A Cohort Study of the Cancer Risks from Radiation to Workers at Hanford

by the Method of Regression Models in Life-Tables

by

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Introduction

In 1977 a report was published[1] of a preliminary analysis of cancer risks from radiation to workers at the Hanford works, Richland, Washington. This report indicated a risk for bone marrow cancers among reticulo-endothelial system (RES) neoplasms, and for cancers of pancreas and, to a lesser extent, lung among solid tumours. These risks showed a definite relation to radiation doses of individual workers.

This report aroused controversy because the estimated increase in risk (per unit dose) at relatively low dose levels (less than 30 rads) was approximately 10 to 20 times greater than would have been expected by extrapolating downwards from somewhat higher doses analysed in previous studies, notably the Japanese atomic bomb survivors (ABCC data)[2]. Therefore, two independent analyses of essentially the same data by different scientists using different methods were made in order to see whether our findings could be confirmed[3,4]. Both studies essentially confirmed the findings in relation to bone marrow and pancreatic cancers but drew different conclusions.

Meanwhile we continued analysing the data[5] and showed that an increase in risk was still observable after simultaneous control for the following factors: sex, age at death, year of death, years worked and level of monitoring for internal exposure to radioactivity (see below). This paper introduced the important concept of concentrating on cancers in tissues which are known (by others) to be sensitive to cancer induction by radiation. In epidemiological studies it is often necessary to subdivide cancers because a particular agent may be inducing some cancers more than others. If this subdivision is done without previous knowledge of tissue sensitivity it will often be necessary to carry the subdivision so far that the subgroups are too small for an adequate statistical test. In the field of cancer induction by radiation this difficulty no longer exists because a wide body of previous experience has shown which tissues are most sensitive[6,7].

Previous reports by us[1,5] and the NCI report[3] used the methodology of proportionate mortality analysis and related the proportion of cancers to cumulative dose. The Battelle[4] report used the SMR approach and was thus able to identify a substantial "Healthy Worker" effect, presumably because of stringent pre-employment health checks etc. In this study the SMR for all causes of death was 75 and for cancers 89. The question arises, how much of this difference is due to inefficient rejection of cancer-prone workers at health checks and how much to radiation? Clearly what is needed is a method of analysis in which <u>nothing</u> is assumed about cancer mortality of Hanford employees in the absence of radiation.

Nature of the Data

The variables recorded and the method of data collection have been described elsewhere[8] and only a few relevant facts are noted here. The present analysis includes employees up to 1975 who wore film badges (and deaths up to 1977) and the main epidemiological facts are summarised in Table 1.

The prime variable is the vector of annual dose of external (or penetrating) radiation as measured by the film badge. Formally these doses are measured in rems to the nearest centirem not rads but this refinement is an illusion since prior to 1960 there was only one type of film in the badge and thus it is impossible to separate the effects of gamma rays, neutrons and x-rays, which have different quality factors. Only cohorts exposed prior to 1960 are yet old enough to have substantial numbers of deaths and this is a major limitation to possible conclusions from any analysis.

Files describing basic epidemiological facts about the population, death certificates and various kinds of radiation exposure are in a good state of quality control and very suitable for analysis. However, the file describing work histories is so poor that the Battelle scientists had to recode all the occupations before using them in their analysis[9]. We have adopted a different approach and decided to kill two birds with one stone by using the level of monitoring for internal exposure as an indication of the occupational risk. In any case this level is strongly correlated with the total external dose (as may be seen in Table 2) and therefore ought to be included in any analysis.

Statistical Methodology

As already mentioned an ideal methodology ought to assume nothing about death rates in the absence of radiation. It ought also to be able to statistically control for any combination of relevant epidemiological variables, as a Mantel-Haenszel analysis can, and be able to include data on both live and dead workers. Ideally it ought also be able to estimate parameters of simple dose effect models (e.g. latent period, doubling dose, linearity of dose-response etc.) as well as testing the null hypothesis of no radiation effect.

A methodology satisfying these criteria was developed in the course of correspondence with interested scientists and an attempt was made to publish in Nature. However, a referee pointed out that the method of Cox[10] on the analysis of Regression Models in Life-Tables (originally supposed to be of use only in clinical trials) had simply been rediscovered. Therefore, the mathematical explanation, in the Appendix, is based on the paper by Cox.

The method divides into two parts: first, a relatively simple calculation to test the null hypothesis of no radiation effects, and second a more complex calculation, based on a transformation of the dose to estimate parameters of a specific dose-effect model. In both calculations the data are first divided into a large number of subgroups by levels of controlling variables. In each subgroup a life-table is constructed, giving for each year of follow-up, the total number at risk, the number of cancers dying in that year, and the mean doses (transformed doses in the second calculation) of these two

categories, cumulated to the year of follow-up or death. One then obtains summary variables for each subgroup by certain summations over years of follow-up and finally a grand summary by summation over all sub-groups. The result is, in the first case, a t-statistic with an approximately normal distribution if the null hypothesis is true and, in the second case, a log-likelihood which measures the goodness of fit of the specific dose-effect model according to which the dose transformation was calculated. By varying the parameters of the dose- effect model one can then calculate maximum likelihood estimates in the usual way.

Results

Validation of the Controlling Factors

In table 1 are shown the levels of the controlling factors used, and in table 3, the definition of cancers of radiosensitive tissues. This definition is the same as the one in a previous paper[5] except that on the advice of experts we have included all RES neoplasms and breast cancer[7].

Before these definitions can be used in the analysis proper, it is necessary to show that the range of controlling factors is adequate. The reason for this necessity may be seen by considering the paper by Sanders[11]. He, in effect, used the same method, but without the mathematical basis and with fewer controlling factors.

He came to the conclusion that radiation exposure, if it did anything, increased longevity, because survivors had higher doses than non-survivors. In fact, using as controlling factors, only sex, year of hire and age at hire, our analysis finds a grand summary t-value for comparing all deaths with survivors of -4.6395 (table 4), which is highly significant and indicative of increasing longevity. But the methods employed in this paper can go further, and do what Sanders did not, namely estimate the magnitude of this effect by fitting a model. Practically any model will show that doses of less than 5 rads seem sufficient to reduce the death rate from all causes by more than half, or equivalently to extend longevity by 10 years! Inasmuch as a not insubstantial number of workers received over 30 rads they should have longevity extended by 60 years and live to be more than centenarians. This conclusion is contrary to the facts, but merely by adding exposure period and internal radiation monitoring to the controlling factors, the grand summary t-value for all deaths may be reduced to -0.4847 (table 4) which is non-significant.

Tests of the Null Hypothesis for Cancers

Having shown that the range of controlling factors is adequate, the appropriate tests now are those of the null hypothesis (of no radiation effect) using the definitions of Tables 1 and 3. Table 5 shows one of the life-tables that are intermediate in this calculation. The grand summary t-values obtained are as follows:- the one for cancers of radio-sensitive tissues is significantly positive

at 2.4701, while the one for other cancers is significantly negative at -2.1957. Why other cancers should show a negative effect is still a mystery: it may be that although the controlling factors are adequate for all causes of death, more control is needed for these cancers. Whatever the reason, the fact that the two different kinds of cancers give opposite results only strengthens the case that the result for cancers of radiosensitive tissues is genuine, since the distinction was made a priori and the test is of radiation effects per se.

Model Fitting: I

Having shown that cancers of radiosensitive tissues gave a significant positive result in the test of the null hypothesis, an attempt was made to fit a simple model (table 6). This first model only allows for variation of the assumed doubling dose and a parameter measuring non-linearity of dose-response. Equal weights were given to doses of radiation at whatever age they were received or at whatever interval before death, so no allowance was made for cancer latency. The log-likelihoods (relative to no radiation effect) for various combinations of the parameters are given in Table 6. These are plotted as log-likelihood curves in Figure 1, and sample dose-response curves equivalent to typical combinations of parameters are plotted in Figure 2. Both theoretical and practical considerations show that in plotting log-likelihood curves the parameter D (doubling dose) should be measured on an inverse scale for best possible interpolation on the curves.

Inspection of the curves in Figure 1 shows that for all values of D, the log-likelihood is higher for E=0.5 (corresponding to a half-power law for the dose-response) than for any other value of E, in particular E=1.0 (corresponding to a linear dose-response). This is interesting because if the very differing estimates of doubling dose (assuming linearity) from ABCC and Hanford data were to be reconcilable, one would expect that the true dose-response relationship should have this kind of downward curvature. By inspection of Figure 1 the maximum likelihood estimate of doubling dose is approximately 30 rads for the linear model and 15 rads for the half-power model.

Model Fitting: II

Following these encouraging results with a simple model a more complicated model (allowing for cancer latency and variation in sensitivity with age at exposure) was fitted (table 7).
The results for this model are:

(a) a maximum likelihood estimate for E of 0.5 (half power dose-response law) with E=1.0 rejected at the 1% level;

(b) a maximum likelihood estimate for D of 15 rads with a 95% confidence interval of 2 to 150 rads;

(c) a maximum likelihood estimate of L (interval between induction and death) of 25 years and

(d) a maximum likelihood estimate of the amount, by which age at exposure must increase in order to increase sensitivity by 2.7183, given by S=8 years, with $S=\infty$ (corresponding to constant sensitivity with age at exposure) rejected at the 1% level.

Conclusions

The main body of data on the carcinogenic effects of penetrating radiation in man previous to the Hanford Study was the ABCC study[2] and the study of ankylosing spondylitics[12]. Both these studies broadly agree that the dose-response relationship for doses greater than about 100 rem shows no evidence of curvelinearity within experimental error and that the doubling dose for radiosensitive cancers (as defined in this paper) is of the order of 200 rem. The two sets of data on latent periods broadly agree with estimates of this paper showing an effect continuing and in some cases still increasing after 20 years. Less has been published on the effects of age at exposure, but what has been would tend to show that the relative risk tends, if anything, to increase with age, though the measured effect is by no means as great as that estimated in this paper.

Thus the main area of disagreement between published studies of Hanford data (which gave a doubling dose of about 15 rad assuming linearity of dose-response) and other human data lies in the dose-response relationship and specifically the doubling dose which implies an effect about 15 to 20 times greater.

If, however, the dose-response relationship estimated in this paper - which implies major downward curvature in the region of 10 rads - is extrapolated upwards to the region of greater than 100 rads, covered in the other studies, then it predicts an effect two to three times lower than linear extrapolation. Furthermore if one takes into account the fact, mentioned previously, that the Hanford study cannot separate the greater radiobiological effect of neutrons, one should probably reduce the difference by another factor of two to three. Thus the

remaining unexplained component of the difference is only a factor of two to three.

This remaining factor is of a magnitude small enough to be accounted for by the increased liability of pre-cancers in general and pre-leukaemias in particular to deaths from infections shortly before they would otherwise be diagnosed as cancers. This fact has recently been confirmed for children's cancers[13], and almost certainly holds true for adult cancers also. This effect could play an important role, since, as mentioned above, there is a strong "Healthy Worker" effect at Hanford whereas the Japanese atomic bomb survivors lived through the aftermath of a catastrophe and the ankylosing spondylitics already suffered from a crippling disease.

Thus putting all the data together can give a reasonably consistent explanation of the observed facts. But one discrepancy remains to be accounted for. That is, the prediction (by others) that (by our estimates) background radiation amounting to about one-tenth of a rem per year should account for more cancers than actually exist. This can be taken account of by three factors. Firstly, the increase in sensitivity with age means that a great proportion of the lifetime exposure to background radiation would occur at a relatively insensitive age. Secondly, the long latent period means the increased risk will only be expressed if the individual manages to survive other causes of death to an advanced age. Thirdly, the simplistic assumption that each cancer case has only one cause is almost certainly wrong. The method of calculation employed in this paper is such that if, for example, radiation worked jointly with smoking (not measured in the data), to produce lung cancer, then radiation would be regarded as contributing to the risk even if there was apparently already a sufficient cause, namely the smoking.

APPENDIX

Regression Models In Life-Tables

A life-table contains information on individuals exposed to various treatments and followed-up for several years. A characteristic feature is that the final fate of some individuals is not known; that is, their survival time is censored and all that is known is that they were alive at the end of follow-up. A crucial assumption is that this censoring time is statistically independent of the final fate whatever it may be. The question at issue is whether the survival curves differ between treatments. In the seminal paper by Cox[9] only one kind of ultimate fate was considered; in other words, if an individual was not alive at the end of follow-up any cause of death was considered of interest. The present problem differs in that only cancers are supposed a priori to be susceptible to radiation induction, so two kinds of ultimate fate, cancer and non-cancer, must be considered. The probability of non-cancer is assumed independent of any radiation, and if the plausible assumption is made that the probability of censoring is also independent of radiation (though it will obviously depend on other treatment factors such as work cohort), then the censored and non-cancers can be considered together, which greatly simplifies the statistical analysis.

Because the data give the radiation doses in yearly exposures and not more finely divided it is convenient to work in discrete time units of one year. The basic method is to divide the data into a large number of treatment sub-groups (480 in the present paper) by the cross-classification of non-radiation-controlling factors. The survival curve of cancers in each sub-group in the absence of radiation is considered arbitrary and estimated by maximum likelihood. The survival curve in the presence of radiation is assumed related to that in its absence by a simple regression model whose parameters can then be estimated by maximum likelihood.

Derivation Of Likelihood Formula

Let the data be divided into G sub-groups indexed by g. Let the follow-up years be indexed by i and j. Let there be K individuals indexed by k. Let individual k be in sub-group G_k and be followed up to year I_k. Let a_k be one if individual k dies of cancer and zero otherwise. Let b_k be one if individual k dies of non-cancer or is censored and zero otherwise. Let $\lambda_A(i,g)$ be the probability of dying from cancer in sub-group g and follow-up year i. Let $\lambda_B(i,g)$ be the corresponding probability of dying from non-cancer or of being censored. Then $[1-\lambda_A(i,g)-\lambda_B(i,g)]$ is the probability of surviving year i in sub-group g. Let X_{ki} be the radiation dose of individual k in year i. Let $\underline{x}_k$ be a vector of length I_k containing these doses. Let the model of radiation effects be that the relative risk of cancer for individual k in year i is increased by the factor $(1+E(\underline{x}_k,i))$ where E is a simple function specifying the model. For example a very simple model has $E(\underline{x}_k,i) = (\sum_{j=1}^{i} X_{kj}/D)$ with equally weighted doses and a constant doubling dose D. Then the overall likelihood is given by

$$\prod_{k=1}^{K}\left\{\prod_{i=1}^{I_k}[1-\lambda_A(i,G_k)(1+E(\underline{x}_k,i))-\lambda_B(i,G_k)][\lambda_A(I_k,G_k)(1+E(\underline{x}_k,I_k))]^{a_k}[\lambda_B(I_k,G_k)]^{b_k}\right\}$$

Let R_{ig} be the survivors to the beginning of year i in sub-group g. Let A_{ig} be the cancers dying in year i in sub-group g and B_{ig} be the corresponding number of non-cancers and censored. So the survivors to the next year are given equivalently by $R_{(i+1)g}$ or $(R_{ig}-A_{ig}-B_{ig})$. Then, using the notation $\sum_{k\in R_{ig}}$ to mean summation over the R_{ig} individuals surviving to year i in sub-group g and a similar notation for summation over the A_{ig} cancers dying in that year, the overall log-likelihood is given by

$$\sum_g\left\{\sum_{k\in R_{ig}}\ln[1-\lambda_A(i,g)(1+E(\underline{x}_k,i))-\lambda_B(i,g)]+A_{ig}\ln[\lambda_A(i,g)]+\sum_{k\in A_{ig}}\ln[1+E(\underline{x}_k,i)]\right.$$
$$\left.+B_{ig}\ln[\lambda_B(i,g)]\right\}$$

Optimum Test Of The Null Hypothesis

Since by year i the doses for years less than i and consequently $E(\underline{x}_k, i)$ and also R_{ig} are all fixed, the only term in the log-likelihood that actually depends on any connection between the doses and the number of cancers is $\sum_{ig}\{\sum_{k\epsilon A_{ig}} \ln[1+E(\underline{x}_k, i)]\}$ and consequently by sufficiency arguments the difference between two such terms is the optimum statistic for testing which of two fully specified models, corresponding to two forms for E, is the better fit. If the null hypothesis of no radiation effect is true the function E and the term it specifies are both identically zero, and so the term corresponding to the model of some effect is the optimum test of that model compared to the null hypothesis. For the very simple model with equal weights and a constant doubling dose the test statistic becomes $\sum_{ig}\{\sum_{k\epsilon A_{ig}} \ln[1+(\sum_{j=1}^{i} x_{kj}/D)]\}$. If the doubling dose under test is large and fixed, then by expanding the logarithm and neglecting a constant of proportionality the effective statistic becomes $\sum_{ig}\{\sum_{k\epsilon A_{ig}} (\sum_{j=1}^{i} x_{kj})\}$ or the total dose of the cancers. Its distribution under the null hypothesis of no radiation effect may be found from the following considerations. If the null hypothesis is true the A_{ig} cancers dying in year i in sub-group g will be a random sample of the R_{ig} survivors who started the year. Therfore the mean under the null hypothesis of the test statistic will be $\sum_{ig}\{(A_{ig}/R_{ig})\sum_{k\epsilon R_{ig}} (\sum_{j=1}^{i} x_{kj})\}$ and its variance can be found by finite population sampling formulae. Hence a t-statistic can be constructed from the observed value and its mean and variance under the null hypothesis. If the number of cancers is reasonably large this t-statistic will be approximately normally distributed under the null hypothesis.

Fitting A General Model Of The Radiation Effect

If one is attempting to fit a general model with adjustable parameters in the function E, because the null hypothesis has been rejected by the previously derived test, one cannot use sufficiency arguments that work for fully specified models since the function E appears in more than one place in the expression for the log-likelihood. So an approach via general maximum likelihood theory appears suitable. Because of the number of parameters involved it would be better to estimate the parameters in λ_A and λ_B by maximum likelihood for a fixed function E, substitute these estimates in the likelihood and then estimate the parameters in E. This approach is made more simple if the likelihood function is first suitably approximated.

Let $E_{ig} = \sum_{k \in R_{ig}} E(\underline{x}_k, i)/R_{ig}$ be the estimated mean excess relative risk in year i in sub-group g. Then if $\lambda_A(i,g)E_{ig}$, the estimated proportion of radiogenic cancers in the R_{ig} individuals who started year i in sub-group g, is small compared with one, the term in the expression for the log-likelihood involving summation over R_{ig} can be approximated by $\sum_{ig}\{R_{ig}\ln[1-\lambda_A(i,g)(1+E_{ig})-\lambda_B(i,g)]\}$ With this approximation the maximum likelihood estimate for $\lambda_A(i,g)$ is $A_{ig}/[(R_{ig}+A_{ig}+B_{ig})(1+E_{ig})]$ and the corresponding value for $\lambda_B(i,g)$ is $B_{ig}/(R_{ig}+A_{ig}+B_{ig})$. The justification for using maximum likelihood estimates at all if R_{ig} is small, when the estimates will be very erratic, is given in terms of the power it gives against the most general forms for λ_A and λ_B in the paper by Cox[9]. Substituting these estimates into the expression for the log-likelihood, simplifying and neglecting constant terms, the log-likelihood becomes $L = \sum_{ig}\{\sum_{k \in A_{ig}} \ln[1+E(\underline{x}_k, i)] - A_{ig}\ln[1+E_{ig}]\}$ or, in other words, the sum over the cancers of the difference between the logarithms of the actual estimate of the relative risk and the mean estmate of matching

TABLE 1

HANFORD STUDY POPULATION.

All Workers Monitored for External Radiation

Specifications		Live Workers	Dead Workers(2) A	B	C	Total
Sex	Males	18009	503	240	3128	21880
	Females	5756	58	31	237	6082
Age at Hire (in years)	Under 25 yrs	8850	35	17	224	9126
	25 - 34	9330	143	61	733	10267
	35 - 44	4048	194	69	935	5246
	45 - 54	1341	143	86	1012	2582
	55+	196	46	38	461	741
Work Cohort (Calendar years)	1943-44	3005	215	132	1457	4809
	1945-49	5947	231	92	1311	7581
	1950-54	4659	83	29	407	5178
	1955+	10154	32	18	190	10394
Employment Period (in years)	0 - 2	8916	206	107	1324	10553
	3 - 7	5812	98	52	626	6588
	8+	9037	257	112	1415	10821
Levels of(1) monitoring for internal depositions of radioactive substances.	1	9087	211	119	1479	10896
	2	6016	154	78	928	7176
	3	2741	114	40	545	3440
	4	5921	82	34	413	6450
	Totals	23765	561	271	3365	27962

(1) 1. Nil.
2. Monitored with negative findings for internal depositions or external contamination.
3. One or more bioassays with positive findings for external contamination.
4. One or more bioassays with positive findings of internal deposition or whole body counts associated with positive bioassays.

(2) A. Cancers of Radiosensitive tissues.
B. Other cancers.
C. Non-cancer deaths.

TABLE 2

EXTERNAL RADIATION DOSES FOR 4 LEVELS OF MONITORING FOR INTERNAL RADIATION

Sex	External Radiation in Rads	Levels of Monitoring for Internal Radiation (1) 1	2	3	4	Total
Males	under 0.01	2609	494	87	21	3211
	0.01 - 0.07	1326	611	149	96	2182
	0.08 - 0.31	1586	1366	376	216	3544
	0.32 - 0.63	894	1019	338	209	2460
	0.64 - 1.27	707	822	523	670	2722
	1.28 - 2.55	321	686	801	1266	3074
	2.56 - 5.11	76	269	325	1064	1734
	5.12 - 10.23	38	96	173	910	1217
	10.24 - 20.47	27	37	69	686	819
	20.48 - 40.95	3	8	33	675	719
	40.96 - 99.99	2	2	1	193	198
	Total	7589	5410	2875	6006	21880
Females	under 0.01	1391	352	58	8	1809
	0.01 - 0.07	574	321	81	17	993
	0.08 - 0.31	829	532	128	43	1532
	0.32 - 0.63	315	243	71	39	668
	0.64 - 1.27	138	204	102	103	547
	1.28 - 2.55	54	84	77	103	318
	2.56 - 5.11	6	20	21	53	100
	5.12 - 10.23	-	8	16	31	55
	10.24 - 20.47	-	2	8	39	49
	20.48 - 40.95	-	-	3	8	11
	40.96 - 99.99	-	-	-	-	-
	Total	3307	1766	565	444	6082

(1) See table 1 for definition of levels.

TABLE 3

DETAILED SPECIFICATIONS OF CANCERS OF RADIOSENSITIVE TISSUES

Cancers of Radiosensitive Tissues		No. of Cases. Male	Female	Total
Alimentary	Stomach	44	2	46
	Large Intestine	69	9	78
	Pancreas	52	5	57
	Other Intestinal	37	3	40
Respiratory	Pharynx	10	-	10
	Lung	215	10	225
Female	Breast	-	19	19
Reticulo-Endothel System	Lymphoma	40	3	43
	Myeloma	10	1	11
	Myeloid Leukaemia	15	-	15
	Other RES	11	6	17
	Total	503	58	561

TABLE 4

Effect of Introducing Different Controls into Comparisons between Live Workers with those Dead from Any Cause

Controlling Factors[1]	t-values[2]
1. Sex, work cohort, hire age.	-4.6395***
2. Ditto plus employment period.	-3.5953***
3. Ditto plus internal radiation monitoring levels.	-0.4847

(1) For factor levels see table 1.

(2) For the null hypothesis of no radiation effect (using cumulative untransformed doses)

*** Significant at the 0.01% level.

TABLE 5

Life Table for Typical Cohort[1]

Year of Follow-up(i)	Survivors to Beginning of Year (R_{ig})		Cancers of Radio-sensitive Tissues Dying in Year (A_{ig})		Deviation (Rads)	Variance (Square Rads)	t-Value
	Number	Mean Dose	Number	Mean Dose			
1-11	414	1.68	-	-	-	-	-
12	414	1.99	-	-	-	-	-
13	414	2.34	-	-	-	-	-
14	414	2.75	-	-	-	-	-
15	414	3.17	-	-	-	-	-
16	413	3.61	-	-	-	-	-
17	413	4.09	-	-	-	-	-
18	410	4.66	-	-	-	-	-
19	409	5.17	1	29.30	+24.13	61.00	+3.09
20	407	5.60	-	-	-	-	-
21	406	6.15	-	-	-	-	-
22	402	6.62	-	-	-	-	-
23	397	6.93	-	-	-	-	-
24	392	7.13	1	0.79	-6.34	106.8	-0.61
25	387	7.42	2	15.28	+15.69	228.6	+1.04
26	378	7.63	1	4.76	-2.87	121.0	-0.26
27	374	7.73	1	6.96	-0.77	127.4	-0.07
28	267	7.50	1	2.17	-5.33	115.1	-0.50
29	162	7.90	-	-	-	-	-
30	134	8.21	4	3.98	-16.92	404.8	-0.84
31	5	8.39	1	12.83	+4.44	27.3	+0.85
32	3	8.60	-	-	-	-	-
33	1	2.21	-	-	-	-	-
Σ	11543 Man-Years	3.50	12	8.60	+12.03	1192.0	+0.34

(1) i.e. Males for the 1945-49 cohorts who were:

(i) 25 to 34 years of age when hired;
(ii) employed for more than 8 years, and
(iii) had 4th grade of monitoring for internal radiation.

TABLE 6 Fitting of Simple Model

Let X_j = dose in follow-up year j, and let the relative risk in follow-up year i be given by $R_i = 1 + (\sum_{j=1}^{i} X_j/D)^E$ where D is the assumed doubling dose and E is the exponent for non-linearity (E = 1.0 gives a linear dose-response relationship).

Model Number	E	D rads	Log-Likelihood Relative to no Radiation Risk.
1	1.0	∞	0.0000
2	1.0	100	1.7046
3	1.0	50	2.5307
4	1.0	25	2.8818
5	1.0	15	2.1187
6	1.0	10	0.3942
7	2.0	∞	0.0000
8	2.0	50	1.1697
9	2.0	25	-0.6964
10	2.0	15	-9.7484
11	0.5	∞	0.0000
12	0.5	50	3.8979
13	0.5	25	4.3815
14	0.5	15	4.5278
15	0.5	10	4.4394
16	0.3333	∞	0.0000
17	0.3333	25	3.9659
18	0.3333	15	3.9173
19	0.3333	10	3.7579

TABLE 7

Fitting of More Complex Model

Let radiation received k years before death have to be multiplied by a factor W_k to give the effective dose,

where $W_k = (k/L) \exp\left[1-(k/L)\right]$

and L is the optimum latent period in years (W_k is less than 1.0 for all k except k equal to L).

Let radiation received at age a have to be multiplied by a factor U_a to give the effect of age at exposure,

where $U_a = \exp\left[(a-40)/S\right]$

and S is the amount in years by which age at exposure must increase to increase sensitivity by a factor e (2.7183). U_a is standardised to give a sensitivity of 1.0 at exposure age 40.

Let the radiation received in follow-up year j be X_j and let the cumulative effective dose by follow-up year i be Z_i,

where $Z_i = \sum_{j=1}^{i} W_{(i-j)} U_{(h+j)} X_j$ and h is the hire age in years.

Let the relative risk in follow-up year i be given by R_i

where $R_i = 1 + (Z_i/D)^E$

and E is the exponent for non-linearity and D is the assumed doubling dose for radiation received at age 40 and death after the optimum latent period (L years).

Model Number	L years	S years	E	D rads	Log-Likelihood
1	any	any	any	∞	0.0000
2	10	∞	0.5	15	4.8748
3	20	∞	0.5	15	5.0972
4	30	∞	0.5	15	5.0483
5	25	20	0.5	30	6.4304
6	25	-20	0.5	30	2.6846
7	20	20	0.5	30	6.4806
8	20	15	0.5	30	7.0649
9	20	10	0.5	30	8.0644
10	20	5	0.5	30	7.3960
11	20	2	0.5	30	0.8342
12	20	8	0.5	30	8.5601
13	15	8	0.5	30	8.3384
14	25	8	0.5	30	8.6314
15	25	8	1.0	30	1.6531
16	25	8	0.3333	30	8.0394
17	25	8	0.5	20	8.8489
18	25	8	0.5	50	8.0931
19	25	8	0.5	100	7.0663
20	25	8	0.5	10	8.6104
21	25	8	0.5	15	8.8558

FIGURE 1

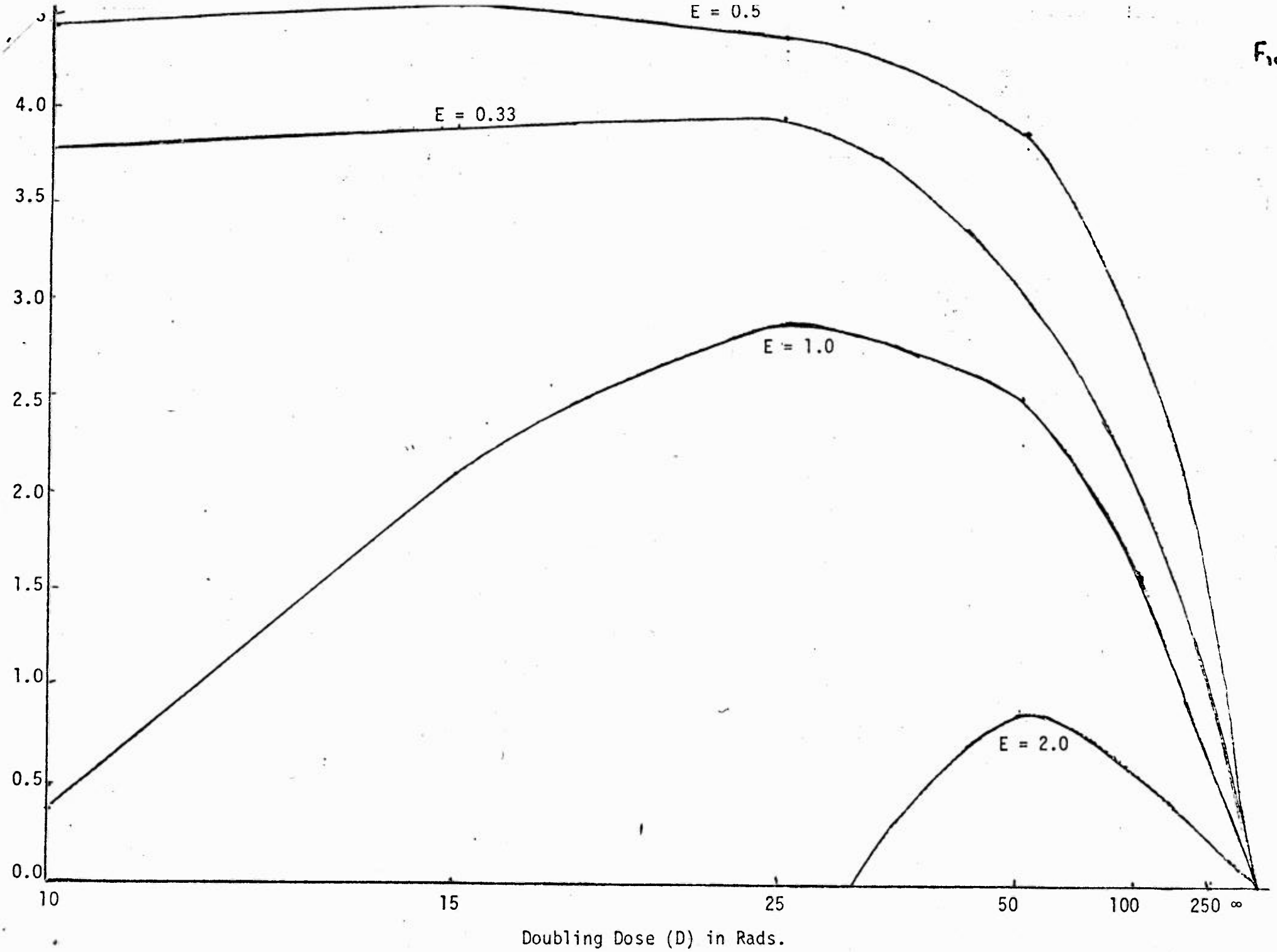
Curves of Log-Likelihood Against Assumed Doubling Dose (D) for Various Values of the Exponent for Non-Linearity (E) Arising in the Fitting of the Simple Model.

FIGURE 2

Typical Dose-Response Curves of Relative Risk (R) Against Cumulative Dose (Σx) for Various Values of the Parameters (D and E) in the Simple Model: $R = 1 + (\Sigma x/D)^E$

Curve A : D = 30 Rads, E = 1.0 (Linear Law)
Curve B : D = 15 Rads, E = 0.5 (Square-Root Law)
Curve C : D = 15 Rads, E = 0.3333 (Cube-Root Law)
Curve D : D = 50 Rads, E = 2.0 (Quadratic Law)

Fig 1


E = 0.5
E = 0.33
E = 1.0
E = 2.0
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
10
15
25
50
100
250
∞
Doubling Dose (D) in Rads.

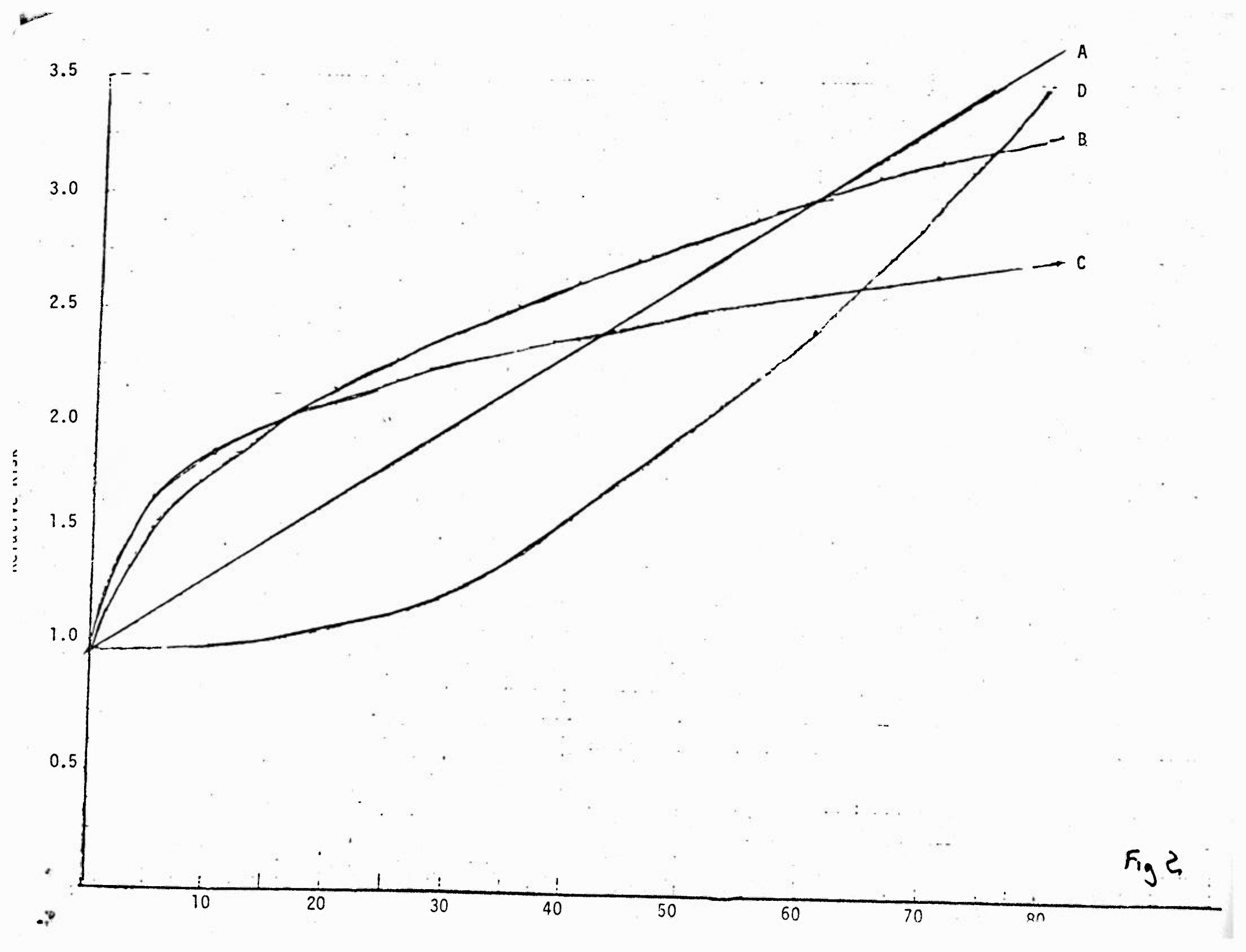


Fig 2