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NOTE

Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

Symbols of United Nations documents are composed of capital letters combined with figures. Mention of such a symbol indicates a reference to a United Nations document.

Annex G

MAMMALIAN SOMATIC EFFECTS

TABLE OF CONTENTS

I. Shortening of the life-span in experimental animals

The experimental effect of single doses on short-term survival

1. The short and long-term effects of whole-body exposure to a single dose of radiation have been studied in a variety of mammals. When "survival time" (duration of life after exposure) is studied as a function of radiation dose, the results with all species have shown fundamental similarities that may be illustrated here with the data of a hypothetical experiment.

2. The plan and results of the hypothetical experiment are shown in table I and figure 1. The animals were young adult males, 100 days old on irradiation. They were of a species with a relatively short life span of 2½ years. Slightly different results would be obtained with females. Greater effects per unit of radiation dose would be obtained with immature animals or with sick animals.

3. The mortality-time curve (figure 1) illustrates three major periods:

(*a*) The acute period lasting about one month, for which the LD_{50} is 600 rem;

(*b*) The intermediate period whose duration of 1.5-2 years depends on the radiation dose, and during which practically no deaths occur;

(*c*) The terminal period during which the population dies out rapidly.

4. Long-term somatic effects develop during the intermediate period and some of them become "limiting factors" for survival in the terminal period. The complete quietude of the intermediate period indicated in figure 1 is therefore misleading—the intermediate period is, in fact, a period of increasing morbidity. The rate of increase may be slow or fast, depending on the radiation dose and also on various biological factors, many of which are predetermined genetically.

5. The long-term decrease in life-span, illustrated in figure 1, is dealt with quantitatively in the sixth column ("Days") of table I. The decrease is not proportional to the acute mortality (column 4). The decrease can also be expressed as a percentage of the normal life span (column 7), which in the present experiment was 900 days. It is useful to express life-shortening in per cent of normal life span for purposes of comparing results of experiments involving species that differ in life-span.

Table I. Hypothetical experiment

The animals (males, 100 days old) received a single whole-body exposure on experiment-day 0. The table records the doses given to the various groups, and the resulting changes in their median life-spans.

Group	Radiation dose rem	Number of live animals		Median survival time of animals alive on day 30 days	Long-term decrease in life-span	
		Day 0	Day 30		Days[a]	Per cent of control[b]
1.....	0	100	100	800	—	—
2.....	300	100	100	710	90	10
3.....	500	100	82	650	150	17
4.....	600	100	50	600	200	21
5.....	700	100	11	530	270	30
6.....	800	100	0	—	—	—

[a] The difference between the datum for group 1 (800 days) and the data for other groups in column 5 (median survival time).
[b] The life span of the controls (group 1) was 900 days.

6. The dependence of biological effect on radiation dose is illustrated in figure 2. In the case of acute mortality (deaths within thirty days of exposure calculated from table I, column 4), the dose-effect curve shows a threshold—the first deaths occur somewhere between 300 and 500 rem. In the case of the long-term decrease in life-span (per cent of normal life-span) the course of the curve as drawn does not show a threshold and indicates that even at the smallest radiation doses there is some decrease in life-span (see paragraph 11).

7. Biological effects not only depend on radiation dose but also on dose rate. In the hypothetical experiment, the animals received a single dose at 50 rem/min. The same results would have been obtained with dose rates of 5 or 500 rem/min. Below 5 rem/min., however, the effect per unit dose diminishes. In the case of acute mortality, it does so relatively rapidly. It may do so quite differently in the case of the various kinds of late injuries, including those shortening the life-span.

The acute LD_{50}

8. Recent determinations of the acute LD_{50} (single, whole-body exposure) for mature mammals are given in table II. Values for immature and senescent animals would be lower than those tabulated. It has been pointed

Table II. Acute x- and gamma-ray LD_{50} of mature mammals[a]

Species	LD_{50} (rads)	Number of determinations
Swine.....	190–310	4
Goat.....	240	1
Dog.....	240–320	6
Man.....	300 (?)	0
Guinea pig.....	380–490	3
Monkey.....	520	1
Mouse.....	520–670	7
Hamster.....	590–800	3
Rabbit.....	680–750	3
Rat.....	790–820	2

[a] The original reports are listed in reference 1. All doses are estimates for the middle-longitudinal axis of the animal under conditions of approximately homogeneous soft tissue dose distribution. The dose rates ranged from 5–60 rads/min. The LD_{50} is that dose killing half the animals within 30 days of exposure. Almost all of the deaths occur within three weeks.

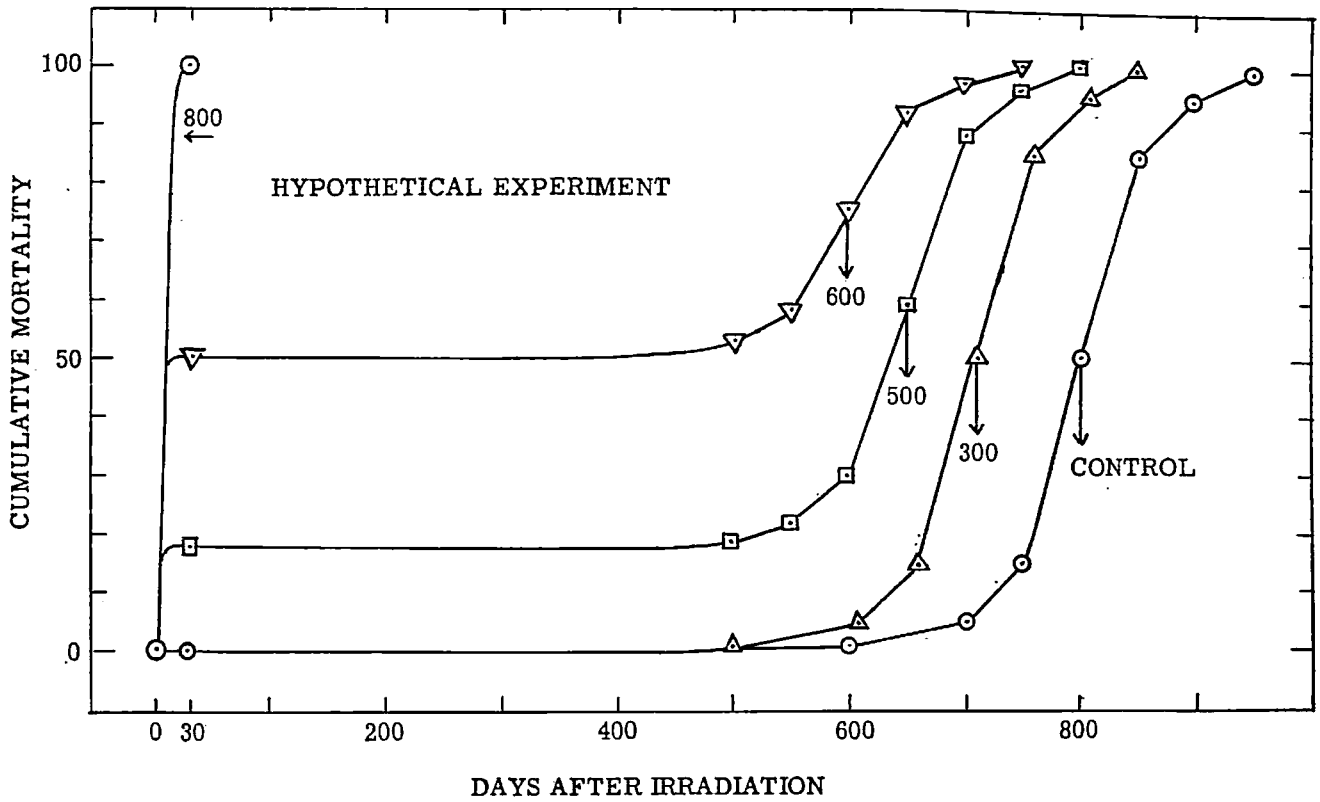

Figure 1. Hypothetical experiment–Cumulative mortality after a single whole-body exposure. The dose in rem is specified for each curve.

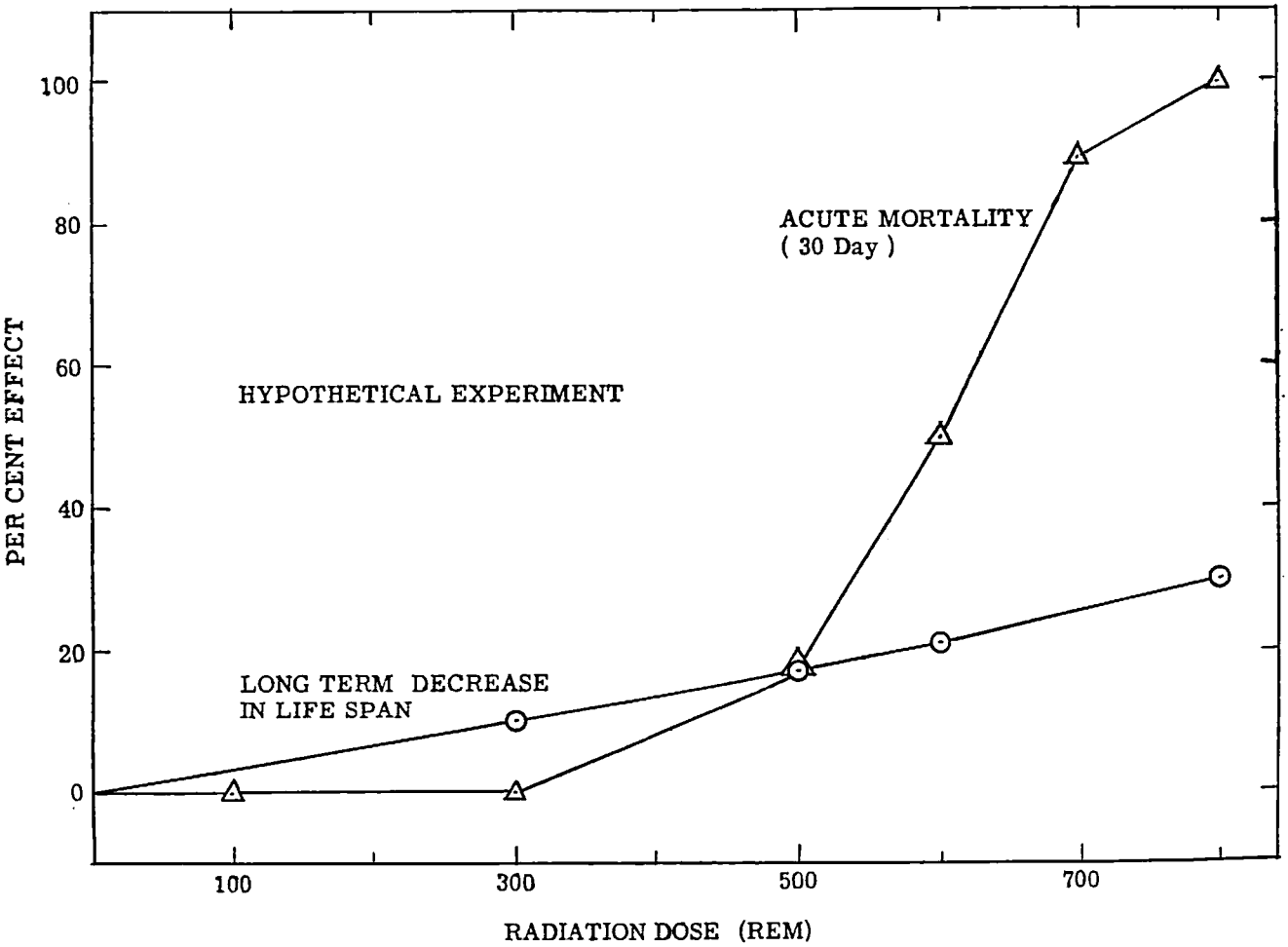

Figure 2. Hypothetical experiment–Effect as a function of dose. Acute mortality shows a threshold whereas long term decrease in life-span does not.

out[1] that the values fall into two groups. Those for the "larger" mammals are in the range 200-300 rem; those for the "smaller" mammals are in the range 400-800 rem. The only monkey listed (M. mulatta) falls into the "small" animal class. The estimate for man is close to the determinations for the guinea pig and dog, suggesting that studies with these species may be of special importance. It is to be noted, however, that the figure for man is speculative.

Acute effects in single organs

9. A very great number of somatic effects have been described that occur within hours, days, or several weeks of irradiation. Doses as low as 5 rem, for example, have a measurable although brief effect on the mitotic index of the skin of mice.[2] In the range from approximately 25 to 200 rem, simple *quantitative* relations between somatic effect and radiation dose have been demonstrated in such organs as the lymph node, spleen, thymus, testis, and intestine,[3] using both microscopic and gross methods of examination (e.g., weighing). In these examples, restitution occurs relatively quickly, during the course of some days or weeks, and often seems complete.

Recovery from whole-body exposure

10. When two or more exposures instead of one are employed, some restitution occurs during the interval(s) between them. One method to study the rate of restitution is to give a non-lethal dose on day 0 and to determine the LD_{50} on various days thereafter. Suppose that the LD_{50} of unirradiated animals is 600 rem. Furthermore, suppose that after 300 rem on day 0 the LD_{50} is:

(*a*) 300 rem on day 1;
(*b*) 450 rem on day 2;
(*c*) 600 rem on day 8;
(*d*) 600 rem on day 20.

It may be concluded therefore that acute recovery from 300 rem was complete by day 8, since by then the LD_{50} had returned to "normal", and half-complete by day 2. Experiments of this type (table III) have shown that the rate of recovery depends on genetic factors, and therefore varies with the strain and species of animal.[4] The rate also depends on the magnitude of the dose—large doses may, so to speak, inhibit the recovery process *per se*.

TABLE III. TIME FOR 50 PER CENT RECOVERY FROM A SINGLE WHOLE-BODY EXPOSURE TO X-RAYS[a]

Animal	*Number of strains*	*X-ray dose (rem)*	*50 per cent recovery time (days)*
Mouse			
Young	1	260	7.4
Adult	6	200–400	1.6–3.0
Adult	1	600	12.0
Rat	2	310	4.9 and 8.5
Hamster	1	320	6.1
Monkey (M. mulatta)	1	260	4.8

[a] Recovery measured under the particular conditions described in paragraph 10. The original reports are listed in reference 4.

The experimental effect of single doses on long-term survival

11. Data on life-shortening in mice and rats after a single whole-body exposure to X- or gamma-rays at the time of puberty or young adulthood are summarized in figure 3.[5] The radiation dose is expressed as a percentage of the acute LD_{50}, e.g., a dose of 300 rem is called 50 per cent if the acute LD_{50} is 600 rem. In the various experiments, the LD_{50} (in r) varied from 500 to 800 r. The curve fitted to the points in figure 3 is on the assumption that life-shortening is directly proportional to dose. For mice and rats it appears that life is shortened by about 10 per cent following a "25 per cent dose". The curve drawn through the points in figure 3 runs straight to the origin, indicating that radiation decreases the life-span no matter how small the dose may be. It is to be noted that the figure only suggests this conclusion, but does not prove it.

12. The data in figure 3 are based on exposure in youth or early adulthood. Comparable data for exposure during middle age or old age are not available.

13. It is known from clinical as well as laboratory evidence that partial-body exposure decreases the life-span much less than whole-body exposure (when the effects of roughly similar doses in rads are compared). There is a paucity of information, however, concerning the quantitative dependence of the life-span on (*a*) the region or organ irradiated and (*b*) the absorbed dose. The data from an experiment of this type are given in table IV.[6] More information of this kind is needed.

TABLE IV. DECREASE IN LIFE-SPAN—PARTIAL AND WHOLE-BODY X-RAY EXPOSURE COMPARED IN THE MOUSE[a]

Region exposed	*Dose (rem)*	*Median survival time after exposure (days)*	*Significantly different from control ($P \leq .05$)*
Control	0	676	—
Entire animal	530	582	Yes
Entire chest	720	646	No
One-half chest	570	654	No
and caudal	1140	591	Yes
2cm. of trunk	1700	525	Yes

[a] Female mice, 170 days old when irradiated. With the doses employed there were no acute deaths. Data from reference 6.

The experimental effect of chronic exposure on long-term survival

14. The experimental literature on the shortening of life by chronic exposure to radiation, and its bearing on the maximum permissible dose for man, are discussed in the article by R. H. Mole,[7] presented in its entirety following paragraph 15. Among other details, the report considers whether a threshold dose exists below which the life-span is unaffected. The report finds the evidence equivocal. A significant conclusion might be established for animals if very great numbers of them were used in such experiments. The report points out, however, that even if such a conclusion were established, its application to the human case would require a theoretical basis to justify such an extrapolation. Such justification is lacking at present.

15. Of the experimental groups referred to in paragraph 14, two (mouse, guinea pig) that received less than 1 rem per week lived a greater total number of days than their respective controls. In a more recent experiment[8] with Sprague-Dawley male rats exposed throughout

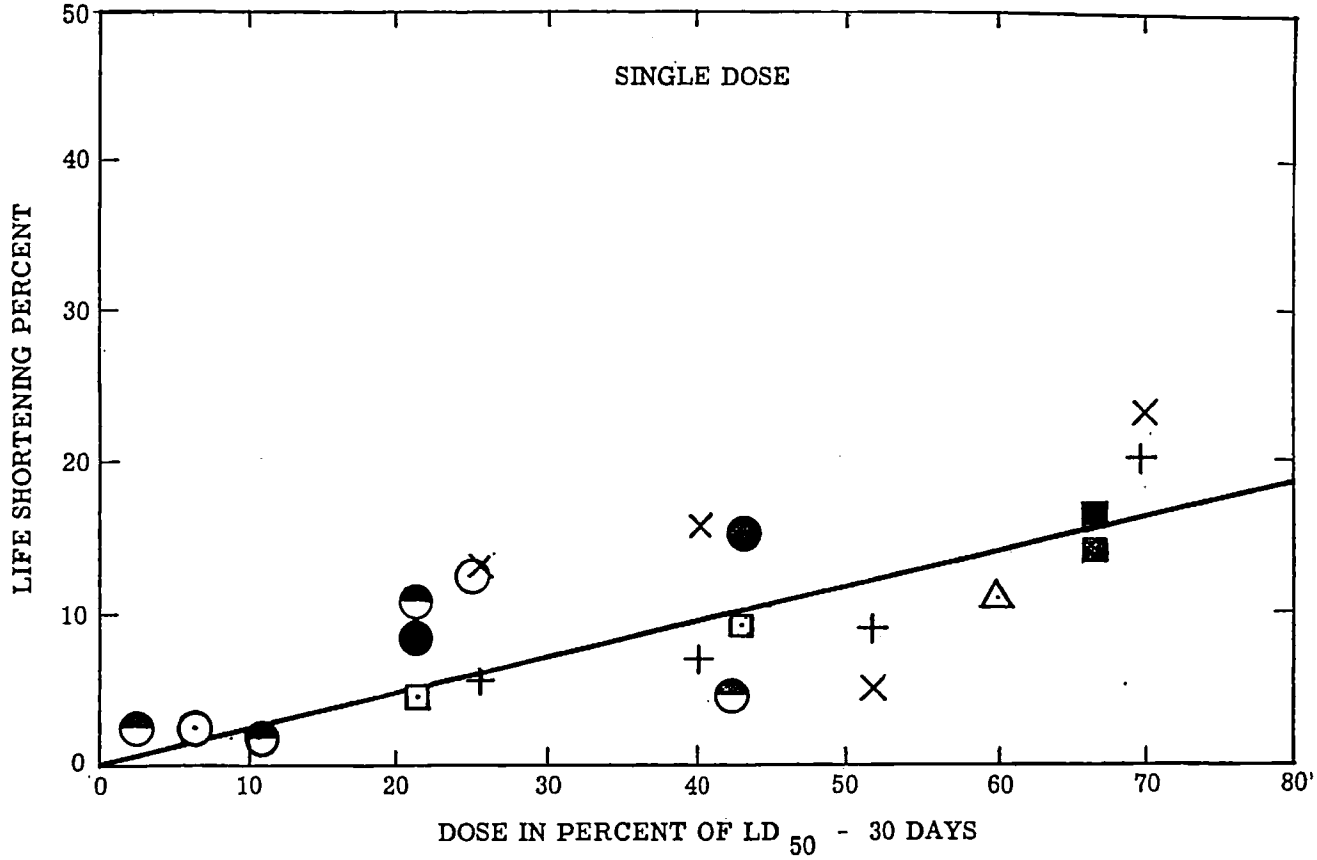

Figure 3. Life shortening (percentage) in mice and rats after a single, whole-body exposure to X- or gamma-rays. The dose is expressed as a percentage of the acute LD_{50}. The figure is taken from reference 5 where the original reports are listed.

adult life to 0.8 r/day of Co^{60} gamma-rays, the median survival times were as follows:

Temperature of environment	*Survival time (days)*	
	Control	*Irradiated*
5° C.....	240	305
25° C.....	460	600

Although there were only twenty-two animals per group, the differences between the irradiated and control groups were consistent throughout the course of the experiment.

Shortening of life by chronic irradiation: the experimental facts* by R. H. Mole

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It is probably true to say that more is known of the biological effects of radiation than of any other environmental hazard except bacteria. Certainly the chronic toxicity of no chemical substance has been investigated as thoroughly as the chronic toxicity of whole-body irradiation by penetrating gamma-rays or fast neutrons. The incentive has been obvious: the very large industrial hazard during the war-time development of the atom bomb, and afterwards the increasingly widespread risk associated with the remarkable development of atomic energy as a source of industrial power and of a unique series of military weapons. Chronic toxicity experiments in the strict sense must cover the whole life-span of the experimental animal and thus take years to carry out, even with the relatively short-lived laboratory mouse. The results of war-time work in the United States have become generally accessible in the past few years[1-5] and work carried out in this laboratory is just beginning to be published.[6] A brief survey of the experimental results relating to shortening of the life-span may provide a few facts in a field of current general interest and perhaps raise the academic question of how the results of chronic toxicity experiments, as such, may be generalized—a question which needs an answer before they may be used to help solve the practical problem of setting safe limits to the environmental exposure of man to irradiation.

Experimental methods

Daily irradiation has been given to animals in a variety of ways, for details of which the original reports should be consulted.[1-7] The more important experimental features are summarized in table I. There are two important differences between the experimental arrangements of Henshaw *et al.*[3] and Evans[2] on one hand, and those of Lorenz *et al.*[4] and of this laboratory on the other. In the first two sets of experiments, the animals had to be transferred individually each day from their living cages to the irradiation boxes and back again, and each daily dose of radiation was given in a few minutes. In the second two sets of experiments, the animals were irradiated in their living cages, undisturbed by additional handling with its accompanying traumatic effects, and the daily dose of radiation was spread over 8-24 hours. In general, the experimental animals were examined

* UN document A/AC.82/G/R.115; also published in Nature *180*, 456-460, 1957. For table 1, figures 1 and 2, and bibliography referred to in this article, see immediately following the article.

daily and the time of death noted. Post-mortem examinations to determine tumour incidence and the cause of death were usually made, but the experimental reports differ very greatly in the detail with which these findings are given. For this reason, and since shortening of life-span is often considered the most sensitive experimental index of the toxicity of chronic irradiation, survival-time is the only experimental end-point considered here.

Results and their interpretation

By chronic irradiation is meant daily irradiation five, six or seven days a week at dose-levels which allow survival for at least six months. All the experiments on chronic irradiation for the duration of life which have ever been carried out, so far as is known, are referred to in table I and, where possible, shown in figure 1. The duration of life of an irradiated group of animals has been expressed as a proportion of its corresponding control and plotted against the weekly dose of radiation on a logarithmic scale. The results from this laboratory are shown in black symbols. They provide the first direct experimental comparison between gamma-rays and fast neutrons for chronic irradiation, where the dose of fast neutrons was measured in terms of energy absorbed in tissue. The relative biological efficiency factor for the fast neutrons used as compared with cobalt gamma-rays was 13.

This factor has been applied to the other two fast-neutron experiments, where the fast-neutron dose was measured in arbitrary units and where a somewhat uncertain conversion factor (table I) has to be used for estimating the tissue dose. In this way the results of all the experiments with fast neutrons as well as those with gamma-rays from other laboratories have been plotted, using open symbols, together with our own results in figure 1. The agreement, when mice were used as experimental animals, is remarkable, and suggests, in spite of the various uncertainties in the comparisons, that chronic irradiation shortens the life of mice in a reproducible manner.

It should be noted that there are eight experimental points at weekly doses of less than 10 r. or its equivalent in neutrons, and that the duration of life in none of these experimental groups was significantly different ($P \geq 0.05$) from its control.

The experimental results have been put down as they were obtained. More sophisticated analyses of some of these results have been made elsewhere.[1,5,6,9,10] The purpose of such analyses has usually been to find some regularity in the results which would allow extrapolations to daily doses smaller than, and to species other than, those used experimentally.

Curve fitting

Three curves have been fitted to the mouse data and are shown in figure 1.

(1) The straight line which provided the relative biological efficiency factor of 13 from our second experiment (Neary *et al.*, II, table I) is clearly a good fit to its results, and is also reasonably close to the only experimental group in our first experiment with a markedly decreased survival-time. The simplest interpretation of such a linear relation is that there is a threshold of between 1 and 2 r. daily below which no shortening of a mouse's life will be produced by daily irradiation. This may be considered confirmed by the repeated experimental failure to find a demonstrable shortening at weekly doses of less than 10 r. (see above). Considering the nature of the data, it would be difficult to have a clearer experimental demonstration of the existence of a threshold.

(2) The biologist, almost as a reflex, attempts to fit a Gaussian curve to quantitative data. Such a curve is shown as a dashed line in figure 1, and clearly fits all the experimental data very well. The meaning of the fit at weekly doses of less than 10 r., where none of the points differs significantly from the base line, is less clear.

(3) Boche (1946, 1954)[1] suggested that shortening of life-span was proportional to the total accumulated dose,

$$t - t_0 = kdt$$

where t and t_0 were the mean life-spans of irradiated and control animals, d was the daily dose of radiation and k was a constant. This curve ($k = -0.04$ for gamma-rays) is shown in figure 1 as a dotted line, which also fits all the experimental points very well.

Curves 1 and 2 are empirical; curve 3 has some claim to a theoretical basis, the idea that the bigger the total dose of radiation the bigger the effect, that is, the shorter the mean life-span. For daily exposures which kill in less than six months, however, the converse is found to be true.[4,9,11] This is not as paradoxical as it may seem, once the importance of recovery processes is appreciated; but it makes data on the effects of high daily doses (on shortening of life by much more than 50 per cent) of little value in helping to decide which is the best of several curves, each purporting to describe the effects of low daily doses.

Curves 2 and 3 are clearly so close together that over the experimentally determined range they cannot be distinguished. (The possibility that this algebraic similarity has a much wider biological significance is being investigated.) Each curve appears to fit all the points better than the straight line of curve 1, but this may be a spurious consequence of experimental uncertainties. In two experiments the exact conversion factor from arbitrary units of fast neutrons to rads is unkown (see above) and factors numerically different from those used (table I) but just as plausible (see literature) would make the fit look less good. There seems to be no intrinsic reason why different mouse strains *should* behave identically, and the curvilinear arrangement of the experimental points may merely reflect differences of strain and of dose.

Each of the second two formulations indicates that there is no absolute threshold for shortening of life by chronic irradiation. The apparent threshold suggested by curve 1 may be thought of either as an absolute or as an effective threshold, depending on whether shortening of life is considered in proportional or absolute terms. If time is necessary for the effects of daily irradiation to show themselves, and if this time is longer the lower the daily dose, then an effective threshold *must* be reached at a dose-level which takes longer than the life-span to produce its effect. If so, each species would be expected to have its own threshold, and the longer the natural life-span the lower this would be. The only relevant experimental data are those of Lorenz *et al.*[4] on chronic irradiation of guinea pigs and these are included in figure 1. The effect of 1.1 r daily was possibly greater than in mice (though still not significantly different from its control) and the apparent threshold possibly a little less. The difference in life-span between mice and guinea pigs is probably not large enough to decide the point, and in an event there are no confirmatory data for guinea pigs as there are for mice.

The data for guinea pigs do show that species differences occur. Boche[1] suggested on, admittedly tenuous evidence, that the constant k (curve 3) is αt_0, where α is the same for all mammals. If this were true, the mouse data should not agree so well, since t_0 for the different mouse strains differed. If the mean mouse t_0 is 600 days, $\alpha = 7 \times 10^{-5}$ (rather different from Boche's own estimate), and this has been used to construct the theoretical curve for guinea pigs ($\alpha t_0 = -0.09$ curve 3, figure 1); the fit to the experimental points is poor.

Nature of the experimental material

In any event, too much should not be read into the results because of the nature of the experimental material. First, the results have all been expressed in terms of mean survival-times. This is really a rather unsatisfactory parameter to use, as may be seen from figure 2, which illustrates the shape of the mortality curve of normal control female CBA mice. The shape of the human mortality curve in the more materially advanced human civilizations is similar, but that of mice with a high spontaneous incidence of leukemia may be very different.[4,12] The mean survival-time and its statistics are markedly affected by the occasional early deaths and no great precision in mean survival-time can be expected. A small decrease in mean survival-time could occur either because of a small increase in the frequency of earlier deaths or because of a small reduction in life-span of the upper two quartiles. In fact, an analysis of cause of death in relation to duration of life is imperative in order to see whether irradiation decreases life-span by increasing the frequency of particular causes of death which kill earlier than the average, or merely by making all causes of death kill at an earlier age.[6]

Second, the nature of a chronic toxicity experiment usually, if not invariably, makes it impossible to randomize treatments and to ensure that the only difference between experimental groups is the treatment being investigated. For example, if animals are arranged at different distances from a source of radiation, the animals will occupy different parts of a room for their whole lives and it will be impossible to be sure that environmental temperature, humidity, degree of air movement and other relevant factors possibly not even thought of are exactly the same for each different dose-group. Thus the differences in, say, mean survival-time between different groups, will be due to the differences in radiation-level plus any other relevant environmental differences. This is not just a theoretical point. Differences of the order of 5 per cent in the mean survival-time of female CBA mice have been found during the past few years not only between different "lots" of controls but also between two sets of randomly chosen controls kept, so far as could be, in the same environment but some 20 feet away from each other.[6] The apparent increase in survival-time at the lowest daily dose used by Lorenz *et al.*[4] (figure 1) may well be due to the fact that the animals at this dose-level were kept without air conditioning in a different room from all the other groups, including the controls. Such variability is to be expected by the biologist, but it should also enjoy caution in extrapolation of the results of analysis of intrinsically inexact data.

Replication on a sufficiently large scale, though often completely impractical, could overcome this particular difficulty. In fact, however, replication is almost completely lacking from the experiments listed in table I. The logic of experimentation is that experiments are repeated and give the same result. Yet with the exception of a still unfinished investigation,[10] no one concerned with duration-of-life irradiation experiments has ever repeated his experiment even once—for which there are perhaps understandable reasons. The nearest to repetition so far has been the two experiments carried out in this laboratory,[6,13] where although the same mouse strain was used the radiation doses were different. From this point of view the value of figure 1 is to demonstrate that an experiment has been done, that is, that the same result has been obtained several times over.

Lastly, it should be pointed out that in all the experiments considered here irradiation has been for the duration of life. This may not be the most appropriate experiment to carry out. Recent,[6,14,15] as well as older,[4,16] evidence has shown that, in some circumstances at least, not all radiation is of equal value, the first of a series of daily doses having proportionately greater effects in shortening life and inducing leukemia than the later daily doses. This is presumably one aspect of the time factor; time is needed for the effects of irradiation to develop to the point where biological damage can be detected,[11,14,17] and/or the reactivity of the biological object may change with age.[11] But if the phenomenon is true of weekly doses of less than 50 r., which has not yet been demonstrated, formulae which give equal weight to each of a series of doses as Boche's, cannot be properly extrapolated. Further, if at relatively high daily doses much of the radiation is wasted, so far as producing an effect is concerned,[11] then an observed linearity of response against total dose (curve 3, figure 1) may imply a decreasing ability of radiation to harm as the daily dose decreased.

There has also been very little work yet on the problem of whether the effect of chronic irradiation is altered by changing the distribution in time of, say, a constant weekly dose. The data of table I and figure 1 suggest that it matters little whether a daily dose is given in a few minutes or spread out over many hours; but other as yet uncompleted observations[14,17] suggest that the delayed effects of irradiation may depend as much on the way the irradiation is given as on the total dose. In these experiments there was no wasted radiation: on the contrary, as much time as possible was allowed for the full development of any damage that radiation may have caused. Such experiments may give a relation between shortening of life and dose of radiation very different from those shown in figure 1, and indeed this might well be anticipated by anyone aware of the normal complexity of biological phenomena. Dose-response curves should not be extrapolated without fully realizing the nature of the experimental material on which they are founded.

Possibilities of extrapolation

It should first be emphasized how unusual it is to pay any attention to the ends of a biological dose-response curve. Normally, the aim of the biologist is to work in the middle ranges and, if irregularities appear at the ends, this is regarded as just to be expected, not necessarily deserving investigation.

The current maximum permissible level of radiation for occupational exposure of man, 0.3 r. weekly (Recommendations of the International Commission on Radiological Protection), is indicated in figure 1. Extrapolation suggests that this dose-level would shorten the lives of mice by nil, 0.02 or 0.2 per cent, depending on which of the three curves described earlier is taken to be

correct. As already shown, the experimental data on chronic irradiation at low doses are not sufficiently exact to distinguish between the curves, and the adequacy of fit at high levels of irradiation seems quite irrelevant. Thus the value of any attempt at extrapolation must depend on whether there is some theoretical reason for preferring one mathematical form to another. When this question is settled, there is the additional problem of extrapolating from one species to another.

One principle of selection often used nowadays in general discussion on radiation as it affects mankind, and at first sight self-evidently sound, is to take the most pessimistic assumption suggested by experiment or theory for the relation between dose and effect. Lorenz[8] used a very similar criterion when discussing the effects of daily irradiation on the difficult tissues and organs of different species. He concluded that man should be considered to be as sensitive as that species of animal found experimentally to be the most sensitive. Clearly this is no absolute criterion; as the range of species examined is widened, the apparent sensitivity of man must decrease. A consistent use of this criterion would involve denying the possibility of chemotherapy, or of selective killing by pesticides. It does not seem realistic to maximize pessimism as a means of choosing the best dose-response curve.

The most plausible reason for thinking that species differences among mammals in their reactions to irradiation are likely to be smaller than in their reactions to chemical agents is that the penetration of radiation into cells is not affected by the series of permeability barriers which every chemical agent has to pass before reaching the site of its action.[18] The uniformity of the acutely killing dose for all mammals gives supporting evidence. However, the chronic toxicity of radiation would be expected to depend on a balance between the continuing damage produced by the radiation and the ability of the irradiated animal to keep pace with the damage by repair. The ability to repair and its rate must depend on many of the structural and metabolic features which distinguish strains and species, and, for this reason, strain and species differences in the dose-response curves for chronic irradiation might be expected. Some of the experimental facts can best be understood in this way.[6]

An alternative view is to assume that the chronic toxicity of radiation is due to processes where repair of damage does not occur, like genetic mutation. It may then be plausibly argued that the genetic material of all mammals is very similar, both physically and chemically, and that therefore dose-response curves will in general be the same for all species. Such a view would suggest that damage should be proportional to total dose, as in Boche's formula (curve 3, figure 1), and would be consistent with the somatic mutation theory of carcinogenesis and the fact of carcinogenesis by ionizing radiation. But there are difficulties in the way of equating damage and total dose, as already suggested, and really very little evidence in support of the mutation theory of carcinogenesis. The theory is an easy one to accept; but even with the most recent advances in technique its testing seems almost impossible to envisage. However, in the experimental animal there is no simple relation between carcinogenesis and dose of radiation, and for mouse leukemia there is good evidence of the great importance of an indirect mechanism.[19] Moreover, the experimental evidence suggests that radiation shortens life apart from inducing cancer, and this is not easy to understand in terms of mutation.

If the results of animal experiments are to be carried over to man, there must either be very good evidence that all mammals behave alike, or sufficient human evidence of similarity with experimental animals to inspire confidence in the process of filling the human gaps from animal experience. It will at least be generally agreed that experimental dose-response relations which cannot satisfactorily account for all experimental results are scarcely worth applying to the human case. In the absence of a satisfactory theory, it seems pointless to expend the enormous experimental effort required to define the relation between daily dose and life-span for mean survival-times of 95 per cent and more of the control: it is only in this region that extrapolation to man is of any particular interest.

I would like to thank my colleagues for allowing me to make use of unpublished material.

TABLE I.

Of preceding paper by R. H. Mole

Reference	Source and type of irradiation G=Gamma rays N=fast neutrons	Unit of dose (conversion factor to rads)	Details of irradiation exposure: Days/week	Details of irradiation exposure: Duration of daily dose	Symbol used in Fig. 1	Experimental animal: Mouse strain	Experimental animal: Age at start of irradiation (days)	Experimental animal: Control life-span from start of irradiation (days)	No. of animals used	Method of reporting survival-time
Henshaw *et al* (ref. 3).....	^{182}Ta G	r.	6	minutes	▽	*CF*[1] (females only)	?	440	820	Median[a]
	Graphite reactor N	r. (2.0)	6	minutes	△					
Evans (ref. 2).....	Cyclotron N	N (2.5)	5	minutes	□	*CF*[1] Swiss	28–42	420 475	500	Median[b]
Lorenz *et al.* (ref. 4).....	Radium G	r.	7	8 hr.	○	*LAF*[1]	52–85	703	240	Mean
Neary *et al.* I (ref. 6).....	Graphite reactor N	rad	6–7	16–24 hr.	■	*CBA*	75–95	780	500	Mean[c]
Neary *et al.* II (ref. 13)...	Graphite reactor N	rad	7	16–24 hr.	▲	*CBA*	45–75	818	320	Mean[c]
	^{60}Co G	r.	7	24 hr.	●	*CBA*				
Thompson *et al.* (ref. 16)..	^{60}Co G	r.	7	24 hr.	+	Rats (Sprague-Dawley, females only)	90–120	585	42+	Mean
Lorenz *et al* (ref. 4).....	Radium G	r.	7	8 hr.	×	Guinea pigs (hybrid)	137–196	1,372	112	Mean

[a] Mean survival times calculated from data provided by Hollaender and Stapleton (1948, personal communication) have been used in fig. 1.

[b] Mean survival-time of the two strains combined were also reported and have been used in fig. 1 because standard errors were also given. However, irradiation stopped when 8–30 per cent of an experimental group was still alive, so that the mean survival times include variable proportions of radiation-free time.

[c] There were real sex differences in control life-span and possibly also in the effects of irradiation. The data have been pooled to make them comparable with those of the other authors.

The data of Henshaw (ref. 7) have not been included because the mean life-span of his controls was less than a year. The data of Boche (ref. 1) have not been included for a variety of reasons: his monkeys had tuberculosis, his mice salmonellosis; the dogs and rabbits were irradiated in small numbers and irradiation stopped after two years, long before the end of the natural life-span; irradiation of the rats also ceased after two years when 16–36 per cent of the lower level and control groups were still alive and were killed, which prevents estimation of mean survival-times.

Evans's X-ray data (ref. 2) have not been included because mean survival-times were not given. The control life-span was not given by Hagen and Simmons (ref. 5). In each of Sacher's (ref. 5) and Mole's (ref. 11) experiments with daily X-irradiation of mice, one experimental group survived about seven months; they are omitted because no groups surviving longer are available and because the relative biological efficiency for X- to gamma-rays for chronic irradiation is not known.

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II. LIFE SHORTENING EFFECTS IN MAN

16. Data were examined relating to the mortality of medical specialists in order to learn if those exposed to X-rays had a shortened life-span. In one extensive analysis,[9] utilizing the mortality data for specialists 35-74 years of age who died during 1938-1942, the *mortality ratio* was calculated for each specialty. The mortality ratio is the ratio of the number of deaths observed to the number that specialty would experience if subject to the specific death rate calculated for all physicians. These mortality ratios are given in parentheses in the last column of table V. It is seen, first, that specialists have a lower mortality than physicians in general; the specialist mortality ratio is only 0.78. Secondly, the various specialties appear to have different mortality ratios, from 0.99 to 0.62.

17. The mortality ratios of the various specialties were recalculated,[10] using the death rate for all special-

ists instead of all physicians (table V). The ranking of the mortality ratios by this method agreed with that of paragraph 16. Eight specialties had mortality ratios greater than unity, but in no case was the difference statistically significant.

18. The extent to which repeated small exposures to X-rays shorten the life of man is a matter of speculation. In the past, radiologists were so exposed, but from the mortality statistics it cannot be demonstrated that the life-span of this group of medical specialists has been shortened relative to that of other medical specialists[11] although this has been suggested.[12] It is known, however, that the incidence of leukemia is increased in these men.

III. Cancer in man

19. It is generally agreed that the incidence of cancer* in man can be increased by exposure to ionizing radiation. Quantitative data will be considered relating the incidence rate of cancer to radiation dose and to time after exposure. For introduction, the method of calculating the incidence rate and the influence of certain variables on it will be discussed briefly.

20. The prevalence of cancer may be defined as the number of cases per unit of population at a specified time, e.g. 15 cases per 10,000 on January 15.

21. The cancer incidence rate R may be defined as the number of new cases per unit of time and population occurring during a specified interval of time, e.g., 5 per 10,000 per annum. Alternatively, it may be said that an estimate of the probability that an individual in the population will acquire a cancer equals 5/10,000 or 5×10^{-4} per annum. R is an important statistic in the calculations to be made below.

22. The total effect of exposing a population to radiation is estimated in terms of the total number of cases, N_x, induced per unit of population. If the rate after exposure is constant at R, and if prior to exposure it was constantly R_o, then $(R-R_o)$ is the number of extra

* Cancer is a generic term and, as used here, includes leukemia and all forms of so-called neoplastic or malignant disease.

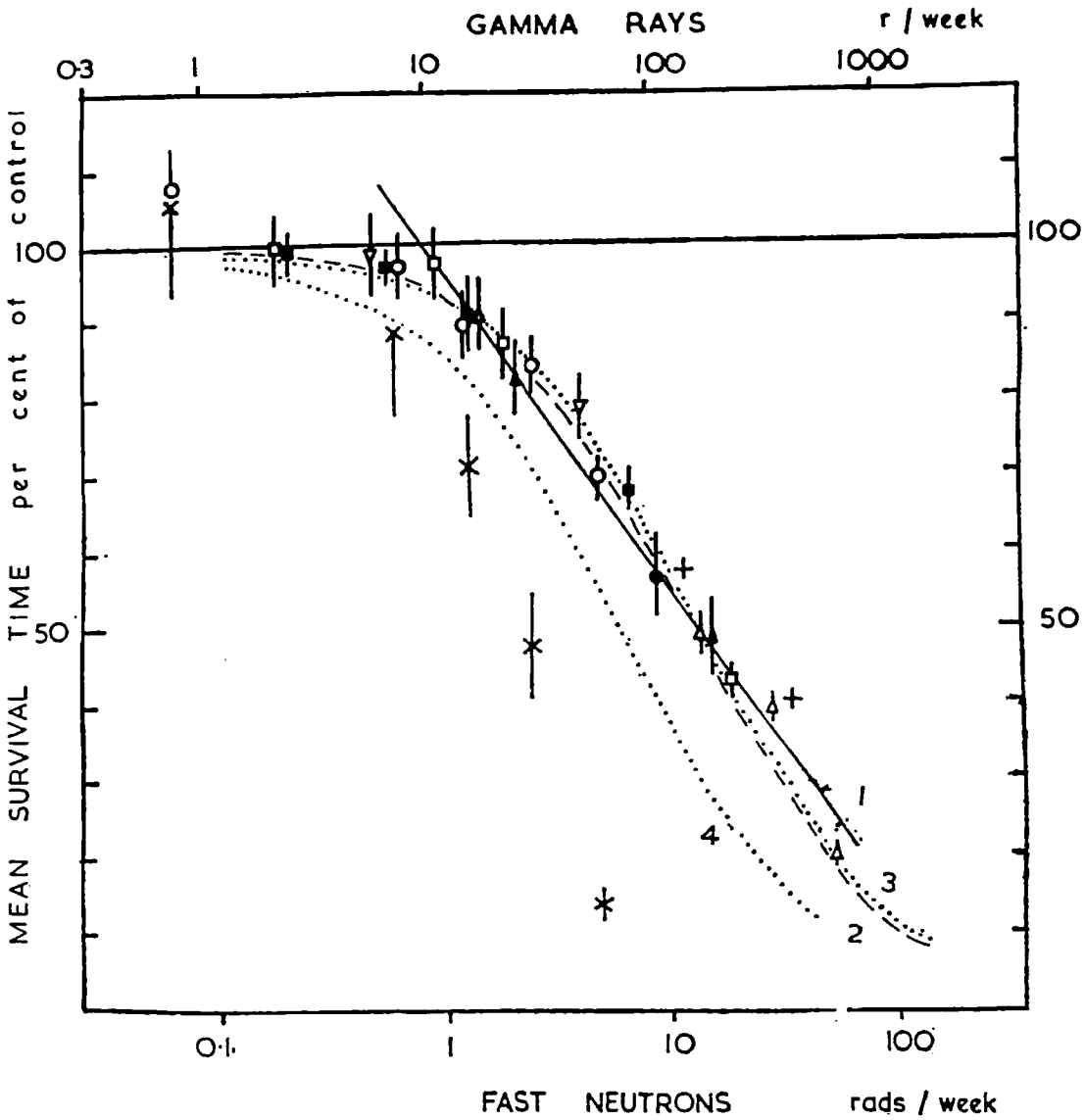

Figure 1 (of preceding paper by R. H. Mole). Mean survival-time (per cent of control) and weekly dose of radiation (logarithmic scale).
The symbols are given in table 1. The curves are numbered as in the text, where they are discussed. The gamma and neutron scales are in the ratio 13:1 (see text).

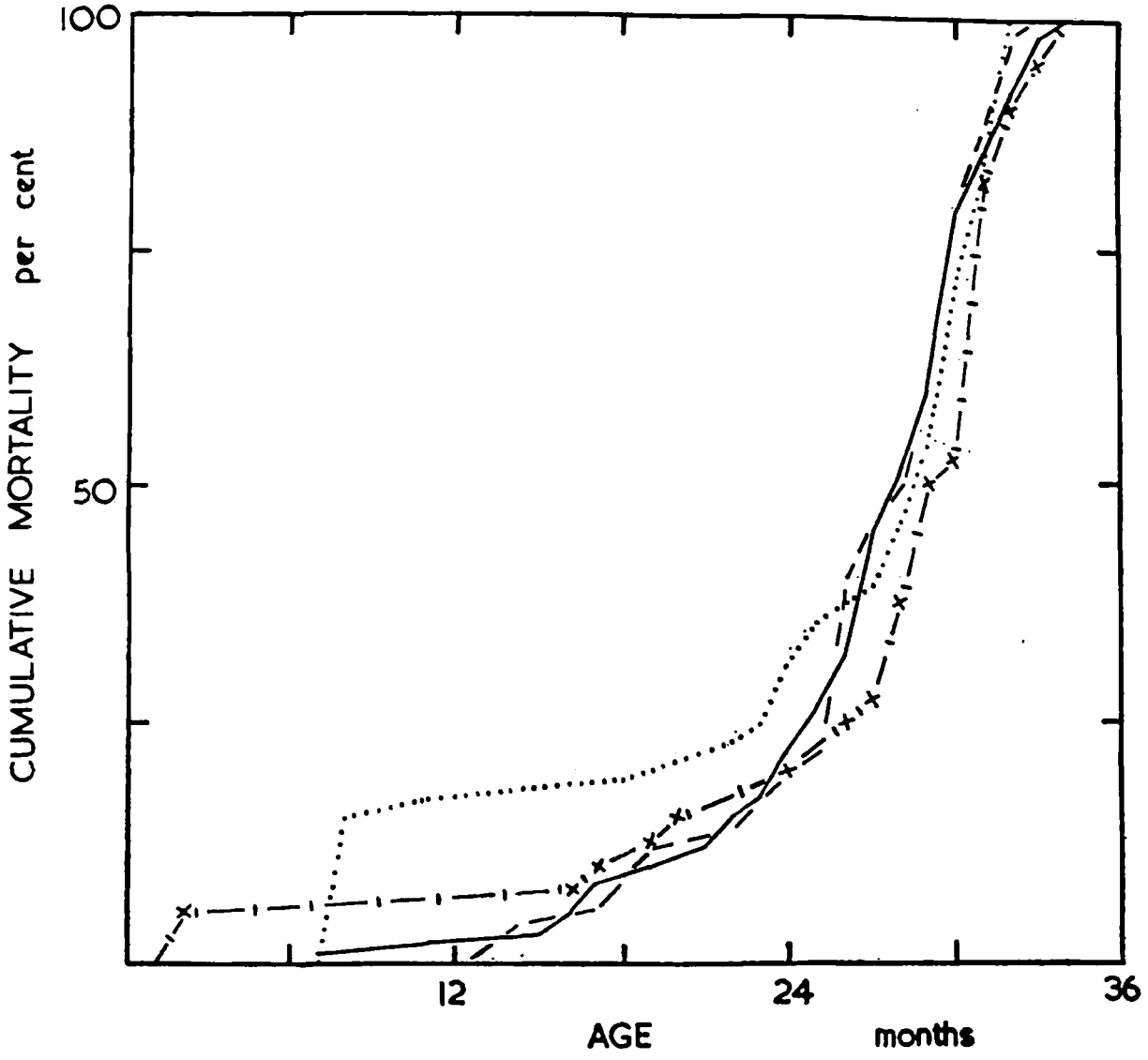

Figure 2 (of preceding paper by R. H. Mole). Cumulative mortality of female CBA mice (four different control groups 1951-54). All times plotted from same starting age of 70 days.

TABLE V. MORTALITY RATIO (ALL CAUSES OF DEATH) FOR MEDICAL SPECIALISTS

Rank	*Specialty*	*Observed deaths*	*Expected deaths*	*Mortality ratio*[a]
1.	Tuberculosis	43	34.2	1.26 (0.99)
2.	Dermatology	60 (58)[b]	47.8	1.25 (0.98)
3.	Roentgenology and radiology	96 (91)[b]	82.4	1.16 (0.90)
4.	Anesthesiology	17	–	– (0.88)
5.	Orthopedic surgery, proctology, urology and industrial surgery	199	179.1	1.11 (0.86)
6.	Neurology and psychiatry	142	133.0	1.07 (0.83)
7.	Public health	99	94.3	1.05 (0.83)
8.	Surgery	360	346.7	1.04 (0.81)
9.	Obstetrics and gynecology	112	116.3	0.96 (0.75)
10.	Eye, ear, nose and throat	502	523.4	0.96 (0.75)
11.	Internal medicine and pediatrics	378	423.6	0.89 (0.69)
12.	Pathology and bacteriology	38	48.1	0.79 (0.62)[c]
	ALL	2,046		1.00 (0.78)

[a] The ratio of (*observed deaths in a specialty at ages 25 to 74 years*) to (*expected deaths on the basis of age specific death rates for all specialists, 1938–1942*). The ratios were calculated from data made available by Dr. M. Spiegelman. The figures in parentheses are the published[9] mortality ratios for specialists based on the age specific death rates for all physicians (instead of all specialists) at ages 35 to 74 (2,046 deaths). Note that the ranking of the mortality ratios is the same for both methods of calculation.

[b] Omitting deaths from leukemia.

[c] Pathology only.

cases per unit of population per annum. In a period of T years,

$$N_x = (R - R_0)T \qquad (1)$$

Although simple in principle, the use of equation (1) is somewhat difficult in practice. First, R is not a constant, but varies with times. In general, exposure is followed by an initial period during which few if any radiation-induced cases occur. The duration of the initial period may be shorter after large doses than after smaller ones. Thereafter, depending on the particular cancer studied and the nature of the population, there will be a second period during which the vast majority of radiation-induced cases occur. This period might last for five years or for twenty-five. We are now only in the process of learning what the duration of such periods may be. Secondly, precise values of R_0 may not be available. In the case of some kinds of cancer there is some evidence that R_0 is changing relatively rapidly (e.g. leukemia). For these, it would be necessary to estimate the changes in R_0 as a function of time independently of the changes in R. Thirdly, the numbers of radiation-induced cases actually dealt with are very small, as will be seen below.

23. Having obtained a method for estimating N_x, it becomes feasible to investigate how N_x depends on the dose of radiation, D. Is N_x, for example, a simple linear function of D, is it a non-linear function or is there a threshold dose below which radiation is without effect? Before attacking such a problem, it is important to note that the same dose may result from a single exposure, multiple exposures, or a long period of continuous exposure. Such differences in dosage may lead to major differences in the end results and therefore must be explicitly dealt with when making comparisons or extrapolations.

24. It is worth special note that the factor of time has entered the problem in more than one way. In equation (1) paragraph 22, there is the term T, often referred to as *period at risk*. In paragraph 23, the role of time in dosage is considered; this may be referred to as *period under exposure*. The period under exposure may last for only a minute and thus be an insignificant fraction of the years at risk. On the other hand, in the case of long-lived isotopes, for example, the period under exposure may be a matter of many years and thus partially or even completely overlap the period at risk.

25. Constitutional factors are known to influence the production of cancer in man. These include race, age, sex, nutrition and other environmental and genetic influences. All of these factors have to be taken into account in discussing the production of cancer in man through exposure to ionizing radiation, especially when comparing the effects in one group with those in another.

26. The total of all human data that can be used for the quantitative analysis of cancer-induction by radiation is meagre. For example, only sixty-eight cases of leukemia are involved in the Hiroshima data of table VII. It is important that full use be made of such data while at the same time recognizing and giving due weight to their limitations. In the case of the calculations, extrapolations and applications that follow, the reader is urged to note the simplifying assumptions that may have entered into the analyses, especially in regard to the following items:

(a) *Absorbed dose.* In what organ is the absorbed dose to be determined? If the dose is not uniform throughout the organ, how shall it be averaged or otherwise expressed? Should the integral absorbed dose be considered?

(b) *Temporal factors.* What allowance, if any, should be made for multiple or continuous exposure? Is each successive year at risk of equal significance?

(c) *Constitutional factors.* What is the nature of the irradiated population with respect to age, general health, genetic constitution, etc.?

(d) *Dose-effect curve.* Is there a threshold? Is the effect a linear or some other function of dose? Can a factor be determined that will relate N_x to D?

Leukemia in man

27. Demographic data relating the incidence of leukemia to radiation exposure come from four population groups whose exposures were either a hazard of war or profession, or were incurred during diagnostic and therapeutic medical procedures.

Atom bomb survivors in Hiroshima

28. The most recent information on the incidence of leukemia in the Japanese survivors of the 1945 atomic bomb is given in a report which is reproduced in paragraph 33 below. From the condensed summary in table VI of the Hiroshima data, it is seen that the incidence of leukemia in the population exposed at 0-1,499 metres from the hypocentre has been twenty times greater than in the population exposed at 1,500 metres and beyond. Thus at the end of 1957, N (0-1,499 m.) = 5570; N ($>$ 1,499 m.) = 280. N is the total number of cases per million persons present at the time of the explosion. Taking the cases at 1,500 metres and beyond as a crude estimate of the natural incidence of leukemia, the number of cases N_x due to radiation may be estimated as 5,570 — 280 = 5,290, or in round numbers 5,300 per million.

TABLE VI. LEUKEMIA IN SURVIVORS AT HIROSHIMA, 1948–1957[a]

	Number of cases[b]		
		Distance (metres) from hypocentre	
Period of onset	*Total*	*0–1,499*	*1,500 and beyond*
1948–49	12	8	4
1950–51	20	18	2
1952–53	23	16	7
1954–55	14	9	5
1956–57	11	5	6
TOTAL: 1948–57	80	56	24
N (cases per 10^6)	835	5,570	280
R (average of cases per year per 10^6)	84	557	28

[a] Data from reference 13. The full report from which these and the data of table VII were taken is given below.

[b] 10,051 persons were exposed at 0–1,499 metres; 85,768 were exposed at 1,500 metres and beyond.

29. The data in table VI indicate that the biennial rate of leukemia in the heavily exposed population reached its maximum in 1950-1951 and has been declining since then. If this tendency continues, practically all cases of radiation-induced leukemia probably will have occurred by 1960, within fifteen years of exposure, so that at lease 80 per cent of them may be said to have occurred already, within ten years of exposure. In these circumstances, the annual rate of leukemia taken by itself is not

TABLE VII. LEUKEMIA INCIDENCE FOR 1950–57 AFTER EXPOSURE AT HIROSHIMA[a]

Zone	Distance from hypocentre (metres)	Dose (rem)	Persons exposed	L (Cases of leukemia)	$\sqrt{L}$	N[b] (total cases per 10^6)	N_x (Radiation-induced cases per 10^6)	N_x/rem	P_L ($N_x/10^6$/year/rem)
A	under 1,000	1,300	1,241	15	3.9	12,087 ± 3,143	11,814	9.1	1.14×10^{-6}
B	1,000–1,499	500	8,810	33	5.7	3,746 ± 647	3,473	6.9	0.86×10^{-6}
C	1,500–1,999	50[c]	20,113	8	2.8	398 ± 139	125	2.5	0.31×10^{-6}
D	2,000–2,999	2	32,692	3	1.7	92 ± 52	−181	−90	-11×10^{-6}
E	over 3,000	0	32,963	9	3.0	273 ± 91	Control	—	—

[a] Based on data in reference 13. Prior to 1950 the number of cases may be understated rather seriously.

[b] The standard error is taken as $N(\sqrt{L}/L)$.

[c] It has been noted [15, 16] that almost all cases of leukemia in this zone occurred in patients who had severe radiation complaints, indicating that their doses were greater than 50 rem.

a good index of the total radiation effect; it is the total number of case N_x that should be employed as such a measure.

30. Considering the exposed population by itself, the segment that was closer to the hypocentre has had the greater incidence of leukemia. However, the quantitative relation between *leukemia incidence in Hiroshima* and *radiation dose* is not yet known. Before such a relation can be formulated it will be necessary to have better estimates of the *absorbed dose in rem* than have been available hitherto. The estimates must be made both for the various dose zones in which the population was distributed, and, also, for every individual case of leukemia, taking into account both its position within the zone and the shielding immediately around it. Such work is under way.

31. None the less, using such data as were available, estimates have been made of the potency of this bomb radiation in causing leukemia.[14] The exposed populations of Hiroshima and Nagasaki were considered to have been exposed in a number of zones for each of which a mean dose was assumed. The extra probability of leukemia occurring in an exposed person per rem and per year elapsed after exposure was then calculated for the population of each zone:

$$P_L = \frac{\text{average extra number of new cases per year (1948–1955)}}{\text{number of persons exposed} \times \text{dose (rem)}}$$

In zones A (1,300 rem), B (500 rem), and C (50 rem), the values of P_L were calculated to be 0.9, 0.7, and 0.7×10^{-6}, respectively. This finding was taken to support the suggestion that the extra leukemia incidence is directly proportional to radiation dose, and conversely, to argue against the existence of a threshold for leukemia induction.

32. P_L might be used in estimating N_x, the total number of extra cases of leukemia that follow a dose of radiation. The average value of P_L in paragraph 31 is 0.8×10^{-6} based on statistics for the years in which the leukemia rate is considered to be maximal. Taking 15 years to be the entire period of leukemia production (period at risk), the total number of cases (per individual exposed per rem) $= 15 \times 0.8 \times 10^{-6} = 12 \times 10^{-6}$. On this basis if each of a million persons receives 1 rem, a total of 12 extra cases of leukemia will eventually develop.

33. It is of interest to apply the above method to the latest data on leukemia incidence in Hiroshima, using the same zoning system and estimates of dose (table VII). Contrary to previous findings, the present findings indicate that P_L decreases markedly as the dose falls, that therefore leukemia incidence is not a linear function of dose, and that a threshold for leukemia induction might occur. In fact, according to table VII a dose of 2 rem is associated with a decreased leukemia rate. It is to be emphasized again, however, that the estimates of dose employed in the present and previous analyses are much too uncertain to permit drawing conclusions relative to the vital points in question. The calculations are made only to illustrate how variable the results may be when inadequate data are utilized.

LEUKEMIA IN HIROSHIMA CITY ATOMIC BOMB SURVIVORS* by

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It has become generally accepted that an increased incidence of leukemia follows the acute or chronic exposure of various experimental animals and of man to ionizing radiation.[1] Recently an attempt has been made to establish a quantitative relation between the probability of radiation-induced leukemia and the unit-dose of radiation received, on the basis of data from studies of various groups of radiation-exposed human beings.[2]

The survivors of the atomic bombings in Hiroshima and Nagasaki, Japan, comprise two such groups. Reports concerning the occurrence of leukemia in these populations over a period through June 1956 have been published at intervals by various staff members[3] of the Atomic Bomb Casualty Commission.[4] In addition, an unpublished compilation of certain specific detailed information requested by the British Medical Research Council was prepared in September 1955.[5] An analysis of these data appeared in a publication of the Medical Research Council[6] and a portion was also published in a report of the National Research Council.[7]

Since that time a review has been made of all the leukemia cases known to the Atomic Bomb Casualty Commission, and a master list has been compiled. Some of the cases on the September 1955 listing have been dropped for various reasons, and many cases have been added. No detailed official report has been published recently in the hope that more adequate dosimetry data might become available. This wish is nearing fulfilment because of the joint initiation of a large programme of

* Science *127*, 699-700, 1958, for table 1 and bibliography referred to in this article, see immediately following the article.

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dosimetry studies in 1955 by the Atomic Bomb Casualty Commission and a group of interested organizations including the Atomic Energy Commission's Division of Biology and Medicine, the National Academy of Sciences — National Research Council, the U.S. Air Force School of Aviation Medicine, Los Alamos Scientific Laboratory, and Oak Ridge National Laboratory. The programme is designed to make possible the assignment of a specific neutron or gamma ray dose or both in rads to the record of each survivor in the Atomic Bomb Casualty Commission's files for whom sufficient pertinent information is available.

A detailed interim report on leukemia in the Hiroshima atomic bomb survivors is presently being prepared by various staff members of the Atomic Bomb Casualty Commission and the National Research Council. It will include the best currently available dosimetry information resulting from the afore-mentioned collaborative effort. However, because of the present interest in data pertinent to radiation leukemogenesis and the desirability of making available current information obtained by the Atomic Bomb Casualty Commission, table I, summarizing results of the leukemia survey in Hiroshima as of December 1957, is presented at this time.

Certain limitations of these data should be pointed out. The programme was initiated in 1947 but the present level of intensity of effort was not achieved until about 1950. Therefore, while it may be assumed that the numbers of cases shown for the years 1950 through 1956 are fairly accurate, the numbers that arose in the preceding years may be understated rather seriously. With respect to 1957, it is probable that additional cases remain to be discovered with onset in that year.

The denominators of the incidence rates are estimates, subject to errors of presently unknown magnitude. The 3 June 1953 Residential Census of Hiroshima was conducted by the Hiroshima Census Bureau and was presumably of a reasonable degree of accuracy. The categorization by distance from the hypocentre was made on the basis of Atomic Bomb Casualty Commission investigations of 50.8 per cent of the males and 44.6 per cent of the females who reported themselves exposed to the bomb. However, it was found that 3.1 per cent of those reportedly exposed were in fact not in the city at the exact time of the bombing.

Apart from the uncertainties regarding the population on 3 June 1953, it may be incorrect to assume that migration in and out of the city during the period from 1950 to the present was the same for persons exposed in different distance categories. However, despite the current lack of pertinent information, the simple expedient of multiplying the June 1953 population values by eight to obtain estimates of person-years at risk has been adopted since the census date is roughly near the midpoint of the interval under study. This procedure seems reasonable at present, although the magnitude of any resultant error is hard to estimate.

In addition to the above-mentioned points, which have to do with the intrinsic accuracy of the data presented, a further caution should be strongly emphasized. The uncertainties involved in inferring radiation dose from distance alone are too large to support conclusions beyond the previously reported qualitative one that those survivors who received large doses of radiation—that is, who were within 1,500 metres of the hypocentre, had a significantly higher incidence of leukemia than those beyond that distance, who received relatively little or none.[3] The relationship of incidence to distance as presented in table I cannot be given a more quantitative interpretation because there are too many variables, as yet unresolved, which cannot be ignored.

TABLE I.
Of preceding paper by Niel Wald
LEUKEMIA IN HIROSHIMA ATOMIC BOMB SURVIVORS WHO WERE RESIDENTS OF HIROSHIMA CITY AT THE TIME OF DIAGNOSIS (DIAGNOSES VERIFIED BY THE ATOMIC BOMB CASUALTY COMMISSION)

Year of Onset	*Total*	*Distance from hypocentre (metres)*				
		Under 1,000	*1,000–1,499*	*1,500–1,999*	*2,000–2,999*	*Over 3,000*
1945						
1946						
1947	3		1		2	
1948	7	2	4		1	
1949	5	1	1	1	1	1
1950	9	3	5			1
1951	11	3	7	1		
1952	11	3	5	1		2
1953	12	2	6	2	1	1
1954	6	2	2	1	1	
1955	8	1	4	2		1
1956	6		1	1	1	3
1957	5	1	3			1
TOTAL	83	18	39	9	7	10
Estimated population*	95,819	1,241	8,810	20,113	32,692	32,963
Number of cases with onset in 1950–1957	68	15	33	8	3	9
Estimated person-years at risk	766,552	9,928	70,480	160,904	261,536	263,704
Annual incidence of leukemia per 100,000	8.9	151.1	46.8	5.0	1.1	3.4

* Based on Hiroshima Census Bureau's Daytime Population Census of Hiroshima City, 3, June 1953.

For example, the presently available estimates of the air dose in Hiroshima have a large uncertainty, the magnitude of which is itself not yet definite. Also, experimental dosimetry studies at Oak Ridge National Laboratory emphasize the need for detailed information, such as is being collected by the Atomic Bomb Casualty Commission, concerning the shielding situation of any particular survivor at any distance. It is conceivable that the radiation received within a light frame house (the most common shielding situation) may vary from an amount almost equalling the outside air dose to one equal to the outside air dose attenuated by perhaps a factor of two, depending on the position of the person in the house.

In determining the relationship of radiation exposure to the incidence of leukemia, such detailed data must be examined not only for each leukemic survivor, but also for enough of the population at risk to permit calculation of statistically significant incidence rates. Until this information becomes available from the dosimetry programme, it is premature to attempt precise quantitation of dose-effect relationships in radiation leukemogenesis on the basis of the Hiroshima and Nagasaki radiation-populations.[8]

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8. Grateful acknowledgement is made for the biostatistical assistance of Mr. Seymour Jablon, National Research Council, and also for the aid of Dr. Lowell Woodbury, head of the Biostatistics Department of the Atomic Bomb Casualty Commission, and his staff. Appreciation is also expressed for the help of Dr. Robert M. Heyssel, who provided the hematological data for 1957, and for the co-operation of the physicians of both the Atomic Bomb Casualty Commission and the city of Hiroshima, who make the long-term Hiroshima leukaemia study possible.

Leukemia in radiologists

34. The most recent estimate of the leukemia death rate for United States radiologists (ages 35 to 74 years) is based on the data of 1938-1952, inclusive.[14] During this period there were 17 deaths, corresponding to an average annual rate of 610 per million. The rate observed in the population at large (corrected for age distribution) was 121 per million.

Leukemia in children

35. Two reports have associated leukemia in children with previous X-ray exposure during infancy or the prenatal period. In the first,[17] a study was made of 1,700 United States children treated during infancy for a condition known as enlargement of the thymus gland. The untreated siblings of the irradiated children served as controls. There were 17 cases of cancer, including 7 of leukemia in the irradiated group; there were 5 cases of cancer, but none of leukemia in the control group (tables VIII and IX).

TABLE VIII. EXPECTED AND OBSERVED RATES FOR CANCER[a]

	Treated children		*Untreated siblings*	
	Expected	*Observed*	*Expected*	*Observed*
All cancers	2.6	17 (?19)	2.7	5
Leukemia	.6	7 (? 8)	.6	0
Thyroid cancer	.08	6	.08	0

[a] Data from reference 17.

TABLE IX. DISTRIBUTION OF NEOPLASIA ACCORDING TO AMOUNT OF RADIATION[a]

	Under 200 r.	*Over 200 r.*	*Unknown*
Number treated	604	804	313
Cases of leukemia	2	5	(?1)
Other cancers	0	4	0
Carcinoma of thyroid	0	6	0
Adenoma of thyroid	0	6	3

[a] Data from reference 17.

36. In a British study[18] of the history of 547 mothers whose children had died before the age of ten from leukemia and other cancers, it was found that 85 of the mothers (15.5 per cent) reported that they had had diagnostic abdominal radiography involving the foetus during the relevant pregnancy. In a comparison series of 547 mothers with healthy and living children only 45 (8.3 per cent) reported radiologic exposure during the relevant pregnancy (table X).

TABLE X. LEUKEMIA AND CANCER INCIDENCE IN OFFSPRING RELATED TO X-RAY EXAMINATIONS IN THEIR MOTHERS DURING THE RELEVANT PREGNANCY[a]

Type of cancer in child	*Number of cases*	*Number of mothers and foetuses exposed to*	
		Abdominal examination	*Examination of other parts of body*
1. Leukemia	269	42	25
Controls (living)	269	24	23
2. Other cancers	278	43	33
Controls (living)	278	21	32
3. Total cancer	547	85	58
Total control	547	45	55

[a] Data from reference 18.

37. The suggestion has been made that a proportion of the leukemias and cancers in the first group, namely

7.2 per cent, may have been caused by the exposure during intrauterine life of the patients in question. However, radiological examination of other parts of the body was not correlated with increased cancer incidence.

38. The data indicate a correlation between leukemia and other cancers in childhood and irradiation of the foetus, although alternative possibilities cannot be excluded. It is possible that some mothers who give birth to leukemic children might be in greater need for diagnostic X-ray service during pregnancy and that in the present cases leukemia or cancer may have resulted independently of exposure sustained during intrauterine life.

39. In any event, the clinical indications for the X-ray examinations of the mothers of these particular children are not known, nor is information available on the types of examinations performed and on the actual doses of X-ray received by the mothers and the foetuses. Additional data and final evaluations of their significance are known to be in course of publication (British Medical Journal).

Leukemia after X-ray therapy for ankylosing spondylitis

40. A dependence of the incidence of leukemia on radiation exposure has been demonstrated in a study of 13,352 cases of ankylosing spondylitis treated during 1935-1954 at 82 radiotherapy centres in Great Britain.[19] In this series, 28 patients were certified to have died of leukemia and 12 of aplastic anemia, as of 31 December 1955. The numbers of expected deaths were 2.9 for leukemia and 0 3 for aplastic anemia. (The over-all death rate per million persons for leukemia in England and Wales has been as follows: 21 in 1935, 34 in 1945, 49 in 1954). A thorough study of the series led to the following tabulation of cases with blood disease:

Group	*Males*	*Females*
Leukemia (A)	35	1
Probable leukemia (B)	5	0
Aplastic anemia	4	0
Undecided	2	2

41. To study the distribution of cytological types, all available cases of leukemia in patients with ankylosing spondylitis, both treated and untreated were tabulated:

	X-ray treated series	*per cent*	*Untreated series*	*per cent*
Lymphatic leukemia	3	(8)	3	(38)
Myeloid leukemia	31	(78)	4	(50)
Monocytic leukemia	6	(15)	1	(13)
Type unspecified	9		0	

There is a relative deficiency of the lymphatic type of leukemia among the X-ray treated cases, and the difference between the two series was found to be just significant ($P = 0.05$).

42. Only male cases of leukemia and "probable leukemia" (groups A and B) were available in adequate numbers for further statistical analysis. After a single course of treatment, the evidence of 10 cases indicated that leukemia occurred within 5 years. When all cases were considered, i.e. those receiving multiple courses over a period of years as well as those receiving a single course in a month or so, it was noted that leukemia was diagnosed within 5 years of the last treatment in 35 of 37 cases.

43. The radiological treatment of ankylosing spondylitis usually consisted of irradiating the spine and the region of the sacroiliac joints. In some cases other regions were also treated. Most (7,215) of the patients in the present series received only one course of treatment, but some (1,119) received as many as four courses over a period of years. Preparatory to examining the relation between leukemia incidence and radiation dose elaborate studies were made so that for each course of treatment in each case there could be determined:

(*a*) *The spinal dose:* the mean dose to the spinal marrow, based on the average of 3 points (upper sacral, mid-dorsal, mid-cervical).

(*b*) *The integral dose:* the integral dose to the whole body.

The distribution of doses in the entire population of 11,287 men was estimated from the doses of a randomly drawn sample of 1,878 men. The dose of each leukemia case was determined individually. For multiple courses of treatment due allowance was made for the years at risk at each dose level. Dose-classes were then established (e.g., 250—499 rem, 500—749 rem), and the crude incidence of leukemia determined in each class. In addition, the standardized incidence of leukemia was determined, i.e., the incidence standardized for age.

44. In studying the dose-effect relationship, the following assumptions were made:

(*a*) The significant parameter of dose is the mean dose to the spinal marrow. (The spinal marrow was always irradiated; the amount of irradiated extra-spinal marrow was variable.)

(*b*) There is an absolute waiting period of one year after exposure during which no cases occur. Thereafter, each year at risk has equal weight. (The authors considered this to be an over-simplification, but used it as a practical method of dealing with the many cases that had received multiple courses of treatment).

(*c*) Fractionation of dose did not diminish its effectiveness.

(*d*) The probability of inducing leukemia is directly proportional to the number of man-years at risk. The number of man-years at risk equals the product of (number of individuals given a particular dose) × (mean years since exposure—1).

(*e*) Constitutional factors may predetermine a greater radiosensitivity in this population, but no allowance can be made for it.

45. Results from these studies are summarized in table XI and figure 4. It is clear that the incidence of

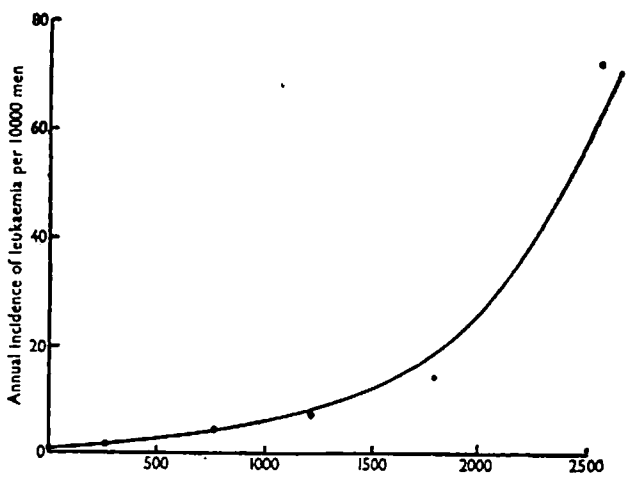

Figure 4. The incidence of leukemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow: all male patients in the study series and 'A' and 'B' cases of leukemia, excluding co-existent cases. (Figure 4 is Figure 1 in the original reference 19.)

leukemia increases with radiation dose and that the relation between them is not linear. The curve through the points in figure 4 is drawn to reach the control rate at zero dose without indicating a threshold for the induction of leukemia. It should be noted, however, that only one case of leukemia received a dose of less than 400 rem and that this case had lymphatic leukemia and had had large doses of extra-spinal irradiation. Therefore the course of the curve between this dose and zero must be regarded as practically undetermined. The slope of the curve between 750 and 1,250 rem appears to be relatively constant and is equal to about 0.6 new cases per year per 10^6 men per rem to spinal marrow.

46. The data for the limited group of patients that received irradiation to the spinal axis only are given in table XII. In this group, 18 patients developed leukemia. Analysis of these data[20] suggested a threshold of 54 rem by one method and of 130 rem by another. These estimates, however, are subject to great uncertainty owing to the small number of cases in the series and the lack of data for the range in question. Statistical analysis indicated that the threshold might lie anywhere between 0 and 460 rem. The slope of the dose-effect curve was about the same as that given in paragraph 45.

Theoretical considerations for estimation of radiation hazards

47. The quantitative statement of a radiation hazard involves the precise relation between the total number of radiation-induced cases N_x and the radiation dose D, throughout an extended range of dosage. At present, such a statement cannot be satisfactorily made for any kind of human cancer. For certain purposes, however, a very crude estimate may be better than none at all and two methods have been proposed with this end in mind.

48. The first method assumes (1) that *all* cancer is caused by ionizing radiation and (2) that the annual cancer rate is directly proportional to the annual radiation dose. The total cancer incidence rate R in the United States, for instance, is now about 2,800 cases per annum per million population. The annual background radiation dose rate is about 0.1 rem, and the dose rate from other sources is perhaps another 0.1 rem. The average annual dose rate per individual is thus about 0.2 rem. The potency factor k is, therefore,

$$k = \frac{2800}{0.2} = 14 \times 10^3, \qquad (2)$$

i.e., 1 rem will produce a total of 14,000 new cancer cases when a population of one million has been exposed. Such a figure appears to be absurdly large. It has been suggested that such a calculation applies only to certain kinds of cancer but not to others. There appears to be no scientific basis for such a selection, however.

TABLE XI.[a] THE NUMBERS OF PATIENTS WHO DEVELOPED LEUKEMIA, AND THE CRUDE AND STANDARDIZED INCIDENCE RATES: AFTER DIFFERENT MEAN DOSES OF THERAPEUTIC RADIATION TO THE SPINAL MARROW: MALE 'A' AND 'B' CASES, EXCLUDING CO-EXISTENT CASES

	Mean dose to spinal marrow (r.)													
	0[b]	*Less than 250*	*250–499*	*500–749*	*750–999*	*1,000–1,249*	*1,250–1,499*	*1,500–1,749*	*1,750–1,999*	*2,000–2,249*	*2,250–2,499*	*2,500–2,749*	*2,750 or more*	*All doses*
No. of men developing leukemia														
'A' cases	—	1	2	6	3	7	2	3	1	2	3	1	1	32
'A' and 'B' cases	—	1	3	6	4	8	3	3	1	2	4	1	1	37
Crude incidence per 10,000 *men per year*														
'A' and 'B' cases	0·49	2·16		4·59		6·99			12·18			63·65		5·98
Standardized incidence per 10,000 *men per year*														
'A' and 'B' cases	0·49	1·98		4·66		7·21			14·44			72·16		5·98

[a] This table was table 19 in the original reference.[19]

[b] The rate given for 'zero' therapeutic dose is the corresponding rate among men of the same age-distribution and observed over the same period, calculated from the mortality from leukemia experienced by the whole male population of Britain.

TABLE XII.[a] THE INCIDENCE OF LEUKEMIA AFTER DIFFERENT MEAN DOSES OF THERAPEUTIC RADIATION TO THE SPINAL MARROW: MALE 'A' AND 'B' CASES GIVEN ONLY SPINAL IRRADIATION, EXCLUDING CO-EXISTENT CASES

	Mean dose to spinal marrow (r.)										
	0	*Less than 250*	*250–499*	*500–749*	*750–999*	*1,000–1,249*	*1,250–1,499*	*1,500–1,749*	*1,750–1,999*	*2,000 or more*[b]	*All doses*
No. of man-years at risk following exposure to dose	—	5,404	7,673	6,573	8,262	7,411	2,782	897	566	679	40,247
No. of men developing leukemia											
'A' cases	—	0	2	4	3	4	0	2	1	1	17
'A' and 'B' cases	—	0	2	4	3	5	0	2	1	1	18
Crude incidence per 10,000 men per year											
'A' and 'B' cases	0·49	1·53		4·72		6·75[c]			8·12[d]		4·47
Standardized incidence per 10,000 men per year											
'A' and 'B' cases	0·49	1·44		4·83		6·82[c]			8·70[d]		4·47

[a] This table was table 20 in the original reference.[19]

[b] Average dose, 2,290 r.

[c] For the group receiving 1,000–1,499 r. the crude incidence is 4·91; standardized incidence 5·06.
For the group receiving 1,000–1,749 r. the crude incidence is 6·31; standardized incidence 6·82.

[d] For the group receiving 1,500 r. or more the crude incidence is 18·68; standardized incidence 19·86.
For the group receiving 1,750 r. or more the crude incidence is 16·07; standardized incidence 16·82.

49. The second method uses the results of the British study of leukemia incidence in a radiation-treated population, discussed above. (The data for Hiroshima have not been used owing to the uncertain dosimetry.) To compensate for the paucity of data, a number of assumptions are made in the following analysis:

(*a*) The significant parameter of dose is the mean dose to the entire red marrow. In uniform whole-body exposure, the doses to the entire red marrow and the spinal marrow are the same. When only the spinal marrow is irradiated, the mean dose to the entire red marrow is probably about 40 per cent of the spinal dose.

(*b*) The total number of years at risk is 15, and each year has equal weight. This assumption was arrived at from the following considerations. The mean period of observation in the British study was 5 years; this would set a lower limit for all types of cases. Those 10 cases of leukemia that received only one course of treatment all occurred within 5 years of that treatment. For the population exposed at Hiroshima the cancer rate began falling after 8 years, and a complete period at risk of 15 years has been suggested. The maximum duration of the period at risk cannot be greater than the duration of life after exposure. In the case of a population of children, this could be 65 years, in the case of the usual mixed population, the average would be about 35 years.

(*c*) Fractionation or protraction of dose does not diminish its effectiveness.

(*d*) Constitutional factors may be neglected.

(*e*) Cancer production is a linear function of radiation dose. Linearity has been assumed primarily for purposes of simplicity. In the case of the British data for doses below 1,300 rem, a linear relation provides a fairly accurate fit.

(*f*) There may or may not be a threshold dose. The two possibilities of threshold and no-threshold have been retained because of the very great differences they engender.

50. The potency factor k, equal to N_x/D, can now be calculated. For a single exposure of the entire red marrow to 1 rem, the average annual leukemia rate is estimated to be 1.5 cases per million persons exposed. If the total number of years at risk is assumed to be 15, k is equal to 1.5×15, or approximately 20 cases per million exposed per rem. These calculations are based on observations following single large exposures. However, under conditions of prolonged exposure at lower dose rates, the period of risk may be longer. In the calculations of chapters V and VII where a *maximum* estimate is wanted, the period at risk is assumed to equal the average remaining life-time of the exposed population (35 years). The value of k has therefore been taken as 52 cases per million per rem in the calculations in paragraph 128 of annex D and in paragraph 61 of chapter V of this report.

51. The use of k to predict the number of cases of leukemia depends on the magnitude of the threshold. If there is no threshold, N_x is equal to the product of k, D, and the number of persons exposed. If a threshold is assumed, there will be no cases in persons who have received less than that dose.

52. Besides the alternative possibilities of a linear relation with or without a threshold, it is possible that a non-linear relationship may exist, as has been found, for example, in the case of many chromosome abnormalities.[21] As noted in paragraph 45 and illustrated in figure 4, the incidence of leukemia in the British study was a curvilinear function of dose, not a linear one. A curve providing a good fit to these data is obtained when leukemia incidence is considered to be proportional to the square of the radiation dose. In general, curves of this type predict a finite incidence of leukemia at small doses. However, this incidence may be very much lower than that predicted by a linear function based on all of the same data.

53. The methods used above to estimate the risk of leukemia after radiation exposure are of general use. They may be applied both to other cancers and also to non-cancerous lesions such as occur in the eye (cataract), the skin and in the bones. Their use is contingent upon the availability of adequate statistical estimates of the incidence of the disease in question related to the radiation doses received by the population at risk. It may be noted that such methods do not depend on detailed knowledge of how the radiation induces the lesion within the cell, e.g. by somatic mutation or some other alleged or hypothetical mechanism. At present, adequate statistical data are not available for bone tumours or for tumours of other organs to make such estimates of risk. However, it is known that pertinent studies are under way for bone tumours in man that are caused by radioactive substances.

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Appendix

LIST OF SCIENTIFIC EXPERTS

The scientific experts who have taken part in the preparation of the report while attending Committee sessions as members of national delegations are listed below. The Committee must also express its appreciation to the many individual scientists not directly connected with national delegations whose voluntary co-operation and good will contributed in no small measure to the preparation of the report.

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back to first page