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Low Level Radiation and the Cancer Controversy

by

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Introduction

The fact that repeated exposure to small doses of gamma radiation is a condition of life on this planet makes it difficult to decide who is on the right track: the pessimists who believe that mutational effects of background radiation are important causes of birth defects and cancer, or the optimists who believe that a little radiation is good for one (hormesis). The advent of man made sources of radioactivity has given epidemiologists several opportunities to study late effects of these additional exposures. However, this work has revealed two problems: how to obtain reliable measurements of the inevitable and the additional exposures (dosimetry) and how to arrange things so that test and control groups have the same risk of dying from natural causes (selection). Recent work suggests that selection bias has more often been the cause of false impressions than faulty dosimetry. Why this is so can be seen in the following attempts to come to grips with both problems: a follow-up of A-bomb survivors by the Radiation Effects Research Foundation (RERF data); a follow-up of workers from the Hanford nuclear weapons facility (Hanford data), and the Oxford Survey of Childhood Cancers (OSCC data).

RERF Data

The Life Span Study or LSS cohort of A-bomb survivors was assembled 5 years after the bombing of Hiroshima and Nagasaki. For the next 15 years the nearest equivalent to a radiation dose was the distance from the hypocentre; it then became possible to work with dose estimates based on bomb simulations at Oak Ridge, and today there are revised estimates based on further work by US nuclear physicists. Meanwhile, RERF had decided that, in spite of their unusual experiences, A-bomb survivors had a normal risk of dying from all causes except cancer.

This conclusion was the result of periodically comparing deaths from various causes with national statistics (SMR analysis) and with a linear model of relative risk (see diagram). For all causes of death there was no difference between the survivors and other persons of the same age and sex; for cancer there was a linear trend with dose (which was steeper for leukaemia than other neoplasms) and for the remaining non-cancer deaths there was no dose trend in either direction. Therefore, according to RERF, there was no reason why cancer risk coefficients should not be based on linear extrapolation of high dose effects.

This recommendation was accepted by the International Commission on Radiological Protection (ICRP) and by the World Health Organization (WHO) and there is still a general concensus that late effects of the A-bomb radiation were always the result of mutations and never the result of cell killing. Nevertheless, given the exceptionally high risk of dying from trauma-related infections before 1950, and the possibility of late effects of marrow damage and other serious injuries, the present interpretation of RERF data is open to question.

For several weeks after the two nuclear explosions there was exceptionally strong selection against all infirmities especially infection sensitivity. This effect was necessarily dose related. Therefore, if it had persisted without interference from later effects of the radiation, the all causes death rate of the LSS cohort would have been lower than normal (healthy survivor effect) and inversely related to dose (internal healthy survivor bias). Deaths from self inflicted injuries have always met the "selection only" requirements and, for diseases of blood and blood forming

tissues, there has always been a rising trend with dose. These exceptions to the rule of no dose related effects for non-cancer deaths were not unnoticed by RERF, but they clearly carried no weight when it came to assessing late effects of the radiation. Nevertheless both observations would fit with the assumption of longstanding competition between selection effects of early deaths and later effects of the radiation.

According to this hypothesis all effects of the bombs were dose related, but a) there was one effect which was only felt at high dose levels (marrow damage) and three effects which were felt at all dose levels (environmental damage, selection and mutations), and b) by 1950, harmful effects of environmental damage were no longer a match for beneficial effects of selection, and beneficial effects of selection were no longer a match for harmful effects of marrow damage. As a result of these differences one would expect the non-cancer death rate of survivors to decrease with dose below the marrow damage threshold and increase with dose above this level. Therefore, a risk model with two degrees of freedom would be more appropriate than a simple linear model (see diagram).

The first opportunity to apply this reasoning to the mortality experiences of the LSS cohort came in 1988 with general release of an RERF data tape. With this tape it was possible for two outsiders (Stewart and Kneale) to show that for all non-cancer deaths (and more especially deaths within 15 years of the bombing, and infection related deaths) there was a biphasic dose response curve whose lowest point was in the middle of the dose scale. This demonstration of late effects of the radiation other than cancer is still awaiting confirmation by RERF. But it is already

reasonable to suggest, first, that the usual method of estimating cancer risk coefficients (by linear extrapolation of high dose effects) is unsafe since late effects of radiation are probably the result of cell killing well as mutations; and second, that the impression left by RERF data - of no cancer risk at low dose levels - cannot be trusted since a "healthy survivor bias" has been demonstrated whose effects would not be restricted either to high doses or to non-cancer deaths.

Hanford Data

The commonest source of man made radioactivity is the nuclear weapons industry. For workers in this industry there is both monitoring of external doses (by film badges) and monitoring of internal depositions of radioactive substances (by urine tests and whole body counts). There are also a few branches of this industry where epidemiologists are preparing the ground for studies of late effects of the occupational exposures by systematic tracing of all causes of worker deaths. For various reasons, including follow-up periods which are often too short for demonstrating cancer effects, only limited use has been made of the mortality data. But enough work has been done to be reasonably certain a) that nuclear workers have lower rates of general mortality than their contemporaries (healthy worker effect), and b) that the proportion of cancer deaths is typically 10 to 20 per cent higher for nuclear workers than for the general public. Furthermore, for one branch of the industry, which has been producing plutonium since 1944 (Hanford), we have the results of two independent analyses of the mortality data: one by Mancuso, Stewart and Kneale (1944-77 deaths), and the other by Gilbert et al (1945-81 deaths).

According to MSK, uneven distribution of the healthiest workers between safe and dangerous occupations has produced a workforce in which the risk of dying from natural causes is negatively correlated with radiation dose (internal healthy worker bias). Partial correction of this bias can be obtained by "job stratification", but full control requires a different type of stratification, i.e. by the frequency (and results) of the monitoring for internal radiation. With this method of control for the internal bias, a relative risk analysis (which allowed each annual dose of external radiation to make a separate contribution to the final result), eventually produced evidence of a cancer risk and showed that this was largely the result of malignant changes in tissues rated (by ICRP) as "sensitive to cancer induction effects of radiation".

Meanwhile, Gilbert et al, who were not convinced that there was an "internal healthy worker bias" and were openly critical of the MSK use of the urine tests and whole body counts, were coming to a somewhat different conclusion. For two types of cancer (myeloma and female genital), there was suggestive evidence of a radiation effect. However, the estimated number of extra (radiogenic) cancers was so small (4 at the outside) that the final risk estimate was in reasonably close agreement with RERF estimates. Therefore, according to one analysis of Hanford data it is safe to base cancer risk coefficients on linear extrapolation of the high dose effects and according to another analysis of essentially the same data it is not safe to do so.

OSCC Data

The first evidence of any cancer risk from diagnostic radiography (or brief exposures to small doses of penetrating radiation) came from a survey which had allowed interviews with mothers to be a means of comparing *in utero* and postnatal experiences of two groups of young children. In one group there were 1299 children under 10 years of age from various parts of Britian who had recently died from malignant neoplasms (with 176 records of prenatal x-rays) and in the other group there were the same number of live children (with only 93 records of prenatal x-rays). Each case/control pair was matched for sex, date of birth, region and interviewer, and the x-ray findings were no different for the examinations with extant records of dates, reasons and findings than for the x-rays claimed by mothers but not otherwise confirmed. Even so, there was no shortage of radiobiologists who were convinced that the case/control imbalance was an artifact caused in one of two ways: either by biased recall of pregnancy events by mothers of live and dead children, or by one or more of the reasons for the x-ray examinations having associations with childhood cancers.

The 1299 case/control pairs included 82 per cent of all the notified deaths in Britain in a three year period (1953-55). Therefore, it was clear that a data collection network, which had required the voluntary cooperation of numerous health departments, could if necessary, be put to further uses. Conseqently, all criticisms of OSCC data have met with the same response, namely, further data collection from "new" case/control pairs, and more safeguards against selection bias.

By 1970 the number of x-rayed cases was sufficient to be reasonably certain that the usual time for practising obstetric radiography (towards

the end of the third trimester) was later than the usual time for initiating a childhood cancer. Ten years later it was possible not only to confirm this impression (of fetal origins for all childhood cancers); but also to show that "routine pelvimetries" were contributing more to the case/control imbalance than x-rays which had association with fetal abnormalities or maternal illnesses, and to show that the cancer risk was greater for a rare group of first trimester x-rays than for the usual run of obstetric x-ray examinations.

By this time the only persons who were still expressing doubts about the causal nature of the association between the x-rays and the early cancer deaths were scientists who found the RERF finding (of no cancer risk at low dose levels) more convincing than the opposite OSCC finding. Therefore, since independent measurements of background radiation were now available for every 10 Km square of the national grid, it was decided to include OSCC data in a test of whether there was any evidence of a cancer effect from this inevitable source of fetal irradiation.

From earlier work it was evident that infections were influencing the frequency of childhood cancers. Therefore, several infection related factors (such as population density, actual illnessess and social class), as well as prenatal x-rays, were included in a regression analysis where the terrestrial gamma ray or TGR component of background radiation for each birth address (of OSCC cases and controls) stood as a surrogate for the inevitable exposures. According to this test, the two sources of fetal irradiation (medical x-rays and background radiation) were having separate cancer effects and the contribution from background radiation was

sufficient to account for most of the OSCC cases. Finally, the regression analysis was also used to show that, if it had not been possible to control for several cancer related factors, there would have been no evidence of the medical x-ray effect and suggestive evidence of a hormesis effect from background radiation.

Summary

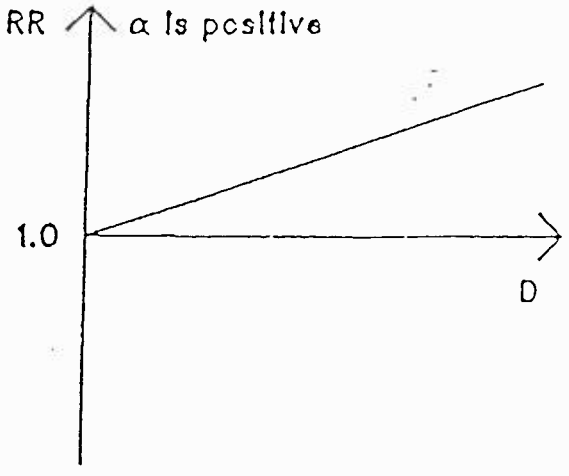
Recent work suggests that selection bias has more often left a false impression of no late effects of radiation than it has exaggerated the cancer risk. The effects of such bias can be seen in RERF data, where a "healthy survivor effect" is dose related; in Hanford data, where a "healthy worker effect" is dose related, and in a recent use of OSCC data, where only control of several cancer related factors prevented an impression of an hormesis effect. There are also signs that the present position of the LSS cohort of A-bomb survivors (as a reliable source of cancer risk coefficients) is unlikely to persist.

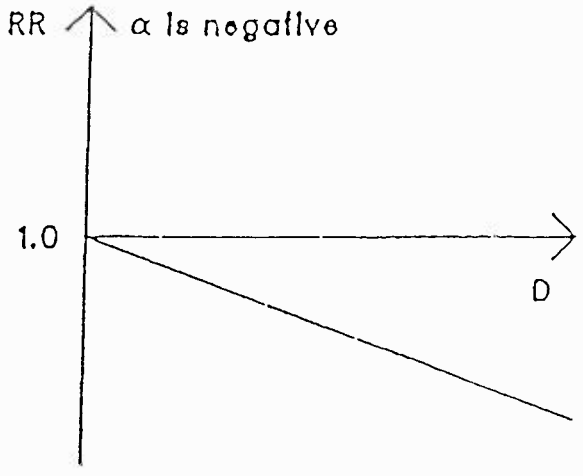
Long after the bombing of Hiroshima and Nagasaki the death rates of survivors were still being influenced by selection and marrow damage. Failure to recognise that this was so has allowed RERF data to be the source of several wrong impressions. For example, an assumption of no late effects of the A-bomb radiation other than cancer, has led to a general belief that extra deaths from aplastic anaemia and myelofibrosis (observed in all high dose studies) have mutational rather than marrow damage origins. But the greatest mistake of RERF statisticians was to require any late effect of the A-bombs to produce a significant trend statistic in a simple linear model of relative risk.

An obvious alternative to RERF data is Hanford data. This would allow a wide range of estimated doses (which often exceeded the threshold dose for chronic marrow damage) to be replaced by a much narrower range of measured doses (too small to cause any immune system damage). But with Hanford data the problem of how best to cope with the "internal healthy worker bias" would still remain. Furthermore, no follow-up of radiation workers could have the same flexibility as the Oxford survey, whose good fortune it was not only to recognise an important key to the problem of cancer etiology (by sifting of past events, as in clinical medicine or crime detection) but also to be in a position to use this key to resolve other problems. Therefore, ironically the survey which was most often criticised for selection bias and inadequate dosimetry, has probably not suffered as much from these basic problems as most surveys of late effects of radiation.

Figure 1. Examples of Linear and Linear-Quadratic Relationships

Linear: $RR = 1 + \alpha D$ where RR = Relative Risk, D = Radiation Dose





Linear-quadratic: $RR = 1 + \alpha D + \beta D^2$