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X-Ray Exposure and Premature Aging

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An hypothesis of an aging effect of exposure to ionizing radiation in humans is proposed and given precise mathematical expression. The assumption is made that the biological changes which occur when humans are exposed to ionizing radiation from medical x ray are comparable to those occuring through the natural aging process, since both factors are known to increase the relative risk of nonlymphatic leukemia. This assumption focuses on this one aspect of aging only. The hypothesis that aging and exposure to ionizing radiation are comparable for increasing the relative risk of nonlymphatic leukemia is tested against the data from the Tri-State Leukemia Survey. It is shown to explain the data in a statistically acceptable way, giving an estimate of 1 rad skin dose exposure to the trunk as comparable to 1 year natural aging. This research raises further questions concerning the effects of exposure to ionizing radiation, and presents a new methodology by which these questions may be researched.

Key words: x ray, aging, leukemia, radiation

INTRODUCTION

There has long been speculation in scientific circles that the biological effect on humans of exposure to ionizing radiation is comparable to the effect of normal aging. Dr. Elkeles (1966), well-known student of both radiation effects and gerontology, has gone so far as to state:

> "Gerontologists have shown keen interest in the effect of chronic exposure to very small doses of radiation. Many believe that this phenomenon may prove to be the key to our understanding of the normal aging process." (p. 895).

Research into mortality and morbidity rates of diseases for persons chronically exposed to low doses of ionizing radiation has shown significantly high rates for cancer (especially leukemia), diabetes, cardiovascular-renal disease, stroke, and hypertension (Gibson et al., 1972; Lea, 1947; German, 1974; Matanoski et al., 1975a, 1975b; Seltser

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and Sartwell, 1965; Burnet, 1974). The conclusion reached by Seltser and Sartwell (1965) in their study of mortality of American radiologists relative to other medical specialists was as follows:

> "These findings warrant the inference that occupational exposure to ionizing radiation on the part of physicians has in the past produced a nonspecific life-shortening effect." (p. 22).

Research presented in this paper moves this speculation into a precise and testable hypothesis. It provides a model for testing the theory that exposure to ionizing radiation has a primary effect of accelerating the natural aging process, and that the observed increase in incidence rates for various chronic diseases among persons exposed to radiation is "normal" for their altered biological age. This model is applied specifically to the relation between exposure to ionizing radiation and the occurrence of nonlymphatic leukemia, as reported in the Tri-State Leukemia Survey.

Bridging the gap between a speculative and nebulous theory and a precise hypothesis which could be tested against a reliable body of data is an important first step in understanding the complex biological interaction between man and his environment. It moves a theory from the hypothetical to the real world.

The data from the Tri-State Leukemia Survey probably represent the best available retrospective data on diagnostic x-ray exposure for leukemia cases and randomly selected controls (Graham et al., 1963). Information on the number of x-ray plates used and site of x ray is converted to the average rads skin dose x-radiation received under standard American diagnostic procedures current in 1959–1962, the time during which the survey was administered. Using this data base, an estimate of the aging effect relevant for today's medical procedures was obtained.

In this analysis, only verified reports of diagnostic x-ray received 1 year or more prior to diagnosis for cases and to interview for controls is considered. The time interval over which the exposure is reported is 20 years, with the bulk of the reporting within the first 10 years prior to diagnosis.

Reconciliation of the findings reported in this paper with the large body of literature relative to the question is not attempted in this paper. A fresh look at previous data reports in the literature reveals no fundamental contradictions, and some clarifications of reported effects of radiation which could not, at the time of writing, be explained. There is some difficulty with the expression "life-shortening effect," which is frequently taken as an averaging over the whole population of the years lost by the premature death of some members of the population. This is not the same concept used here. Life-shortening effect or aging as used here refer to the stress on the individual which undermines his biocommunication facility, reducing his ability to cope with life and maintain healthy homeostasis. Such breakdown is associated with debilitating illness prior to death and actual premature termination of life.

FORMULATING THE HYPOTHESIS

Most theories of biological aging posit a breakdown in biofeedback, so that gradually the organism becomes unable to cope with the stresses caused by daily living. Whether the information needed to trigger an appropriate reaction to restore well-being is totally absent or is blurred (an "error" message, or misinformation), the result is the same. It is well known that the biochemical carriers of information in the human organism

are subject to alterations with time and with exposure to ionizing radiation (Lea, 1947. German, 1974). There may well be more than one identifiable bioinformation system, and the gradual breakdown of one such system may be associated with a syndrome of clinical manifestations.

Key to recognizing the similarity in the results of aging and of exposures to low level x ray is the undramatic, hardly perceived but cumulative damage which results from each. We do not seem to be dealing with extensive cell damage and destroyed tissue, but rather with injured cells able to continue functioning and even reproducing themselves within the body. Because of nonrepair or misrepair of slight damage, these cells introduce error into some biological information system. When the error level reaches a certain point, it becomes clinically observable in terms of some inability of the organism to control the internal environment and restore homeostasis.

In terms of leukemia, this is manifested as an inability to maintain a normal cell population in the blood.

The question posed is the following: Can an increase in age proportional to amount of ionizing radiation received be shown to account fully for the significant increase in relative risk of nonlymphatic leukemia in a real sample of cases and controls with known exposures? As in any scientific inquiry, if the real data reject the hypothesis, the question is settled in the negative. When the real data support the hypothesis, further research is required and the hypothesis must be taken into consideration with respect to past scientific-medical experience and with respect to plans for future protection of public health.

Since it is valid to hypothesize that both natural aging and exposure to low levels of ionizing radiation bring about a comparable gradual breakdown in the biofeedback mechanism which may be clinically manifested as leukemia, it should be possible to devise a simple way to test the validity of this hypothesis. Mathematically expressed, we can posit the existence of a number k_0, and calculate for each person an exposure age, e, as follows:

$$e = c + k_0 r$$

where c is the person's chronological age and r is the number of rads skin dose of ionizing radiation to which he or she has been exposed. We then posit as a testable hypothesis that persons of the same exposure age have the same probability of contracting leukemia. In effect, we are saying that exposure age e measures both aging and radiation exposure in interchangeable quantities. For example, if $k_0 = 1$, a person 45 years old with 15 rads skin dose exposure to ionizing radiation would have the same probability of contracting leukemia as a person 58 years old with 2 rads skin dose exposure. Both would have exposure age 60, and it would matter little whether the "age" was acquired in the natural course of events or through the exposure.

The Tri-State data provided the reliable information with which to test the hypothesis and evaluate k_0. Since the nonlymphatic leukemia types have shown a strong relation to radiation for males over 45 years of age, this subgroup of cases and controls was used as the first test of the hypothesis against factual human data (Gibson et al., 1972). An age effect hypothesis would be expected to be either more clearly acceptable in this group or more easily rejected. If the hypothesis proves acceptable, the technique could then be used to more carefully explore other subgroups. The research design required fully accounting for the increased relative risk of nonlymphatic leukemia in this subgroup by an age shift for both cases and controls, directly proportional to the skin

dose of x ray to the trunk, which each had received. See Appendix A for further technical discussion of the measurement of radiation exposure relative to verified information available in the Tri-State survey.

THE TRI-STATE DATA

The Tri-State Leukemia Survey was administered in selected areas of New York State, Maryland, and Minnesota, between 1959 and 1962. All reported cases of leukemia and a random sample of controls were interviewed. The population base for the study was about 13 million, and the random sample controls were chosen at a rate of approximately 1 per 3,000.

The adult sample of the survey, those 15 years and older, includes 1,400 leukemia cases and 1,370 random controls. Detailed information on disease history, mobility, exposures to suspected hazards, and personal history was gathered (Gibson et al., 1972; Graham et al., 1963). Verification techniques included contacting all medical personnel, hospitals, and laboratories mentioned. Detailed information on the site and number of diagnostic x-ray plates taken was obtainable for about half of the sample, and only such verified reports were used in this study. Verification techniques could not be shown to have introduced any bias with regard to age distribution or diagnostic x-ray exposure for cases or controls.

Table I gives the age distribution by leukemia type in the Tri-State Survey data. The acute lymphatic leukemia cases were eliminated from the present adult study because the preponderant occurrence of this type of leukemia is in children. The chronic lymphatic leukemia cases were eliminated both because the age distribution of these cases significantly differed from that of the myeloid and monocytic type of leukemia cases, and because this type of leukemia has never been shown to be radiation-related. The etiology of the lymphatic leukemias appears to be different from that of the myeloid leukemias.

Because of further limitations on the data imposed by the requirement that subjects be male, over 45 years of age, with verified trunk x ray, it was important to attain the largest possible sample size for cases. Since the Kolmogorov-Smirnov test (Siegel, 1956) showed the age distributions to be homogeneous, it was decided that the sample of nonlymphatic leukemia cases could be pooled. This includes all leukemias not diagnosed as either acute or chronic lymphatic leukemia.

Table II gives the age distribution of the base population from which the Tri-State information was collected.

Table III gives the D values, the maximum difference in percent between the two cumulative relative frequency curves being compared. The probability of a D value this large or larger occurring under the homogeneity hypothesis is given.

TESTING THE AGING HYPOTHESIS

If the hypothesis of equivalent effect for natural aging and exposure to diagnostic x ray is acceptable, then when cases and controls of the "correct" exposure age are compared, i.e., when k_0 is found, the incidence rates of nonlymphatic leukemia for those reporting more x-ray exposure should be the same as the incidence rate for those not so exposed. This would mean, in terms of our previous example, that the 45-year-old man having 15 rads of exposure to ionizing radiation would not have a greater relative risk of nonlymphatic leukemia than the 58-year-old man having 2 rads exposure. In some way

TABLE I. Age Distributions by Leukemia Type – Tri-State Survey

Age	AM No.	AM Relative cumulative frequency	CM No.	CM Relative cumulative frequency	OTH No.	OTH Relative cumulative frequency	AM and CM No.	AM and CM Relative cumulative frequency	AM, CM, and OTH No.	AM, CM, and OTH Relative cumulative frequency
15–24	19	5.7	9	3.5	7	3.1	28	4.7	35	4.3
25–34	27	13.8	15	9.3	12	8.5	42	11.9	54	10.9
35–44	25	21.3	29	20.6	17	16.1	54	21.0	71	19.7
45–54	48	35.7	32	33.1	26	27.7	80	34.6	106	32.7
55–64	79	59.5	57	55.3	41	46.0	136	57.6	177	54.4
65–74	85	85.0	72	83.3	62	73.7	157	84.2	219	81.3
75+	50	100.0	43	100.0	59	100.0	93	100.0	152	100.0
Sample size	333		257		224		590		814	
Mean age	57.67		59.37		62.31		58.41		59.48	

Notes: AM is acute myeloid or monocytic leukemia, CM is chronic myeloid or monocytic leukemia, and OTH includes all nonlymphatic leukemia cases for which one of the above diagnoses could not be made.

The categories AM and CM are referred to as M-type leukemias, and the AM, CM, and OTH categories are referred to as nonlymphatic leukemias in the text.

TABLE II. Age Distribution Based on 1960 Census Data for Areas Involved in Tri-State Leukemia Survey

Age	Number of persons	Relative cumulative frequency
15–24	2,183,654	16.8
25–34	2,301,104	34.5
35–44	2,502,232	53.7
45–54	2,287,864	71.3
55–64	1,869,281	85.7
65–74	1,273,975	95.5
75+	583,860	100.0
Σ	13,001,970	

TABLE III. Tri-State Leukemia Survey – Age Distributions. Kolmogrov-Smirnov Test Values Under Hypothesis of Common Underlying Distributions

Cumulative relative frequencies compared	D Value	Probability
Census vs AM	35.6	.00
Census vs CM	38.2	.00
Census vs OTH	43.6	.00
AM vs CM*	4.5	> .20
Census vs AM and CM	36.7	.00
Census vs AM, CM, and OTH	38.6	.00

*This was a two-sample test. All other are one-sample tests since total census data give accurate frequency information.

their experience may be considered comparable, whether acquired by exposure to time or exposure to ionizing radiation. To test this hypothesis, age adjustment for radiation exposure must be made for each case and each control, using for each the same k value. It must also be shown that, with this adjustment, persons having greater exposure to ionizing radiation no longer have greater relative risk of leukemia than others in their exposure age cohort. What has previously been reported as a radiation effect could then be equally well explained as an aging effect. The usual measure of the ratio of incidence rate of disease among those with high exposure to radiation relative to those with low exposure, namely the relative risk statistic, is used (Bertell, 1975a, 1975b; Cornfield, 1950/1951). A relative risk of one indicated that the incidence rates of disease in the population exposed to more ionizing radiation and in the population not so exposed are the same.

It is possible to predict the behavior of the relative risk statistic as the value of k changes, where k is the estimate of years of aging per rad exposure. If k is taken to be zero, i.e., no age adjustment is made for exposure, we would expect to have a risk of disease in the exposed group relative to the unexposed group of greater than one. Under the aging hypothesis, this is because the exposed persons are biologically in an older age

bracket where disease incidence rate is higher. This increased risk would also be true for $k = 0$ if radiation exposure were directly related to leukemia.

As k increases through a set of values k_i, we obtain for each k_i a new set of ages for each case and each control: $e_i = c + k_i r$. This will slightly alter the cohorts matched for comparable age. Under the aging hypothesis, each increase in k brings each individual case and control closer to "true" biological age, which is assumed to be the determining factor in incidence rate for nonlymphatic leukemia. If, however, radiation has a unique random effect not comparable to aging, such age adjustment would not eliminate this effect. We would expect the relative risk for higher exposure to ionizing radiation vs lower exposure either to remain elevated or to change in a random way. What we are then looking for is quite demanding of the real data, namely, one value of k which, when used to adjust the ages of each of the cases and controls in the sample, will eliminate (reduce to one) the increased relative risk of nonlymphatic leukemia with increased exposure to ionizing radiation.

Under the age hypothesis, if k is "too large," the age shift assumed is too great, and we expect the risk of disease in the exposed group relative to the unexposed group to be less than one. This is because the exposed group is biologically younger than others in the given classification, therefore having a smaller incidence rate of disease. Again, if radiation damage is independent of age, this continual decrease in relative risk would not be expected.

The test consists in observing the behavior of the relative risk statistic as k increases through small positive values. Monotonic decrease of relative risk through one supports the aging hypothesis. Persistently high relative risk or random changes would reject the aging hypothesis. Thus theory is examined in the light of real data.

Table IV gives the results of the analysis of the risk of nonlymphatic leukemia for males exposed to 5 or more rads skin dose from trunk x ray, relative to those exposed to less than 5 rad skin dose. Each line in Table IV summarizes an analysis of the total sample, 269 male controls and 214 male nonlymphatic leukemia cases. The first column indicates the value of k, the assumed aging per rad of exposure, which was used in calculating the exposure age of each case and control. Each summary relative risk is a composite of the relative risks within cohorts matched for exposure age. See Appendix A for the discussion of rad skin dose assigned to diagnostic procedures. The rad skin dose was used so that the results of the analysis could be interpreted in terms of current medical diagnostic procedures. The rad unit is also basic to dialogue with health physicists who are evaluating the effects of industrial exposures to ionizing radiation.

Table IV clearly conforms to the pattern predicted under the aging hypothesis. In fact, it is so remarkable that the reader may mistakenly think it is inevitable. The acceptable range of k values is found by noting the probabilities associated with a χ^2 test of the exposure-age-adjusted summary table. This is the probability of the occurrence of the relative risk because of random variation. The values of k between the two horizontal lines cannot be rejected on the 5% level. The k value marked with an asterisk is the estimate of k_0 for this body of data, namely, $k_0 = 0.60$.

In order to test the stability of the estimate of aging effect, i.e., of acceptable k values at even higher levels of radiation exposure, the entire analysis was repeated using as the exposure group those who had received 10 or more rads skin dose, and then repeated again using those who had received 15 or more rads skin dose.

As can be seen in Fig. 1, there is a stable band of values for k, between $k = 0.60$ and $k = 1.45$, which is common to all three analyses. The point estimate, $k_0 = 1$, i.e.,

TABLE IV. Relative Risks of Nonlymphatic Leukemia for Males Over 45 Years of Exposure Age With Trunk X-Ray Exposure of 5 or More Rads

No. years aging per 1 rad exposure	Age-adjusted relative risks	Probability
0.00	1.57	.0017
0.05	1.56	.0022
0.10	1.51	.0036
0.15	1.44	.0101
0.20	1.36	.0295
0.25	1.31	.0522
0.30	1.23	.1220
0.35	1.21	.1558
0.40	1.16	.2706
0.45	1.06	.6489
0.50	1.03	.7952
0.55	1.03	.7718
0.60*	1.00	.9797
0.65	0.99	.8869
0.70	0.94	.5978
0.75	0.93	.5253
0.80	0.92	.4436
0.85	0.90	.3839
0.90	0.94	.5678
0.95	0.92	.4392
1.00	0.93	.5078
1.05	0.91	.4003
1.10	0.89	.3138
1.15	0.90	.3348
1.20	0.88	.2145
1.25	0.87	.2009
1.30	0.86	.1787
1.35	0.85	.1325
1.40	0.84	.1138
1.45	0.82	.0513
1.50	0.79	.0323
1.75	0.76	.0071
2.00	0.74	.0020
2.25	0.71	.0004

*For this body of data $k_0 = 0.60$.

1 rad skin dose exposure to the trunk is equivalent to 1 year natural aging, is a statistically acceptable explanation for the occurrence of nonlymphatic leukemia among those exposed to ionizing radiation. Key to understanding the significance of this finding is the observation that no greater aging per rad needs to be assumed to account for increased leukemia among those exposed to more than 15 rads than for those exposed to more than 10 rads. This is true, although for k = 0, i.e., for no exposure age adjustment, the relative risk of nonlymphatic leukemia for persons having more than 10 rads exposure is 2.00, with probability 0.00, and the relative risk for persons with more than 15 rads exposure is 2.35, with probability 0.00. Both risks decrease with increases in k, and both become 1 at k = 0.95.

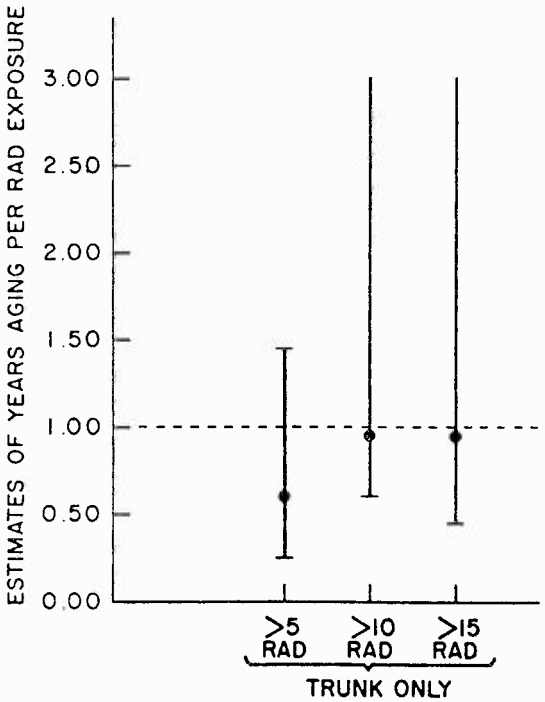

Fig. 1. Statistically acceptable estimates for the rad skin dose (mR in air at skin entrance) equivalent to one year natural aging, for the Tri-State Survey data. Each line represents a 90% confidence interval for k_0 using the indicated cut-off.

The slight discrepancy between the first analysis and the two using higher rad exposure levels may be explained by noting that the cases and controls reporting higher levels of exposure were also those reporting abdominal x ray. The value of k_0 would be expected to rise under the supposition that irradiation of major components of the hemopoietic system was the relevant exposure involved in the etiology of leukemia. The k value is remarkably stable and the age shift accounts for the previously reported increased relative risk of leukemia with exposure to medical x ray in a statistically acceptable way.

What seems clear, then, is that it is possible to account totally for the radiation-related increase in relative risk of nonlymphatic leukemia in this data by a simple and well-defined age shift which depends on the level of exposure only. For trunk exposure in males aged 45 and older, this age shift is most probably between 0.60 years and 1.45 years per rad skin dose. The easily remembered formula "1 rad is equivalent to 1 year natural aging" is consistent with my findings.

DISCUSSION

This analysis would have been impossible without precise information on each case and control. Prospective studies and human surveillance systems designed to evaluate environmental hazards need similar careful design if they are to yield meaningful infor-

mation. This has many implications for gathering of routine health statistics. Such fine analysis cannot be carried out using vital statistics as presently collected and published. An adequate gathering of factual data is required to test further the implications of these results.

A second implication of this study has to do with methodology. If we wish to answer the epidemiological questions of the 1970's, we must update our statistical methodology and discover creative new uses of standard techniques. These new approaches to statistical methodology are needed so that the increased precision of information is not lost because of inadequate mathematical techniques, and scientific hypotheses are not neglected because they are not formulated with analytical precision.

The questions of excessive use of diagnostic x ray and the combination of medical exposure with excessive environmental pollution must be faced as important public health problems requiring immediate national attention.

Implications of this study for medical use of diagnostic x ray, especially when the purpose of such patient exposure is to further basic research or to prevent malpractice suits, are serious. It seems advisable to begin steps immediately to curtail unnecessary x rays or x rays not directly beneficial to the person receiving them. Patient records should show a cumulative account of all diagnostic x ray received, including dental. Informed patient, or guardian, consent should be required before each exposure.

Analyses of other radiation-related diseases, such as coronary, atherosclerosis, cataracts, and various solid tumors, in a way comparable to this study of nonlymphatic leukemia, are needed. These studies would perhaps clarify some of the mechanisms of aging, as well as reveal the more generalized effects of ionizing radiation. It is imperative that the effects of low level radiation on humans be further researched before we implement elaborate diagnostic x ray techniques and/or make an irrevocable commitment to pollute the environment further with hazardous radioactive material.

Appendix B has been added to give the mathematical reader a deeper insight into the underlying theory which prompted this research and the future directions which measurements of low level radiation effects may be expected to take.

APPENDIX A

Coding of the verified diagnostic x-ray data in the Tri-State Survey includes the exact number of plates used in medical examinations of four body sites: teeth, chest, abdomen, and extremities. The latter category included head and neck examinations.

For the purpose of this paper, the two categories, chest and abdomen were selected. In the years since the survey was collected there has been a change in the radiation exposure in terms of rads skin dose per plate for these examinations; hence a conversion from number of plates to rads skin dose was indicated. This conversion provides a more meaningful tool of communication, not subject to the variations noted in the measurement by plate.

Conversion of number of x-ray plates used to rads skin dose received was based on estimates for medical practice in the United States for 1960 made by the Bureau of Radiological Health, Department of Health, Education and Welfare (Gitlin and Lawrence, 1966). Abdominal x-ray conversion was 790 mrad skin dose per plate. No overall estimate of rads skin dose per chest x-ray plate is given, so a weighted average assuming that 90% of such exposures were standard chest radiographic examinations of the lungs, and 10% were cervical or thoracic spine or other upper trunk examinations, was used. These

percentages were reported for the general public, and were verified for a random sample of the Tri-State Survery. An estimate of 167 mrad skin dose x-radiation was used for each verified chest plate reported.

Further research involving estimates of bone marrow dose per diagnostic procedure would be expected to yield further information on the etiology of leukemia.

There is also evidence that irradiation of the liver and spleen, or other specific organs, may be of special biological interest with respect to aging. A recoding of the Tri-State Survey information would be needed to answer these questions.

APPENDIX B

The original insight into the equivalence of 1 rad exposure to ionizing radiation and 1 year of natural aging came through the fortuitous applications of a newly developed mathematical technique to both aging and exposure to diagnostic trunk x ray. This new technique will be presented in detail in another paper "On estimating leukemia risk per x-ray plate," which is in preparation. It was designed to quantify an increase in relative risk of disease for exposure to an environmental hazard which admits of measurable degrees, such as numbers of x-ray plate exposures, packs of cigarettes smoked per day, years of natural aging, etc.

Application of the mathematical theory to trunk x-ray exposure and to natural aging showed an increase in relative risk of nonlymphatic leukemia of 5 to 6% with each plate and/or year. The striking similarity was not immediately accepted as indicative of equivalence, but was used rather to formulate a precise hypothesis which could be rigorously tested in the manner described in the body of this paper.

For the reader interested in the technique involved in quantifying the relative risk of nonlymphatic leukemia per year of aging, a brief explanation is given here.

Table II gives the age distribution according to the 1960 census for the appropriate areas from which the Tri-State survey data were drawn. From this distribution two theoretical distributions, T_5 and T_6, were derived; T_5 and T_6 represent cumulative relative frequency functions assuming a relative risk of $(1.05)^t$ and $(1.06)^t$ of leukemia for t years beyond 15 (Table V). The theoretical expected frequencies are obtained as follows:

From the relative frequencies in the census data, we determine that $p(20) = 0.168$

TABLE V. Theoretical Cumulative Relative Frequency Curves for Relative Risks $(1.05)^t$ and $(1.06)^t$ for t Years Beyond 15*

Age	T_5	T_6
15–24	3.6	2.4
25–34	9.7	7.1
35–44	20.5	16.0
45–54	36.7	30.7
55–64	58.3	52.2
65–74	82.2	78.4
75+	100.0	100.0

*This table is derived from Table II, the age distribution of the population from which the Tri-State information was drawn. See text for explanation of the methodology involved in the derivation.

is the probability of being in the 15–24-year age category; p(30) = 0.177 is the probability of being in the 25–34-year age category, and so on.

Under the hypothesis that the relative risk of leukemia for each year of natural aging is 1.05, the probabilities for the cases are obtained:

$$q(20) = \frac{(1.05)^5\ p(20)}{S}$$

is the probability of a case being in the 15–24-year category, and

$$q(30) = \frac{(1.05)^{15}\ p(30)}{S}$$

$$q(40) = \frac{(1.05)^{25}\ p(40)}{S}, \text{ and so on,}$$

where S is the sum of all the numerators. The cumulants can then be formed.

This definition conforms to the usual meaning of relative risk or odds ratio, since the odds for getting leukemia in the 25–34-year age category relative to the 15–24-year age category would be:

$$R.R.* = \frac{q(30)\ p(20)}{p(30)\ q(20)} = (1.05)^{10}.$$

Figure 2 shows the observed cumulative relative frequency function for the cases against the band predicted when there is a 5 to 6% increase in relative risk with each year of natural aging.

The deviation of the cumulative relative frequency function of the combined acute myeloid, chronic myeloid, and nonlymphatic leukemias could not be distinguished statistically from the predicated curves T_5 and T_6, based on a relative risk of (1.05) and (1.06) per year of natural aging, with the Kolmogorov-Smirnov test (Siegel, 1956). The maximum deviation between the cumulative relative frequency curve of the cases and the theoretical curve T_5 was +4.0; its maximum deviation from T_6 was −3.8. Both values are acceptable random deviations, in a 90% confidence interval. Separate analyses for males and females showed consistent and similar results.

The comparison of the subsample of those cases with verified x-ray reports and the census data revealed no age bias caused by the verification procedure.

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*R.R. is the ratio of disease incidence in one subgroup of a population to the disease incidence in another subgroup. As used here, the subgroups are persons 25–34 years old and persons 15–24 years old.

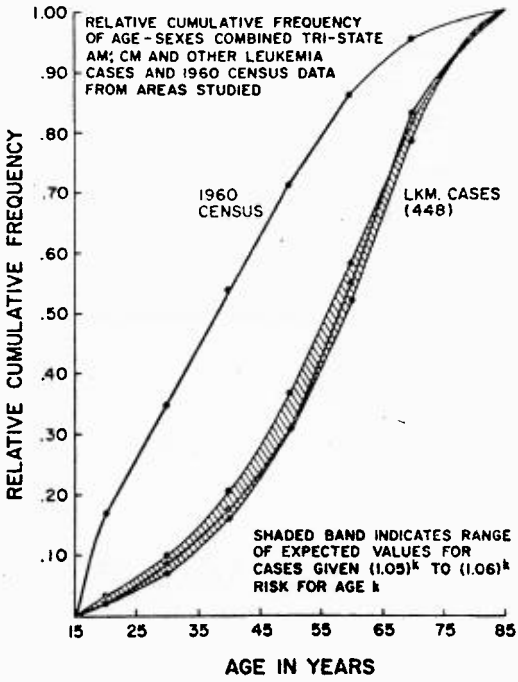

Fig. 2. Mathematical model for predicting the age distribution of the leukemia patients in the Tri-State survey. Leukemia types are as noted in Table I.

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