a father and mother. However, there was a major difference in the vital status of their children. None of the 219 child-referents were known to have died, whereas 102 of the 222 child-cases had died prior to the parental interview.

Study Results:

Living in WCP: There was no difference between cases and referents in the proportion of subjects who were born in WCP. There was no difference in the proportion of time the subjects had lived in WCP or in the length of time spent in WCP prior to being diagnosed. There was no difference between the cases and referents in the proportion of children diagnosed by 5 years of age who were born in WCP. There also was no difference in the proportion of participants age 0-19 who were born in WCP. There was statistically significant evidence that children diagnosed before 60 months of age and born in WCP were diagnosed at an older age than those born outside WCP. Investigators interpreted this finding as evidence that there may have been a prenatal risk factor in WCP.

The proportion of cases and referents who shared various attributes related to living in WCP was statistically similar. There was no clear evidence

that being born in, nor living in, WCP was a risk factor for developing childhood leukemia.

Emissions and pollution of the general environment: The study results indicated that residence within 0.5, 1.0, or 2.0 miles of municipal wells contaminated with TCE at levels above the allowable maximum contaminant level (MCL), within the boundaries of one or more federal EPA Superfund areas, within 0.5, 1.0, or 2.0 miles of any Arizona Department of Environmental Quality "Water Quality Assurance Revolving Fund" sites, and within 0.5, 1.0, or 2.0 miles of any of one of 162 different sources of airborne volatile organic chemicals in Maricopa county were not risk factors for leukemia. Also, proximity to gas stations was analyzed and showed no risk of living within 200 feet or 200 yards of a station.

Having lived within 3 miles of the gasoline tank storage facility was a significant risk factor (OR = 2.2 95% CI = 1.04,). However, no participants had lived within one mile of the tank farm; those who had lived within two miles had an OR of 1.8; and living within 5 miles, but not 4 miles, was a risk factor. Thus the results appear to be inconsistent.

Solvent Exposure: Parental occupational exposure to 11 different solvents and all the solvents combined was not associated with childhood leukemia. Household exposure through hobbies was assessed by evaluating 10 specific activities. Two findings were significant, with model building as a risk factor (OR 1.9; 95% CI 1.1 to 3.4; p=0.02) and use of power tools as a protective factor (OR 0.33; 95% CI 0.17 to 0.66; p=0.002), both of which could be markers for some other factor. The "father only" analysis indicated that automobile/truck repair was

a risk factor (OR 1.6; 95% CI 1.03 to 2.50; p=0.033). The elevated risks were not linked to residence in WCP or to cases of AML.

When inferring exposure from residential characteristics and activities, two significant associations were found. Parking the car in a lot 100 feet from the residence was protective (OR 0.85; p=0.047), and children who spent less than one hour per day outdoors seemed to have elevated risk (OR 1.23; p=0.044).

Pesticides: Parental occupational exposure to pesticides was not associated with childhood leukemia. Analysis of household pesticide use only revealed an elevated risk associated with use of liquid concentrate ant and cockroach pesticides (OR 3.3; p=0.036).

Other: Other exposures that were associated with childhood leukemia included: (OR between 1.8 and 5.0) living near various industries (based on potentially biased parental recall); cigar/pipe smoking by father; child's consumption of ham, bacon or sausage, hot dogs, hamburgers, coffee, and colas; (OR between 1.0 and 1.8) cigarette smoking by father or any parent; marijuana smoking by non-parents; black and white TV use by child; and child's consumption of grapefruit or grapefruit juice and charcoal broiled meats.

Other exposures that were assessed but no association found: skin application of mosquito repellants; living near industries that emit chemicals into the air; ionizing radiation to the mother or child; family history of cancer or leukemia; vehicular traffic exposure (time commuting to school); incense burning at home; cigarette smoking by mother; various household appliances; moving or number of residences; schooling in WCP or near contaminated wells; source of

drinking water; playing in irrigation water; plastic water pipes in home; public or private swimming pool use; c-section or other birth-related operations; perinatal complications; herbicide exposures of parent while in military; parent's occupation or industry; child's consumption of oranges and orange juice, apples and apple juice, bologna etc., and milk.

Study Conclusions:

Investigators noted that there were some weak associations, as indicated above, but their finally conclusion was as follows: "The reason or reasons for the elevated number of leukemia cases from WCP observed between 1965 and 1986 was not specifically identified in this study". (Flood et al., 1997)

Follow-Up of Childhood Cancer Study in Maricopa County Standardized Incidence Ratio of Area F to Area R Maricopa County for 1991-1995 (ADHS, 1997)

This study was undertaken to compare incidence rates for childhood leukemia (ages 0-19 years) in a previously defined combined census tract area that comprises WCP (Area F) in Maricopa County. The comparison standard area (Area R) was comprised of all of Maricopa County excluding the 4 suspect areas (including WCP). This study compared childhood leukemia in area F with area R for the years 1991-1995.

During the period of 1991-1995, childhood leukemia incidence was found to be no higher in area F than the comparison standard area R. The standardized rate ratio (SRR) for area F standardized to area R for 1991-1995 was calculated to be 1.04 (95% CI 0.597, 1.812). The observed number of cases

for area F was 15 during this time period and 14.43 were expected. The data indicated that the incidence of childhood leukemia in WCP from 1991-1995 was not significantly different than area R. (ADHS, 1997)

Chapter 5

EPIDEMIOLOGIC CRITIQUE OF THE WOBURN AND WEST CENTRAL PHOENIX STUDIES

Hypotheses

The multiple studies in Woburn, Massachusetts and West Central Phoenix (WCP), Arizona advanced various *a priori* hypotheses to account for the apparent excess of childhood leukemia in these areas. However, the two regions differed starkly in the focus of hypotheses. In Woburn, hypothesis generation quickly- focused on environmental exposures related to the contaminated wells and the industriplex. Conversely, WCP studies took a much broader approach, in that hypotheses were advanced that addressed virtually all the potential risk factors for childhood leukemia. However, like the Woburn studies, WCP studies did tend to focus on environmental exposures.

Initial studies in both Woburn and WCP explored the possibilities of an epidemic of childhood leukemia through descriptive analysis of mortality and incidence data. As a related hypothesis, the possibility of residential clustering was explored by both groups. Woburn and WCP researchers also collected a variety of demographic and family medical history data for *post hoc* analysis. The Woburn investigators then turned to exploring the possible connection between exposure to contaminated drinking water, soil, and air and the onset of childhood leukemia as well as other various health outcomes. In WCP, the focus was then directed at testing as many hypotheses as possible, as evidenced by the long list of risk factors examined.

In Woburn and WCP, none of the studies conducted advanced a single *a priori* hypothesis to test the potential for an infectious origin of the excess leukemia cases. Investigators did make reference to the possibility of an infectious origin in their reviews and in some anecdotal findings, but they did not set out to evaluate this important potential causal pathway.

Case Definition

The studies conducted in Woburn and in WCP were relatively consistent in their definition of a childhood leukemia case. Cases were typically defined as individuals age 0-19 at the time of onset of leukemia and in most cases with a histiologically confirmed leukemia type. Also, residence at the time of diagnosis within the community of interest was a criterion. In the case-control studies as well as some of the descriptive studies, the specific subtypes were noted but not stratified by type. While the Woburn cases were predominantly ALL and the WCP more of a mix ALL and AML, neither group of studies treated the subtypes separately in the study, with one exception. In the final case-control study in WCP, investigators conducted their proximity to the fuel tank farm analysis by stratifying on AML and non-AML. This was the only identifiable instance in which the subtype of leukemia was considered in analysis. In all other instances the ALL and AML cases were aggregated together into the "childhood leukemia" category.

This aggregation of ALL and AML cases was likely done to increase sample sizes, but is a serious problem in the design of the studies. Both studies defined cases as children with any type of leukemia, which even included one

case of CML in Woburn, and did not stratify their analyses on subtype. As previously stated, even though many previous childhood leukemia studies have lumped ALL and AML together, ALL and AML are distinctively different in their epidemiological breakdown and thus presumably in their etiologies. For this reason, the results of the Woburn and WCP studies could have been biased toward the acceptance of null hypotheses.

The Woburn data presented the actual final breakdown of childhood leukemia cases by subtype over the study period (Table 12), while the WCP data presented the final breakdown for only a sub-sample of WCP-related participants that were utilized for the fuel tank farm analysis and sub-typed by only AML and non-AML (Table 13). However, given the population statistics for childhood leukemia, it is fair to assume that most, if not all, of the non-AML cases were in fact ALL cases, and that this sub-sample was representative of other WCP cases.

Table 12:

Childhood Leukemia Cases in Woburn from 1/69 to 8/89 by Cell Type

Cell Type	Cases
Acute Lymphocytic Leukemia (ALL)	17
Acute Myelogenous Leukemia (AML)	3
Chronic Myelogenous Leukemia (CML)	1
Total	21

Table 13:

Childhood Leukemia Cases Sub-Sample in WCP 1965 to 1990 by Cell Type

Cell Type	Cases
Acute Myelogenous Leukemia (AML)	4
Non-AML (likely all ALL)	23
Total	27

Both of the tables above clearly demonstrate that ALL comprised the majority of the cases. Thus, it would have been prudent to analyze ALL separately from the other subtypes.

Case Ascertainment

Following the previous case definition, studies in Woburn and WCP selected cases on certain spatial and temporal criteria. Both study groups selected cases from specific geographic locations, typically census tracts, and categorized them by the time period in which incidence or mortality occurred. Other than the preconceived notions of clustering that influenced the selection of certain temporal-spatial criteria, there is nothing clearly wrong with the way in which cases were ascertained. Because clustering of childhood leukemia cases, or any cancer for that matter, can occur randomly, the possibility exists that investigators in both areas could have missed important cases through inclusion of only certain specific areas. The case ascertainment in Woburn was more likely to be susceptible to this bias, since researchers focused on the residents only within the small community of Woburn, while in WCP the entire population of Maricopa County was taken into consideration.

Control Selection & Matching

Controls for both study areas appeared to be selected fairly consistently. Controls were randomly selected and community-based, and were typically matched on age and sex and occasionally on other demographic variables. Some of the controls were also matched on residential status or proximity to the case, but not all were, as this was one of the main proxies for exposure to

various environmental agents. Matching on an exposure variable is clearly ill advised, as it strongly biases the results towards the null hypothesis. Putative factors cannot be teased out if they are matched on and therefore masked in the analysis.

Ascertainment of Exposure to Risk Factors

In Woburn, the main childhood leukemia risk factors considered were related to the presence of environmental contaminants. The consumption of water from two contaminated municipal wells, Wells G and H, was the key exposure evaluated by investigators. The main contaminant of these wells that was evaluated in the studies was TCE, but other environmental toxins were also considered. Other potential exposures evaluated included such factors as family medical history, parental smoking, parental occupation, and breast-feeding.

In contrast to Woburn, the WCP studies did not concentrate on a single exposure like municipal drinking water. Rather, the WCP investigators examined virtually every potential childhood leukemia risk factor known. The investigators evaluated such factors as water quality, air quality, parental smoking, parental occupation, place of residence, solvent exposure, pesticide exposure, family medical history, ionizing radiation, types of food eaten, perinatal complications, and many more. Thus, exposure assessment was much broader in WCP than in Woburn.

The case-control studies conducted in Woburn and WCP relied heavily on proxy measures for exposure and on parental recall. In Woburn, parents of cases and controls were interviewed by trained interviewers, and in most cases

by the same interviewer, both by telephone and in person. The ideal was to conduct an interview with both parents simultaneously in-person. The interviewers were not blinded to the status of cases and controls and were likely not blinded to the study hypotheses, as they were quite narrow. Also, in the final study there was only one main hypothesis to test - exposure to Wells G and H. In WCP, trained interviewers were not blinded to the status of the cases and referents, but they were blinded to the numerous study hypotheses. WCP interviews were conducted primarily by telephone with the parents (one or more parent or a surrogate) of the study participants. In both Woburn and WCP, structured interview questionnaires were utilized to collect exposure data on the cases and controls.

The methods used by investigators in Woburn and WCP were not grossly biased, but an unblinded interviewer can introduce bias to the results. While it would be extremely difficult to blind an interviewer to the status of the cases or control, efforts should have been made in Woburn to ensure that the interviewer was blind to the hypotheses. Additionally, parental recall of exposure information was fraught with bias, both because of the time elapsed since the incidence of the leukemia and the strong preconceived notions of the parents about cause of their child's leukemia. The latter is most striking in Woburn, where many in the community had already drawn a causal link in their minds between exposure to contaminants from the well water and the onset of childhood leukemia. This bias is evidenced by the intense media coverage at the time of the investigation which subsequently led to the writing of a book on the Woburn childhood leukemia story

which was made into a 1999 feature film "A Civil Action". The media induced public bias would have made it nearly impossible to have blinded the interviewers.

In addition to interview data collected from parents, investigators also collected environmental samples and used proxy measures of environmental exposures, such as proximity to fuel tank farms or high levels of vehicle commuting in WCP and proximity to the industriplex in Woburn, to assess exposure to potential putative agents. The collection of environmental samples was most vigorously conducted in WCP, where investigators collected such things as carpet dust samples, air and soil samples, and direct magnetic field measurements within residences. The evaluation of proxy measures and environmental sampling in both Woburn and WCP was comprehensive, but little data was collected that would be useful in assessing the infectious etiology hypothesis.

Ascertainment of Exposure to Confounding Variables

In WCP and in Woburn, investigators controlled for basic demographic confounders as well as certain potential environmental confounders. Demographic variables such as age, sex, race, and socioeconomic status were matched in most cases so as to control for any covariation. Also, depending on the study hypotheses, certain environmental exposures were controlled for to determine if a specific putative risk factor was significantly associated with the outcome. The final study in Woburn controlled for numerous environmental factors in order to test the Wells G and H exposure hypothesis.

Analytic Methods and Study Conclusions

The descriptive studies in Woburn revealed that there was in fact an excess of childhood leukemia in the period 1969-1989, which was largely comprised of ALL cases. In West Central Phoenix, descriptive studies identified an excess of childhood leukemia, but stated that only AML was statistically significantly elevated. The case-control studies conducted in Woburn and WCP utilized a variety of univariate and multivariate statistical methods to analyze the data collected, but they both relied on the calculation of odds ratios based on contingency tables to present their findings. These odds ratios are potentially biased by differential misclassification through recall bias of parents of cases versus parents of controls. The parents of cases would be more likely to recall exposures, as their child's illness had caused them to closely focus on what exposures may have occurred and to look for reasons to explain the illness. Conversely, parents of controls would not have necessarily focused on particular exposures their child may have had, and they would likely be more objective in recalling exposures. For example, in Woburn parents of cases would have been strongly biased on recall of their historical exposure to water from the contaminated wells, and parents of cases in WCP would have likely succumbed to recall bias on the myriad of potential exposures they were questioned on. This differential misclassification can lead to an increase or decrease in magnitude of association and even a reversal in the direction of association which may have been the case in Woburn and WCP. This differential misclassification may account some of the seemingly spurious findings in WCP such as the association

found between grapefruit consumption and childhood leukemia. The use of these contingency tables could have also produced results biased towards the null as a result of the potential for non-differential and independent misclassification in exposure assessment. Potential for independent misclassification existed in both Woburn and WCP. In addition, the final Woburn study implemented a dose-response trend analysis to make their final conclusions, which is described below. Due to non-availability of the original data from the Woburn and WCP studies, the analytic methods utilized by the researchers and the subsequent results cannot be validated for accuracy (i.e. data cannot be re-analyzed to confirm results). Therefore conclusions made by the investigators must be viewed with caution for this as well as other reasons.

In Woburn, the final and "conclusive" study conducted to investigate the excess of childhood leukemia relied on very weak results on which to base their causal conclusions. The results were for the most part statistically insignificant, and those that were modestly significant were based on a very small case sample size of 19 and were not entirely consistent with each other. The results lacked consistency in that both an association and lack of association was found between the childhood leukemia and contaminated water. The study concluded that the incidence of childhood leukemia in Woburn from 1969 to 1989 was associated with the mother's "potential for exposure" to contaminated water (with TCE as the suspected agent) from Wells G and H during pregnancy. There are several problems with accepting this conclusion. First, the chemical trichloroethylene (TCE) has been identified as the most

common contaminant of public wells (ADHS, 1997), and the chemical is not known to be a leukemogen in mammals. Second, earlier studies in Woburn noted that the number of childhood leukemia deaths began to rise from 1959-1963 (SMR = 120), before the wells were drilled in 1964, and continued to rise in the period in which the wells were drilled 1964-1968 (SMR = 169). However, in the period following well drilling, 1969-1973, the rate was lower than expected (SMR = 50). Rates did begin to increase again between 1974-1978, but this increase occurred over ten years after the opening of Wells G and H. The increase could also have been a result of improved screening methods. Earlier research also noted that childhood leukemia mortality was not elevated during the period 1949-1958, but childhood leukemia mortality began to rise in 1959-1963. Therefore, a factor introduced during the late 1950's would be a more likely cause (MDPH, November 1981). Third, the odds ratios related to exposure to water from Wells G and H *in utero* or *in vivo* were statistically insignificant, so no direct association could be made.

Finally, the conclusion that the potential for exposure to the contaminated water *in utero* was associated with childhood leukemia in Woburn was based upon an extremely weak analysis. After finding no significant association with direct exposure to well water, investigators parameterized the cases in three exposure categories: Never, Least, or Most exposed. The adjusted odds ratios for the Least and Most categories relative to the Never group were as follows: Least (OR = 3.53; 95% C.I. 0.22, 58.14), Most (OR = 14.30; 95% C.I. 0.98, 195.60). Even though the Most category flirted with statistical significance, the

confidence interval was cavernous. Lacking statistically significant results utilizing the trichotomous parameterization method, investigators turned to trend analysis, finding a slightly significant trend across the three groups. Basing a conclusion on a barely significant trend analysis of categorical variables that were not statistically significant on their own, calls that conclusion into question. The investigators also appear to have misused trend analysis by basing the trend on only three data points. Consequently, I assert that the "conclusive" findings of the MDPH in Woburn are anything but conclusive.

The findings in final case-control study in WCP are also based upon somewhat inconclusive evidence. First, the investigators took an unfocused approach in the study of the childhood leukemia cases in WCP and surrounding Maricopa County. Investigators set out to test virtually every hypothesis they could think of, with the exception of the infectious etiology hypothesis. Thus, it is not surprising that they found a few weak associations. Given the number of variables evaluated and analyzed, one would expect to find a few such associations just by random chance, due to the inherent probability of detecting errant associations in data analysis. The investigators made multiple comparisons which can increase the overall probability of incorrectly rejecting a null hypothesis, as statistical significance includes a probability of error (e.g. $p = 0.05$ or 5% chance of error). The weak associations identified were also not necessarily biologically coherent, consistent with previous research, or intuitive. For example, the finding that living within 3 or 5 miles of the gasoline tank farm was weakly associated with childhood leukemia fails for the several reasons. (1)

It is inconsistent that there was less risk associated with living within 2 miles versus 3 miles and that there was a risk for living within 5 miles but no risk associated with living within 4 miles of the tank farm. (2) While investigators did separate the cases into AML and non-AML in this particular analysis, their findings were based on the aggregated childhood leukemia cases. (3) Benzene is the leukemogenic agent in gasoline, but it has only been associated with AML and not ALL, as noted earlier in this paper, and the findings were based on a large number of ALL cases. The WCP case-referent study also had spurious findings. Parental smoking by the father was associated with leukemia, but smoking by the mother was not associated. The finding that use of power tools was a protective factor (OR 0.33; 95% CI 0.17 to 0.66) is seemingly nonsensical, although it could be that this is some sort of marker for another protective factor such as high socioeconomic status. These examples, along with the weak association found with random food products and other risk factors, demonstrate the shortcomings of examining a childhood leukemia cluster by making multiple comparisons.

While studies in Arizona apparently took far too broad an approach to examining the excess of leukemia among children in WCP, it is also clear that studies in Woburn too quickly focused on specific environmental exposures, to the detriment of other potential putative risk factors.

Chapter 6

CONCLUSIONS

Descriptive & Analytic Epidemiological Methods: Woburn & WCP Studies

The CDC developed a systematic and integrated approach for responding to reports of cancer or other disease clusters in 1990. The method involves four basic stages as follows:

Stage 1. Initial Contact and Response - The purpose of this preliminary stage is to collect information from the person(s) or group(s) first reporting a perceived cluster in a specific location.

Stage 2. Assessment - This stage involves the evaluation of two concurrent issues: (1) whether an excess has actually occurred and (2) whether the excess can be linked etiologically to some exposure. The first issue must be satisfactorily evaluated in order to proceed to the second issue, which may or may not be clear at this stage in the cluster investigation.

Stage 3. Major Feasibility Study - The purpose this portion of the investigation is to determine the feasibility of performing an epidemiologic study linking the health event and a specific putative exposure.

Stage 4. Etiologic Investigation - This final phase of the investigation, which is followed by analysis of the data collected, is intended to elucidate the potential disease-exposure relationship. This step is a standard epidemiologic study, for which all the preceding effort has been preparatory. (CDC, 1990)

Evaluating the childhood leukemia studies in Woburn and West Central Phoenix (WCP) in light of the CDC's cancer cluster guidelines reveals some of the strengths and deficiencies of these studies. Health officials in both Massachusetts and Arizona apparently satisfactorily implemented Stage 1. There was a concerted response to the allegations of the presence of childhood leukemia clustering in these areas. After proceeding to the assessment phase in Stage 2 both Woburn and WCP investigators employed basic descriptive techniques. The study of the distribution of childhood leukemia in Woburn and WCP was conducted through evaluation of person, place and time relative to clustering. The investigators did satisfactorily identify the types of childhood leukemia cases and the spatial-temporal relationship of these cases in determining if excesses of childhood leukemia did in fact exist. The investigators in both study groups conducted multiple analyses of both childhood leukemia incidence and mortality to determine the nature of the clustering. After succeeding in determining the presence of elevated ALL rates in Woburn and elevated AML rates in WCP, the methodology began to break down.

It is apparent that as the investigators were in the analytic planning phase, equivalent to Stage 3, a major bias was introduced. In order to make the studies more feasible, investigators increased the sample sizes by aggregating ALL, AML and even CML into the definition a childhood leukemia case. This misclassification of caseness would later diminish the quality of the study results as these subtypes of childhood leukemia have distinctive etiologies.

The subsequent etiologic investigation, Stage 4, in both Woburn and WCP went even further astray of sound epidemiology and science that one would find in most peer-reviewed studies. In spite of the advanced nature of the infectious etiology hypothesis at the time the final conclusive studies were being conducted, there was not a single *a priori* hypothesis to examine the potential of an infectious origin. The investigators were also prone to inductive reasoning in quickly focusing on environmental exposures to the detriment of other potential putative agents. This was most pronounced in the Woburn studies, that were very narrowly focused on the well water contamination. Not only was this a very narrow approach to investigating the leukemia cluster, but it was also bad science in that there was no biologically coherent evidence to suggest that TCE exposure could even be leukemogenic.

Investigators in both Woburn and WCP failed to take a deductive approach with strict hypothesis formulation and testing, and they also failed to utilize statistical and mathematical modeling techniques (see example on page 101) that could have elucidated an undetected association. The haphazard hypothesis testing in WCP and the narrow and unscientific hypothesis testing in Woburn led to truly inconclusive results.

Support for the Infectious Etiology Hypothesis: Literature Review

Kinlen asserted that:

1) The influx of individuals into an isolated community produces conditions in which leukemia is more likely to occur.

2) Isolated communities (susceptible individuals) newly exposed to migrants (infected individuals) from elsewhere could experience an unusual exposure to some hypothetical infectious agent or to otherwise common infections for which no immunity happens to exist.

3) This exposure, in turn, increases the risk of childhood leukemia.

4) Consequently, isolated communities may experience "mini-epidemics" because they are too small to maintain common infections in endemic form, which could lead to a cluster of ALL (Kinlen, 1988).

Greaves asserted that ALL may be due to two separate genetic events:

1) spontaneous mutation of a pre-B-cell in utero

2) proliferation of the mutated pre-B-cell when exposed to a later antigenic challenge (i.e. an infectious agent) (Greaves, 1988)

Freda Alexander advanced an Aberrant Response Model (ARM) that unifies the Kinlen and Greaves models. The ARM states that a substantial portion of ALL cases arise as a rare host response to certain patterns of exposure to common infectious agents. (Alexander, 1993).

Support for an infectious etiology hypothesis was identified in numerous studies. An association between population mixing and childhood leukemia was observed in Hong Kong (Alexander et al., 1997), Greece and Italy (Kinlen and Petridou, 1995), and the United Kingdom (Kinlen and Hudson, 1991) (Langford, 1991) (Alexander et al., 1990) (Alexander et al., 1992) (Alexander, 1992). Kinlen also identified increased childhood leukemia trends in cities within the UK that had greater commuting levels (Kinlen et al., 1991) (Kinlen, 1993). Recent

evidence has also supported the infectious etiology by indicating that childhood leukemia epidemics arise regularly in moderately densely populated areas and also sporadically in areas which are somewhat less densely populated (Alexander et al., 1999). Also, in a more recent study there was highly significant evidence of space-time clustering based on place of birth and time of diagnosis, particularly for ALL cases age 0-4 years (Birch et al., 2000).

The potential infectious etiology of childhood leukemia is additionally supported by observations of birth order and parental immune system function (James, 1990) (Meelemkjaer, Alexander and Olsen, 2000). The role of viral agents in the development of other human cancers and suspected ALL putative infectious agents also supports infectious etiology hypothesis (Morris, Eddleston and Crook, 1995) (Toren et al., 1996) (McCool, 1996) (Smith et al., 1997) (Davies and Ross, 1997).

Support for the Greaves model has been found in the growing body of evidence around the possibility of in utero infectious origin with the identification of the potentially antigen induced non-hereditary TEL-AML1 gene fusion abnormality in children with ALL (Greaves et al., 1997) (Felix, 1999) (Wiemels et al., 1999) (Magalhaes et al., 2000) (Knox et al., 1983). Leukemogenic animal models of infectious origin have also been elucidated (Goldman and Jarrett, 1984).

Evaluation of individual causal criteria demonstrate the rigor of the infectious etiology in light of the evidence in the literature. The first criteria of time order (infection precedes ALL) seems to be met in many of the ecological

studies. The proxies for exposure, such as population influx and population mixing, have been demonstrably shown to precede "epidemics" of ALL in children; and there is evidence of dose-response relationship through identification of greater risk in areas with much higher population increases over a defined period (Kinlen, 1988) (Kinlen et al., 1990) (Alexander et al., 1990) (Kinlen & Hudson, 1991) (Kinlen et al., 1991) (Alexander et al., 1991) (Langford, 1991) (Alexander, 1992) (Alexander, 1993) (Greaves & Alexander, 1993) (Kinlen & Petridou, 1995) (Alexander et al., 1996) (Alexander et al., 1997). These same studies have an inherent weakness however, in that the applicability of the findings to the individual level would be fallacious. The ecological nature of the previously noted studies, while they demonstrate the potential mechanism of an infectious origin, precludes the necessary conclusion that an individual case of ALL could have resulted from an infection linked to population mixing. Nevertheless, the consistency of the ecological studies within themselves and with other biological infectious models would indicate that the hypothesis is valid.

The biologic and epidemiologic evidence that supports the infectious hypothesis has been most clearly demonstrated in animal leukemogenic models and other human cancer models (Morris, Eddleston and Crook, 1995) (Toren et al., 1996) (McCool, 1996). The coherence and consistency of the studies and evidence withstanding, the strength and specificity of association between infection and childhood ALL does not provide conclusive support for the hypothesis. The fundamental problem is the lack of understanding of the potential infectious agent(s) that precipitates the disease. Without knowing what

the specific agent(s) is, no specificity of association can even be considered, and likewise strength of association is nearly non-existent when the specific exposure is a mystery. The continued research to identify a specific agent(s), such as the JC virus or an EBV-type virus, should rectify this in the future.

The other concern from the hypothesis supporting studies is the laboratory-based studies. Sample sizes in these studies are critically lacking. Reliance on very few subjects has provided the evidence we have to date on potential agent(s) and possibilities of in utero exposure (Smith et al., 1997) (Greaves et al., 1997) (Felix, 1999) (Wiemels et al., 1999). However, while we lack conclusive evidence of specific infectious agents, the hypothetical modeling of ALL clusters when certain population mixing criteria have been met seems to intuitively point a causal finger at an infectious origin.

Support for the Infectious Etiology Hypothesis: Woburn & WCP Studies

Review of the study results from Woburn and WCP indicate that there is at least some anecdotal evidence in support of the infectious etiology hypothesis present in these reports.

In Woburn, one of the earlier studies revealed that four of the ALL cases to date had been born in the same 6-month period (CDC, 1981). This indicates that there was potential for some common *in utero* exposure. While investigators in Woburn would have interpreted this as the potential for exposure to some sort of toxin, it could also be argued that the *in utero* exposure could have been an antigenic challenge in concordance with Greaves' hypothesis. Another finding in Woburn that potentially implicates a challenge of the child's immune system was

the statistically significant association identified between developing childhood leukemia and being breast-fed as a child (OR = 10.17; C.I. 1.22, 84.58) (MDPH, 1997). At first glance it may seem counter-intuitive that breast-feeding would be a risk factor, in that if there was an infectious agent responsible for the cases of ALL, breast-feeding should be protective as a result of the antibodies passed from mother to child. However, since the infectious etiology of ALL could be the result of a combination of antigenic challenges or even a lack thereof, it is plausible that breast-feeding could increase risk by reducing the necessity of the child's immune system to respond to new antigenic challenges. In this scenario, the antibodies conferred to the child from breast-feeding may actually make the child susceptible to leukemogensis because the child did not uniquely experience the antigen or antigens and develop antibodies on their own.

In the WCP studies it was found that children who spent less than one hour per day outdoors seemed to have an elevated risk for childhood leukemia (OR 1.23; p=0.044) (ADHS, 1997). This finding suggests a potential lack of antigenic challenges as a child, or at the theoretical critical times, due to minimal mixing with peers through playing outside. This finding could also be looked at from another direction by saying that the child would experience more opportunity for exposure to potentially leukemogenic infectious agents due to spending more time indoors in crowded situations with less ventilation. Another interpretation of this result, from an infectious etiology point of view, would be that the child is generally less healthy due to a more sedentary lifestyle (or sedentary childhood could be a marker for a sickly child who could not go out to

play), which could make the child's immune system more susceptible to an infectious agent.

Admittedly, these findings and the subsequent interpretations of them are anecdotal and conjectural, but this new approach could lead to future hypothesis generation in the exploration of the infectious etiology hypothesis.

The Infectious Etiology Hypothesis - Evaluation of Listed Objectives in Light of Woburn and WCP

2.1) Evaluate if Woburn and West Central Phoenix were relatively isolated from newcomers and did not experience a great deal of population mixing prior to the ALL epidemic.

This hypothesis was not supported by any information or data collected within the Woburn and WCP studies. The two communities are both suburban and quite close to major urban centers, so it is unlikely that indigenous residents could have been isolated to any appreciable extent. The City of Woburn currently only has 35,943 residents, but it resides in Middlesex County, which has a population of 1,417,868. Likewise, WCP is within Maricopa County, which has a population of 2,696,198. Thus, it is unlikely that either community was isolated prior to the excesses of childhood leukemia in the late 1960's.

2.2) Evaluate if Woburn and West Central Phoenix experienced (a) an influx of newcomers and (b) experienced increased incidence of ALL in children (age 0 to 19) following an influx of newcomers.

(a) There were no data collected or evidence available to suggest that an appreciable influx of newcomers took place prior to the increases in ALL

incidence in WCP. However, in Woburn there was a significant increase in population between 1940 and 1960. The population increased by 58% in this two decade period, jumping from 19,751 in 1940 to 31,241 by 1960. Presumably, the majority of this increase was a result of urban dwellers in Boston and other metropolitan areas relocating to a more rural location. (b) A significant increase in ALL did occur in Woburn, but only AML was significantly increased in WCP compared to national averages.

2.3) Evaluate if Woburn and West Central Phoenix experienced significant mixing of newcomer and indigenous populations prior to and during the elevated incidence of ALL in children (age 0 to 19).

No data were available in the subject studies to support this hypothesis, and there is no way to determine if newcomers did mix with indigenous populations, as these two groups are not quantifiable. However, a crude proxy for mixing in general is the current population density. In Woburn, there are 2,835 people per square mile and in Maricopa County there are 293 people per square mile (this number is low due to the large land mass of counties in Arizona). Thus, in Woburn it is reasonable to assume that a fair amount of population mixing occurs and has occurred in the past. Also, in 1960 the Woburn section of route 93 opened which allowed more commuting and influx of non-Woburn residents. This too would have likely led to greater population mixing than previously experienced and this occurred prior to the epidemic of childhood ALL. In WCP it is also likely that population mixing does and has occurred much more than in rural areas.

2.4) Evaluate if the cases of ALL occurred primarily in children (age 0 to 19) born in Woburn and West Central Phoenix and whose parents were indigenous to the community (susceptibles) or vice versa in the case of susceptibles moving into an infected population (urban to rural or rural to urban).

The data from the final Woburn study neither support nor refute this hypothesis. At least 10 of the 21 cases of childhood leukemia were born in Woburn. This is based on the number of cases that were exposed to water from Wells G and H *in utero*, but it does not rule out the possibility that the remainder of the cases were born in other areas of Woburn. Data from the final case-control study in WCP does not support this hypothesis in that only 10 of 23 cases diagnosed in WCP were actually born in WCP. Of course it is not specified what number of the 10 born in WCP or the 13 not born in WCP were actually ALL cases. Also, these 23 cases were not all of the cases in WCP as they were only the cases used in one of the residential comparisons (this was the only source of this type of data in the WCP studies).

2.5) Evaluate if the increased incidence of ALL in children (age 0 to 19) Woburn and West Central Phoenix was a result of an aberrant response to an infectious agent(s) (*in utero* or *in vivo*) introduced by the newcomers.

This hypothesis is not generally supported by any of the study results, with the exception of the previously noted evidence under the "Support for the Infectious Etiology Hypothesis" heading.

2.6) Evaluate whether susceptible indigenous children exposed to the infectious agent(s) at the ages of 3-4 were more likely to develop ALL according to the typical peak in ALL incidence at that age.

This hypothesis does have some support from the Woburn and WCP studies. In Woburn, 9 of the 21 childhood leukemia cases (43%) occurred in the 0-4 age group. This was the largest percentage for any of the 5-year age groups (Table 14). In WCP, there were 18 childhood leukemia cases identified that were born in WCP, and of these seven (39%) were diagnosed at the age of 3 or 4 (Table 15).

Table 14:

Childhood Leukemia Cases in Woburn from 1/69 to 8/89 by Age Group

Age at Diagnosis	Cases
0-4 years	9
5-9 years	4
10-14 years	7
15-19 years	1
Total	21

Table 15:

Childhood Leukemia Cases Born in WCP 1965 to 1990 by Age

Age at Diagnosis	Cases
0 years	0
1 years	1
2 years	0
3 years	2
4 years	5
5 years	1
6 years	0
7 years	2
8 years	1
9 years	1
10 years	1
11 years	1
12 years	0
13 years	1
14 years	0
15 years	0
16 years	0
17 years	1
18 years	1
19 years	0
Total	18

Conclusions and Recommendations

To date, no one has able to demonstrate the Kinlen model of rapid exposure of susceptibles, observed in the UK, Hong Kong, Italy and Greece, or the inverse of it in North America. It could be that there are cases of infected individuals moving into susceptible communities in North America as well, but it is quite possible that infectious model follows the inverse approach in North America. It would appear that both WCP and Woburn were close enough to urban centers that, rather than the communities having a high proportion of susceptibles at a critical age for leukemogenesis, they could have had a high

proportion of the leukemogenic infection(s) at a non-critical age. Thus new age-specific susceptibles could have moved into these communities and later developed the aberrant response of ALL. This model seems to fit well with the Greaves model of an *in utero* antigenic exposure or exposures. Clusters of cases are observed in suburban areas, to which susceptibles from rural locations would be likely to migrate. Comprehensive population-based studies and mathematical modeling could make answering these questions possible. The following description of my proposed mathematical simulation model is an example of the epidemiological techniques that could have been utilized in Woburn and WCP and that can be implemented in the future:

The mathematical simulation model would be developed to mirror the processes of a typical infectious agent. The reference agent would be the Epstein-Barr Virus, which is hypothesized to be similar to the ALL agent if not the actual agent. The model would generate an over-representation of cases in the 2 to 5 range to mimic the known ALL peak incidence. This would be done to determine if the modeled peak coincides with the actual peak in the population given the assumed time of exposure. The model would assume that rural populations would have low level endemnicity of the EBV-type agent and urban populations have high endemnicity of the EBV-type agent. This allows the urban children to be infected prior to the critical age (1-3 years) that predisposes a child to ALL, while rural children remain susceptible. This would allow the model to determine age-specific susceptibility.

The model would be compartmentalized to predict the dynamic interaction between parasitic and host populations. The host population would be segregated into susceptible, latent but not yet infectious, infected, and recovered-and-immune individuals. The basic reproductive rate, known threshold host densities, and direct & indirect transmission routes of EBV would be factored into the mathematical model as well. The model would also take into consideration the threshold host densities for maintenance of EBV in a population through deterministic means (influx of population) and stochastically from either epidemic or endemic fade-out.

Ultimately the model would consist of dynamical equations that would produce a predicted outcome of ALL cases based on the relevant epidemiological and demographic parameters selected for the analysis. These parameters include but are not limited to the following: baseline community population, childhood ALL Incidence statistics, percentage of population increase in 5-year increments, percentage change in population density, number of births and families in a community, poverty level and per capita income, education level, and commuting levels. The model would conform to the guidelines set forth in Infectious Diseases of Humans: Dynamics and Control by Roy M. Anderson and Robert M. May, with specific reference to Chapter 6 (The basic model: dynamics).

The mathematical simulation model would produce an expected ecological outcome and a statistical comparison would be made between the expected and observed ecological outcome. The comparison for the observed cases in the

final analysis would be the predicted "cases" according to the mathematical model. If no significant difference exists when the observed and predicted data are compared then it would be interpreted as support. If a difference does exist then results would be viewed as support for the null hypothesis rather than merely a conclusion of a fault in the model. The use of this or other mathematical models could significantly advance the elucidation of the childhood ALL infectious etiology hypothesis in North America and elsewhere.

In addition to demonstrating the need to use modeling to evaluate the infectious etiology hypothesis, the childhood leukemia studies conducted in Woburn and West Central Phoenix illuminate the shortcomings of cluster analysis. Childhood leukemia cluster studies are hampered by deficient sample sizes for statistical analysis, as well as strong sociological biases within the community and political pressures to find an answer quickly. Also, childhood leukemia cluster analyses in Woburn, WCP, and elsewhere have all failed to identify a single putative agent. To circumvent these negative aspects of cluster analysis, large population-based case-control studies must be implemented to increase sample sizes and test the infectious etiology hypothesis. Additionally, the erroneous results from making multiple comparisons in the WCP studies demonstrates the need to generate strict *a priori* hypotheses for testing in future studies. Future studies must also avoid aggregating ALL with AML and other leukemia cell types, to account for the separate and distinct etiologies.

The Woburn and WCP clusters were exhaustively studied for over a decade and at great expense, but no truly conclusive results were obtained. The

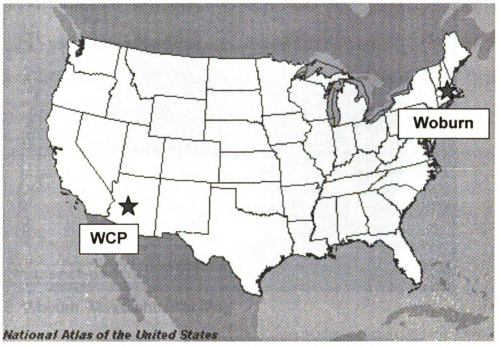
data from these studies should therefore be made available to other researchers for viable hypothesis testing. The datasets should not be unavailable, rather they should be downloaded to some sort of centralized clearinghouse such as SEER. Future studies need to be directed away from specific clusters and need to focus on the population as a whole. Careful retrospective and prospective studies need to be undertaken to assess the potential infectious etiology of ALL, with comprehensive collection of data on residence history, mobility, population density, and level of interaction or mixing with others in the community. This will facilitate the analysis of the infectious etiology of childhood ALL.

APPENDICES

APPENDIX A

LOCATION OF WOBURN, MA AND WCP, AZ ON U.S.MAP

Figure 1: Location of Woburn, MA and West Central Phoenix, AZ on U.S. Map



APPENDIX B

MAPS OF WOBURN, MASSACHUSETTS

Figure 2: Location of Woburn, MA on Massachusetts Map

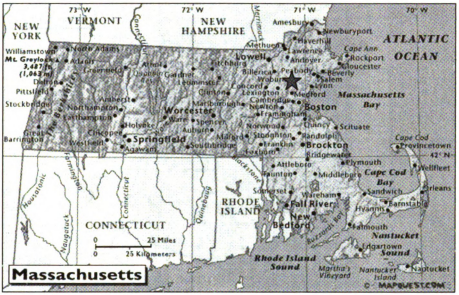
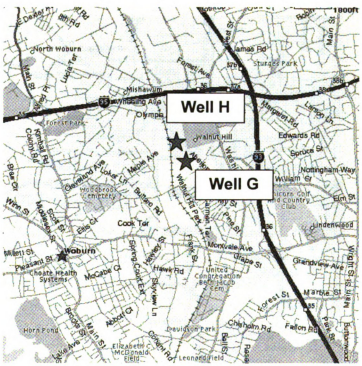


Figure 3: Woburn, Massachusetts Map

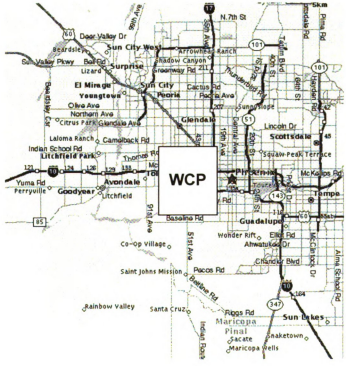


APPENDIX C

MAPS OF WEST CENTRAL PHOENIX, ARIZONA

Figure 4: Location of West Central Phoenix, AZ on Arizona Map

Figure 5: West Central Phoenix, Arizona Map



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