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Detection of Late Effects of Ionizing Radiation: Why Deaths of A-Bomb Survivors Are So Misleading

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'I know that most men—not only those considered clever, but even those who are clever and capable of understanding the most difficult scientific, mathematical, or philosophic problems—can seldom discern even the simplest and most obvious truth if it be such as obliges them to admit the falsity of conclusions they have formed, perhaps with much difficulty—conclusions of which they are proud, which they have taught the others, and on which they have built their lives.'

Leo Tolstoy, 1898

Besides the International Commission on Radiation Protection (ICRP), the main arbiters of supposedly safe levels of radiation exposure are the UN Scientific Committee on Effects of Atomic Radiation (UNSCEAR), the US National Academy of Sciences Committee on Biological Effects of Ionizing Radiation (BEIR), and the UK National Radiation Protection Board (NRPB). According to these authorities, late effects of radiation are usually the result of mutations (stochastic effects) and the only exceptions to this rule are teratogenic effects caused by exposing embryos to relatively high doses; sterility and impaired fertility from similar involvement of testis or ovary, and lens opacities or cataract (non-stochastic effects). Therefore, since there is spontaneous realignment of broken chromosomes after exposure to radiation,[1] there has been general acceptance of the following ICRP recommendations:[2]

(i) 'The frequency of cancer effects per unit dose will be lower following exposure to low doses or doses delivered at slow dose rates.'

(ii) 'Risk estimates based on linear extrapolation of high dose effects should be used with great caution and explicit recognition of the possibility that the actual risk at low doses may be lower than that implied by a deliberately cautious assumption of proportionality.'

(iii) 'Even on the assumption of no threshold dose for stochastic effects, the prevalence of radiation-induced cancer among workers will remain at an acceptably low level provided occupational exposure rates remain below 5 rems per annum.'

These recommendations are consistent with: (i) animal experiments;[3] (ii) studies of radiotherapy patients (eg, ankylosing spondylitis);[4] (iii) a uniquely large study of high, medium and low doses (ie, the follow-up of A-bomb survivors first by the Atomic Bomb Casualty Commission [ABCC] and later by the Radiation Effects Research Foundation [RERF];[5,6] and (iv) negative findings of several low dose studies.[7] There are, however, two studies of exclusively low doses whose findings suggest that the usual method of risk estimation (ie, by linear extrapolation of high dose observations) may be grossly underestimating the cancer risks of radiation workers and background radiation. The two aberrant studies are the Oxford Survey of Childhood Cancers (OSCC data)[8] and an analysis of Hanford data by Mancuso, Stewart, and Kneale (MSK).[9]

Over a period of more than 20 years sufficient support for OSCC findings has accumulated for clinicians to be now working on the assumption that there is a cancer hazard associated with obstetric radiography.[10–12] More recently, other scientists have confirmed the original MSK findings (ie, they too have found a significant dose trend for myelomas and pancreatic tumors in Hanford data).[13–16] Nevertheless, only MSK and Gofman[16] have drawn the obvious conclusion, namely, that there is, in these occupational data, evidence of a cancer effect at supposedly safe dose levels.

The reason why there is so much reluctance to ascribe *any* cancer effects to low level radiation is because no such effect has ever been observed in ABCC or RERF data. It is usually taken for granted that this negative finding applies to workers as well as to A-bomb survivors. However, this is tantamount to forgetting how unique were the circumstances which

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led to the collection of ABCC data; and how little we still know about late effects of natural disasters.

Before the first post-war census of Japan (on 1 October 1950) made possible a systematic follow up of A-bomb survivors, virtually nothing was known about late effects of radiation or civic disasters. It was, of course, realized that radiation could erode skin and bones and that complete recovery from many forms of trauma was impossible. But, epidemiology was still in its infancy; there was no previous study of a cohort wholly composed of people who had survived a major catastrophe, and none has followed. Therefore, even today there is still no one with the requisite authority to insist that if such a group has what seems to be a normal death rate, this could only be an artefact caused by the parent population losing a high proportion of individuals with a weak hold on life during the height of the disaster and acquiring new cripples.

The parent population of the A-bomb survivor study population included thousands of people who died from acute effects of marrow damage as well as more usual blast injuries.[17] Therefore, in ABCC data, late effects of marrow damage might be having a greater effect on general mortality than more obvious lesions. In laboratory animals, even extensive destruction of red marrow is quickly followed by a return to normal levels of marrow cellularity and peripheral blood counts.[18,19] However, this resilience on the part of haemopoetic stem cells is deceptive since it hides the fact that, from now onwards, there will be defective immune responses and other signs of reduced proliferative capacity. Therefore, there could be late effects of the A-bomb radiations that (a) were extremely difficult to recognize; (b) masked the prevalence of all cancers by causing premature infection deaths; and (c) provided ideal conditions for mutations of haemopoetic stem cells to cause an early epidemic of acute myeloid leukaemia.

In spite of these possibilities, both analysts and assessors of RERF data have continued to find the normal non-cancer death rate reassuring rather than puzzling. For example, when Stewart expressed doubts about the general applicability of ABCC risk estimates,[20] the BEIR Committee of 1972 conceded the possibility of a 'disaster effect' but finally concluded that this would be 'very small and would have no practical effect on risk estimates derived from ABCC data.'

The fact that so many influential people on prestigious boards have expressed the same opinion has naturally biased scientists in other disciplines. They too have come to accept (on authority only) that OSCC and MSK risk estimates are either irrelevant or plain wrong since this is in unison with assertions that sensitivity to cancer induction by radiation is much reduced after birth (ICRP)[2] and that 'the Hanford study, as presented by MSK, does not represent a valid statistical interpretation of the actual data.' (NRPB)[21]

Though constantly repeated, these are only assertions, and all the NRPB criticisms of the MSK analysis have been rebutted.[22] However, the primary purpose of this review is not to vindicate this analysis but to alert epidemiologists to the possibility that in all studies of high dose effects there may be a joker in the pack.

ANIMAL EXPERIMENTS

Even in laboratory animals exposure to ionizing radiation has never been followed by any specific disease other than cancer. There has, however, been more life shortening than could easily be accounted for by the extra cancer deaths. Therefore, radiobiologists are reasonably certain that high level radiation has non-specific effects akin to 'accelerated aging'.[23] From experiments with radiation and other marrow poisons[18,19] we have also learned that destruction of haemopoetic stem cells is followed by defective immune responses and other weaknesses which have associations with old age but could also cause death from aplastic anaemia long after subsidence of all acute effects of marrow damage.

A-BOMB SURVIVORS

The follow-up of Japanese A-bomb survivors has produced a uniquely large data base for detecting stochastic and non-stochastic effects of A-bomb radiations. According to a long series of ABCC and RERF reports, all tests of non-stochastic effects have been uniformly negative. Hence the following claims: 'in atomic bomb victims up to the present, the series has indisputably shown no evidence of life shortening that could not be explained by increasing appearance of leukemia and solid tumors' (UNSCEAR)[24] and 'analysis of the whole material and its major components provided no support for the belief that diseases other than cancer are involved in the late mortality effect.' (RERF)[5]

According to RERF, only 415 of an estimated 70 000 deaths of 285 000 A-bomb survivors (1950–74) were radiation-induced and there were no extra deaths apart from leukaemia (200) and other cancers (215). Nevertheless, a recent test of the hypothesis of radiation accelerated aging contains the following sentence: 'A superficial association between mortality for diseases of blood and blood forming organs and radiation rests entirely on the carcinogenic effect of radiation, especially the leukaemogenic effect.'[25] This is one of several attempts by RERF to ascribe to 'misdiagnosis' a finding which is at variance with the hypothesis of no

late effects of the A-bomb radiations apart from cancer. The awkward finding is a death rate for aplastic anaemia which has always been much higher than normal and is still showing a highly significant dose trend.

Why RERF find it so necessary to assume that Japanese doctors are constantly mistaking leukaemia for aplastic anaemia (and never making the opposite mistake) is not clear, since radiation is a known cause of both diseases. However, the most likely reason is the apparent absence of a much commoner effect of marrow damage, namely, heightened sensitivity to infections.

It was this anomaly which eventually led Stewart[26] to formulate the following hypothesis: Exceptionally hardy persons had the best chance of surviving all effects of the bombing and they would be unlikely to lose this initial advantage unless personal involvement in acute radiation effects led, *via* marrow damage, to acquired loss of immunological competence. Therefore, since all effects of the bombing were dose related, *via* hypocentre distances, some *permanent* marrow damage can be assumed, otherwise the non-cancer death rate would have been inversely related to dose.

According to Land, this was an untestable hypothesis and other analysts of RERF were equally skeptical.[27] However, even on the basis of published data,[6] Stewart and Kneale have shown that removal of cardiovascular diseases from 'diseases other than cancer' left a large residual group which (a) included all the infection deaths and (b) had a dose response curve that was not flat but U-shaped.[28] According to this analysis the downward slope of this biphasic curve shows that below 50 rad, selection effects of early deaths were much stronger than other effects of the bombing; and the upward slope at high dose levels show that above 50 rads other mortality effects of the bombing were at least twice as strong as the selection effects. Therefore, when estimates of cancer effects of radiation are based on A-bomb survivors, there should be both a 'correction factor'—based on the downward slope of the U-shaped curve—to allow for later effects of early deaths, and control for all non-fatal effects of the blast, the radiation and social consequences of the general devastation.

As a result of not recognizing the downward slope of the dose response curve for infection deaths, official estimates of the cancer risks of A-bomb survivors could be an order of magnitude lower than the actual risk. This would not only account for the present (order of magnitude) difference between ICRP and MSK estimates of the cancer effects of low level radiation but would also make it unnecessary to assume that there is no return to fetal levels of cancer sensitivity in old age.

SPONDYLITIC DATA

In the follow-up of patients with anklyosing spondylitis, there was no question of early deaths confusing the issue.[4] However, all skeletal diseases have associations with other causes of death. Therefore, it is arguable that the exceptionally high death rates for ulcerative colitis and pneumonia reported in a recent paper[29] occurred independently of the fact that both the thorax and the large intestine were heavily exposed. However, no side effect of ankylosing spondylitis could be the reason why the ratio of observed to expected deaths (in several SMR analyses) has always been consistently higher for aplastic anaemia than leukaemia. This finding is explained in the same way as the comparable finding for A-bomb survivors, namely, 'misdiagnosis'. Again, there is no mention of an obvious alternative, namely, a non-stochastic effect of high marrow doses.

FETAL IRRADIATION

Only one study of fetal irradiation effects has flatly contradicted the Oxford Survey of Childhood Cancers. This is the one where cancer deaths of 1297 A-bomb survivors who were exposed *in utero* were compared with national statistics.[30] The observed number of deaths (1) was not significantly higher than the expected number (0.75). Therefore, for several years it was assumed that all studies of fetal irradiation with positive findings were suffering from a common fault caused by a hidden association between childhood cancers and the reasons for x-raying pregnant women. How this unlikely hypothesis was finally and effectively rebutted can be seen in two papers which show the results of including over 10 000 case/control pairs from the Oxford survey in a Mantel–Haenszel analysis of several factors with x-ray associations including the reasons for the examinations, the x-ray findings and the exposure ages of the fetuses.[31,32] This analysis makes it impossible to doubt that there was some masking of carcinogenic effects of the A-bomb radiations even though there is still no official recognition of this possibility.

RADIATION WORKERS

MSK risk estimates for Hanford workers were originally based on an analysis of the mean doses of two groups of dead workers (cancers and non-cancers).[9,22,33] They have since been confirmed and amplified in a full cohort analysis of more than 30 000 live and dead workers by a more orthodox methodology, ie, a Cox analysis by the method of regression models in life tables.[34] There are several features of Hanford data which make it both unwise to base risk estimates upon a conventional SMR analysis and

difficult to discriminate between genuine findings and artefacts. For example, the 'healthy worker effect' is not only exceptionally strong for workers in this reprocessing plant, but also much stronger for workers in dangerous than safe occupations. How the statistical problems associated with these biases were finally solved is explained in the latest MSK publication.[35]

Hostility to the results of the first MSK analysis was so forcefully expressed that Dr Mancuso first lost his DOE contract and then had most of his data impounded. His place as coordinator of health studies of workers in all DOE controlled nuclear installations has since been taken by Dr Lushbaugh from the Oak Ridge Associated Universities. One consequence of this change is that the meticulous MSK methodology has been replaced by 'subcohort studies of radiation associations by the nested case-control design.'[36]

According to this methodology only victims of diseases with a significant excess of deaths in a conventional SMR analysis (and matched controls of these cases) are included in further tests of radiation associations. Furthermore, since the stated purpose of these tests is to discover whether *all* the extra deaths (according to the SMR analysis) are radiation-induced, they are most unlikely to have any positive findings.[37] It is difficult to see what useful purpose is being served by this work, since even the scantiest knowledge of statistics is sufficient to show that, as a method of detecting the necessarily small cancer effects of small doses of radiation, the nested case-control design has only a fraction of the power of the MSK modifications of the Cox methodology.

CONCLUSIONS

The sheer size of the RERF data base and the fact that it alone has coverage of high, medium and low doses[38] has had a profound effect on past and present ideas about health effects of low level radiation. In report after report, the Japanese study is described as (a) a uniquely large study that has provided 'indisputable' evidence of no life shortening effects of radiation other than cancer; (b) a completely reliable source of risk estimates for cancer effects of low level radiation; and (c) a source of risk estimates which show that linear extrapolations of high dose effects can be counted upon to exaggerate the dangers of occupational exposures or leakage of radioactivity from various sources such as the waste products of reprocessing plants.

These opinions have been repeated so often and over such a long period that very few scientists are prepared even to consider the possibility that the reason why there is incompatibility between MSK risk estimates and ICRP recommendations is because official interpretations of RERF data are seriously flawed. Therefore perhaps the time has come to consider the logical consequences of certain axioms.

Few things are more certain than that large-scale disasters are causes of irreparable trauma. Furthermore no one has contradicted the following RERF statement: 'with mortality in the immediate area of the hypocenter essentially 100% except for those who were heavily shielded, and falling rapidly with distance from the hypocenter, selection is an indisputable fact, not an issue.'[23] Irreparable trauma has associations with high rates of mortality and the selection referred to by RERF has associations with low rates of mortality. Therefore, even if there were no special effects of radiation, survivors from a nuclear explosion could only have an apparently normal death rate if mortality effects of the permanent lesions and equally permanent effects of early selection were in equilibrium and evenly balanced.

According to RERF, all non-cancer effects of two explosions which all but destroyed two large cities were so short-lived that in less than five years the slate was wiped clean. In my view this was impossible and certainly less likely than that analysts of ABCC and RERF data began by paying too little attention to certain, inevitable consequences of the explosions and ended by not recognizing the relevance of later work even when this showed (i) that complete recovery from extensive marrow damage is rarely, if ever, possible[18,19] and (ii) that there was a biphasic dose response curve for infection deaths.[28]

The more recent findings are important since they show that the death rates of people who have survived acute effects of A-bomb radiations have little or no bearing on the cancer risks of radiation workers. Fortunately for these workers, we have in their own occupational and health records an excellent alternative to RERF data. Judging both by Hanford data and by the records of a few workers from Rocky Flats in Colorado and Sellafield in Britain (who are currently subjects of compensation claims), the standard of record keeping in all branches of the nuclear industry is exceptionally high. Furthermore, there are now several nuclear installations which have been producing plutonium long enough for their work forces to be mines of information on two subjects of great importance, namely, the safety of radiation workers and the probable consequences of allowing the manufacture of plutonium to make annual additions of man-made radiations to natural or background radiation.

REFERENCES

[1] Cole A F, Shonka *et al.* CHO Cell Repair of Single and Double Strand DNA Breaks Induced by Gamma and Alpha Radiations. In: *Molecular Mechanisms for DNA Repair* Part B

665–676. P C Hanawalt and R B Setlow (eds). New York, Plenum Press, 1975.

[2] International Commission on Radiological Protection. Recommendations of the ICRP. Publication 26, Pergamon Press, 1977.

[3] Committee on the Radiological Effects of Ionizing Radiation. The Effects on Populations of Exposure to Low Levels of Radiation. Nat. Acad. Press, Washington DC, 1980.

[4] Court-Brown W, Doll R. Leukemia and Aplastic Anemia in Patients Irradiated for Ankylosing Spondylitis. Medical Research Council Special Report Series No. 295. London, HMSO, 1957.

[5] Beebe G W, Kato H, Land C E. Life-Span Study Report 8. Mortality Experience of Atomic Bomb Survivors 1950–74. RERF TR1-77, Hiroshima 1977.

[6] Kato H, Schull W J. Cancer Mortality Among Atomic Bomb Survivors 1950–78. Life Span Study Report 9. Radiation Effects Research Foundation (RERF TR12-80), Hiroshima, 1980.

[7] Court-Brown W M, Doll R, Hill A B. Incidence of leukemia after exposure to diagnostic radiation *in utero*. *Brit Med J* 1960; **2:** 1539–41.

[8] Stewart A M, Kneale G W. Radiation dose effects in relation to obstetric x-rays and childhood cancer. *Lancet* 1970; **1:** 1185–8.

[9] Mancuso T F, Stewart A M, Kneale G W. Radiation exposures of Hanford workers dying from cancer and other causes. *Health Physics* 1977; **33:** 369–84.

[10] Ford D D, Paterson J C S, Trueting W L. Fetal Exposure to Diagnostic X-Rays and Leukemia and Other Malignant Diseases in Childhood. *J Nat Cancer Inst* 1959; **22:** 1093–1104.

[11] MacMahon B. Prenatal X-ray exposure and childhood cancer. *J Natl Cancer Inst* 1962; **28:** 1172–91.

[12] Bross I D J, Natarajan N. Leukemia from low level radiation. Identification of susceptible children. *N Engl J Med* 1972; **287:** 107–10.

[13] Hutchison G B, MacMahon B, Jablon S, Land C E. Review of Report by Mancuso, Stewart, and Kneale of Radiation Exposure of Hanford Workers. *Health Physics* 1979; **37:** 207–20.

[14] Comptroller General Report to the US Congress. Problems in Assessing the Cancer Risks of Low Level Ionizing Radiation Exposure. Washington, DC, General Accounting Office, 20548, 1981.

[15] Darby S C, Reissland J A. Low levels of ionizing radiation and cancer—are we underestimating the risk? *J R Statist Soc* 1981; **144:** Part 3: 300–14.

[16] Gofman J W. The Question of Radiation Causation of Cancer in Hanford Workers. *Health Physics* 1979; **37:** 617–39.

[17] Okhita T. Acute effects of A-bomb radiations. *J Rad Res* (*Tokyo*) 1975; **16** (Suppl): 49–66.

[18] Botnick L E, Hannon E C, Hellman S. Multisystem stem cell failure after apparent recovery from alkylating agents. *Cancer Research* 1978; **38:** 1942–7.

[19] Hendry J H, Lajatha L G. The response of haemopoetic colony-forming units to repeated doses of X-rays. *Radiation Research* 1972; **52:** 309–15.

[20] National Academy of Sciences Report to the Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR), Washington DC, Chapter VII, p. 167, 1972.

[21] Reissland J A. An assessment of the Mancuso Study. National Radiological Protection Board, NRPB R-79, 1978.

[22] Stewart A M, Kneale G W, Mancuso T F. The Hanford Data—A Reply to Recent Criticisms. *Ambio* 1980; **9:** 66.

[23] Casarett G W. Similarities and contrasts between radiation and time pathology. *Adv Gerontol Res* 1964; **1:** 109–63.

[24] Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR *2* para 376, 1972.

[25] Beebe G W, Land C E, Kato H. The hypothesis of radiation-accelerated aging and the mortality of Japanese A-bomb victims. In: *Late Biological Effects of Ionizing Radiation.* IAEA, Vienna, Vol. *1*, 3–25, 1978.

[26] Stewart A M. Delayed effects of A-bomb radiation: A review of recent mortality rates and risk estimates for five-year survivors. *Journal of Epidemiology and Community Health* 1982; **36:** 80–6.

[27] Kristof N D. New study of A-blast survivors versus radiation health rate. In: *The Washington Post*, 9 July 1982.

[28] Stewart A M, Kneale G W. Non-cancer effects of exposure to A—bomb radiation. *Epidemiol Comm Health* 1984; **38:** (2), 108–12.

[29] Smith P G, Doll R. Mortality among patients with ankylosing spondylitis after a single treatment course with x-rays. *Brit Med J* 1982; **284:** 449–60.

[30] Jablon S, Kato H. Childhood cancer in relation to pre-natal exposure to atomic bomb radiation. *Lancet* 1970; **2:** 1000–3.

[31] Kneale G W, Stewart A M. Mantel–Haenszel analysis of Oxford data. I. Independent effects of several birth factors including fetal irradiation. *J Natl Cancer Inst* 1976; **56:** 879–83.

[32] Kneale G W, Stewart A M. Mantel–Haenszel analysis of Oxford data. II. Independent effects of fetal irradiation subjects. *J Natl Cancer Inst* 1976; **57:** 1009–14.

[33] Kneale G W, Mancuso T F, Stewart A M. Re-analysis of data relating to the cancer risks of radiation workers. In: *Late Biological Effects of Ionizing Radiation.* IAEA, Vienna, *2*, 387–410, 1978.

[34] Kneale G W, Mancuso T F, Stewart A M. Hanford Radiation Study III: A cohort study of the cancer risks from radiation to workers at Hanford (1944–77 Deaths) by the method of regression models in life-tables. *Brit J Indust Med* 1981; **38:** 156–66.

[35] Kneale G W, Mancuso T F, Stewart A M. Job-related mortality risks of Hanford workers and their relation to cancer effects of measured doses of external radiation. *Brit J Indust Med* 1984; **41:** 6–14.

[36] DOE Radiation Epidemiology Contractors Workshop. Program and Working Papers. Washington, DC, Office of Energy Research, 1982.

[37] Reyes M, Voelz G *et al.* Case Control Study of Brain Tumors Among White Males Employed at the Rocky Flats Plant. Los Alamos National Laboratory, LA-UR-83-946, 1983.

[38] Land C E. Estimating cancer risks from low doses of ionizing radiations. *Science* 1980; **209:** 1197–1203.