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Etiology of leukemia

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THE ETIOLOGY OF LEUKEMIA

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This thesis was inspired by the memory of

Donna Canar Bernstein who was victimized by Leukemia...

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VERITAS PER RATIONEM

TRUTH THROUGH REASON.....

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The Purpose of the Thesis

As the title of this paper might suggest, the purpose of this thesis is to determine a cause for leukemia. This was my original intention before I undertook the writing of this monograph. I first delved into the field of leukemia by talking to patients and relatives of patients with leukemia in hopes of finding some common link with all these cases. Admittedly, I was often times discomfitted in my trying quest; and at times felt that perhaps leukemia evolved spontaneously. This thought frightened me, and in fact caused me to think back to the days when Pasteur resolved the question of spontaneous generation by means of a very simple experiment. I could not think of anything so ingenious to relieve my frustrations.

I was driven to read books on heredity, and studies attempting to show the familial characteristics of leukemia. I was not placated to say the least.

I began to read current research reports in the field of leukemia and became impressed with the incrimination of viruses in certain animal leukemias; such as, mouse and chicken leukemias. I studied the behavior of the viruses and was very much impressed with their close link with intracellular particles and with their analogous behavioral patterns and their responses to the behavioral patterns and responses of genetic material, per se.

Could this be the key in my search for an answer?

I went back and analyzed my interviews with leukemic patients, and attempted to substitute an infectious agent for the missing link. The picture seemed to focus more clearly in my own mind.

With this seeming revelation, I reread reports and literature on leukemia and substituted this infectious agent for the missing link. It seemed feasible and at times too simple an answer, and yet it fitted the picture.

In the first half of this thesis I will give a summary of my literature review, and in the second half I will present the results of a questionnaire which was sent to a series of leukemic patients in the hopes of realizing the initial purpose of this thesis.

Part I. Review of the Literature

Before undertaking the study of leukemia, I proceeded to question patients as to their living conditions and exposures to external factors which may have played some part in the contracting of leukemia. There was no definite pattern unless one was inclined to incriminate an infectious agent in the cause of leukemia, transmitted perhaps by means of animals, food, or even through reproductive channels.(As may be implicated in the rare case of congenital forms of the disease.)

My first hint of a possible association with foods and animals came when I noticed the high incidence of leukemia in various nations primarily dependent on cattle and dairying in providing for the countries economy. I also became impressed with the low incidence of leukemia in countries with a low economy compared to that of the United States, such as Japan and India, areas where statistics had earnestly been collected. There has been a trend to associate leukemia with individuals in the higher income brackets, and the conclusion has usually been that this was due to the better medical care received by these people, and subsequently better diagnosing. This way of thinking doesn't bear out in the case of the Japanese, who have carried on an intense study of leukemia ever since the Hiroshima and Nagasaki atomic bomb explosions. A look at this research in conjunction with a review of radiological influences

on leukemia will be discussed later. Even with this stepped up investigation, Japan has one of the lowest incidences of leukemia known today.

To give the reader an idea of the incidence of leukemia and aleukemias in the world, I will present the following chart on the mean annual death rates of these diseases for the years indicated.(See Chart I.)

Let's look at the general epidemiological reports as given by the World Health Organization.(2)

Age-standardized rates indicate that leukemia mortality is high in the white population of the U.S.A., in Denmark, and in the Jewish population of Israel, and relatively low in Finland, France, Ireland, Northern Ireland, Italy, and Japan.

In New York City, Leukemia mortality is about twice as high among the Jewish population as among either Catholics or Protestants.

Others have recently noted that leukemia mortality among the Jewish population of Israel after the age of 45 was lower for Afro-Asian born, than for the European born or native born Israelis.

In the U.S.A., Minnesota has had for some time the highest leukemia mortality of any state, this appears to be the peak of an area of generally high mortality stretching across the north of the country west of the Mississippi. Rates are generally low in the south-east. Among the eastern states, Vermont has an unusually high rate. Correlating this with a few facts

Chart I

Mean annual death-rates from leukemia and aleukemia by sex in 1950-52 and 1956-58(1)
(Rates/100,000 live born)

Country	Year	Males(all ages)	Females(all ages)
America			
Canada	1950-52	5.1	4.1
	1956-58	6.2	4.6
U.S.A.			
total	1950-52	7.1	5.1
	1956-58	8.0	5.7
white	1950-52	7.5	5.4
	1956-58	8.4	6.0
non-white	1950-52	3.9	2.8
	1956-58	4.8	3.3
Asia			
Japan	1951-53	2.0	1.5
	1956-58	2.9	2.1
Europe			
Denmark	1950-52	7.3	5.1
	1956-58	9.1	6.6
Finland	1950-52	3.5	3.4
	1956-58	5.4	4.8
France	1950-52	4.6	3.4
	1956-58	6.5	5.1
Gr.Fed.Rep.	1950-52	4.8	3.5
	1956-58	6.2	4.7
Ireland	1950-52	3.5	2.5
	1955-57	4.7	3.3
Italy	1950-52	4.0	2.9
	1956-58	5.2	3.9
Nether-	1950-52	5.3	4.2
lands	1956-58	6.6	5.3
Norway	1950-52	6.1	5.1
	1956-58	7.8	5.8
United King.			
Eng.&Wales	1950-52	419	4.0
	1956-58	5.9	4.7
Scotland	1950-52	4.5	3.8
	1956-58	5.5	4.2
Sweden	1950-52	7.2	5.3
	1956-58	8.1	5.8
Switzer-	1950-52	5.9	4.5
land	1955-57	6.6	4.7
Oceania			
Australia	1950-52	5.1	4.1
	1956-58	5.8	4.7
New Zea-	1950-52	6.3	4.2
land	1955-57	7.3	6.0

from the Encyclopedia Americana, I found that the regions in which the greatest amount of milk is produced rank in the following order;

The East North Central States
The West North Central States
North Atlantic States
South Central States
Western States
South Atlantic States

Wisconsin produces more milk than any other state(The total yearly production being nearly twice as much as in Minnesota which ranks second.) New York is third in total production, followed by Iowa, Illinois, California, Michigan, Pennsylvania, Texas, Missouri, Kansas, Nebraska, North Dakota, Oklahoma, Tennessee, Kentucky, and South Dakota, in the order named.

Another report studied areas with standardized mortality ratios for leukemia and found the following states to be significantly above the U.S. average;(4)

Minnesota, Montana, Idaho, Nebraska, New York, Kansas, Iowa, Wisconsin,&California.

Montana and Idaho are not listed as being high in Dairy production as are the other states; but checking into the industries in these states, I found that both states are used widely for grazing purposes, and Idaho has an active dairy industry in its own right.

We have seen that there is a high incidence of leukemia

in the Jewish population of Israel and New York. If I may embrace my previous premise, and analogize this with the fact that some authors have stated that one of the reasons for a high incidence of coronaries in these people is probably due to their high intake of dairy products, could I say that this same correlation also exists in the instance of leukemia?

I will not analyze every state or country in this study, but will choose Denmark to discuss, since it has one of the highest incidences of leukemia in the listings by the W.H.O.

A lot of study is coming out of Denmark in regards to Bovine Leukosis, since this disease is so prevalent there, and since Denmark's population is so highly afflicted with leukemia itself.

I would like to begin this discussion with a brief summary of a series of articles from Modern Veterinary Practice by Dr. Hans Jorgen Bendixen.(5,6,7,8,9)

"One type of bovine leucosis shows a typical enzootic occurrence, a neoplastic tumorous disease caused probably by a transmissible agent, probably of virus nature. Under Danish conditions, this type is met in about 80% of the reported cases of leucosis. The other 20% of the cases show a typical sporadic occurrence, and give no evidence of transmissibility, among these are leucosis among young animals and the so-called skin leucosis of adult animals.

The disease which is, as a rule, demonstrable hematologically, runs a relatively chronic course and may last for the whole lifetime of the animal without visible changes of functional troubles. If, and when, the disease passes into the clinical phase, it runs a fatal course of varied duration, depending on the speed of growth of the proliferations. Histologic examination will reveal a proliferation of the cells belonging to the reticulohistocytary series, a reticulosis.

The disease may run a very acute course, for example, in splenic rupture as a sequel to gross leukotic infiltrations in that organ. Internal hemorrhage, followed by sudden death, may occur without the animals having shown any preceding signs of illness.

Generally, however the course is more prolonged. Subacute cases may run for several days, and chronic cases for months. Not infrequently, the specific alterations, tumerous changes in lymph nodes and palpable organs, for example, develop relatively early so that the diagnosis can be made without difficulty.

However, in 60% of the cases in our material the practicing veterinarian could find nothing but nonspecific symptoms on his first examination, mainly weariness, inappetence, and emaciation."

I would like the reader to keep the above statistics and remarks well in mind. Why, may you ask, am I dwelling on this

form of leucosis? If the reader is alert, he will see a clinical course which is astonishingly similar to human forms of these diseases.

And again you may ask, why so much emphasis on the early findings of this disease and the late findings? It may be enlightening to the reader to know that the only way lymphomatous diseases are detected, prior to marketing of the animal in Nebraska, amd most likely in other states as well, is by the gross finding of enlarged lymph nodes in the suspected animal. What about the animal which doesn't manifest these nodes? More than likely this animal goes to the dinner table. It was noted that in carcasses condemned in 1962 in the U.S. among the cattle, calves, sheep, lambs, and swine, that gross malignant lymphoma was found in 6,241 animals; cattle predominating with 3,786 cases. What about the various occult forms of the disease, or those forms which get by the inspectors unrecognized?

For Denmark as a whole 4.1 cases of leucoses per 100,000 head of cattle per year are found. (This incidence is very close to the incidence which can be calculated from figures given for the U.S.)

I would now like to continue to quote from Dr. Bendixen's articles.

"The lymphatic system is most often the site of tumorous changes. In 98% of the cases in the medical clinic, one or more

swollen lymph nodes have been observed on clinical observation. However, universal enlargement of lymph nodes has been observed in only 58%. Swollen lymph nodes have been found in nearly all leukotic calves submitted to the medical clinic. Universal enlargement is relatively less frequent in the adult animal.

In countries(in Denmark) of Western Zealand, Lolland, and Eastern Jutland an incidence of up to about 40 cases per 100,000 head of cattle per year is characteristic.

In leucosis herds where a new breed is introduced, leucotic cases will soon be found in both breeds.

It can be concluded that earlier theories of the cause of leucosis, stating that this disease is primarily caused by hereditary, toxic, or nutritional disorders, cannot be confirmed by Danish investigations. On the contrary, bovine leucosis in Denmark seems to occur in such a way as if it were an enzootic of a very chronic nature.

It is known that from 2 to 6 years may elapse, from the time of the purchase of animals in a leucosis herd, before the first clinical cases are found."

If one were to look at a map of Denmark and keep in mind the following points,

I. In countries of Western Zealand, Lolland, and Eastern Jutland an incidence of up to about 40 cases per 100,000 head of cattle per year is characteristic.
II. The W.H.O. states that in Denmark leukemia incidence rates are higher in the provincial towns than in the rural areas.

he will notice that Copenhagen, the capital, is surrounded on the north by Zealand, on the south by Lolland, and to the west by Eastern Jutland; and that the largest provincial towns are in East Jutland.

In order to emphasize the far-reaching effects of such findings, I would now like to quote a few excerpts from the Encyclopedia Americana.(11)

"Despite not having especially fertile soil or advantageous climate, Danish agriculture is highly developed. Of the country's total area, 75% is cultivated, and 30% of the population is engaged in farming.

Cattle and poultry raising rank most important in agriculture.

Under normal conditions Denmark's foreign trade is of considerable importance. The chief exports are bacon, butter, eggs, cattle, and fish.

Goods of agricultural origin account for 75 per cent of the exports."

In the closing discussion from Dr. Bendixen's articles he states;

"The infectious theory is confirmed by transmission experiments by Gotz, et al. 1956 and by the isolation of a virus from a leucosis cow reported by Hjarre, 1958 and Thorell 1958. Control experiments are, however, not yet terminated.

Papparella, 1959 and Montemagno, 1959 have reported that

they are able to grow a virus in hen eggs inoculated with material from cattle suffering from leucosis.

It is estimated that the disease is spreading rather slowly to districts where it was formerly unknown. Communications from Western Germany, Eastern Germany, and Sweden show that the incidence may reach a considerably higher level."

Since I've spent a lot of time on the potential role of the virus in bovine leukosis in Denmark and its ramifying implications, I would like to direct my thoughts now to a more familiar region, right here in the United States. During a recent seminar at Ames, Iowa in September of 1962, a talk given by Ray M. Dutcher Ph.D. went something as follows;

"The bovine lymphosarcoma is believed to be caused by a virus. One means which appears to be present in the spread of the disease is the exchange of herd stock.

The group at the University of Pennsylvania school of Veterinary Medicine are of the opinion that an agent is present in bovine lymphosarcoma which is toxic to the chick embryo. Reactions on the standard tissue cultures have been observed which are similar to those noted when a known pathogenic viral agent is introduced.

Tissue cultures of bovine lymphosarcoma have been grown and a zone of perinuclear clear areas have been uniformly noted. Under phase contrast microscopy these clear areas have been

found to contain RNA material.

Excluding epidermoid tumors of the eye, the lymphomas are the most common neoplasms of cattle, sheep, and dogs.

In a type of sarcoma (malignant lymphosarcoma) which occurs among children in Central Africa, much work has been done concerning a suspected insect vector."

I would like to interject here and cite the above article mentioned by Dr. Dutcher.

The article reads as follows(12):

"Five years ago (1957) it became evident that the majority of malignant neoplasms observed in children in Uganda were but differing manifestations of a single distinctive tumour syndrome. The most frequent and characteristic presenting feature of this condition is a tumour involving one or more quadrants of the jaw. Other sites where tumors are commonly found include the kidneys, adrenals, ovaries, liver, thyroid, heart, intestine, and the extradural space in the spinal canal.

Tumour distribution constituted a belt across tropical Africa with a tail running down the East Coast. Moreover there were areas in the belt, in spite of dense population, the tumour didn't exist. More detailed examination of tumour distribution in Uganda and Kenya indicated that the limiting factor distribution pattern was an altitude 5,000 ft. above sea level."

In conclusion the author states:

1. The tumor is dependent on altitude.
2. The critical altitude falls as the distance from the equator increases.
3. Altitude is therefore considered to be only a limiting factor in so far as it reflects temperature.
4. The actual limiting factor appears to be a minimum temperature of about 60 degrees fahrenheit.

The author in closing hinted the possibility of a vector agent being involved in the transmission of the disease.

I now will refer to a study on bovine lymphosarcoma from which the following information was derived(13).

"An attempt has been made to characterize lymphosarcoma of cattle with regard to clinical manifestations, pathologic alterations, and familial distribution of cases in high incidence herds.

According to data from a total of 89 cases it is evident that, in many respects, the cattle disease resembles lymphosarcoma of man. There is localized neoplastic proliferation of lymphoid tissue which results in diffuse infiltration of organs or formation of discrete solid tumor masses. These are locally destructive and invasive. The process probably spreads by metastasis and, in time, becomes widely disseminated. Some animals develop leukemic peripheral blood with massive bone marrow involvement; in many others, the blood and marrow appear normal throughout the course of the disease.

The common clinical picture is one of emaciation, pallor,

a history of progressive weight loss, and decreased milk production. Enlargement of palpable lymph nodes is an outstanding feature.

Analysis of pedigree data from cattle with lymphosarcoma in six multiple case herds indicates that the probability of chance occurrence of the disease in these related animals is extremely remote."

The author goes on to mention that the data are compatible with a concept of vertical transmission of an infectious agent.

In the discussion of this article a small historical account was alluded to, some of which I would like to insert here.

"It was reported that European workers had recognized the occurrence of lymphosarcoma in related animals as early as 1896. In 1915 it appeared to attain almost epizootic proportions in East Prussia. Later, the appearance of bovine lymphosarcoma in Silesia was attributed to introduction of these East Prussian cattle.

An extraordinary high incidence of lymphosarcoma in cattle from Southeastern Sweden (SRB breed) and an almost negligible incidence in Northern Swedish cattle (SKB breed) provided an interesting experiment when attempts were made to upgrade milk production of the Northern cattle through importations of SRB breeding stock in the late 1940's. During a five-year study of Northern herds in which lymphosarcoma was diagnosed,

the majority of cases appeared among the imported Southern Swedish cattle of their offspring."

From these studies it seems as though some agent is transmitted and probably is transmitted in many instances through the father or mother.

Deviating slightly from the research of the animal itself, I would like to take some license here and point out the locales from which the U.S. has acquired its beef and dairy cattle and the year these cattle were imported. Try and keep in mind the areas of high leukemic incidence by referring back to Chart I. on page 5, as you read the report. I regret that I have no figures on the incidence of leukemia in the small island regions.

The common Dairy Breeds are as follows(14):

Ayrshire cattle: Originated in South-West Scotland.
Importation in U.S., 1822.

Holstein-Friesian: Originated over 2,000 years ago in Western Europe, in the area now known as Holland or Netherlands.
Importation to U.S., 1795

Guernsey: Originated on the island of Guernsey. One of the islands in the English Channel.
Importation to U.S., 1833

Jersey: Originated in the island of Jersey in the English Channel.
Importation to U.S., 1850

The common beef cattle are as follows:

Shorthorn: Originated in England.
Importation to U.S., 1783

Hereford: Originated in West England.
Importation to U.S.,(?)

Aberdeen Angus: Originated in Scotland.
Importation to U.S.,(?)

Galloway: Originated in Scotland.
Importation to U.S.,(?)

Red Danish: Originated in Denmark.
Importation to U.S.,(?)

Curiously enough, in the little county of Aberdeen, Scotland the W.H.O. reports a high incidence of leukemia. If we were to look at the industry there, we would find(15);

"Approximately half of the land is used for agricultural purposes, the remainder is forest. Oats, barley, and potatoes are the principal crops. The county is noted for its cattle and sheep and the related dairy industry."

Again, take a relatively small country like New Zealand which can be noted to have a high incidence of leukemia, and look at the findings on industry and agriculture(16).

" The extremely favorable climate of New Zealand to a large extent accounts for the high agricultural productivity of the country. Of New Zealand's total area of some 66 million acres, almost 43 million are in occupation for primary production. Approximately 37 million acres are devoted to pastoral production; of this total, about 5 million acres are used for dairy farming, leaving approximately 32 million acres, or nearly half of New Zealand's total land area , for sheep farming.

The outstanding feature of mutton and lamb production since World War II has been the rapid development of the fat-lamb industry; lamb is one of New Zealand's principal exports, third in value to butter and wool only.

Dairying is second only to sheep-farming in economic importance. Pastures provide the principal cattle fodder.

The greater part of dairying is devoted to the production of butter and cheese; after World War II, the manufacture of processed milk and the production of casein markedly increased."

I would now like to discuss Japan along these same agrarian lines. Before delving into this aspect, I would like to allude to some statistics, the substance of which I will present in more detail later when I discuss radiological influences in leukemia. Tomonaga has compiled figures showing increased leukemia in those people exposed to the atomic bomb. Even today, the significance of these findings is not yet clear. Tomonaga has shown an increase in leukemia in the years of 1947 through 1960. However, there also seems to be an associated rise in the nonexposed population as well as the exposed population in his study. It's this fact which I would like to emphasize at this point, as I endeavor to enlighten the reader in regards to the agricultural developments of the country (17).

" Japanese agriculture has only a limited livestock industry despite the preponderance of highlands. There are two principal reasons for this:

1. There is a lack of good natural pasture land, because the native wild grass is coarse and unnutritious and generally crowds out the valuable forage grasses.

2. Farming is limited to the cultivation of the soil for the produce derived directly from it, because in a densely populated country with limited food resources the food value

produced from an acre under grains is 6-7 times larger than the food value of the meat or milk that can be obtained by feeding the grain to livestock. Cattle and horses are raised chiefly for draft purposes and for stable manure. The total number of cattle prior to World War II averaged 1,800,000 and reached a peak of 2,300,000 in 1945. In the immediate post war period the number was considerably reduced, but it was estimated that in 1949 it attained the 1945 level(note spikes for leukemia on following graphs). By 1953 the livestock industry was above prewar levels in virtually every category; the most notable gains were in cattle, horses, sheep, and poultry.

As we know, the basic diet of the Japanese is essentially rice. Whether this factor alone is of significance in the decreased spread of leukemia in Japan still remains to be determined.

Before closing on this aspect of leukemia I would like to call to the reader's attention the ubiquitous nature of this disease.

Holm(18) in his book states that leukemias were recognised as an independent group of diseases in 1845 through Craigies, Bennetts, and in particular Virchow's studies. (Virchow was the one who introduced the term leukemia.)

Ever since this time leukemia has been observed in a

multitude of other animals, such as, horses, pigs, dogs, cats, mice, birds, fowl, monkeys, lions, buffaloes, deer, sheep, elephants, and opossums.

The term leukemia in animals means a lot of different things to various people in this field and is subject to wide debate. As an example, the Merck Veterinary Manual(19) under the disease heading referred to as Canine Malignant Lymphoma, finds this entity synonymous with or undifferentiated from Lymphoblastoma, Lymphosarcoma, Lymphocytoma, Lymphatic leukemia, and Pseudoleukemia.

There seems to be quite a large area open for clarification in the various forms of leukemia in animals, and quite a lot of study too long neglected in this field still to be done.

Radiation in the Field of Leukemia

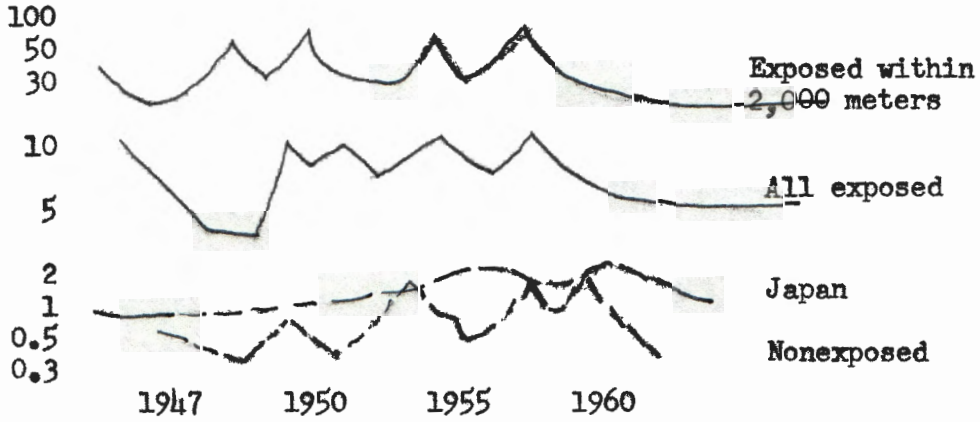
There has never been any definite proof that radiation is a cause of leukemia; however, the atom bomb reports from Japan have seemed to imply a seeming correlation. Also experimental research, which will be discussed later, seems to demonstrate an augmenting influence from x ray and also a possibly synergistic role in the causation of leukemia. I would like to quote an article from the W.H.O. in order to show the skepticism that still remains in regards to radiation.

Segall(20) in 1961 investigated the relationship between terrestrial background radiation and leukemia mortality in northern New England. Equivalent uranium concentrations of underlying bedrock were used to estimate population exposure to natural radiation in each of some 1,000 townships. No association between estimated radiation level and population income, urbanization, availability of medical care, ethnic composition, or population mobility was present. Some differences between radiation levels in the proportion of foreign born persons were present. Age-adjusted leukemia mortality rates were determined for four background radiation categories. No statistically significant association between level of background radiation and leukemia mortality was demonstrated, nor were any trends discernible.

I would now like to present the Japanese data(21).

Graph 1

Annual incidence of leukemia in Nagasaki and in Japan as a whole.



Graph 2

Leukemia among persons exposed at under 2.000 meters in Nagasaki and Hiroshima by year of onset.

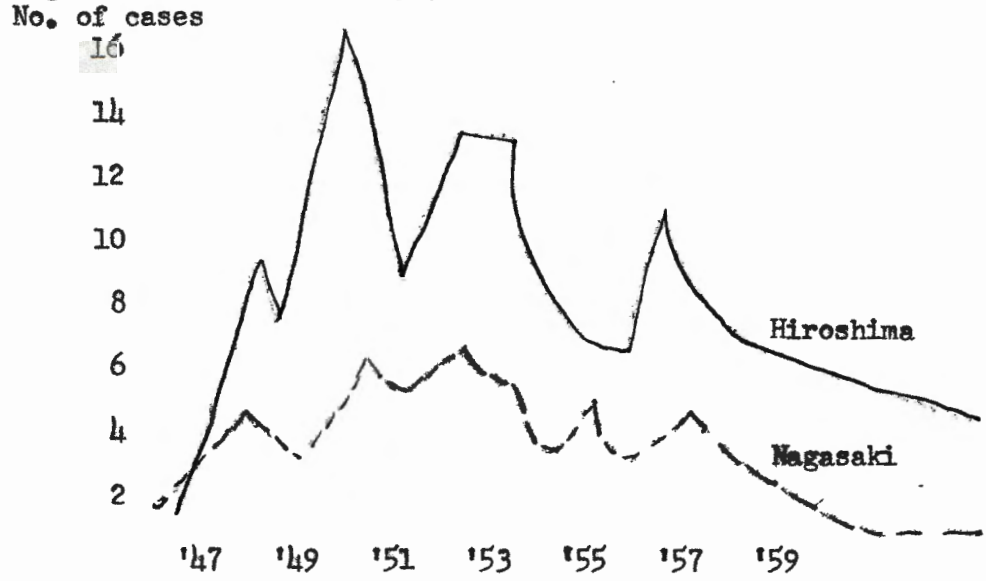


Table 1

Incidence of leukemia in residents of Nagasaki and Hiroshima according to distance from hypocentre, 1947-1959.

Exposure distance	Nagasaki		Hiroshima	
	cases	rate per 100,000 pop. per year	cases	rate per 100,000 pop. per year
0-999	6	100	20	100
1000-1499	22	54	40	27
1500-1999	5	10	19	7.1
2000 and over	34	3.4	18	1.8
total exposed	67	6.0	97	7.0
nonexposed	40	1.7	53	2.0
exposed and nonexposed(total)	107	3.0	150	3.4

Incidence for all Japan 1947-1958 Cases: 20,305 Rate: 1.9

In regards to the types of leukemia, it was noticed that there was a total absence of lymphocytic leukemia. The significance of this fact is not yet evident.

The chronic granulocytic leukemias seem to be disproportionately clustered in the zoney exposure under 1500 meters as compared with the acute leukemias, although this distance is not statistically significant.

For persons exposed at under 1500 meters the rate of each type of leukemia is significantly greater than even the total leukemia rate for all of Japan. In Hiroshima there is a tendency to a higher incidence of chronic granulocytic leukemia among those exposed at a short distance. In Nagasaki the ratio among those exposed at a short distance is almost the same as that in Japan as a whole, but remarkably lower than in those exposed at a great distance and in the non-exposed.

It seems evident that no definite conclusions can be drawn from these findings and the conclusive proof of radiation as a sole mediator for leukemia remains to be elucidated.

In regards to fetuses exposed the article goes on to say that;

" In the Nagasaki and Hiroshima survivors exposed in utero, no case of leukemia has been identified to date."

Before concluding on the radiation hazard I would like to reveal some more statistics and reports concerning radiation effects in man.

First lets get an idea of the degrees of various tissue susceptibilities to x ray.

According to Cronkite and Bond(22) the listing of mammalian tissue in an order of increasing magnitude of resistance to radiation damage is as follows;

1. Spermatogonia
2. Lymphocytes
3. Erythroblasts
4. The rest of the classical hematopoietic tissues.
5. Lining of the small intestinal tract
6. Stomach
7. Colon
8. Skin
9. Central Nervous System
10. Muscle
11. Bone
12. Collagen

On the hypothesis that changes such as radiation-induced bone marrow aplasia would be reflected first in the mitotic index, (A ratio of dividing to nondividing cells) some researchers investigated the mitotic index of human bone marrow in healthy

individuals and a group of accidentally irradiated patients. A dose-dependent fall was noted on the fourth post irradiation day. The index returned to normal after four weeks but was found to be significantly elevated 4½ months after exposure. However, the control mechanism that ordinarily would suppress DNA synthesis after doubling the amount prior to mitosis seemed to be inoperative, and giant cells were produced. Furthermore, it appeared that the mechanisms that ordinarily initiate cell division were also disturbed after radiation exposure. Ribose nucleic acid(RNA) synthesis seemed unimpaired.

The initial response of the myelocytic cell series to midlethal doses of radiation is the development of a neutrophilic leukocytosis very shortly after exposure.

In human survivors of the acute radiation syndrome, the minimum granulocyte level is generally reached 14-28 days post-irradiation. In fatal cases the count continues to fall until death.

The response of the granulocytic series indicates primary damage to the proliferation pool of myeloblasts and their daughter cells in the bone marrow. Morphologic changes can be seen in the immature granulocytes 24 hours after irradiation. It is possible that subtle damage to mature cells also occurs since hypersegmentation of the nuclei of some of the mature granulocytes has been observed, but this does not lead to

removal of these cells from circulation in the immediate post-irradiation period.

The response of the lymphoid tissue to total-body irradiation consists of rapid disappearance of lymphocytes, both from the circulating blood and from the lymph nodes, thymus, spleen, and other tissues.

Although there is abundant evidence that x radiation interferes with the rate of DNA synthesis in growing tissue it is not established whether this metabolic alteration is the primary effect of x radiation injury, or if the effect of x radiation on DNA synthesis is indirect. Even if the effect of x radiation on DNA synthesis is indirect, the elucidation of that effect may lead to the unraveling of the nature of the primary injury.(23)

Another author goes on to show some typical effects caused by irradiation. The early effects of large doses of irradiation are erythema and blistering of the skin, followed later by telangiectasis and atrophy of the dermal papillae, with loss of sweat-glands, hair follicles, and sebaceous glands and eventual extensive scar formation. Later changes on these surface tissues may include the formation of carcinomas and sarcomas. Similar but less marked changes are present in the deeper tissues. The lymphatic and hematopoietic system is manifest first by a depression of the total leukocyte count, particularly

the lymphocytes, and later by anemia.(24)

Therapeutic irradiation may produce less marked clinical effects, although subtle changes may be seen in dividing cells in the body. These changes show during mitosis as stickiness of the chromosomes with anaphase lagging, or may be seen as structural chromosome abnormalities. These chromosome abnormalities include an increased number of cells showing a total count significantly differing from the modal count, an increased incidence of polyploidy, and the presence of abnormal chromosomes such as dicentrics, fragments, and ring forms.

It has been demonstrated that chromosome irregularities may be detected for several months after radiotherapy.

Other authorities have reported persistence of chromosomal aberrations for 29 months.

I think that with the empirical data showing the detrimental effects of radiation and also its altering characteristics of the in vivo cell that we must seriously think of radiation as being involved in leukemogenisis or as taking a part in its inception.

Just to show the complexity in trying to involve radiation as the sole etiology of leukemia, a few rather extensive studies will be introduced here.

The case records of 13,352 patients presumed to have ankylosing spondylitis and given x ray treatment for this

condition at 81 British radiotherapy centers between 1935 and 1955 were analyzed in retrospect by Court-Brown and Doll. Wide-field x ray therapy had been administered to the full spine, and sometimes to the pelvis and extraspinal areas, in dosages ranging from 112r to more than 3,000r in from one to eight courses of therapy. In this population 33 proven and 5 probable cases of leukemia were found. The expected number of cases in this population was 2.9.(25)

Retrospective studies of leukemic children have disclosed five instances of therapeutic radiation, but none for thymic enlargement, among 677 children dying of leukemia.

Other studies show:

Five histories of thymic irradiation among 856 leukemic children, a history of thymic irradiation in 4.3 per cent of 261 leukemic children compared with 0.8 per cent in a comparable group without malignant disease; and a history of x ray therapy in eight instances, including five for thymic enlargement, among 65 leukemic children; with only two instances in 175 living siblings and none in 65 matched dead controls.

Further significance of radiation will be considered in the following presentation of todays laboratory research being conducted in the field of leukemia and cancers in general.

Laboratory Research in the Field of Leukemia and Allied Diseases

Over 25 neoplastic diseases caused by viruses are presently known in vertebrates and man as evidenced from their being transmitted by cell free filtrates(26).

Frog kidney carcinoma(Lucke, 1938)
Cartilaginous tumors in newts with Lucke virus(Rose & Rose 1952)
Chicken leukemia(Ellerman & Bang 1908)
Chicken Sarcoma (Rous, 1911.)
Chicken osteosarcoma(Rous, 1912)
Chicken angiosarcoma (Rous, 1913)
Chicken lymphomatosis (Furmester et al.,1946)
Mouse mammary carcinoma(Bittner, 1936)
Mouse leukemia (Gross, 1951)
Mouse chloroleukemia(Graffi, 1956)
Mouse leukemia(reticulum cell, Friend, 1957)
Mouse parotid carcinoma (Gross, 1953)
Mouse sarcoma(Gross, 1955)
Rat leukemia(Thurzo, Svec et al., 1956)
Rabbit fibroma(Shope, 1932)
Rabbit papilloma(Parsons & Kidd, 1936)
Tumors induced in mice, rats, hamsters, and rabbits by S.E.Polyoma virus(Stewart, Eddy et al., 1957, 1958)
Dog oral papilloma(De Monbreun & Goodpasture, 1932)
Horse cutaneous papilloma(Cook and Olson, 1951)
Pulmonary adenomatosis of sheep (Dungal, 1946)
Deer fibroma (Shope, 1955)
Cattle papillomatosis (Magalhoes, 1920)
Human condyloma acuminatum(Waelsch, 1917)
Human laryngeal papilloma(Ullman, 1932)
Fish melanoma(Nigrelli, 1952)

It has been found that inoculation of the Rous virus, and other viruses as well, under proper conditions results in the induction not only of the connective tissue sarcoma but of lymphomatosis and erythroblastosis as well.

Therefore, in the discussion of leukemia research, disregard for other tumor research would be imprudent, and therefore leukemias and cancers will be considered as part of the

same family and introduced in this light.

In regards to the transmission pathways of the S.E. polyoma virus, it is known that in affected animals the virus is eliminated with urine, feces, and saliva. It was also found in water and the bedding from cages in which the animals were kept.(28)

Antibodies to the virus have indeed been found in mice of various strains, which indicates that they are infected with this virus, although to a different degree. The antibodies were found in 100% strain AK mice of the Cross colony although absent in mice of the same strain but of another colony. They were mostly found in mice kept in the same room as the experimental ones affected with tumors and infected with the S.E. polyoma virus.

Magrassi et al.(29) (1950, 1951, 1958) administered into the brain, abdominal cavity, or bone marrow of guinea pigs leukotic material of humans either affected by leukosis or having succumbed from this disease. The result was the development in guinea pigs of disease of a definite clinical and histopathological pattern and transplantable from one animal to another.

Mas y Magro(30) described a series of experiments in which blood from leukemic patients was inoculated into the scarified skin of guinea pigs. The blood and marrow were interpreted

as myelogenous or lymphatic leukemia, depending on the source of the human cells. Transmission of leukemia from one animal to another occurred after the animals were caged together for 8 months.

Bergolz(31,32) reported leukemogenic activity of cell-free extracts from cases of acute leukemia in man. Saline extracts were prepared from brain, spleen, lymph nodes, marrow, and blood and inoculated into low-leukemic strains of mice. These filtrates, injected by various routes, produced leukemia in 34% of the mice, with an average latent period of 3.7 months. Subsequent experiments showed that the nuclear fraction of human leukemic tissues possessed the greatest leukemogenic activity and that the active principle consists of lipomucleoproteins.

Transmission of human leukoses in rats was followed by Riman and Vesely in 1951(33). The administration to one day old Wistar rats of a fraction obtained by differential centrifugation from bone marrow or leukocytes of patients affected with various forms of leukoses resulted in reticulosis with or without infiltration, tumors of the lung and hemorrhages under the skin and internal organs. After 2 months there appeared, in the experimental rats, tumors of lymphoid origin consisting of atypical reticular cells. The disease could be passed from rat to rat by means of liver homogenates.

Parnes and Ssunzova(34) in 1959 accomplished transmission to mice of human leukoses. They administered to newborn mice, within the first hours of postnatal life, spleen tissue and blood clots of leukotic patients.

Five to six months thereafter leukoses developed in part of the mice. Out of 174 mice 27 developed the disease, mostly after administration of material from acute leukosis. In control groups no disease was recorded.

Schwartz, et al.(35)(1957, 1959) report that injection of filtrates from the brain of patients who had died from acute leukosis(like the leukotic material of mice) greatly accelerates the appearance of leukosis in mice of the leukotic strain AKR.

It has been shown that extracts of leukocytes and blood serum of leukemic(especially acute) patients contain a factor which alters and disturbs cell metabolism, protein and nucleic acid metabolism, as well as enzymatic activity.

Dmochowski et al. (36) (1959) found in ultrathin sections of lymphatic nodes of patients with various forms of leukosis inclusions have been detected which contain virus like bodies; 90mu in diameter, with an inner zone surrounded by one or two membranes.

In the cells of lymphatic nodes cultivated in vitro, pathological changes have been noted, such as an increased granularity of the protoplasm, vacuolization, inclusions and

cell disintegration. No such changes were recorded in control cultures of lymphatic nodes of non-leukemic patients.

Moloney(37) isolated and described a mouse leukemia virus in 1960. After transferring a sarcoma 37 from A/LN mice to BALB/c mice for 3 tumor generations, cell-free extracts, prepared from the tumor, produced a lymphoid leukemia in BALB/c mice.

Serial passage of cell free extracts of leukemic nodes and spleen has resulted in 100% leukemia induction in adult mice after a latent period of approximately 2½ months. This agent shows a remarkable lack of strain and species specificity. It is leukemogenic for many inbred and hybrid strains of mice. In addition, leukemia developed in newborn Sprague-Dawley rats inoculated with filtrates of the mouse leukemia and this could be serially transmitted in rats or back to mice. The virus is antigenic in a heterologous species(rabbit) and specific antiserum neutralizes its leukemogenic properties. Preliminary studies indicate that it is an RNA containing virus. Electron microscopic studies demonstrate an extracellular particle with a diameter of 90 to 110mu. Biologic activity is retained after freezing or lyophilization and is destroyed by heating at 56 degrees C for 30 minutes.

At the present time in the mouse, four different morphological types of viruses have already been found, and the

interpretation of these findings still remains quite uncertain.(38)

A. Mammary tumors of mice considered to be induced with the milk agent.

There were observations of two different kinds of virus like particles present in mammary carcinoma cells and also in hyperplastic nodules of the mammary gland.

1. A predominantly intracellelar particle(A-particle) of doughnut shape, measuring around 70mu, is found in great numbers in the Golgi area. Such particles form inclusion bodies which are visible in the light microscope.

2. A predominantly extracellular particle(B-particle) of about 105mu in diameter with an eccentric nucleoid is visible in many intercellular spaces, and also in some intracellular vacuoles of tumor cells.

B. Virus-like particles in various other mouse tumors (melanomas, sarcomas, plasmocytomas, and ascites tumors.)

It has been shown by various authors that in all these tumors A-particles occur either isolated and scattered throughout the cytoplasm in connection with the endoplasmic reticulum or in the dense clusters in the Golgi-zone, forming there inclusion bodies very similar to those seen in mammary tumors.

C. Spontaneous and induced leukemias

Spleen, thymus, and lymph nodes from AKr mice with spontaneous lymphoid leukemias contain virus like particles of a new type designated as type C.

A small number of similar particles have also been found in the leukemic organs of Gross's filtrate induced leukemia, and a significant number were present in Friend's and Moloney's leukemias, though the diameter of the particles may not be identical.

In addition to the C-type, A-type particles also are present simultaneously in the infiltrated organs.

D. Leukemia, Hodgkin's disease, and malignant tumors

Dmochowski et al. have published electron micrographs showing virus like particles about 86mu in diameter in lymph nodes of one acute lymphatic and one acute myeloid leukemia. Later these authors reported similar observations in 5 of 11 cases of human leukemia and Hodgkin's disease. Only small numbers of particles were found, sometimes only after several weeks of examination.

The three diseases in birds of the leukosis complex, visceral lymphomatosis, myeloblastosis, and erythroblastosis, representative of host response by the lymphoid, myeloid, and erythroid hematopoietic tissues to virus infection are directly transmissible in reproducible patterns by inoculation appropriate previous passage materials.

It has been possible to differentiate unequivocally between the BAI strain A(myeloblastosis) and the Engelbreth Holm strain R(erythroblastosis) viruses.

The agent of myeloblastosis in birds diseased with BAI strain A is a spheroidal particle of about 120mu diameter in shadowed electron micrographs.

Research into the field of radiation has proved very intriguing.

Cell-free extracts of leukemic tissues of mice in which leukemia had arisen as a result of irradiation proved capable of inducing leukemia in some cases in mice of non-leukemic lines, and it was possible to passage the disease serially in cell-free extracts and filtrates of leukemic tissues. Cross-neutralization experiments with the sera of rabbits immunized with the Gross virus and the agent discovered in the irradiated mice showed that these viruses were closely related.(40)

These experiments showed that irradiation "activates" the Gross virus which is present in the mouse organism in latent form. It is interesting to note that in these experiments the "activation" of another viral agent, the parotid-tumorvirus (polyoma virus), was observed.

Gross(41) x irradiated one to three months old C3H mice with a dose of 150-200r given to the whole body on four to six occasions at weekly intervals. 53% of the 154 irradiated mice developed leukemia at 9 months of age, and certain other tumors also arose. None of the sibling control mice developed leukemia at the age of 14 months. Irradiated C57 mice reacted

similarly at nine months of age, 60% developed lymphatic leukemia as compared with a 1% incidence in the control animals at the age of 22 months. Thymectomy prevented radiation leukemogenesis, as shown earlier by Kaplan. The radiation-induced leukemias were transplantable by cell graft only within the inbred strain in which they originated. Leukemia induced by radiation in low leukemia C3H mice was transmissable by cell free filtrates. The incidence was low and only 40-60% of the filtrates proved to be active. Parotid tumors also rose in some of the animals. One of the most potent filtrates was serially passed in newborn C3H mice. The first passage caused leukemia in 37% of mice within 9.3 months. In the eighth passage, the incidence of leukemia was above 80% and the latency period approximated 5 months. The potent viral agent recovered from radiation induced leukemia has been designated as "passage X" strain.

Cross-neutralization experiments between "passage A" and "passage X" viruses indicated common antigenic components.

Upton(42) demonstrated that adult RF mice can be made susceptible to the inoculation of cell-free leukemic filtrated after whole body irradiation.

Perhaps we're not just dealing with a virus alone, or perhaps the definition of a virus may be variable.

Hays(43) and her associates, in 1957, reported leukemia

induction by RNA extracts of leukemic AK mice. In a recent report, Hays describes slightly but significantly higher and earlier occurrence of leukemia in certain hybrid mice inoculated with DNA-RNA preparations from leukemic Ak mice.

Recent evidence in human leukemias show definite abnormal vacuolizations of leukemic cells, highly indicative of some foreign particle, and there also are noticeable chromosomal abnormalities specific to the leukemic cell or cancer cell, per se, which may be indicative of some intracellular disruption.

Researchers today seem to be standing on the threshold of the conquest of leukemia and allied diseases.

Part II. Presentation of Questionnaire

The chief purpose of the questionnaire was to see if an infectious agent could be located for leukemia. An emphasis was placed on the animal contacts, dietary habits, and sources of drinking water of the patients. Also an effort to show a correlation with radiation and immunizations was undertaken.

In no way will I claim that the results of this questionnaire are confirmatory in the establishment of an etiology for leukemia. However, I feel this type of study would prove to be more fruitful if conducted on a wider scale.

Methods and Materials

A questionnaire and an introductory letter to the questionnaire were sent out to 103 patients with leukemia or related diseases which were diagnosed in the last 4 or 5 years.
There were 85 returns, or 83% of 103.
There were 12 unclaimed letters from patients who had moved and left no forwarding address or had passed away.

Only 82 questionnaires were analyzed in the statistics because the slowness of some of the returns conflicted with the time alotted for the completion of the thesis. However, the general pattern of findings was not interferred with, and the data represents a typical account of the results of the questionnaires.

The Accompanying Letter to the Questionnaire

Dear

This questionnaire is being brought to you by Senior Medical Student Sam Shukert under the auspices of Dr. Peyton Pratt with the sole purpose of accumulating enough vital information which can be used in directing our efforts as well as other reseacher's in discovering a cause for a wide variety of malignant diseases. These include Leukemias, Hodgkins, and Lymphomatous diseases. This letter is being sent to families who have members presently afflicted with one of these diseases, and to families who have lost one of their loved ones in the ravages of one of these dreaded illnesses. We apologize for our stirring up any tender feelings, but we know that in the United States alone, 15,000 to 20,000 people will die each year as the pall of these merciless diseases takes its toll.

The evidence to date indicates that an infectious agent may be responsible for causing these diseases.

The importance of such a survey, which according to the latest literature has not been conducted in this country, cannot be overemphasized; and the urgency with which you reply is of utmost importance.

Any request on your part for additional information will be met with in a personal manner.

All information will be considered confidential.

Thank you for your co-operation and sincere effort in wanting to be part of a team designed to reveal one of life's challenging mysteries.

Yours Truly,

Sam Shukert

The Questionnaire

USE BOTH SIDES OF PAPER IF NECESSARY
USE A QUESTION MARK WHERE YOU DON'T KNOW THE ANSWER
REMEMBER! EVERY LITTLE BIT HELPS, AND FEEL FREE TO EXPAND ON ANY PARTICULAR POINTS.

PATIENT'S NAME_____

PATIENT'S OCCUPATION_____

MOTHER'S OCCUPATION_____

FATHER'S OCCUPATION_____

PAST RESIDENCES OF PATIENT(ESTIMATE YEAR) AND INDICATE LAST RESIDENCE:

DIETARY HISTORY OF PATIENT:
LIST THREE MOST COMMON FOODS EATEN: 1. 2; 3.

SPECIFY IF WOULD PARTAKE IN:

	YES	NO	PASTEURIZED	UNPASTEURIZED
MILK				
CHEESES				

SPECIFY IF WOULD EAT:

			(HOW COOKED)		
	YES	NO	RARE	MEDIUM	WELL
BEEF					
MEAT PORK					
LAMB					
POULTRY					
FISHES					

INDICATE SOURCE OF DRINKING WATER
PRIVATE WELL___ CITY WATER___OTHER_____

GIVE ANY HISTORY OF CONTACT WITH FARM ANIMALS, HORSES, OR HOUSE PETS:
(BE BRIEF BUT SPECIFIC)

GIVE HISTORY OF AN ALLERGY OR INFECTION FROM ANIMALS:

HAS PATIENT HAD WARTS? YES___ NO___
ALSO DURING ILLNESS YES___ NO___
BEFORE ILLNESS YES___ NO___

WAS PATIENT EVER EXPOSED TO X-RAY PRIOR TO ONSET OF ILLNESS?
(IF AFFIRMATIVE, BE SPECIFIC)

CHECK, IF PATIENT HAD ANY OF THE FOLLOWING IMMUNIZATIONS:
POLIO__ DIPHTHERIA__ TETANUS__ WHOOPING COUGH__ SMALLPOX__.

WAS THE MOTHER EVER EXPOSED TO X-RAY DURING HER PREGNANCY WITH PATIENT? YES__ NO__

DID THE MOTHER HAVE AN INFECTION DURING HER PREGNANCY WITH THE PATIENT? YES__ NO__
(IF AFFIRMATIVE, SPECIFY ILLNESS)

DID OR DOES ANY OTHER MEMBER OF THE FAMILY HAVE GRANULOCYTIC LEUKEMIA, LYMPHOCYTIC LEUKEMIA, MONOCYTIC LEUKEMIA, HODGKINS, LYMPHOSARCOMA, OR POLYCYTHEMIA RUBRA VERA? (IF YES, SPECIFY RELATIONSHIP TO PATIENT, AND SPECIFY DISEASE)

IS THERE ANY OTHER INFORMATION WHICH YOU YOURSELF THINK IS PERTINENT TO THE UNDERSTANDING OF THE PATIENT'S DISEASE?

DO YOU HAVE ANY THEORIES OF YOUR OWN WHICH YOU FEEL ARE RELATED TO THE PATIENT'S DISEASE PROCESS?

MANY THANKS FOR YOURTIME AND EFFORT.

A Breakdown of the 82 Cases Studied

	Abbreviations which will be used	Number of cases	Per cent of 82 replying
Acute granulocytic leukemia	AGL	8	9%
Acute lymphocytic leukemia	ALL	26	32%
Chronic lymphocytic leukemia	CLL	18	22%
Chronic granulocytic leukemia	CGL	9	11%
Acute monocytic leukemia	AML	3	4%
Polycythemia rubra vera	PRV	2	2%
Lymphosarcoma	LS	7	9%
Hodgkins disease	H	4	5%
Erythroleukemia		1	1%(excluded)
Agnogenic myeloid		1	1%(excluded)
Subacute granulocytic leukemia		1	1%(excluded)
Lymphoma		1	1%(excluded)
Acute granul. or lympho. leukemia		1	1%(excluded)
Total		82	100%

The last 5 cases will not be entered into the detailed breakdown of the findings, because of their poor representation for individual group studies.

Not a complete compilation of every question will be undertaken. Take the case of the question asking for the mother's occupation. In this particular instance 99% of the Mothers were housewives or homemakers. No attempt to associate this

finding with the etiology of leukemia is made.

However, the purpose for finding out the father's occupation, takes on a different light. The chief motive in this instance was to reveal the possibility of contagion from animal to man, and the farmer would be likely carrier in this regard. In my study 30 out of 82 patient's had fathers who were farmers, or 37% of all fathers.

Even though we live in an agricultural region, this percentage seems significantly higher than that which one would expect.

The search for past residences was queried in order to find a possible common pool for an infectious agent. Since most patients moved around at one time or another and exact dates were not obtained, no attempt was made to group these individuals geographically.

Looking at the dietary history of the patient, I first asked the patient to list the 3 most common foods eaten.

The main purpose of this question was to stimulate the patient's mind to think about the succeeding questions which concerned the specific indulgence of various food items.

As the reader analyzes the findings, the reader must keep in mind that the cause of leukemia is not yet proven; and what I'm trying to demonstrate is that possibly milk, meat, or whatever it may be, could transport an infectious agent.

The results are as follows:

69 out of 82 patients drank milk, or 84% of 82.

18 patients drank unpasteurized milk, or 22% of 82.

7 patients didn't drink milk, or 9% of 82.(see chart 1)

CHART 1 (Study of Patient's Milk Habits)

Disease	Pasteurized	Unpasteurized	No milk
AGL(8)	5	1	2
% of 8	62	13	25
ALL(26)	21	4	1
% of 26	81	15	8
CLL(18)	15	3	1
% of 18	83	17	5
CGL(9)	8	2	0
% of 9	89	22	0
AML(3)	2	1	1
% of 3	67	33	33
PRV(2)	2	0	0
% of 2	100	0	0
LS(7)	6	1	1
% of 7	86	14	14
H(4)	3	1	1
% of 4	75	25	25

It is evident that in some cases I am talking about only 4 patients(as in Hodgkins disease) and I have supposedly 5 patients as the total for those drinking pasteurized, unpasteurized, and no milk. The reason for this apparent discrepancy is that some people drank both kinds of milk. In order

to give a true account of the returns, all answers were tabulated. This is the way I will treat all information used in my study, and I hope this will not interfer with the reader's interpretation of the statistics but will be looked upon as a more accurate representation of the data.

Of those who ate cheeses(see Chart 2), 66 ate them pasteurized, or 81% of the 82 cases.

7 patients ate them unpasteurized, or 9% of 82.

12 patients didn't eat cheeses, or 15% of the cases.

There were only 3 people in my study who didn't indulge in either milk or cheeses.

One case was a Hodgkins disease, one a Lymphosarcoma, and one was a Chronic lymphocytic leukemia.

All were elderly, and the possibility of them never eating or drinking any milk products is highly unlikely.

However, all three of these patients partook in some form of meat product, so that if an infectious agent is responsible for these diseases, it could have been obtained from one of the investigated food products.

Chart 2(Study of cheeses)

Disease	Pasteurized	Unpasteurized	No Cheeses
AGL(8)	7	0	1
% of 8	87	0	13
ALL(26)	21	2	4
% of 26	81	8	11
CLL(18)	15	2	2
% of 18	83	10	10
CGL(9)	8	0	1
% of 9	89	0	11
AML(3)	3	0	0
% of 3	100	0	0
PRV(2)	1	0	1
% of 2	50	0	50
LS(7)	5	0	2
% of 7	71	0	29
H(4)	3	0	1
% of 4	75	0	25

The next group of figures will concern the meat products. I will not break down any statistics on the lamb eaten, for it seems that this delicacy was very rarely enjoyed. Approximately 30 patients ate lamb, and some of these emphasized the fact that they seldom ate it. However, everyone ate beef, even the infant who had to get it strained.(See Chart 3)

Chart 3 (Study of Meats)

	Beef			Pork				Poultry				Fish			
	Rare	Med	Well	Rare	Med	Well	No	Rare	Med	Well	No	Rare	Med	Well	No
Total	2	26	63	1	7	69	7	0	4	73	2	0	5	66	11
% of 82	2	32	77	1	9	84	9	0	5	89	2	0	6	81	13
Diseases															
AGL(8)	0	5	3	0	1	6	1	0	1	6	1	0	1	6	1
% of 8	0	62	38	0	12	75	12	0	12	75	12	0	12	75	12
ALL(26)	1	4	21	0	0	23	2	0	0	25	0	0	1	21	4
% of 26	4	15	81	0	0	89	8	0	0	96	0	0	4	81	10
CGL(9)	0	2	7	0	1	8	0	0	1	7	1	0	1	7	1
% of 9	0	22	78	0	11	89	0	0	11	78	11	0	11	78	11
CLL(18)	0	6	14	0	3	13	3	0	1	16	1	0	1	15	2
% of 18	0	33	78	0	17	72	17	0	6	89	6	0	6	83	11
AML(3)	1	3	2	1	0	3	0	0	0	3	0	0	0	3	0
% of 3	33	100	67	33	0	100	0	0	0	100	0	0	0	100	0
V(2)	0	1	2	0	0	2	0	0	0	2	0	0	0	2	0
% of 2	0	50	100	0	0	100	0	0	0	100	0	0	0	100	0
LS(7)	0	2	5	0	1	6	0	0	0	6	1	0	0	6	1
% of 7	0	28	72	0	14	86	0	0	0	86	14	0	0	86	14
H(4)	0	0	4	0	0	3	1	0	0	4	0	0	0	3	1
% of 4	0	0	100	0	0	75	25	0	0	100	0	0	0	75	25

Some patients didn't fill in either yes of no on some questions, as in the instance of one patient with acute lymphocytic leukemia.(See Poultry above)

The next study concerned the source of drinking water. People claim that the well water is uaually state tested. From personal interviews this was not always shown to be the case, also no specific viral studies are done in the general routine procedure of testing this water. (See Chart 4)

Chart 4 (Study of Drinking Water)

	Private Well	City Water
Total	41	56
% of 82	50	68
Diseases		
AGL(8)	3	5
% of 8	38	62
ALL(26)	10	19
% of 26	38	73
CLL(18)	8	13
% of 18	44	72
CGL(9)	7	4
% of 9	78	44
AML(3)	2	2
% of 3	67	67
PRV(2)	0	2
% of 2	0	100
LS(7)	5	3
% of 7	71	43
H (4)	3	2
% of 4	75	50

My next approach wasto find out if there was any animal contact. I've attempted to differentiate whether the patient was in contact with farm animals, which would include horses, cows, chickens, and hogs, or whether there was contact with domesticated animals such as dogs, cats, or rabbits. This latter group was combined in my study with "Animals in general". In other words, if a person came in contact with farm animals and domesticated animals, I included this in the colum

"Animals in general" and also in the column "farm animals". If a person just came in contact with domesticated animals, this finding was also included in the column "Animals in general". Therefore if the reader wishes to know the number of patients who just came in contact with domesticated animals, then all he has to do is subtract the column "farm animals" from "Animals in general".(See Chart 5)

I would like to make a comment on the one lymphosarcomatous patient who supposedly never had contact with farm animals, or animals of any sort. Since this seemingly egregious discrepancy in my data stuck out like a sore thumb, I inquired into the life of the patient and found out that the patient was married to a farmer for around 20 years prior to the onset of her disease. However, the patient had such a distaste for animals that she lived in the city and would not go on the farm. Whether this could represent an animal to human to human form of cycle, I will leave up to further investigation.

It might be worth-while to point out to the reader the high percentage of lymphosarcomatous patients who drank out of private wells, and also had contact with farm animals. Unfortunately the smallness of this series limits its import.

Chart 5

	Contact with farm animals	Animals in general	None
Total	43	68	14
% of 82	52	83	17
Diseases			
AGL(8)	4	6	2
% of 8	50	75	25
ALL(26)	11	23	3
% of 26	41	88	12
CLL(18)	8	14	4
% of 18	44	78	22
CGL(9)	5	8	1
% of 9	51	89	11
AML(3)	2	3	0
% of 3	67	100	0
PRV(2)	1	1	1
% of 2	50	50	50
LS(7)	6	6	1(See preceding page)
% of 7	86	86	14
H(4)	3	4	0
% of 4	75	100	0

My next means of approach, I consider somewhat of a failure in my search for an etiology. I wanted to know if there were any allergies or infections incurred by the patient from exposure to animals. I received only one positive reply or possibly two, but these were both of an uncertain nature.

I nexted asked about the incidence of warts before and during the illness. This was an attempt to associate a virus to both entities. The results showed that 8 patients of the 82

had warts during their illness, and 19 out of 82 patients had warts prior to the onset of their illness.

In my approach to radiation encounter, I was rather general and nonspecific in regards to dates of exposure or the amount of exposure; however, as one can see this information would be difficult to get. It might be of interest to know some of the sources of patient contact with radiation, which I feel may have been over-looked by some of the recipients of the questionnaire. The reason I say this is because a lot of these radiation sources were supplied voluntarily by the interviewee with some air of doubt as to their importance in regards to the question asked.

1. Teeth x ray
2. Chest x ray
3. Diagnostic x rays
   a. Fractures
   b. Barium studies
4. Environmental sources

Out of 82 patients, 39 had been x rayed prior to their illness.(See Chart 6)

Chart 6

Diseases	Number x rayed prior to illness
ALL(26)	10
AGL(8)	4
CLL(18)	10
CGL(9)	5
AML(3)	1
LS(7)	4
H(4)	1
PRV(2)	0

My next study was a report of previous immunizations. The reasons for my interest in this knowledge were as follows;

1. The possibility that an agent was introduced which could react adversely under favorable conditions.
2. The possibility that an agent which was introduced might synergize with an already present foreign agent, and thus inaugerate a new virulence.
3. The possibility that an agent which when introduced might behave adversely when stimulated by radiation.

The preceding concepts were acquired from recent animal studies in the field of viral eriology of neoplastic diseases as presented earlier.

It was found(See Charts 7&8) that 22 patients out of 82 had a complete series of immunizations, 45 patients out of 82 had smallpox vacinations, and 36 patients had polio immunizations(oral or parenteral).

Before I discuss the above findings I would like to continue to the next question in which I asked whether or not the mother of the patient was exposed to x ray while pregnant with the patient. I realized that the older patient may have no recollection of this data, and the value therefore of this information is mainly limited to the infant patient, whose questionnaire was filled out by the parent.

Out of 82 patients, I received 9 affirmative answers. 8 of these patients had acute lymphocytic leukemia. One of the affirmatives included an elderly lymphosarcomatous patient.

In breaking down the data on immunizations,I would like to present this information in a slightly different manner.

I will only utilize the four largest groups for this study, the ALLs, AGLs, CLLs, and the CGLs. As the reader studies this data, he must keep in mind the afore-mentioned reasons for my initial interest in immunizations, and the possible association of a multiple number of factors working together to create a virulent agent.

I made five columns for each group of diseases studied in an effort for the reader to easily make associations of facts if they so exist. (See Charts 7&8)

Key to Charts 7&8

* means affirmative reply

absence of an * means either the answer was no or that the patient didn't answer.

Where specific immunizations are filled in, means that a complete series of immunizations was not received, and the patient received only that shot designated.

Chart 7

Disease and individual patients	Contact with farm animals	Contact with domestic animals	Complete series of immunizations	Mother x rayed while pregnant with patient	Patient x rayed prior to illness
AGL(8)					
1.	*		Diphtheria		*
2.		*	*		
3.		*			*
4.	*		Polio		*
5.	*				
6.			*		*
7.	*				
8.	Not filled out				
ALL(26)					
1.	*		*		
2.		*	*		*
3.		*	*		
4.		*	All except Smpx.		*
5.		*	*		*
6	Not filled out				
7		*	*	*	*
8.	*		*	*	
9.		*	*		*
10.		*	*	*	
11.		*	*		*
12.		*	*		
13.	*		*		
14.	*		*		
15.	*		*		*
16.			*	*	
17.		*	Whooping cough		
18.	*		Smpx. & polio		
19.	*		Polio & diphtheria	*	
20.	*		*		*
21.	*		Whooping cough	*	
22.		*	*	*	*
23.			*		
24.		*		*	
25.	*		Smpx.		
26.	*				*

Chart 8

Disease and individual patients	Contact with farm animals	Contact with domestic animals	Complete series of immunizations	Mother x rayed while pregnant with patient	Patient x rayed prior to illness
CLL(18)					
1.		*	Tetanus & smpx.		*
2.	*		Smpx.		
3.		*	Smpx.		
4.	*		Smpx.		
5.		*	Smpx. & polio		*
6.	*				
7.		*	Whooping cough		*
8.	*		Polio, whp.c., smpx.		*
9.	*				*
10.	*				
11.			Polio		*
12.	*	*	Smpx. & whp.c.		*
13.	Not filled out				
14.			Smpx.		
15.			Polio		*
16.	*		Smpx.		*
17.		*			*
18.	*				
CGL(9)					
1.	*		Polio		
2.		*			*
3.			Polio, & diphth.		*
4.	Not filled out		Smpx. & whp.c.		
5.		*			*
6.	*		Smpx.		
7.		*			*
8.	*		Diphth., tetanus, smpx.		*
9.	*		All except smpx.		

In finding out whether the mother had any infection while pregnant with the patient, I only received 5 affirmative answers;

2 had kidney infections, 1 had the flu, 1 had diarrhea, and 1 had measles.

When I asked for other members of the family who may have had a leukemic form of illness, I found out that 5 patients out of 82 had another member of the immediate family with one of the illnesses asked for.

To this list could probably be added two more families whom I talked to individually but had not sent out any questionnaires to, since I wanted to receive random samplings, to which I had no prior history.

Lastly in my questionnaire, I asked for individual theories or further information which could be useful in revealing the cause of the patient's illness. The various replies will be summarized below.

1. Contact with chemicals
   a. Insecticides
   b. Hair sprays
   c. Medicines
2. Insecticides on foods
3. Contact with other people with cancer
4. Contact with radiation
5. Alcoholism

Part III. My Personal Hypothesis Concerning the Genesis and Conquest of Leukemia and Allied Diseases

I feel that Leukemia may be related to cancers in general and possibly is a different expression of a common disease agent.

The role of an infectious agent, whether a virus or an analogous particle, seems most tenable.

I feel that the infectious agent enters the host cell, and disrupts the normal cellular metabolism by creating a new monitoring system through disturbances chiefly in the chromosomal architecture or cellular cytoplasm.

This new arrangement can feasibly respond differently to normal body stimuli, and therefore laboratory studies may show imbalances in the normal body chemicals and hormones.

In leukemia we are often times confronted with a pancytopenia prior to recognition of any massive increase in one of the cellular elements.

I explain this as being due to the bodies all out attempt to suppress the leukemic cell and in turn the body manages to suppress the normal cells as well. When the leukemic cell becomes refractory and gains prominence, the normal cellular elements remain depressed. However, when antileukemic agents are used and the increased proliferation of the leukemic cell is finally suppressed, the body is capable of responding now with the normal cellular elements, which will show a gradual return to normal levels.

I like to regard the leukemic or cancer cell as a "cell individual", having(if I may speak metaphorically) a mind of its own, and a body of its own; and therefore, this cell must be considered and treated as a different species, a species not under the same influences as the host species(*).

There would be no common antibody in this system, but selective antibodies for each individual neoplasm would be apropos. In other words each neoplasm must be thought of as being composed of individual or independent cells, and in each person who may have a similar cancer, the cancers can only be considered identical morphologically, not genetically.

Exp. Though my skin looks the same as someone else's skin, I know that homologous skin grafts are not possible, because of genetic differences.

I feel that the agent causing cancer may be isolated and destroyed, or through preventive means, eliminated from human contact.

However, if this agent is always carried from individual to individual and even passed in utero, as the case may be, I feel that antiviral or antiserum treatment may be impractical once the agent has become intracellular or has created an intracellular derangement. Therefore, as in the case of other diseases of the body, the cell must be considered as the in-

* See references 44,45,46,47,48,49,50.

fective agent, a daughter agent, now comprised of a new architecture capable of replicating itself in a manner which will not respond to prevailing bodily inhibitors.

*Treatment would consist of developing specific antibodies to the malignant cell(daughter cell).

If an outside reservoir is definitely established, then the role of preventive medicine is self-explanatory.

Leukemia and allied diseases must no longer be thought of as incurable diseases, but must be looked upon in a new light and approached accordingly.

* See references 51, 52, 53.

Summary

In Part I of my thesis I pointed out a number of countries which had high incidences of leukemia. Using these countries, I tried to show that there may be an association of leukemia with the cattle and the dairy industries, and used Denmark as a prototype upon which I based this concept. A review of the bovine leucoses in this country was presented, with the implication that humans may contract the same disease from direct animal/ contacts, or indirectly through the various food products, esp. dairy products.

I tried to show that Japan's low incidence of leukemia may be due to its agricultural and dietary habits. A review of the atomic bomb reports from Japan were given in an effort to show the uncertainty with which we implicate radiation as a sole cause for leukemia.

Other studies on radiation were also given in order to re-emphasize this point.

Laboratory research in leukemia was presented in an effort to show the close connections of radiation and infection in the causation of leukemia. Also the presentation of this research was meant to show the reader the tremendous strides which are being taken in an effort to conquer leukemia and the allied diseases.

Part II was a presentation of a questionnaire sent to a series of leukemic patients. The questionnaire was patterned after some of the laboratory research findings on leukemia, with the purpose of trying to show that there may be similarities in the human and laboratory animal milieu. The questionnaire was also used as an attempt to locate a possible source of infection in foods and animals. No infectious agent could be implicated from the results of the questionnaire alone.

Part III was my attempt to formulate the present research findings and my own findings into a workable hypothesis on the etiology and treatment of leukemia.

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