APPENDIX-B

The Safe-Dose Fallacy: Summary of Three Remarkably Similar Reports

Part 1. Gofman 1990: Proof That There Is No Threshold Dose or Dose-Rate
Part 2. UNSCEAR 1993: "Sometimes Misrepair Can Occur"
Part 3. NRPB 1995: Evidence "Falls Decisively" against a Threshold
Part 4. Alpha Particles, Xrays, and the Major Medical Journals

By "Safe-Dose Fallacy," we refer to the mistaken idea that no cancer-risk occurs from ionizing radiation if a dose is below a certain level (below a "threshold dose"). Appendix-B expands on the very brief discussion in Chapter 2, Part 6.

The threshold hypothesis, with respect to radiation carcinogenesis, has been invalidated in three major reports: Gofman 1990, UNSCEAR 1993, and NRPB 1995. (UNSCEAR is the United Nations Scientific Committee on the Effects of Atomic Radiation. NRPB is Britain's National Radiological Protection Board.)

• Part 1. Gofman 1990: Proof There Is No Threshold Dose or Dose-Rate

The no-risk speculation about low-dose radiation has been tied for a long time to the fact that cell-nuclei have massive capacity to repair DNA damage (Part 1c). Once upon a time, nearly everyone (myself included) hoped that carcinogenic lesions might invariably be repaired --- correctly --- whenever the repair-system was not overwhelmed by "too much" radiation-induced damage all at once.

In the 1970s, however, it was already clear that perfect repair of injured human chromosomes did NOT occur, even when low total doses of radiation were received very slowly from weapons-testing fallout or chronic occupational exposures. And some evidence was already solid that radiation-induced human CANCER is associated with very low doses and dose-rates. But might there be a safe dose (no-risk dose) at even lower levels?

Between 1970 and 1990, it was frequently asserted that the safe-dose issue could never be settled, because of the limits of epidemiology. In Gofman 1990, however, we were able to prove, by any reasonable standard of biomedical proof, that no safe dose or dose-rate exists with respect to radiation carcinogenesis.

The key breakthrough lies in recognizing that the relevant way to define the lowest possible dose and dose-rate of radiation is NOT in fractions of a rad. The RELEVANT definition occurs in "tracks" per cell (Gofman 1971, pp.275-276; Gofman 1981, pp.405-411; Gofman 1986, pp.6-14). We will show why, by explaining "tracks" in Section 1a, below.

1a. The Least Possible Amount of Damage to Repair

• - (1) "The dose from low-LET ionizing radiation is delivered by high-speed electrons, traveling through human cells and creating primary ionization tracks" (Gofman 1990, p.18-2). Low-LET radiation includes xrays, gamma rays, and beta particles.

• - (2) When genetic molecules are damaged by ionizing radiation, each cell-nucleus attempts to un-do the damage by repair. The damage done by a single primary ionization track is the LEAST POSSIBLE damage which the repair-system ever can face. "Fractional tracks do not exist. Either a track traverses a nucleus somewhere (one nuclear track) or it does not (zero nuclear track)" (1990, p.19-2).

• - (3) "For disproof of any safe dose or dose-rate, it is more important to establish the dose in terms of the average number of tracks per nucleus, than to establish it in terms of rads. The reason is that the lowest conceivable dose or dose-rate with respect to repair is not a millionth or any other tiny

fraction of a rad or centi-gray. The lowest conceivable dose or dose-rate is one track per nucleus plus sufficient time to repair it" (1990, p.18-3,4).

• - (4) "Because the minimal event in dose-delivery of ionizing radiation is a single track, we can define the least possible disturbance to a single cell-nucleus: It is the traversal of the nucleus by just one primary ionization track" (1990, p.19-1). The traversal is complete in a tiny fraction of one second.

• - (5) "Single, primary ionization-tracks, acting independently of each other, are never innocuous with respect to creating carcinogenic injuries in the cells which they traverse. Every track --- without help from any other track --- has a chance of inducing cancer by creating such injuries" (1990, p.18-2).

• - (6) "... Any lesion which can be inflicted in a nucleus by a PAIR of tracks, can also be inflicted by a single track acting ALONE ... The earlier parts of this chapter leave no doubt that events [injuries] at multiple, separate sites are certainly producible by a single track, acting alone" (1990, p.19-8).

1b. What Dose in Rads Delivers an Average of ONE Track / Nucleus?

• - (7) Because a single primary track represents the least possible challenge to the repair-system in a cell-nucleus, we wanted to find out if there is solid human evidence of radiation-induced Cancer as a result of doses which deliver just one track or a few tracks per nucleus. If such evidence exists, it indicates that repair is not always perfect, even when the challenge is about as low as it can ever get. In other words, it would be DIRECT evidence that the hypothesis of a no-risk dose is false, with respect to radiation-induced cancer.

• - (8) So a necessary step in our analysis was figuring out what dose in rads (cGy) delivers an average of ONE primary track per cell-nucleus. Chapters 20, 32, and 33 in Gofman 1990 show how such doses were derived, step-by-step. The doses vary with the diameter of the cell-nucleus and with the energy of the radiation.

• - (9) The values in the box apply to cell-nuclei with an average diameter of 7.1 micrometers (p.20-3). The heading "Medical Xrays" refers to diagnostic xrays with an average energy of 30 KeV, generated when the peak kilovoltage across the xray tube is 90 KeV. The heading "596 KeV Gammas" refers to gamma rays from radium-226 and daughters. Several additional sources of radiation are evaluated in Tables 20-M and 20-"0" of Gofman 1990.

Radiation	Average number of tracks per nucleus	Tissue-dose in rads (centi-grays)
Medical Xrays	1 track	0.75 rad
	10 tracks	7.48 rads
	134 tracks	100.00 rads
596 KeV Gammas	1 track	0.34 rad
	10 tracks	3.40 rads
	294 tracks	100.00 rads

From Gofman 1990, Table 20-M.

• - (10) When the AVERAGE number of primary tracks per nucleus is one, then:

37 percent of cell-nuclei experience no primary track at all;
37 percent of cell-nuclei experience one primary track;
18 percent of cell-nuclei experience two primary tracks;
6 percent of cell-nuclei experience three primary tracks;

1.5 percent of cell-nuclei experience four primary tracks;
Half-percent of cell-nuclei experience more than four primary tracks.
(From Table 20-N of Gofman 1990).

1c. How Many Tracks at Once Can Overwhelm the Repair System?

• - (11) In our 1990 analysis, we reviewed the existing experimental evidence on what radiation doses are required to overwhelm the repair-system for genetic molecules. In Gofman 1990, p.18-4, we quote Albrecht Kellerer, one of the leading experts on the issue:

"There is, at present, no experimental evidence for a reduction of the repair capacity or the rate of repair at doses of a few gray [a few hundred rads] which are relevant to cellular radiation effects" (Kellerer 1987, p.346). And: "There is little or no evidence for an impairment of enzymatic repair processes at doses of a few gray. Studies, for example by Virsik et al on chromosome aberrations, have established characteristic repair times that are substantially constant up to 10 Gy [1,000 rads], that is, up to the highest doses investigated" (Kellerer 1987, p.358).

• - (12) We also reviewed the existing evidence on the time required to finish repair (Gofman 1990, Chapter 18). Numerous studies indicate that cell-nuclei finish whatever repair they can perform on genetic molecules within 3 to 6 hours, even after doses of 100 to 400 rads.

• - (13) "The dazzling speed of repair has an extremely important implication for settling the threshold issue. It means that certain HIGH-dose evidence can reveal a great deal, as we will explain" (Gofman 1990, p.18-5).

1d. Existing Human Evidence of Cancer from Minimal Doses

• - (14) The relevant high-dose evidence comes from studies of breast-cancer rates among women who received serial fluoroscopies in the course of pneumo-thorax treatment for tuberculosis (see entries in the Reference list for Boice 1977, Boice 1978, Boice 1981, Howe 1984, Hrubec 1989, MacKenzie 1965, Miller 1989, Myrden + Hiltz 1969).

Because the women had so many fluoroscopic exams over months and years of treatment, their breasts accumulated radiation doses ranging from about 150 rads to over 1,000 rads (Gofman 1990, Chapter 21). But each exposure delivered single doses of 1.5 to 7.5 rads at a time. Such doses deliver, respectively, an average of just 2 or 10 tracks per cell-nucleus, as we see from paragraph 9 above.

• - (15) These are very nearly the lowest POSSIBLE doses and dose-rates, with respect to challenging the repair-system in a cell-nucleus. If the repair-capacity of cell-nuclei is not overwhelmed by the tracks from hundreds of simultaneous rads (paragraphs 11 and 12, above), we can regard 10 tracks per nucleus, on the average, as nearly minimal.

• - (16) Referring to the Nova Scotia Fluoroscopy Study of female tuberculosis patients, we wrote (1990, p.21-2):

"If carcinogenic injury was produced in the irradiated women at their first fluoroscopy exposure-session, but if repair-systems were able to perform flawless repair afterwards, then that particular exposure-session would have left no residual harm, in terms of any increased risk of future breast-cancer." And:

"Similar carcinogenic injury inflicted at EVERY subsequent fluoroscopy session would also have been without residual harm, if a flawless repair-system operated at a total dose per exposure-session of 7.5 rads. And thus, after accumulating 850 rads in this fashion, the irradiated women would have had NO radiation-induced breast-cancer." And:

"The Nova Scotia Study is certainly not a high-dose study; at every critical step along the way, it is a test of how perfectly the repair-system can un-do carcinogenic injury produced by 7.5 rads, or 10 nuclear tracks on the average --- a LOW dose and dose-rate." Between exposures, ample time elapsed for completion of repair-work (paragraph 12).

• - (17) The repair-system FAILED the test, conclusively, not only in the Nova Scotia series of women, but also in additional pneumo-thorax series in Canada and in Massachusetts. The evidence of excess Breast Cancer in the fluoroscoped women is very solid, and shows a positive dose-response. This evidence of radiation-induced human cancer is widely acknowledged and cited, but not many people recognize that it shows REPAIR-FAILURE even after a challenge which was MINIMAL.

• - (18) Our disproof of any threshold dose or dose-rate includes six additional studies from the mainstream literature which show radiation-induced cancer when the average number of tracks per cell-nucleus ranged from 0.3 track to 12 tracks (Gofman 1990, Table 21-A). They are the Israeli Scalp-Irradiation Study (Modan 1977, 1989); the Stewart In-Utero Studies (1956, 1958, 1970); MacMahon's In-Utero Study (1962); the British Luminizer Study (Baverstock 1981, 1983, 1987); Harvey's In-Utero Study of Twins (1985); Modan's Study of Breast-Cancer in the Scalp Irradiation Study (1989). The evidence against any threshold embraces infants in-utero, children, adolescents, young women, high-energy gamma rays, medical x-rays, acute single doses, acute serial doses, and chronic occupational doses.

• - (19) "In recent years, it has been fashionable to suggest that epidemiologic investigations can not usefully address the low-dose radiation question. The epidemiologic studies described here make it apparent that this is incorrect ... When the effort is made to evaluate the doses in such studies, in terms of tracks-per-nucleus, then it becomes evident that studies whose doses are not 'next-to-zero' are nonetheless studies of truly minimal doses and dose-rates" (Gofman 1990, p.21-19).

1e. Failure of Repair: "The Troublesome Trio"

• - (20) It is the COMBINATION of epidemiology with track-analysis which reveals that we already know that (a) repair has failures even when the repair-system has the least possible challenge, and (b) the failure has CANCER consequences. We do not need impossible-to-obtain studies at doses like 10 milli-rads or 10 micro-rads --- because the least possible challenge to the repair-system occurs at much higher doses.

• - (21) "One can look with awe, humility, and gratitude at a system of repair with the capacities demonstrated by the DNA repair-system. But an independent analyst, or a realist of any stripe, does not casually dismiss the troublesome trio: Unrepaired lesions. Unrepairable lesions. Misrepaired lesions" (1990, p.18-6). And:

"One cannot fault the repair-system in cell-nuclei for leaving a relatively small number of injuries unrepaired, or misrepaired, or for having some inherent inability to repair every conceivable type of injury inflicted at random by the tracks of high-speed electrons ... " (1990, p.18-6).

• - (22) "... the human epidemiological evidence on dose versus cancer-response provides no support for the speculation that repair makes each rad less carcinogenic as dose falls. If that were the net result of repair, the shape of dose-response would be concave-UPWARD. But what is seen in the A-Bomb Study and in others is NOT concavity-upward. The finding is either supra-linearity or linearity --- both of which are inconsistent with the speculation that repair processes make each rad less carcinogenic as dose and dose-rate fall" (1990, p.18-6, 18-7).

• - (23) "Our entire experience with human radiation carcinogenesis should have made it evident that the problem we might be facing is that --- regardless of dose-level --- some fraction of radiation injury to nuclei is unrepaired ... some fraction is unrepairable ... and some fraction is misrepaired" (1990, p.18-7).

1f. Not "Hypothetical": Fatal Cancers from Minimal Doses

• - (24) "The radiation-induced cancers arising from the unrepaired lesions at low doses do not wear a little flag identifying them as any different from cancers induced by higher doses of radiation, or induced by causes entirely unrelated to radiation. Therefore, threshold proponents cannot argue that the cancers arising from the lowest conceivable doses of radiation will somehow be eliminated by the immune system or any other bodily defenses against cancer. Such an argument would require the elimination of cancer in general by such defenses. Instead, we observe that cancer is a major killer ... So the proposition would lead to a non-credible consequence, and must be rejected" (Gofman 1990, p.18-2).

• - (25) What about the speculation that low radiation doses may induce a net health benefit, by stimulating DNA repair or by stimulating the immune system? "When excess fatal cancer is observed in humans after such exposures [minimal doses and dose-rates], the excess has occurred DESPITE any possible stimulation of the repair- and immune-responses by low-doses. The NET result is injury, not benefit. I wish it were otherwise" (1990, p.18-2).

• - (26) "By reasonable standards of proof, the safe-dose hypothesis is not merely implausible --- it is disproven ... We conclude with a warning: Disproof of any safe dose or dose-rate means that fatal cancers from minimal doses and dose-rates of ionizing radiation are not imaginary. They are really occurring in exposed populations. Proposals, to declare that they need not be considered, have health implications extending far beyond the radiation issue ..." (1990, p.18-18).

• Part 2. UNSCEAR 1993: "Sometimes Misrepair Can Occur"

UNSCEAR 1993, written by the United Nations Scientific Committee on the Effects of Atomic Radiation, is a 922-page report (with no index) which presents a lot of valuable information and analysis. Pagination in the report is consecutive from beginning to end, but paragraph numbers start over with each annex. Below, we will separate the page number and the paragraph number by a slash.

Although authors of its nine big sections (called "annexes") are not identified, the total international membership of the Committee is identified on page 29. The biggest delegations are from Canada (9), China (7), France (9), Germany (7), Japan (11), Russian Federation (12), United States (11). Staff and consultants are identified on page 30.

• - (27) In its introduction, the report states: "The combination of epidemiology and radiobiology, particularly at the molecular and cellular levels, is a useful tool for elucidating the consequences of low doses of radiation" (1993, p.27/184). That very combination is the essence of our proof, above, that there is no threshold dose with respect to radiation carcinogenesis.

• - (28) UNSCEAR also affirms our premise in paragraph 24, when it states: "Epidemiological studies of human groups exposed to low-LET radiation show that a range of neoplasms are represented in excess and, broadly, that these do not differ markedly from those arising spontaneously in the population ... no unique neoplastic signature of human radiation exposure is, as yet, apparent" (p.578/153).

2a. The Smallest Possible "Insult" at the Cellular Level

• - (29) UNSCEAR 1993, like Gofman, recognizes the importance of using an APPROPRIATE definition of the lowest possible radiation dose or dose-rate. And it embraces our "microdosimetric approach to defining low doses and low dose rates" (p.680/321):

"Photons deposit energy in cells in the form of tracks, comprising ionizations and excitations from energetic electrons, and the smallest insult each cell can receive is the energy deposited from one electron entering or being set in motion within a cell." See paragraphs 1-4 above.

• - (30) The only conversion offered by UNSCEAR between tracks and dose in rads (centi-grays) is for cobalt-60, which produces a far more energetic gamma ray than the 596 KeV gammas presented above in our paragraph 9. Says UNSCEAR (p.680/321):

"For cobalt-60 gamma rays and a spherical cell (or nucleus) assumed to be 8 micrometers in diameter, there is an average of one track per cell (or nucleus) when the absorbed dose is about 1 mGy [0.1 cGy or rad]. The dose, corresponding to one track per cell, on average, varies inversely with volume and is also dependent on radiation quality, being much larger for high-LET radiation."

• - (31) At page 696, UNSCEAR supplies Table 17, "Proportion of a cell population traversed by tracks at various levels of track density." It is like Table 20-N in Gofman 1990. For instance, it shows what percentage of cells experience 0, 1, 2, 3, 4, and more tracks per cell-nucleus, when the average track density is ONE track per cell-nucleus. The percentages are the same as we show in paragraph 10, above.

• - (32) The UNSCEAR authors define the region of "definite" single-track action as the dose-region where not more than TWO PERCENT of the cell-nuclei experience more than a single track. "In this dose-region, there are so few radiation tracks that a single cell (or nucleus) is very unlikely to be traversed by more than one track" (p.628/42). For cobalt-60, the two-percent criterion means a tissue-dose of 0.2 mGy. Two percent is an arbitrary choice which seems completely unrelated to the repair-issue --- even though UNSCEAR agrees with us that the repair-issue is a critical part of the threshold-issue, as we will show. However, after choosing cobalt-60 and a dose of only 0.2 mGy (20 milli-rads), the UN authors are correct in saying that there are no corresponding human or animal data (p.628/42).

2b. UNSCEAR: The Carcinogenic Potency of a Single Track

• - (33) "The most basic, although not sufficient, condition for a true dose threshold is that any single track of the radiation should be totally unable to produce the effect" (p.630/54).

• - (34) "Radiation is able to induce a diversity of genomic lesions, ranging from damage to single bases to gross DNA deletions and rearrangements" (p.578/153).

And: "Biophysical analyses based on Monte Carlo simulations of track structure show clearly that all types of ionizing radiation should be capable of producing, by single-track action, a variety of damage to DNA, including double-strand breaks alone or in combination with associated damage to the DNA and adjacent proteins" (p.632/63).

And: "In all these mechanistic models, a single radiation track from any radiation is capable of producing the full damage and hence the cellular effect" (p.632/64).

• - (35) "There is compelling evidence that most, if not all, cancers originate from damage to single cells ... Point mutations and chromosomal damage play roles in the initiation of neoplasia" (p.8/37).

And: "Single changes in the cell genetic code are usually insufficient to result in a fully transformed cell capable of leading to cancer; a series of several mutations (perhaps two to seven) is required ... The whole process is called multi-stage carcinogenesis" (p.8/38). And: "It is possible that radiation acts at several stages in multi-stage carcinogenesis, but its principal role seems to be in the initial conversion of normal stem cells to an initiated, pre-neoplastic state" (p.8/39).

• - (36) "... the majority of neoplasms originate from damage to single cells. In principle, therefore, the traversal of a single target cell by one ionizing track from radiation has a finite probability, albeit low, of initiating neoplastic change" (p.556/26).

• - (37) Our topic here is real-world human evidence relating to the threshold-issue for radiation-induced cancer. We omit unrelated references by UNSCEAR to dose-response curves induced in various experiments, although we are interested in such experiments (see Gofman 1990, Chapter 23). With respect to the threshold-issue, we quote UNSCEAR:

"Multi-stage models of carcinogenesis could lead to expectations of a dose threshold, or a response with no linear term, under particular, highly restricted sets of assumptions" (p.636/84). But, "it would be difficult to conclude on theoretical grounds that a true threshold should be expected even from multi-stage mechanisms of carcinogenesis, unless there were clear evidence that it was necessary for more than one time-separated change to be caused by radiation alone" (p.633/69).

2c. UNSCEAR: "Sometimes Misrepair Can Occur"

A threshold-dose for radiation-induced cancer is a dose below which there is NO risk of radiation-induced cancer. A safe dose.

• - (38) As long as there are any primary tracks at all occurring in a biological tissue, a radiation dose is occurring. UNSCEAR acknowledges that "the dose and dose-rate region of main practical relevance in radiation protection (0-50 mSv per year) [0-5 rems per year] is characterized by small average numbers of tracks per cell with long intervals of time between them. Effects are, therefore, likely to be dominated by individual tracks, acting alone" (p.628/43). This is precisely the

point made in Gofman 1990, p.20-7.

• - (39) "Cells are able to repair both single- and double-strand breaks in DNA over a period of a few hours, but sometimes misrepair can occur" (p.625/28).

• - (40) "The extent to which radiation-induced DNA damage may be correctly repaired at very low doses and very low dose rates is beyond the resolution of current experimental techniques. If DNA double-strand breaks are critical lesions determining a range of cellular responses, including perhaps neoplastic transformation, then it may be that wholly accurate cellular repair is unlikely even at the very low lesion abundance expected after low dose and low-dose-rate irradiation" (p.634/74).

• - (41) "It is highly unlikely that a dose threshold exists for the initial molecular damage to DNA, because a single track from any ionizing radiation has a finite probability of producing a sizable cluster of atomic damage directly in, or near, the DNA. Only if the resulting molecular damage, plus any additional associated damage from the same track, were always repaired with total efficiency could there be any possibility of a dose threshold for consequent cellular effects" (p.636/84).

• - (42) "Biological effects are believed to arise predominantly from residual DNA changes that originate from radiation damage to chromosomal DNA. It is the repair response of the cell that determines its fate. The majority of damage is repaired, but it is the remaining unrepaired or misrepaired damage that is then considered responsible for cell killing, chromosomal aberrations, mutations, transformations and cancerous changes" (p.680-681/323).

• Part 3. NRPB 1995: Evidence "Falls Decisively" against a Threshold

In October 1995, Britain's National Radiological Protection Board released a 77-page report entitled "Risk of Radiation-Induced Cancer at Low Doses and Dose Rates for Radiation Protection Purposes" (NRPB 1995). Its five authors are Cox, Muirhead, Stather, Edwards, and Little.

• - (43) Chapter 2 of NRPB 1995 reviews the existing human epidemiologic evidence and concludes (p.25/61): "It is important to note that the studies of low-LET exposure considered in this chapter are consistent with a linear trend in cancer risks at low doses without threshold." This statement embraces the pneumothorax-fluoroscopy studies (p.13/23).

• - (44) Chapter 5 of NRPB 1995 reviews "Cellular and molecular mechanisms of radiation tumorigenesis." There, the authors also state the now-familiar definition of the lowest possible dose and dose-rate from ionizing radiation:

"It may be argued ... that a single radiation track (the lowest dose and dose rate possible) traversing the nucleus of an appropriate target cell, has a finite probability, albeit low, of generating the specific damage that will result in tumour-initiating mutation" p.58/27).

• - (45) The authors consider existing evidence relating to the reduction of radiation risk by so-called cellular "adaptive" responses and immune-system responses. In particular, they discuss issues raised in UNSCEAR 1993 and in UNSCEAR 1994 (Annex B). The authors reach the same conclusion that we do: Such cellular responses do not provide any threshold dose with respect to post-repair genetic damage. NRPB concludes (p.75/21):

"Whilst adaptive responses or other protective mechanisms may influence the risk of tumour development, they do not provide a sound basis for judgement that tumorigenic response at low doses and low dose rates of radiation is likely to have a non-linear component which might result in a dose threshold below which the risk may approach zero."

3a. NRPB on Special Difficulties in Repairing Radiation Damage

The NRPB authors understand very well that imperfect repair is the key to the absence of any threshold dose. The following excerpts from their 1995 report show they understand that ionizing radiation has the power to induce some UNREPAIRABLE damage to chromosomes and DNA, and that a difference exists between action by primary ionization tracks, and action by the free radicals which are produced by normal cellular metabolism (see Appendix-C of this book).

• - (46) "Radiation-induced damage to DNA nucleotide bases and to the sugar-phosphate backbone on one strand of the DNA duplex closely resembles the cellular damage that occurs through normal endogenous metabolic processes" (p.59/28).

"It is generally accepted that, in the absence of exogenous agents, each cell in the human body sustains 5,000 to 10,000 DNA damage events per hour [they cite Ames 1989 and Billen 1990], principally as a consequence of thermodynamic instability and attack by chemical radicals produced via endogenous biochemical reactions; this damage is believed to contribute to natural cancer risk" (p.59/29).

• - (47) "On this basis, arguments have been made [they cite Billen 1990 and Abelson 1994] that the small increment of additional cellular DNA damage resulting from low dose radiation exposure will have an insignificant effect on the frequency of gene and chromosomal mutations, and by implication, on cancer risk. This would be a valid hypothesis if the DNA damage resulting from spontaneous endogenous processes were to be IDENTICAL with that induced by ionising radiation. There is, however, strong evidence that this is not the case and, consequently, that the hypothesis lacks credibility" (p.59/30).

• - (48) "The vast majority of endogenous DNA lesions takes the form of DNA base damage, base losses, and breaks to one of the sugar-phosphate backbone strands of the duplex. Such single-strand DNA damage may be reconstituted rapidly in an error-free fashion by cellular repair processes ..." (p.59/31).

• - (49) "In contrast, although a single ionising track of radiation will also induce single-strand damage when an energy-loss event takes place in close proximity to one DNA strand, a cluster of such loss events within the diameter of the DNA duplex, of about 2 nanometers, has a significant probability of simultaneously inducing coincident damage to both strands. In support of this, an approximately linear dose-response for double-strand break induction by low-LET radiation is observed, confirming that breakage of BOTH STRANDS of the duplex may be achieved by the traversal of a SINGLE IONISING TRACK and does not demand multiple-track action ..." (p.59/32). And:

"There is also evidence that a proportion of radiation-induced double-strand breaks are complex and involve local multiply damaged sites --- LMDS [they cite Ward 1991-a] ..." (p.59/32).

• - (50) "A given fraction of radiation-inducible double-strand damage will be repaired efficiently and correctly, but error-free repair of all such damage even at the low abundance expected after low dose exposure should not be anticipated" (p.60/33). And:

"Unlike damage to a SINGLE-strand of the DNA duplex, a proportion of double-strand lesions --- perhaps that component represented by LMDS --- will result in loss of DNA coding from BOTH strands. Such losses are inherently difficult to repair correctly, and it is believed that misrepair of such DNA double-strand lesions is the crucial factor underlying the induction of chromosomal aberrations and gene deletions that represent the principal hallmarks of stable mutations induced by ionising radiation of various qualities" (p.60/33). And:

"Double-strand DNA losses may in principle be repaired correctly by DNA recombination, but there is evidence that radiation-induced DNA damage may be subject to error-prone illegitimate DNA recombination which can result in the forms of gene and chromosomal mutations that are known to characterise malignant development" (p.60/33).

• - (51) "The importance of DNA double-strand damage and its repair for the radiation response of cells is further supported by studies indicating, firstly, that the repair of such damage is the principal determinant of dose and dose-rate effects after low-LET radiation and, secondly, that genetically determined cellular radiosensitivity is predominantly associated with deficiencies in DNA double-strand break repair. Finally, there is evidence that it is the difference in the QUALITY and not the QUANTITY of induced DNA double-strand lesions that principally provide for the increased biological effectiveness of high-LET radiation such as alpha particles compared with low-LET radiation such as xrays and gamma rays; these observations are best explained by experimental and computational data indicating that, overall, DNA double-strand lesions in cells induced by high-LET radiation are more complex and less likely to be repaired correctly than those induced by low-LET radiation ..." (p.60/34).

• - (52) "In summary, a coherent argument may be assembled that at low doses and low dose rates of low-LET radiation, DNA single-strand damage either is repaired in an error-free fashion or is an insignificant component of tumour risk. For double-strand DNA damage, there is good reason to believe that repair has an error-prone mutagenic component irrespective of damage-abundance and, by implication, will, even at very low doses, contribute to tumour risk" (p.60/36).

• - (53) "It may be concluded ... that existing data from both in vitro and in vivo [radiation] studies support a linear rather than a threshold-type response for neoplasia-initiating gene mutations" (p.61/38).

3b. NRPB's Conclusion on a Threshold Dose

• - (54) "It is concluded ... that data relating to the role of gene mutations in tumorigenesis, the monoclonal origin of tumours, and the relationship between DNA damage repair, gene/chromosomal mutation and neoplasia are well established and broadly consistent with the thesis that, at low doses and low dose rates, the risk of induced neoplasia rises as a simple function of dose and does not have a DNA damage or DNA repair related threshold-like component" (p.75/21). And:

• - (55) The following statement by the NRPB authors is remarkably similar to paragraph (26):

"In consideration of a broad body of relevant cellular and molecular data, it is concluded that the weight of the evidence, in respect of the induction of the majority of common human tumours, falls decisively in favor of the thesis that, at low doses and low dose rates, tumorigenic risk rises as a simple function of dose without a low dose interval within which risk may be discounted" (p.68/80).

• Part 4. Alpha Particles, Xrays, and the Major Medical Journals

The facts and logic in Parts 1, 2, and 3 above are applicable not only to xrays and other low-LET ionizing radiation, but are applicable also to high-LET ionizing radiation, such as alpha particles (see Appendix-A). Therefore, it should surprise no one that, in 1997, Hei and co-workers demonstrated that traversal of human-hamster hybrid cells, by a single alpha particle per cell, can induce structural chromosomal mutations (Hei 1997; commentary by Little 1997; see also Riches 1997). From some elegant experimental work, Hei et al report (Hei 1997, p.3765):

"Although single-particle traversal was only slightly cyto-toxic to [these] cells (survival fraction $\sim$ 0.82), it was highly mutagenic, and the induced mutant fraction averaged 110 mutants per 100,000 survivors ... These data provide direct evidence that a single alpha particle traversing a nucleus will have a high probability of resulting in a mutation and highlight the need for radiation protection at low doses."

While one chance in 1,000 per cell may not sound like "a high-probability," one must remember the PER CELL part of the finding. There are approximately 600 million typical cells in one cubic centimeter of human tissue (calculation in Gofman 1990, p.20-5). Mutation-induction by alpha-particles is explored further in Wu 1999.

Underway at NCRP: Evaluation of the Linear NonThreshold Dose-Response Model

The National Council on Radiation Protection and Measurements (NCRP is described in our Reference List) has undertaken an evaluation of the threshold issue, under its Scientific Committee 1-6 (Arthur C. Upton, Chair). Here, we do not quote from the online draft report (October 1998) because draft reports are subject to change or non-publication.

Comment: Time for a Policy-Change

In view of Parts 1, 2, and 3 of this Appendix, we urge that editors and reviewers at the major medical journals challenge any submitted paper which uncritically incorporates the safe-dose fallacy. With respect to mutagenesis and carcinogenesis by xrays and other classes of ionizing radiation, the epidemiologic and experimental evidence "falls decisively against" any safe dose (risk-free dose).

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