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Low-dose Radiation Carcinogenesis

THE PRINCIPLE that radiation causes cancer, life shortening and an array of other pathological disorders, is well accepted [1, 2], yet the quantification of sequelae at the lower endpoint of the dose–response curve is still controversial [3]. Since the presence of a significant effect at very low doses would have strong financial implications, social and economic flavours blur the assessment of available information. Let us not forget that in contrast with high dose irradiation, delivery of low-dose radiation (LDR) is mostly in our hands, while health policy is a compounded balance of risks and resources.

The controversy focuses on the inconsistency of and ensuing discrepancy in risk estimates, between results coming from studies based on populations actually exposed to low doses [4–11], and extrapolations derived from high-dose studies. The latter include primarily studies of A-bomb survivors in Hiroshima or Nagasaki and individuals exposed to therapeutic irradiation [12–15], where, with a few exceptions [16, 17], no increased risk has been detected at levels below 0.1 Gy. The former comprise populations exposed to fallout, those residing in the vicinity of nuclear reactors, patients affected by scattered radiation following X-ray therapy, workers in the nuclear industry and children exposed *in utero*.

Unfortunately, the interpretation of the direct LDR findings is confounded by inadequate dosimetry, small sample sizes, lack of adequate controls, simultaneous exposure to extraneous carcinogenic factors, and possibly by erroneous measurements as well.

One major problem is that doses used in the computation of risk estimates are usually based on group exposure rather than on the individual subject. For instance, tilting of an irradiated child's head, or a neglect on the part of a technician to turn off the X-ray machine, result in a much higher exposure level than estimated retrospectively. Dosimeters inadequately used by technical personnel will have a similar effect, as would an occasional higher discharge from a nuclear reactor [18, 19]. Another constraint is that in order to demonstrate a true effect at a low dose, exceedingly large population samples are needed. Consequently, the literature is weighted by low-dose studies, where an excess risk was found, while studies showing negative findings are discriminated against, and yield a "publication bias" [20]. However, perhaps the strongest factor of uncertainty, in this context, stems from the virtual impossibility to distinguish between a genuine radiation effect, and the contribution of other established carcinogens, to which the subjects could have been simultaneously exposed, e.g. chemicals in the workplace of nuclear industry employees.

The issue of LDR carcinogenesis has reached impetus with the slowly accumulating data on excess leukaemia near nuclear installations in the UK. Roman *et al.* [8] demonstrated a significantly increased incidence of leukaemia among children younger than 5 years of age in and around the West Berkshire area, which was limited to less than 10 km from the nuclear establishment. Likewise, Gardner and colleagues [9, 21] found an increased risk for leukaemia in children born to mothers in the Seascale parish but not in those born elsewhere but attending school there. More recent and highly publicised findings by Gardner *et al.* [10, 22], relate to an apparent early paternal exposure. Yet, that particular comparison was based essentially on only 4 cases of leukaemia (out of 46), and 3 control children (out of approximately 300), whose fathers had been exposed to over 10 mSv in the 6 months preceding conception, and to over 100 mSv in total, and confounded by maternal age and proximity of residence to the nuclear plant. Furthermore, home exposure to dust, or contaminated paternal clothing, could have contributed to the observed effect. Gardner and coworkers' findings were supported, to a certain extent, by McKinley *et al.* [23], but in their study the fathers were also more significantly exposed to wood dust and chemicals. A whole array of studies, in other British locations [24–27] and elsewhere [28–31], failed to confirm an excess cancer risk near nuclear installations, suggesting that other factors (e.g. higher discharge, chemical carcinogens, contaminated dust, etc.) played a much stronger role in the reported leukaemogenesis than ionising radiation. Data based on civil or military populations exposed in the course of experimental nuclear testings [5, 6, 11, 32, 33] in the Southwestern US and the Pacific Ocean, are also hard to construe.

The simultaneous exposure to a multitude of chemical substances and "the healthy worker effect" constitute two principal obstacles for a definitive assessment of the effect of LDR on nuclear industry employees. The most illustrative controversy in this respect is probably the study of Hanford employees [7, 34–36], where the only genuine finding may be an excess of multiple myeloma, in persons who have had a cumulative exposure above 0.15 Gy. Studies of British Atomic Energy employees [37, 38], showed a significantly increased mortality

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from prostatic cancer, particularly in young employees and an excessive incidence of skin and bladder cancer. However, all three conditions are highly dependent on the frequency of screening, which was obviously higher in the exposed group; a diagnosis of prostatic cancer is rarely looked for in young men.

The Oxford childhood survey, started by Alice Stewart and her associates in the 1950s [39], has consistently shown about a 2-fold increase in cancer following a diagnostic intra-uterine X-ray exposure at a dose of approximately 0.02 Gy. Several other studies showed similar results [40–44], albeit not all of them [45, 46]. Many of these studies have been criticised on three grounds: (a) the fact that mothers of children who died of cancer would have a better recall of their X-ray history, (b) that the reason for the X-ray examination, could have been related to tumour development, and (c) the incompatability of the observations with the lack of an effect among A-bomb survivors [47]. The immense information ascertained over the past 4 decades suggests that the findings are probably genuine. Still, they are difficult to reconcile, unless one accepts the contention of a relatively higher susceptibility of fetal tissue to radiation.

Follow-up series of subjects exposed to LDR in the process of high-dose medical therapy have also contributed to the controversy. One example is the Israeli cohort of 10 834 children irradiated for tinea capitis in the 1950s [48], showing a significant excess of thyroid and breast cancer [49], following an estimated average dose of only 0.09 Gy and 0.018 Gy to the respective tissues. An augmentary role by the simultaneously irradiated pituitary guard could not be ruled out.

Finally, although with one possible exception [50], no excess cancer risk has been demonstrated due to high background radiation [51], a prolonged exposure to low doses of radon in domestic facilities has been noted to affect lung cancer development [52–56]. Small cell carcinoma of the lung has been implicated in particular [56].

The recent disclosure of a higher than originally assumed radiation exposure of the population in Washington State, in the late 1940s, highlights the futility of deriving risk estimates from populations that have been only apparently exposed to LDR. Indeed, there were some hopes that more refined information may emerge from modern nuclear accidents which apparently have been more numerous than we have been told. Alas, the reports from the Three Mile Island incident show doses too infinitesimal to enable meaningful estimates, even under the more extreme approach to risk derivation, while the reports based on the Czernobyl disaster indicate, at least at present, that detailed dosimetry will be hard to come by. Thus, the question of concrete carcinogenic risk estimates following LDR exposure will stay with us for years to come: it's there, but how much of it?

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EC Proposal for Directive Can Destroy the Possibilities of Cancer Research

THE EC Commission has prepared a proposal for a directive regarding the protection of individuals in relation to the processing of personal data.

The proposal aims at establishing uniform regulations which at European level protect the fundamental rights of individuals by means of a high level of protection. The superior intentions of the proposal can only be sympathised with, but these intentions cannot reasonably be looked at separately. They should be looked at and weighted in close connection with other aspects, which are also of importance to individuals. This also applies to research into diseases, including epidemiological cancer research, and the prevention of diseases, which presupposes that causes and factors, which are known, contribute to the disease.

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Most alarming are the demands of the proposal for a directive for: informed consent of the data subject at the time of registration, informed consent of the data subject when communicating data to third parties, and data that cannot be processed for other purposes than those for which they were collected.

These demands will, to a wide extent, make register-based epidemiological research impossible. As an example it can be mentioned that informed consent will make it impossible to interpret stored data, as we do not know the criteria which form the basis of the recording of the data subject or the lack of same. This will make files incomplete, and reduce the value of research. Informed consent in connection with communicating data concerning health to third parties may have unintended effects on the data subject, who is informed by an existing register about a disease, which the person in question has not previously been informed about, therefore such information should always be given through the data subject's own physician. For deceased