LATE EFFECTS OF EXPOSURE TO IONIZING RADIATION

Why further studies of exclusively low dose situations are urgently needed

by

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Introduction

According to ICRP 26 the most reliable method of risk estimation for cancer effects of low level radiation is by linear extrapolation from effects observed at much higher levels[1]. This recommendation still stands and is clearly the result of the Radiation Effects Research Foundation in Hiroshima (RERF) assuming that all late effects of the 1945 exposures to A-bomb radiation were the result of mutations (stochastic effects)[2]. There are, however, a number of observations which conflict with the hypothesis of no chronic effects of non-stochastic lesions such as radiation burns and marrow damage.

The source of RERF risk estimates is an unusually large cohort which was assembled five years after the bombing of Hiroshima and Nagasaki (so called Life Span Study or LSS population of A-bomb survivors). By this time the devastated areas had been rebuilt and life in the two cities was proceeding normally. Furthermore, according to RERF, deaths from non-stochastic effects of the radiation had ceased and, for five year survivors (or persons who were still alive on October 1st, 1950), there was henceforth a normal risk of dying from all natural causes except cancer.

These conclusions were the result of including the LSS population in a relative risk or RR analysis which recognised eight positions on a T65 dose scale. On this scale under 1 rad was the lowest and over 400 rads the highest dose. The average was appreciably higher for 19374 survivors from Nagasaki (42 rads), than for 60,482 survivors from Hiroshima (34 rads), and for doses above 100 rad, which is close to the threshold for extensive tissue damage, there were even greater city differences (14% and 5%). These differences were originally supposed to be due to the two bombs

having different neutron components. However we have since learnt that the neutron/gamma ratio was equally small for each explosion.

From 1950 onwards death rates of the LSS population compared favourably with national rates. Also - on certain assumptions - the RR analysis was compatible with there being no extra deaths from causes other than cancer. These assumptions are, first, that most of the deaths ascribed to rare blood diseases such as aplastic anaemia, etc were really leukaemias and, second, that for any cause of death a dose related risk was bound to show as a linear trend on the T65 dose scale. Not everyone agreed with these assumptions. But whenever objections were raised they were either over ruled or ignored[3-5]. Apart from doubts about the extra deaths from aplastic anaemia, the main concern was about how long acute effects of the blast and the radiation continued to affect the mortality experiences of the survivor cohort.

For several months after July 1945, both cities experienced extremely high death rates, also rates which were inversely related to hypocentre distances and considerably higher for Nagasaki than Hiroshima[6]. There was gross dislocation of all essential services (which meant harsh living conditions for everyone) and no antibiotics to cope either with widespread injuries or with an epidemic of acute bone marrow damage[7]. The latter caused thousands of deaths from infections as well as unusual blood conditions. Therefore, an early (dose related) effect of each nuclear explosion must have been selection in favour of persons with exceptionally high levels of immunological competence.

This selection has never been disputed and has even described as "an indubitable fact and not an issue"[8]. But according to RERF the mortality effects were too short lived to have much effect on five year survivors. This opinion was the result of, first, assuming that, until they disappeared, any selection effects of early deaths would necessarily show as a linear trend in an RR analysis, and then finding either no such trend (Nagasaki), or an effect which was "too small to have influenced the response to radiation in any important way" (Hiroshima)[8].

Though there was no precedent for the early epidemic of acute bone marrow damage it clearly introduced the possibility of permanent damage to the immune system and to sources of red blood corpuscules. Therefore, failure to find any evidence of selection in the LSS population could be due, not to the early deaths having shortlived effects, but to the favourable attributes which prevented such deaths being gradually eroded by an unrecognised effect of the radiation, namely, chronic marrow damage.

The follow-up of 5 year survivors was mainly for the purpose of observing cancer or stochastic effects of the radiation, but it was also prepared for other late effects of the blast or the radiation (non-stochastic lesions) and for a reduced risk of dying from all natural causes (selection effect of early deaths). There was bound to be competition between the selection and other effects, but the resultant mortality effect would either be different for different causes of death or not remain the same for any length of time. Therefore, since all effects of the bombing were necessarily dose or distance related, it was assumed that all late effects would show in a relative risk analysis as a linear trend or

dose response curve which continually increased or decreased with radiation dose.

Time and again the RR analysis showed no signs of upward nor downward trends of mortality for any non-malignant disease except aplastic anaemia (which was suspect because of its associations with leukaemia and other neoplasms). Therefore, RERF has repeatedly concluded that all members of the LSS population had either avoided or completely recovered from all acute effects of the holocaust. This unlikely conclusion met with no opposition and it soon became accepted practice to base all radiation risk estimates upon linear extrapolation of the cancer experiences of high dose survivors[9].

Unfortunately for this convenient method of risk estimation, the linear trend test is not suitable for detecting mortality effects of two radiation effects which have opposite effects on general mortality and different dose thresholds. For example, only high dose survivors were at risk of chronic marrow damage, but even the zero dose group was affected by the high death rates of 1945-46. Therefore for extra deaths from defective immune responses or insufficient supplies of red blood corpuscles (marrow damage) the threshold dose was much higher than the selection threshold (or the early death effect which reduced the risk of later deaths). As a result of this difference the two contrasting effects would show in a relative risk analysis, not as positive or negative linear trends but as quadratic or U shaped dose response curves.

In a series of RERF mortality reports only six groups of non-malignant

diseases are recognised and only one infection is separately identified (tuberculosis). Even so, there are in the latest report (1950-78 deaths) many examples of U shaped dose response curves and, for the largest group of non-cancer deaths (composed mainly of infection related causes) this shape of dose response curve is a constant feature of deaths in seven consecutive periods[2]. There also exists a review of this report which shows the effects of comparing cardiovascular with other non-malignant diseases[5]. For the "other" group (which was twice as large as the one containing all neoplasms) there was no mistaking the fact that, from 1950 onwards, the ratio of observed to expected deaths decreased with dose below 100 rad and increased with dose above this level.

How the non-cancer death rates of Hiroshima and Nagasaki survivors compared with national statistics can be seen on SMR analysis of 1950-74 deaths from the same non-malignant diseases[8]. For each diagnostic group the ratio of observed to expected deaths (SMR) was higher for the city with 14% of high dose survivors (Nagasaki) than for the city with only 5% of these survivors (Hiroshima), and in both cities the SMRs for tuberculosis and other infection deaths were considerably higher than the ratios for cerebrovascular accidents and other cardiovascular diseases. Furthermore, at dose levels above 100 rad, the observed number of deaths from diseases of blood and blood forming tissues was nearly 5 times as high as the expected number.

Finally, the basic tabulations for the next mortality report (1950-82 deaths) are now available (as a floppy disc). Therefore it is possible to observe the effects of fitting the data for various causes of death to the

following quadratic dose-response curve -

$$RR = 1 + (D-25) + (D-25)^2$$

where RR = relative risk

= coefficient of the linear component of risk.

= coefficient of the quadratic component.

D = radiation dose in rads (T65 estimate)

25 rads = average dose for the LSS population.

Table 1 shows the results of applying this formula to the following groups:- all causes of death, all non-malignant diseases and infections etc. For each group there is a quadratic or U shaped curve of dose response, and for the two sets of non-cancer deaths there is also evidence of a negative linear trend (i.e. a greater risk at the lower than the upper end of the T65 dose scale). These results are clearly due to longstanding competition between selection and non-stochastic effects of the radiation. Therefore it is no longer necessary for RERF to insist that most of the deaths ascribed to aplastic anaemia were really cases of leukaemia.

This was the conclusion reached after a systematic but biassed search for diagnostic errors i.e. by inspection of the cases diagnosed as aplastic anaemia but not the cases diagnosed as leukaemia. Even these "one way" corrections were not sufficient to make the anaemia deaths conform with the hypothesis of no late effects of radiation apart from cancer (table 2). They did, however influence the interpretation of a similar excess of aplastic anaemias in a British study of late effects of radiotherapy[10]. This survey was confined to cases of ankylosing

spondylitis. Therefore it was in no position to detect any life shortening effects of radiation apart from cancer. But once again, by forcing the data to conform with a false hypothesis, the true significance of the extra deaths from aplastic anaemia was missed.

It is of course, quite easy to mistake leukaemia for aplastic anaemia, but it is equally easy to make the opposite mistake. Therefore, even without the tests for quadratic dose response curves in table 1, the extra deaths from aplastic anaemia should have raised a suspicion of chronic marrow damage (and consequent difficulty in maintaining a proper supply of red blood corpuscles). The tests for quadratic as well as linear components of the radiation effects are important because they show that late effects of marrow damage were not confined to a rare blood disease, and were even sufficient to more than counterbalanced a strong selection effect of early deaths. In other words we can now safely assume that following exposure to high level radiation there is a high risk of cancer latency deaths, (or events which automatically mask the cancer risk). Therefore linear extrapolation of high dose effects is bound to underestimate the cancer risks of low level radiation (or doses which lie below the threshold for non-stochastic effects). A greater risk of cancer latency deaths in Nagasaki than Hiroshima would also explain why the cancer risk (per unit dose) has always been greater in this city than in the city with only 5% of high dose survivors, and a greater risk for children and old persons would account for the well known concentration of radiogenic cancers in young adults.

To sum up, lasting effects of extensive marrow damage can be inferred

from several surveys of high level radiation and are the main reason why linear extrapolation high dose effects should not be used to estimate risks of small doses. This method of risk estimation is such an integral part of ICRP recommendations that there may be difficulty in introducing radical changes. Nevertheless, without more studies of exclusively low dose situations, we remain in danger of grossly underestimating, not only the cancer hazards of radiation workers, but also the cancer and genetic effects of large and small leakages of radioactivity from nuclear installations.

References

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Table 1.

1950-1982 Deaths of A-bomb survivors (Unpublished RERF data)

T65 Dose in rads	All Causes of Death Obs	O:E	Non-Malignant Diseases Obs	O:E	Certain Non-Cancers(1) Obs	O:E
0	12798	1.00	9518	1.01	4478	1.02
1-	9563	0.99	7099	1.00	3385	1.01
10-	5170	0.99	3769	0.98	1735	0.97
50-	1476	0.98	1056	0.96	465	0.90
100-	1029	1.01	688	0.95	315	0.91
200-	455	1.09	279	0.93	123	0.85
300-	215	1.17	140	1.09	59	0.94
400+	333	1.36	201	1.15	104	1.23
Total	31043		22750		10664	

			t	sig		t	sig		t	sig
RR:(2)	α	$-7.56\ (10^{-5})$	-0.38	n.s.	$-6.95\ (10^{-4})$	-2.15	*	$-14.75\ (10^{-4})$	-4.18	***
	β	$1.54\ (10^{-6})$	2.70	***	$1.97\ (10^{-6})$	2.86	***	$3.45\ (10^{-6})$	3.42	***

(1) i.e. tuberculosis, digestive diseases and a residual group of other infections etc

(2) $RR = 1 + \alpha(D-25) + \beta(D-25)^2$.

where α = coefficient of linear component, β = coefficient of quadratic component, RR = Relative Risk, D = Radiation dose in rads.

Significance levels: *** < 0.001, * < 0.05.

Table 2.

1950-74 Deaths of A-bomb Survivors from Diseases of Blood & Blood Forming Tissues (from Beebe et al 1978[8]

T65 dose in rads	Observed[1] No:	"Corrected"[2] No:	Expected[3] No:	Ratio Obs : Exp	Ratio Correc : Exp
0 - 9	63	51	46.2	1.36	1.10
10 - 99	30	24	16.1	1.86	1.49
100 +	24	13	4.8	5.00	2.71
Total	117	88	67.1	1.74	1.31

(1) as recorded on death certificates

(2) after haemological review of 59 cases

(3) National Statistics (which are based on death certificate data without the necessity of any haemological review)