A Cytodynamic Two-Stage Model That Predicts Radon Hormesis (Decreased, then Increased Lung-Cancer Risk vs. Exposure)

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Summary

Lung-cancer mortality (LCM) is elevated in underground miners who chronically inhaled mutagenic, cytotoxic α-decay products of radon gas. Studies of LCM associations with residential-radon exposure (RRE) levels remain inconclusive, but indicate at least the plausibility of a negative LCM-RRE association over a restricted exposure range. Recently, this possibility was investigated using a "cytodynamic 2-stage" (CD2) cancer model developed at LLNL.[1] The new model accounts for interrelated killing, regeneration, critical DNA damage, and possibly incomplete exposure of tracheobronchial stem cells; it also presumes non-threshold, low-dose linearity for radon-induced critical DNA damage. This model was fit to combined data on LCM vs. estimated radon exposures for (i) white males in 1,601 U.S. counties[2] (considered controversial because these data exhibit a negative LCM-RRE association), and (ii) white male Colorado Plateau uranium miners.[3] The CD2 fit obtained not only predicts the combined residential/miner data, but also predicts the inverse dose-rate (IDR) effect (i.e., the higher risk for a given total exposure of longer duration) observed for radon-exposed miners, and has parameter estimates that all are realistic when compared to experimental data.[1] As shown in Figure 1, both the nonlinear CD2 and linear BEIR IV risk models predict substantially increased risk above 10 pCi/L, but below this concentration, risks

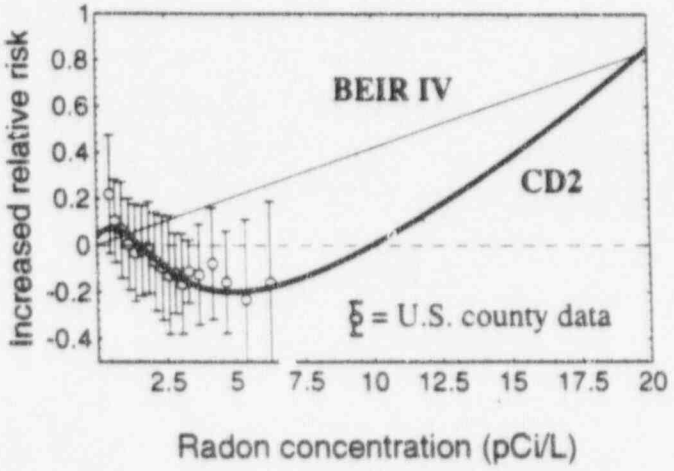

Figure 1. CD2 model fit (bold) to combined data on increased relative risk (IRR) for LCM among Colorado Plateau uranium miners[3] (data not shown), and on mean IRR for LCM rates vs. corresponding mean residential ^{222}Rn concentrations for U.S. white males in 1,601 counties grouped into 15 subsets[2] (data points); also shown are the standard linear (BEIR IV[3,4]) risk model (light), and zero IRR (dashed). IRR = 0.8 corresponds to a 5.4% lifetime LCM risk. Due to IDR effects accounted for, the CD2-predicted residential risk is higher at 20 pCi/L than the BEIR IV estimate based only on underground-miner data.

predicted by the two models diverge dramatically. For 20-pCi/L residential radon exposures—the approximate household concentration implied by the efflux design criterion used recently for DOE's uranium-bearing Nevada Low-Level Waste Facility.[5]—the CD2 model predicts a substantial risk that is *larger* than that predicted by the BIER IV model (Fig. 1). CD2 model plausibility thus bears directly on the scientific basis for risk assessments concerning residential radon exposure and related waste-management issues (e.g., optimal design of uranium-bearing low-level waste sites).

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1980-1981	Science Policy Analyst, U.S. Library of Congress, Congressional Research Service, Science Policy Research Division, Washington, DC.
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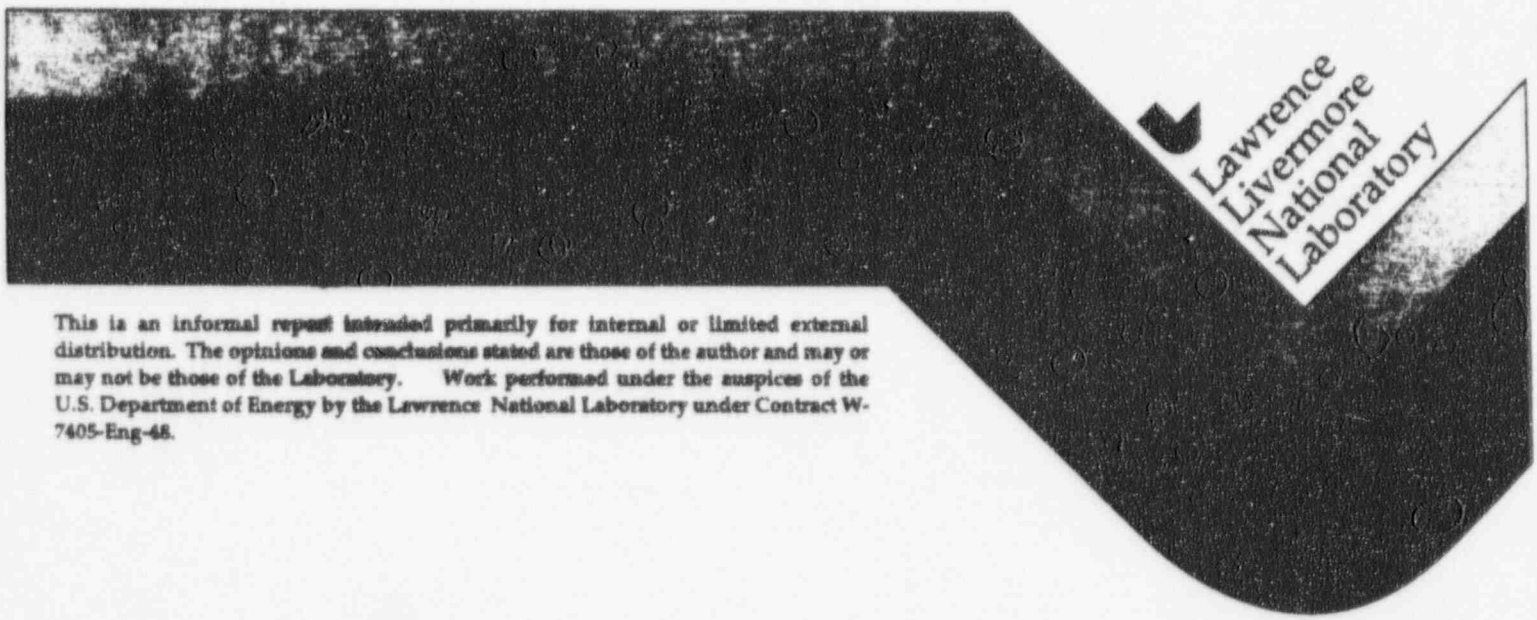

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A Cytodynamic Two-Stage Model That Predicts Radon Hormesis (Decreased, then Increased Lung-Cancer Risk vs. Exposure)

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Running Title: Cytodynamic Two-Stage Model

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Abbreviations: CD2 = cytodynamic 2-stage, CD2S = simplified CD2, CK2 = 2-stage cell-kinetic, CP = Colorado Plateau uranium miner cohort, LCM = lung cancer mortality, LCR lung-cancer risk, RR = relative risk, RRC = residential radon concentration, SD = standard deviation, SN = smokers+nonsmokers, USR = U.S. residential, USWM = U.S. white male, WLM = Working Level Month.

Abstract

Lung-cancer mortality (LCM) is known to be elevated in (even nonsmoking) underground miners who chronically inhaled the mutagenic, cytotoxic α-decay products of radon gas. Studies of LCM associations with residential-radon exposure (RRE) levels remain inconclusive, but indicate at least the plausibility of "radon hormesis" (defined here as a negative LCM-RRE association). The plausibility of radon hormesis was assessed here using a "cytodynamic 2-stage" (CD2) cancer model, which adapts a widely used mechanistic 2-stage (CK2) model to account for interrelated killing, regeneration, mutation, and incomplete exposure of stem cells in tracheobronchial epithelium. The CD2 model, a simplified (CD2S) model positing exposure of all stem cells, and a CK2 model were each fit to published data on LCM vs. estimated radon exposures for both (1) white males in 1,601 U.S. counties and (2) white male Colorado Plateau uranium miners (the largest U.S. mining population studied). The former residential data are considered controversial because they exhibit a negative LCM-RRE association. All three models used presume non-threshold, low-dose linearity for radon-induced mutations. The CD2 (but neither the CK2 nor CD2S) fit was found to be consistent with both the combined residential/miner data and an expected inverse dose-rate effect among radon-exposed miners. Furthermore, all the estimated CD2 parameter values are reasonably consistent with available biological data. In particular, the fraction (~2%) of stem cells predicted to be virtually unexposed is proposed to lie within ciliated submucosal-gland ducts—beyond the range of most radon-decay α-particles. It is concluded that radon hormesis is a plausible prediction of multistage carcinogenesis theory.

Key Words: Alpha, cancer, cytotoxicity, dose-response models, epidemiology, high-LET, hormesis, lung, multistage, mutation, radon, risk.

Introduction

Radioactive radon gas (^{222}Rn) diffuses through rocks and soil, accumulating in enclosed areas such as underground mines and homes. Inhaled radon-decay progeny emit α-particles that are genotoxic and cytotoxic, even at very low doses (1,2). Radon exposure is known to increase lung-cancer risk (LCR) in experimental animals (3,4) and in underground miners of uranium, iron, tin, etc., studied in the U.S. and elsewhere (5-28). The largest study population of U.S. miners involves Colorado Plateau (CP) uranium miners located in Rocky Mountain areas (AZ, CO, NM and UT) [see (5,10,14)]. Mine dust and cigarette-smoke particulates may be important etiologic cofactors in radon-related LCR; e.g. a significant LCR increase was not observed among 359 Japanese Thorotrast patients, in whom the administration of the X-ray contrast medium $^{232}ThO_2$ decades ago caused subsequent long-term, continuous exhalation of high (mine-equivalent) concentrations of α-emitting ^{220}Rn (29). The data on underground (including CP) miners indicate that there is a substantial inverse dose-rate effect for radon-enhanced LCR in miners: cumulative exposures clearly resulted in higher risk when incurred over a longer duration (10,13,30). Combined data from 11 studies of miners also indicate that radon exposures do not materially increase mortality from cancers in tissues other than lung (31).

Residential radon concentration (RRC) is typically ~2 orders of magnitude less than historical concentrations in mines (~50 to 800 pCi/L); RRCs in the U.S. have an average of $\bar{C} \approx 1.25$ pCi L^{-1} and range from <0.5 to (for >1% of homes) >8 pCi/L; corresponding exposure rates average ~0.24 WLM y^{-1} and range from ~0.10 to ~1.5 WLM y^{-1} (32-34).[1] Estimates of LCR due to RRC are generally based on relative risk

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[1]One *working level* (WL) = exposure to any combination of radon progeny in 1 L of air resulting in 1.3×10^5 MeV of potential α-particle energy (≈ 100 pCi L^{-1} ^{222}Rn with daughters at ~50% of their equilibrium concentrations in radon gas); 1 *working level month* (WLM) = 170 WL h; 1 pCi L^{-1} ^{222}Rn = 37 Bq m^{-3} = $f_o f_e(10^{-2}$ WL pCi^{-1} y)(51.6 WLM WL^{-1} y^{-1}) = 0.1935 WLM L y^{-1} pCi^{-1}, assuming f_o = 75% (occupancy) and f_e =

(RR) regression (i.e., linear extrapolation) from excess LCR based on studies of underground miners, and motivate current RRC guidelines such as the U.S. EPA's 4-pCi-L^{-1} action level (13,23,25,33,36-39). Epidemiological studies have examined the expectation that LCR and RRC should be positively related. Recent studies reporting a positive association, and/or claiming consistency with LCR extrapolation from occupational to residential settings, include: a retrospective mortality study of 752 residents of Essex County, New Jersey, exposed to elevated RRCs from industrially contaminated soil (40); a case-control study involving 433 female cases in New Jersey reporting some elevated odds ratios of questionable statistical significance (41); and two case-control studies involving 210 and 1,360 Swedish lung-cancer cases, respectively, indicating significant ~2-fold risk elevations among cases in the highest examined exposure categories (≥ ~4 to 11 pCi/L) (42,43).

In contrast, several case-control and large ecological studies have reported no clearly significant positive, and even some significant negative, LCR/RRC associations. In particular, recent case-control studies involving 308 female cases in Chinese city of Shenyang, 538 cases among nonsmoking females in Missouri, and 738 male+female cases in Winnipeg, Canada, all found no significant positive association of LCR and RRC ($p > 0.05$) (44-46). Interestingly, all three of these studies report odds ratios that are <1 for most RRC ranges above the smallest considered in each study. Among related ecological studies, a significant negative correlation was found between county-average distributions of RRC and lung-cancer mortality (LCM) for males and for females in all 55 counties of England and Wales ($p < 0.01$) (47). Relatively (albeit nonsignificantly) decreased LCM was observed for ~3,000

50% (progeny equilibrium) (13,33,35). Cumulative lifetime exposure is calculated with reference to total lifespan (e.g., 70 y) minus a tumor-latency period (e.g., 5 y; see Methods). Due to biological and physiological factors, residential exposure may typically result in a dose to target cells in bronchial epithelium that is K times as large as the dose caused by the same level of exposure to underground miners; the estimate $K \approx 70\%$ (33,35) is assumed in this study.

inhabitants of the Misasa radon-spa area of Japan compared those in a nearby non-spa area (48). LCR was found to be (again nonsignificantly) inversely related to radon exposure for males and had no apparent trend for females in 67 counties in Florida (49), but a significant inverse LCM/RRC association was found for residents of 37 counties in Washington (50). A similar study of male+female LCR in 427 Norwegian municipalities reported that "no positive trend could be shown with increasing radon exposure" other than a significantly elevated regression coefficient for small-cell-carcinoma incidence *per se* in females (51). Finally, analyses of county-level data on LCM and RRC covering most of the U.S. population assembled by Cohen and coworkers indicate a highly significant ($p \approx 0$) negative correlation between RRC and LCM (but not mortality for other types of cancer) for males and for females, even after adjustment for >50 potentially confounding factors involving socioeconomic status, smoking prevalence, geography, altitude and climate (52-56). The corresponding RR-regression slopes were most recently estimated by Cohen to be discrepant by ~20 standard deviations from corresponding positive BEIR IV estimates based on linear-no-threshold theory (13).

Firm conclusions about radon risk at residential concentrations cannot be drawn from the studies mentioned above (and others that are smaller, unpublished in peer-reviewed journals, and/or have less direct focus on RRC/LCM association *per se*), because of limited statistical power, RRC measurement errors, and possible unidentified confounders (14,16,57). However, data from these studies clearly include a multiplicity of nominally or statistically significant negative associations, and so comprise *at least* a *plausible* basis for "radon hormesis" (here defined as a negative LCM-RRE association). "Hormesis," or induced low-dose benefit (e.g., arising from stimulated adaptive humoral/immune responses and/or DNA repair), has been proposed to explain observed or possible reductions in tumors, mortality, and other endpoints with increasing dose (58-65). By definition, hormesis contradicts linear-no-threshold RR-regression models now applied to risk

extrapolation for residential radon. Linear models are typically justified as prudent and mechanistically reasonable in view of radon's demonstrated carcinogenicity and ability to cause un- or mis-repaired somatic DNA damage likely to contribute to multistage carcinogenesis (13,39). In contrast, proposed hormesis models have been nonmechanistic, focused on dose-rate rather than dose-response effects, and/or only descriptive of possible risk-reduction mechanisms (56,58-65), and are typically uncited in risk assessments for radon and other environmental carcinogens.

A two-stage cell-kinetic model is now used extensively for mathematically modeling epidemiological and experimental carcinogenesis data (66-76). As applied recently in analyses of data on radon- and other radiation-induced tumors in rats and humans, such models explicitly incorporate birth and death rates for postulated premalignant cells (77-79) and cannot predict hormesis because they imply only positive dose-response slopes [see (70,72)]. However, such models are unrealistic insofar as they ignore: (1) expected dose-induced killing of normal (in additional to premalignant) cells via irreparable DNA damage expected by such potent genotoxic agents as radon-related and similar-energy α-particles (2,80-86) and other high-LET radiations used for cancer chemotherapy [see (13,87)]; (2) increased effective mutation rates expected to arise with increased cell division and/or regenerative hyperplasia associated with Point (1) (52,69,88,89); and (3) the likelihood of some virtually unexposed stem cells involved in tissue regeneration. Points (1)-(2) are reasonably self-evident, but Point (3) is more controversial (reasons for its *prima facie* plausibility are discussed in Appendix 1). Point (3) was never considered important in previous radon-related studies, most likely because it does not affect risk calculated using linear-no-threshold risk models (which effectively consider only average target-cell dose(s)). But such an unexposed stem-cell population, as well as Points (1)-(2), may all affect radon risks predicted by newer, biologically based cell-kinetic cancer models. The present study examines whether such effects include a prediction of radon hormesis that is plausible, insofar as corresponding predictions

concerning dose-rate effects, cell turnover, and radon-induced cell killing are in accordance with available data. To this end, the "cytodynamic 2-stage" (CD2) model described in Methods was developed to predict how α-radiation from inhaled radon-decay products might influence LCR in a way that reflects Points (1)-(3) discussed above. This model, and two simpler related ones, were fit to combined U.S. residential (USR) and occupational CP data sets cited above (13,56), using methods described below. The fits obtained, well as corresponding dose-rate-effect and cytotoxicity predictions, are characterized in the Results section. The Discussion section considers how the results obtained bear on the plausibility of radon hormesis.

Materials and methods

Exposure and Mortality Data. Data on lung cancer mortality rates for U.S. white male (USWM) smokers+nonsmokers (SN) and corresponding estimated residential and occupational radon-exposure levels were obtained from the Cohen and BEIR IV studies cited (13,55,56). The residential data compiled by Cohen (56) comprise estimates of relative risk (RR) for LCM in white males adjusted for age and estimated smoking prevalence by county (vs. USWM rates), and corresponding mean RRCs for 1,601 U.S. counties (representing ~90% of the U.S. population in 1,729 counties, minus that in the three major retirement states: AZ, CA, and FL). These USR data are summarized by mean RR values (RR_i, i = 1,...,18), and corresponding values (σ_{RR_i}) of the standard deviation (SD) of each of these means, for counties within 18 corresponding RRC intervals with means (C_i) ranging from ~0.5 to ~6.5 pCi L^{-1} (56). For the present analysis, the SD (σ_i) of each set of n_i county-specific RR values pertaining to RR_i was calculated as $n_i^{0.5}\sigma_{RR_i}$, using n_i and σ_{RR_i} values indicated by Cohen (56) Each RR_i value was converted to corresponding cumulative LCM risk (and the latter's SD was obtained from σ_i) via multiplying by BEIR IV's estimated background rate, $r_0 = 0.067$, for USWM SN based on 1980-84 data (13). Corresponding average exposure rates E_i (in WLM y^{-1}) were calculated directly[1]

from C_i, were assumed to be continuous over an expected 70-y lifetime, and were not adjusted for possible changes in residence(s) outside counties of death; the latter changes tend to shift C_i toward $\bar{C}$, but are estimated to involve a relatively small fraction of the U.S. population outside the major retirement states (55,56).

In addition to the summary USR data described, BEIR IV summary data were used that estimate RR for LCM in white male CP miners, adjusted for age and birth cohort and grouped into 7 exposure intervals <2,000 WLM [(13), Table 2A-1]. To convert to cumulative LCM risk, the RRs and correspo..ding SDs were multiplied by an estimated background risk, r_0^*, for CP SN. It is expected that $r_0^* < r_0$ based on U.S. LCM comparisons at regional, state, and county levels indicating persistent, relatively low LCM rates in Rocky-Mountain areas (52,55,56,90-93). A cumulative LCM risk of $r_{CPN} = 0.063$ is implied by LCM data for CP nonsmokers exposed to ≤2,000 WLM (12). The BEIR IV analysis of smoking- vs. exposure-related effects in CP miners showed that LCM in all non-/minimal smokers (0-4 cig./day, reflecting ~30% of total person-y) was ~9.1-fold higher than that in those who were virtually unexposed [(13), Table VII-9]. The corresponding risk estimate for *un*exposed CP nonsmokers, $r_{CPN}^* = r_{CPN}/9.1 = 0.0069$, is ~62% of BEIR IV's estimated cumulative LCM risk ($r_N = 0.0112$) for USWM contributing to r_0. Interestingly, ~62% is also the estimate obtained as the product of the ratio ($r_{M/I}$) of U.S. mortality to incidence rates for lung cancer, and the ratio ($r_{I(CO/US)}$) of Colorado to U.S. incidence rates for lung cancer, where $r_{M/I} = 0.81$ and $r_{I(CO/US)} = 0.72$ are estimated from corresponding age-adjusted (1950- or 1970-standard) rates (94). For virtually unexposed CP miners, BEIR IV's estimated RR for smoking vs. no/minimal smoking was ~6.0, which is rather less (by ~50%) than that estimated for USWM [(13), Table VII-9]. A relatively low RR for smoking was also indicated in earlier CP studies (5,9,10). In the present study, r_0^* was therefore assumed to be $r_{CPN}^*[(0.30 \times 1) + (0.70 \times 6)] = 0.031$.

The midpoint of each BEIR IV exposure range was assumed to be experienced by corresponding workers for 7 y starting at age 35, which approximate tyical CP

values (5,9,10,12,13). It was further assumed that the percent of residential exposure time during non-mining and mining years was 100% and 76% (= [1–(170 h/760 h)]), respectively (13), and that all CP miners had residential exposure to a radon concentration of $2\bar{C}$ [cf. (10)].

Models of Carcinogenesis. To simplify model descriptions, dependencies on time t and exposure rate $E(t)$ are generally suppressed. The CD2 model (Fig. 1) incorporates a 2-stage cell-kinetic multistage model of carcinogenesis [see (72)], hereafter referred to as a "CK2" model (Fig. 1, dotted box), whereby normal stem cells (S) each with probability μ_1 (per cell division) add one to the population of premalignant ("intermediate") cells (P), which in turn each tend to proliferate clonally and give rise with probability μ_2 to a malignant cell (M). The CD2 model adapts this CK2 structure by specifying cytotoxic loss of S cells, either immediately at rate k_i, and/or at rate k_r to a pool (D) of cells that are reproductively dead but otherwise functionally normal. The CD2 model also posits a reservoir of $100(1-f_x)\%$ resistant/unexposed cells (R), which play an enhanced role in replacing killed S cells. Each R-cell is assumed with probability μ_1' to add one to a population of premalignant (Q) cells, which in turn each give rise with probability μ_2' to an M cell, via processes analogous to those independently involving S and P cells. Transitions from S to P to M and from R to Q to M are assumed to be stochastic, but P- and Q-cell net-proliferation kinetics could be modeled either deterministically [e.g., (72)] or stochastically [e.g., (66-69)]. For the present study, the transition and clonal-growth processes are assumed to be those specified by the "MVK" 2-stage stochastic model of Moolgavkar and coworkers (71,73,77,95). Thus, the production of new malignant cells by each of the $S \rightarrow P \rightarrow M$ or $R \rightarrow Q \rightarrow M$ pathways is taken to be a doubly stochastic "filtered" Poisson process, in which each new premalignant (P and Q) cell undergoes an independent exponential birth-death process leading to stasis, clonal expansion, or extinction. Cytodynamic relations among S, D, and R cells in the CD2 model under cytotoxic conditions, and corresponding effects on Q-cell kinetics (involving

an additional, unitless parameter, c), are modeled deterministically as described in Appendix 2, where other model assumptions are listed. With these assumptions, a discrete exposure scenario involving N dose rates $C(t_i-t_{i-1})$ (where $i = 1,...,N$, $t_0 = 0$, and $t_N = t$) implies a cumulative tumor-mortality risk by time $t+\tau$ that is an analytic function of eight parameters: m, s, f_m, f_R, b, r_{km}, g, and c (see Appendix 2). This expression was used for modeling without adjustments reflecting maturation, so estimates approximate lifetime-average values for SN.

For comparison, fits were also obtained using two related models. First, a simplified CD2 model (CD2S) (Fig. 1, dashed box) was used that represents the CD2 model conditional on $f_R = 0$ and $b_S = b+G(t)$, where $G(t)$ is defined in Appendix 2. Second, an even simpler (CK2) model was used representing the CD2S model conditional on: $k_r = G(t) = 0$, m_i (y^{-1}) here independent of cell-division rates, either $(b_P-d_P) = g + c[1-\exp(-sE)]$ or $(b_P-d_P) = g+sE$, and $b = d_P/b_P$ with b here independent of E. The CK2 model with $(b_P-d_P) = g + c[1-\exp(-sE)]$ is identical to "Model B" referred to in the 2-stage analysis of individual-level CP data by Moolgavkar (78), conditional on zero values for parameters used there to reflect changes caused only by smoking.

Data Analysis. The CD2, CD2S and CK2 models were fit to the combined summary USR and CP data described by minimizing χ^2, the inverse-variance-weighted sum of squared differences between data-derived and model-predicted risks, using *Mathematica®* (96) to implement calculations of model-specific risks, corresponding dose-rate effects, and standard procedures (97) for Levenberg-Marquardt numerical optimization to estimate parameter values and their standard errors. The effects of dose rate on CP-related risks predicted by each model were examined by plotting RR as a function of mine-exposure duration, and by comparing these plots to similar RR data (based on the same reference point: RR=1 at ~2 y) appearing in reports by Lubin and coworkers (24,30). All risk calculations for this purpose used 38.5 y (i.e., the same value assumed for CP miners) as the

midpoint of all exposure durations. Mean lethal dose, D_0 (in cGy), to radon-α-exposed cells implied by each (CD2 or CD2S) model fit was calculated as $D_0 = X/(r_{km}s)$, where X (cGy WLM^{-1}) is biologically effective dose per unit radon exposure. Target cells in tracheobronchial epithelium receiving the greatest dose are the most likely to be killed, and thus to play the greatest role in consequent tissue regeneration. Secretory+basal cells in lobar/segmental bronchi are estimated to receive a higher dose (~2.5 cGy WLM^{-1} under typical mining and residential conditions) than likely targets in bronchioles and alveoli, and at the former site secretory cells receive about twice the dose to basal cells (35,98). Thus, X = 3.3 cGy WLM^{-1} was assumed, and an SD estimate for D_0 was obtained based on the variance estimates obtained for r_{km} and s.

Results

Parameter estimates and corresponding goodness-of-fit statistics obtained for the CD2, CD2S and CK2 fits to combined USR/CP data are summarized in Table 1. The data and model fits are shown in Fig. 2. As noted in Table 1, the CD2S and CK2 fits were not improved by increasing the values of c and s, respectively, above zero, so these parameters were dropped for these fits. Additionally, the CK2 fit was better under the linear than the exponential assumption regarding net-growth of premalignant cells, so the linear assumption was used for this fit. From Table 1 and Fig. 2, it is evident that the CD2 and CD2S fits are consistent with the data considered, whereas the CK2 fit is not ($p < 10^{-6}$). The inadequate CK2 fit is not due to an inability of this model to reflect the summary CP data (an excellent fit was obtained to these data alone). Rather, optimization to the combined USR/CP data forced the CK2 model to reflect its smallest attainable initial slope consistent with larger risk values included in the CP data.

In contrast to the positive linear slope predicted by the CK2 fit low exposures, the CD2 and CD2S fits are more complex. The CD2 fit for USWM SN (Fig. 2a) has a slope that is positive at a hypothetical "zero" exposure level, that decreases to zero at

an exposure level corresponding to the smallest mean RRC (~0.4$\bar{C}$) reflected in the USR data, that becomes negative thereafter before increasing once again to zero at a RRC of ~3.8$\bar{C}$ (≡ a 65-y cumulative exposure of ~60-WLM), and that thereafter becomes and remains positive. The corresponding predicted LCM risk is ~r_0 (the USWM background risk) at three different RRC values: 0 pCi L^{-1}, $\bar{C}$, and 8.0$\bar{C}$ (≡ ~125 WLM). The slope of the corresponding CD2S fit is initially negative, then decreases somewhat before increasing to zero at a RRC of ~8$\bar{C}$, and thereafter becomes and remains positive, with a corresponding predicted LCM risk of ~r_0 both at $\bar{C}$ and at 40$\bar{C}$ (≡ ~630 WLM). CD2 and CD2S dose-response slopes are not constrained to have the signs indicated by the fits obtained here; rather, they may be negative, zero or positive depending on r_{km}, as illustrated in Fig. 3.

Figure 4 plots the RR values predicted by each model fit for CP miners exposed to 300, 600, and 900 WLM over different exposure durations, relative to corresponding risks predicted after a reference exposure time of ~2 y (see Methods). This figure also compares these RR predictions to the estimates for miners obtained by Lubin and coworkers based on 11 studies of LCM in underground miners including the CP miners (24,30). It is apparent from Fig. 4 that the CD2 model predicts an inverse dose-rate effect similar to that estimated for CP and other miners, whereas the CD2S model predicts a proportional dose-rate effect rather than an inverse one. The CK2 model fit jointly to the USR/CP data predicts virtually no dose-rate effect, but this model is clearly capable of doing so. E.g., all fits were excellent under the [false] premise that each USR data point carries only one degree of freedom, in which case the CD2 and CD2S dose-rate effects were virtually unchanged, and the inverse dose-rate effect predicted by the CK2 model predicted RRs increasing to only ~2 at 30 y for a 900-WLM exposure.

Mean lethal dose (D_0, ± 100% × SD / D_0) values of 18 and 31 cGy (± <5%) are implied (as described in Methods) by the values estimated for r_{km} and s using the CD2 and CD2S models (Table 1), respectively.

Discussion

Statistical rejection of the CK2 model fit jointly to Cohen's USR (56) and BEIR IV CP (13) data on LCM risk vs. RRC is not surprising, in view of the facts that this model is constrained to have positive dose-response slopes and that the negative correlation exhibited by the USR data is highly significant (56). This result simply illustrates the fact that while CK2-type models may predict a smaller initial dose-response slope than often predicted by linear RR-regression (e.g., fit to CP data), they are incompatible with the expectation of reduced LCM risk at low doses that is postulated by radon hormesis and by Cohen's interpretation of USR radon data (52,55,56). Consequently, this result would be unchanged had a different approach been used to characterize elevated risk in the CP cohort and/or to estimate parameter values, such as analysis of individual-level CP data using maximum-likelihood methods [cf. (78)].

In contrast, the CD2 and CD2S fits obtained are both consistent with the combined USR/CP data considered, but only the CD2 fit predicts an inverse dose-rate effect similar to that observed for CP and other underground miners (10,24,30). Consequently, the CD2 model may provide a plausible mechanistic basis for radon hormesis, whereas the simpler CD2S model cannot. As has been pointed out (78), a mechanistic 2-stage model may predict an inverse dose-rate effect because, depending on the exposure scenario, the duration of any exposure-induced net proliferation of intermediate cells tends to have a greater impact than cumulative risk within this framework. The CD2-implied inverse dose-rate effects thus arise from this model's integration of predicted mutagenic and mitogenic effects, without reference to hypothesized biophysical (e.g., cell-cycle "window-of-sensitivity") phenomena peculiar to high linear-energy-transfer radiation (99-101).

The biological plausibility of the CD2 model fit obtained may be further assessed by comparing the CD2 parameter estimates to available data. The CD2 estimate for b^{-1} (~3 months) is consistent with the range of directly or indirectly

measured turnover times for normal tracheobronchial epithelial cells in rats (27 to 60+ d) and hamsters (97-159 d) (102-105), the ~3-6-month turnover times previously assumed for purposes of radon dosimetry (98,106), and the enhanced rate of bronchial-epithelium renewal expected in persons chronically exposed to irritants such as cigarette smoke (see Appendix 1). The CD2 estimate of bm (6.5×10^{-8} y^{-1}) is consistent with estimates of ~10^{-8}-10^{-7} y^{-1} made for somatic *hpgrt*-gene-mutation rates in human T-lymphocytes (which are considered reasonable estimators of somatic human-oncogene mutation rates) (107-110).

The CD2 estimate for f_R (1.9%) implies that the R-cell compartment hypothesized in this model is only a small fraction of the major (S) compartment of stem cells considered to be involved, which is consistent with relevant histological and microdosimetric variabilities (see Appendix 1). For example, this f_R estimate is consistent with the hypothesis that R-cells in the major bronchi are stem cells contained in the proximal half of each submucosal-gland ciliated duct descending from the surface epithelium, assuming an equal density of stem cells per mm^2 of ductal and surface epithelia (see Appendix 1).

The parameter r_{km} clearly determines the extent of any hormesis predicted by the CD2 model (see Fig. 3), by virtue of the fact that r_{km} and s specify an effective mean lethal dose to nuclei of exposed cells in bronchial epithelium (see Methods). The D_0 value (18 cGy, ± <5%) implied by the CD2 fit is ~3.5-fold lower than those (averaging ~65 cGy) made for Chinese hamster ovary and other cell lines exposed to radon-derived or radon-simulated α-particles (81,83,84), and ~2-fold lower than that (39 cGy) made for normal diploid human lung fibrocytes exposed to radon α-particles (82). This discrepancy could indicate that the CD2 fit obtained is biologically implausible if radon-induced cell killing (in S and/or P cells) and local tissue regeneration were evenly dispersed over the exposed epithelial surface of the primary target (often considered the segmental bronchi—see Introduction). However, regional variations in particulate deposition can cause doses that are

elevated (~1.3-fold) in bifurcation zones, and dramatically elevated (~10- to 50-fold) in carinal ridges (where bronchi divide), relative to average tracheobronchial doses—particularly when mucociliary clearance is impaired by cigarette-smoke exposure (106,111). Radon-enhanced lung carcinogenesis may also primarily affect those sites receiving such relatively elevated local doses (106,111). The D_0 estimate implied by the CD2 fit for average surface epithelium is thus likely to correspond to a somewhat higher, and hence more plausible, D_0 value in relatively heavily exposed bronchial regions.

It is concluded that radon hormesis (a negative LCM-RRE association) is a plausible prediction of multistage carcinogenesis theory, based on the finding that eco-epidemiological data suggesting such an effect, as well as data on clearly elevated LCM in underground miners, are jointly predicted by a mechanistic 2-stage model that realistically accounts for radon-induced cell killing, cell proliferation, and (non-threshold, low-dose linear) DNA damage. Consequently, current estimates of cancer risk posed by household radon exposures appear to be more uncertain than previous calculations indicate (33,112). In view of the scope of current and planned reductions in residential radon exposures (38), this conclusion highlights the need for more rigorous tests of the biological assumptions and epidemiological predictions of CD2-like models of radon's impact on lung cancer. A more general form of the CD2 model applied here to radon may pertain to environmental chemical carcinogens that are both genotoxic and cytotoxic (see Appendix 2); such applications are currently being investigated.

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Appendix 1:

The Likelihood of Unexposed Stem Cells in Bronchial Carcinogenesis

Lung-cancer in underground miners is considered to arise primarily in upper tracheobronchial regions, which may reflect historical prevalence of non-occupational (smoking-related) lung cancer in males (13,23,35,113,114). Radon microdosimetry has thus focused on the first 4-16 tracheobronchial-airway generations, where epithelial stem-cell targets traditionally were considered basal-cell nuclei ≥ 22 μm (averaging ~50 μm) below surface epithelium (6,13,37,80,115-123), but now are thought also to include nuclei of secretory cells located closer to the epithelial surface (23,35,98,124-128). Considering the ~10-20-μm layer of cilia/sol + mucous/gel overlying tracheobronchial epithelium, all currently hypothesized targets are thus typically within the ~47-μm and ~71-μm ranges of radon-derived 6.0-MeV ^{218}Po and 7.7-MeV ^{214}Po α-particles, respectively. However, several considerations indicate it is likely that some target cells are likely to be unexposed.

Stochastic variation alone in dose delivered to target nuclei at median depths indicates that most target cells would not be hit after 30 y exposure to the mean U.S. RRC (127). But human bronchial-epithelium normally contains undulated/ irregular regions with thicknesses varying from the median by a factor of ~1.4 to 3 (115,117,128-130). Both histologic studies and microdosimetric calculations indicate that ≥10% of basal cells in radon-exposed *normal* upper-bronchial epithelium would be beyond radon-derived α-particle range (117,120,122). The percentage of unexposed cells would be greater within normally occurring regions of local bronchial hyperplasia or squamous metaplasia (where basal cells typically stack), and greater still in regions subjected to chronic cigarette smoke, mine dust, or respiratory dysfunction (13,131-133).

Virtually unexposed stem cells are also likely to exist in the submucosal glands of human bronchial epithelium. These glands, involved in regulating airway surface liquids, have ciliated ducts that emerge from beneath the bronchial surface

throughout tracheobronchial generations 0 to ~8-11, predominantly in generations 2 to 5 where their surface density is ~1 mm^{-2} (130,133-136). They each consist of numerous serous and mucous tubules that distally terminate at corresponding acini and proximally all connect to a collecting duct (~800 μm long in the main bronchus), which in turn narrows to form a nonbranching ciliated duct. Each ciliated duct is ~350 μm in length and ~80 μm in external diameter (again in the main bronchus—smaller dimensions apply to the smaller bronchi), consisting of a 20- to 30-μm-thick epithelial layer that is "identical to and continuous with" the cells of the bronchial surface, including ciliated, columnar, and goblet cells (130,135,137). Virtually all stem cells that might exist in ciliated ducts would be out of range of inhaled α-activity deposited in the upper airways if this activity were nearly all trapped and removed by respiratory surface liquids. The fraction actually removed remains uncertain, but is considered to be in the range of 70 to 100% (35), or to be 99.3% (with the remainder retained near epithelial basement membranes and from there cleared to lymph nodes) (23). While submucosal-duct stem cells have not been identified experimentally or in histological descriptions, the *potential* for such cells to exist and contribute to cell renewal in bronchial-surface epithelium is indicated by observations (133,138) that:

(i) many common virally and bacterially caused respiratory diseases involve extensive, yet efficiently repaired, destruction and denuding of surface epithelium in the larger bronchi (so it would appear unlikely that all such repair is effected solely through migration and/or outgrowth of surrounding undamaged surface-epithelial cells);

(ii) in the case of diphtheria, occasional islets of bronchial mucosa survive undamaged, and epithelial repair proceeds from these zones if recovery occurs;

(iii) squamous metaplastic changes associated with toxic respiratory exposures frequently extend down into submucosal-gland ducts;

(iv) bronchogenic carcinoma tends to spread initially along the bronchus within the mucosa; and

(v) small-cell anaplastic ("oat-cell") carcinomas, which arise primarily in the major bronchi, arise from Kultschitzky-type exocrine cells found both in bronchial submucosal glands and in bronchial surface epithelium.

The *likelihood* that stem cells within submucosal-gland ducts *normally* contribute to renewal of bronchial epithelium is suggested by the known role of mucosal/glandular ducts as a source of progenitor cells for epithelial renewal in small intestine, epidermis, liver, and mammary tissue (139-142). This likelihood is further indicated by recent studies showing that a pluripotent stem cell regenerates both human bronchial epithelium and human bronchial submucosal glands, and that an antigen specific to both bronchial basal cells and cells in bronchial-gland ducts is also expressed in a variety of lung carcinomas (143-145).

Appendix 2:
Mathematical Desription of the CD2 & Related Models

In the CD2 model, the fraction f_R specifies the ratio R/S_0, where S_0 is the normal size of S absent cytotoxicity. The rates b_T and d_T (y^{-1}) are mean birth and death/differentiation rates, respectively, for cell types $T = S, D, P, R$, and Q. It is assumed that $(b_P/b_S) = (b_Q/b_R) = n$, where n is a constant. Under non-cytotoxic conditions, it is assumed that: a single rate constant, g (y^{-1}), governs net proliferation of P and Q cells (i.e., $b_P - d_P = b_Q - d_Q = g$); $b_S = b_D = b(1-f_R)$ and $b_R = d_S = b$; and $d_R << b$ (so $d_R = 0$), where b^{-1} (y) is the mean R-cell turnover time. For cells of type T, the rate of induced reproductive death is assumed to be $k_r = f_x KsEr_{km}$, where s (y WLM^{-1}) and r_{km} (unitless) are scaling factors, $K = 1$ for mining exposures and $K = 0.70$ for residential exposures (33,35)[1], and f_x=1 is assumed for S and P cells. Similarly, corresponding mutation rates are assumed to be $m_T = b_T f_m m_i(1 + f_x KsE)$, where m_i (with i=1 for T={S,R}, and i=2 for T={P,Q}) are estimated mean rates (per cell division, e.g., $\mu_1 = f_m m_1(1+KsE)$), and f_m is a unitless factor set to 1 for USWMs but

estimated for CP miners. The factor f_m represents a potential (e.g., healthy-worker-related) contribution to the expectation that $r_0^* < r_0$, which here is assumed arbitrarily to involve the relative size of effective mutation rates only (results were virtually unchanged when $f_m b$ was used for this purpose rather than $f_m m$). Finally, tumors are assumed to be lethal at time $t+\tau$ conditional on $M(t) \geq 1$, where τ is an assumed tumor-latency period.

Cytodynamic relations among S, D, and R cells in the CD2 model are described here in a general form (relevant to chemical as well as radiation carcinogenesis), incorporating an additional assumption that the rates of birth (b_T) and mutation (m_T) of type-T cells are multiplied by $(1-f_b)$ for $T=\{D,S,P\}$ and by $(1-f_{bx})$ for $T=\{R,Q\}$, and that death rates (d_T) defined there are increased by $f_b b_T$ for $T=\{D,S,P\}$ and by $f_{bx} b_T$ for $T=\{R,Q\}$, where f_b $(0 \leq f_b \leq 1)$ is a function of dose specifying the extent of "mitotic" cytotoxicity (e.g., involving intermediate states of DNA-adduct repair that are lethal if unrepaired prior to mitosis), and where $f_{bx} = f_b / f_x$. By definition, $f_b = 1$ for D cells. A deterministic, Verhulst feedback-inhibition submodel specifies how b_R increases to ensure that $S(t)+D(t)$ tends toward $S(0) = S_0$, under the assumptions that D cells are "perceived" by R cells as being normal S cells, and that $R(t) = R(0) = R_0 = f_R S_0$ for all t (i.e., that the increases in b_R to offset R-cell losses are virtually "instantaneous" on the time scale considered). Equations (1)-(14) below give corresponding birth and death rates specifying the general CD2 model:

$$b_S = b(1-f_R)(1-f_b) \quad (1)$$

$$d_S = b + k_i + k_r + f_b b(1-f_R) \quad (2)$$

$$b_D = b(1-f_R)(1-f_b) = 0 \quad (3)$$

$$d_D = k_i + b(2-f_R) \quad (4)$$

$$b_R = [b + G(t) + f_x(k_i + k_r)]/(1 - 2f_{bx}) \quad (5)$$

$$b_P = n b_S \quad (6)$$

$$d_P = b_P - [g + k_i + k_r + f_b n b(1-f_R)] \quad (7)$$

$$b_Q = nb(1-f_{bx}) \quad (8)$$

$$d_Q = b_Q - \{g[1 + c(b_R-b)(g/b)] + f_x(k_i + k_r) + f_{bx} nb\} , \quad (9)$$

where

$$G(t) = G(\infty) + a\{1 - ([S(t)+D(t)]/S_0)\} \quad (10)$$

$$dS(t)/dt = (b + G(t))f_R S_0 + (b_S - d_S)S(t) \quad (11)$$

$$dD(t)/dt = k_r S(t) + (b_D - d_D)D(t) \quad (12)$$

$$G(\infty) = f\{b + f_R^{-1}[k_i + k_r + 2f_b b(1-f_R)]\} - b \quad (13)$$

$$f = S(\infty)/S_0 = \{1 + k_r[k_i + b(2-f_R)]^{-1}\}^{-1} . \quad (14)$$

The general CD2S model is specified by Eqs. (2)-(4), (6), (7), and (10)-(12) evaluated conditional on $f_R = 0$, and with Eqs. (1), (6), (13) and (14) replaced by:

$$b_S = b(1-f_b) + G(t) \quad (15)$$

$$d_P = b_P - \{g[1 + c(b_R - b)(g/b)] + k_i + k_r + f_b n b\} \quad (16)$$

$$G(\infty) = k_i + k_r \quad (17)$$

$$f = \{1 + h[2(1-f_b)]^{-1}\}/(1 + h) \text{ , where } h = k_r/(b+k_i) , \quad (18)$$

respectively. The scaling constant c (unitless) in Eqs. (9) and (16) specifies in each case that the indicated premalignant cells respond to signals that enhance the normal-cell birth rate by increasing their death rates, where this increase is proportional to the birth-rate increase over its normal value, b. The parameter a (y^{-1}) in Eq. (10) governs the speed of S-cell replacement.

For application to radon (see Methods), Eqs. (1)-(18) were evaluated with $f_b = f_{bx} = 0$, and it was additionally assumed for the CD2 model that:

(1) $f_x = 0$, given that the limited track length of radon-decay α-particles in bronchial epithelial tissue is likely to imply that a small fraction (f_R) of stem cells (e.g., those that may lie within ciliated submucosal-gland ducts) are virtually unexposed (see Appendix 1);

(2) a in Eq. (10) is sufficiently large to ensure that $S(t) \mid E$ approximates its respective steady-state value, $S(\infty)$ (defined above), relatively quickly for all E values considered, where it is understood that for sequential exposures E_i during time intervals $\{t_{i-1}, t_i\}$, $S(t)$ above is defined as $S_i(t-t_{i-1})$ such that $S_i(0) = S_{i-1}(\infty)$ and $S_0(\infty) = S_0$, and where analogous relations hold for D;

(3) the rate (k_i) of dose-induced immediate ("interphase") cell death is ~0, i.e., is negligible compared to k_r at the exposure levels considered here;

(4) $n = 10$, based on values ranging from ~5 to ~20 reported in studies comparing growth kinetics in a variety of potentially premalignant proliferative foci and

surrounding normal tissues (146-149);

(5) $S_0 = 10^8$ cells, based on an estimate that $<10^8$ basal cells are in bronchial regions primarily at risk for radon-induced lung cancer in humans (119), and the assumption that S cells probably also include other (e.g., secretory) cells (see Introduction);

(6) $\tau = 5$ y, based on latency values of 2.5 to 10 y (more recently ~5 y) used in epidemiological studies of lung cancer among underground mining cohorts (5,10,13,25,31,78); and

(7) $m_1 = m_2 = m$, based on similar va[illegible]ained initially for separate estimates of m_1 and m_2, and the similar quality of fits obtained with and without this assumption.

Assumptions (2)-(7) and (6)-(7) were also made for the CD2S and CK2 model applications (see Methods), except that $S_0 = 10^7$ cells was assumed for the CKM model [as in (78)]. Under these assumptions, the models were evaluated using formulae equivalent to Zheng's analytic solution to the piecewise-continuous 2-stage stochastic "MVK" (CK2) model, which during each ith interval (using his notation) involves corresponding rates of mean occurrence (ν_i), birth (β_i), death (δ_i), and mutation (μ_i) of premalignant cells (150). Dropping the i-subscript, the latter three rates correspond directly to the rates b_P, d_P, and m_P, or to the rates b_Q, d_Q, and m_Q, as defined above and in Methods. The expressions used for ν in the CD2 ($S \rightarrow P \rightarrow M$) and CD2S, the CD2 ($R \rightarrow Q \rightarrow M$), and the CK2 models are fS_0m_P, $f_RS_0m_Q$, and S_0m_P, respectively, as defined above and in Methods. In the CD2 model, survival functions Σ_S and Σ_R are calculated for independent $S \rightarrow P \rightarrow M$ and $R \rightarrow Q \rightarrow M$ processes, respectively, with cumulative risk calculated as $1 - \Sigma_S\Sigma_R$.

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Figure Legends

Figure 1. "Cytodynamic 2-stage" (CD2) model of bronchial-epithelium carcinogenesis influenced by α-radiation from inhaled radon-decay products. The model incorporates a mechanistic 2-stage (CK2) framework (dotted box), whereby normal epithelial stem cells (S) may each with probability μ_1 (per cell division) give rise to a premalignant cell (P), which may proliferate clonally and with probability μ_2 give rise to a malignant cell (M). The CD2 model adds a reservoir of unexposed cells (R) that play an enhanced role in replacing S-cells lost, e.g., at rate k_r to a pool of reproductively dead cells (D). R-cells may progress to premalignant (Q) and malignant (M) cells via the same processes independently involving S and P cells. Rates of birth (b) and death/differentiation (d) are specified for each cell type, f_R is the ratio R/S under normal conditions, and bold arrows indicate potential cytotoxic/mitotic induction. In a simplified CD2 (CD2S) model (within dashed border), f_R is assumed to be 0.

Figure 2. CD2 , CD2S, and CK2 model fits made jointly to **(a)** Cohen's data relating mean lung-cancer mortality rates for U.S. white males and corresponding mean levels of residential radon concentration in 1,601 U.S. counties grouped into 15 subsets (56), and **(b)** BEIR IV lung-cancer mortality data for radon-exposed Colorado Plateau miners (13). Cohen's residential data are reexpressed in (a) as mean lifetime lung-cancer fatality risk (± 1 SD) vs. corresponding cumulative radon exposure in WLM. Note that (a) and (b) involve residential (continuous 65-y) and occupational (residential + 7 y of mining) exposures, respectively.

Figure 3. Plots of CD2-predicted risk as a function of cumulative radon exposure are shown for five different rates of reproductive cell killing (k_r), with other parameter values set to those corresponding to the CD2 fit shown in Fig. 2(a). The rate k_r is specified by $k_r = 0.7sEr_{km}$, where E (WLM y^{-1}) is radon exposure rate, s (=3.91) is a fitted scaling constant, and the five different r_{km} values used are indicated. The bold plot is the CD2 fit shown in Fig. 2(a).

Figure 4(a-c). Relative risk (RR) of lung-cancer mortality in Colorado Plateau (CP) miners predicted by the CD2 fit shown in Fig. 2(b) is plotted as functions of mine-exposure duration for cumulative exposures of 300, 600 and 900 WLM (solid curves); corresponding RR predictions based on the CD2S fit are also shown (long-dashed curves). RR is here relative to risk predicted for the reference duration of ~2 y (solid point on short-dashed line indicating RR=1) used by Lubin and coworkers (30) in a similar analysis of combined RR data from 11 studies of underground miners, including the CP miners. For comparison, the plots above include RR values (open circles) and corresponding 95% confidence limits (CLs) reported in the latter study for total exposures of **(a)** 200-400, **(b)** 400-800, and **(c)** >800 WLM (points shown at durations <35 y). The RR point in each plot for the ≥35-y duration was obtained from a similar study (24); the relative deviations of the (unreported) 95% CLs from this point in each plot were approximated as those reported for the preceding time point shown. In each plot, the CD2 curve rising above the RR=1 line predicts an inverse dose-rate effect similar to that indicated by the data shown, whereas the corresponding CD2S curve falling below the RR=1 line does not. Note that the CD2 and CD2S models were not fit to the data points shown in **(a-c)**; rather, the CD2 fit obtained to other (U.S. residential and CP) data happens also to be fairly consistent with the dose-rate-effect data shown above.

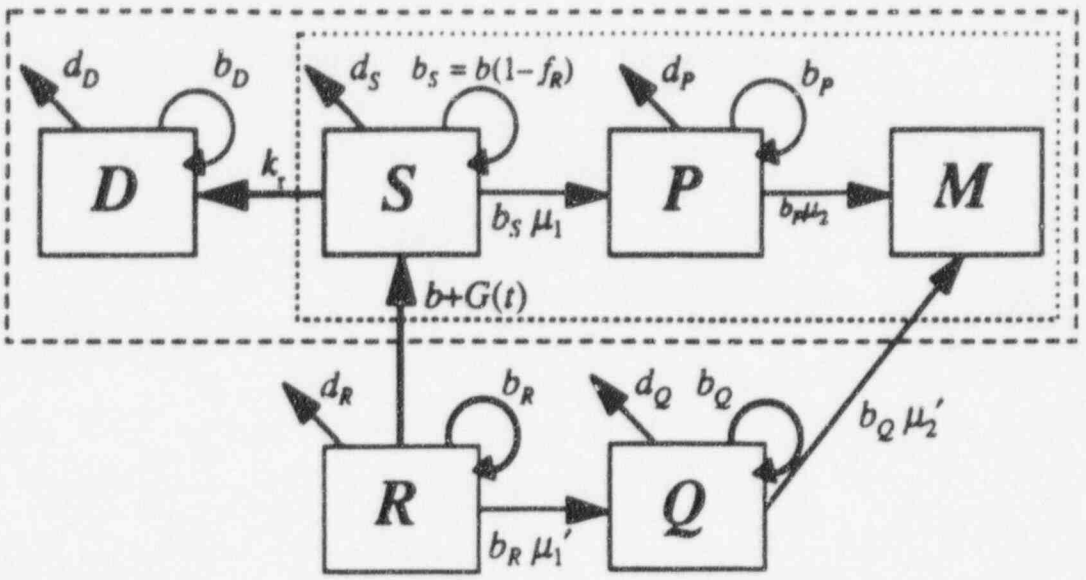

Figure 1

(K.T. **Bogen,** "Application of a Cytodynamic Two-Stage Model ..."; Up = ↑)

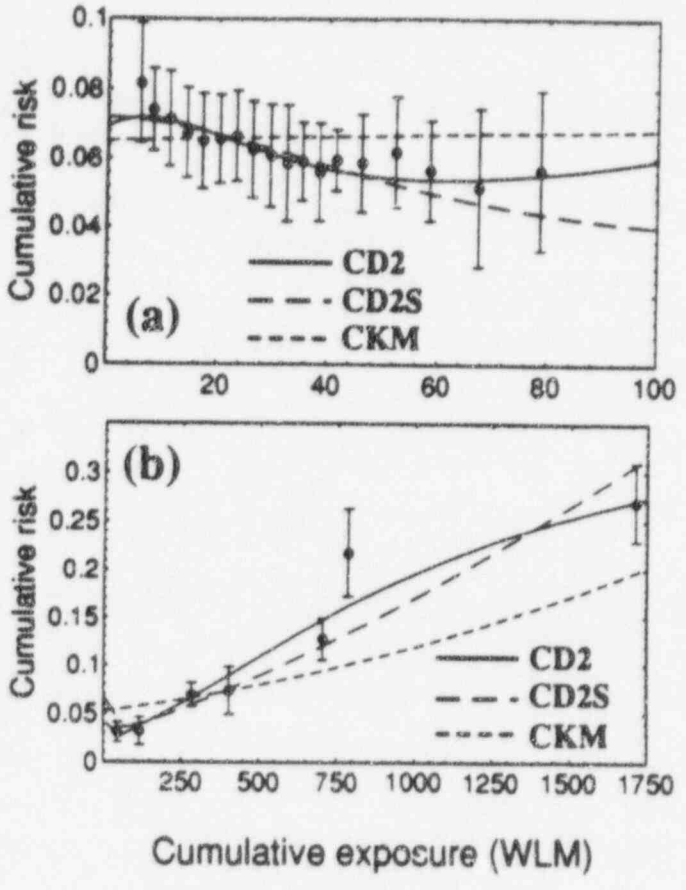

Figure 2

(K.T. Bogen, "Application of a Cytodynamic Two-Stage Model ..."; Up = ↑)

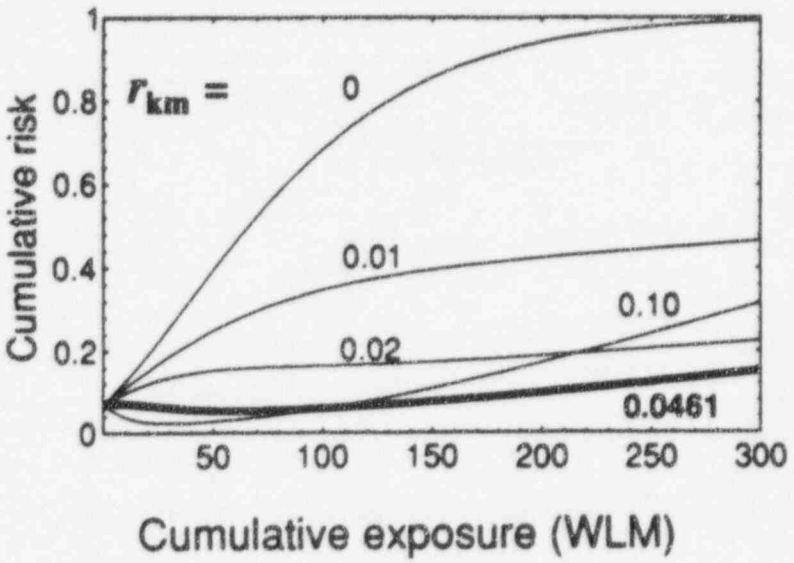

Figure 3

(K.T. Bogen, "Application of a Cytodynamic Two-Stage Model ..."; Up = ↑)

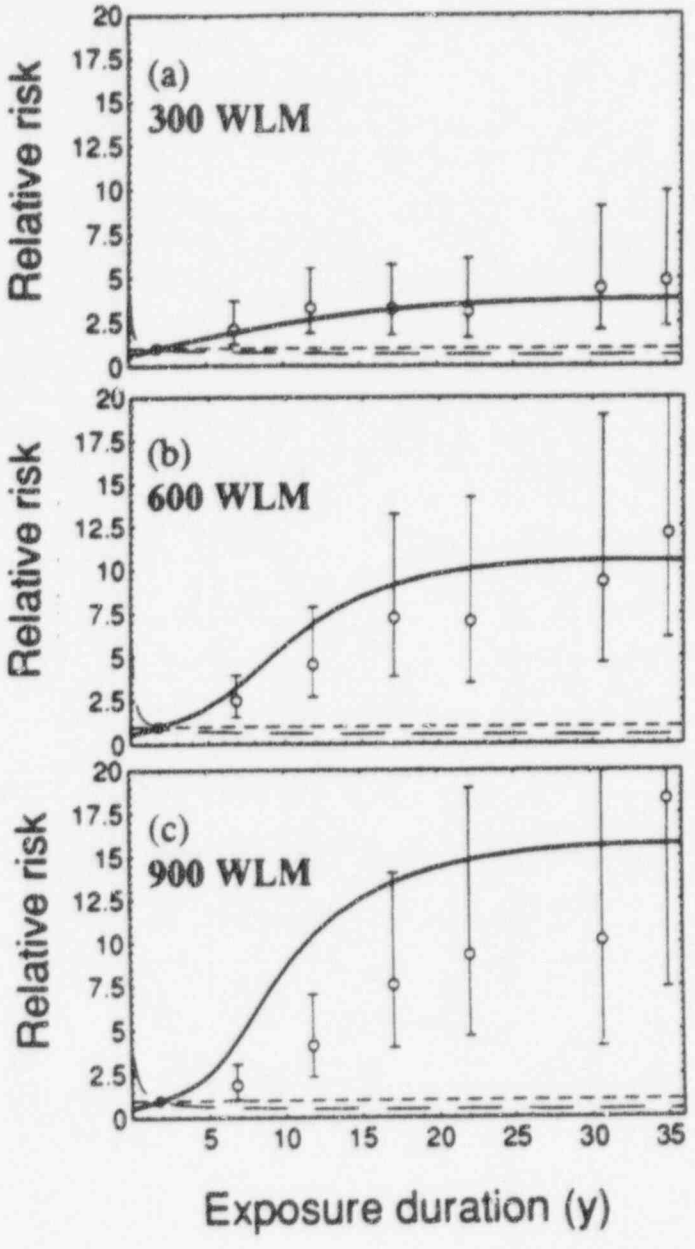

Figure 4

(K.T. Bogen, "Application of a Cytodynamic Two-Stage Model ..."; Up = ↑)

RADIATION HORMESIS: EVIDENCE FOR RADIATION STIMULATION AND SPECULATION REGARDING MECHANISMS

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Abstract—Ionizing radiation is generally believed to be harmful at all levels of exposure, yet, the scientific basis for this assumption is weak to non-existent. Indeed, there is a considerable body of evidence which suggests the contrary, namely, that low doses of radiation, under certain circumstances, may be beneficial. This literature is reviewed, together with some suggested mechanisms.

THE RADIATION PARADIGM

The great majority of people, both scientists and nonscientists alike, share certain assumptions regarding exposure to ionizing radiation. Put very simply, it is believed that radiation exposure: (1) is harmful at all dose levels, but (2) is increasingly harmful at high dose levels, and (3) there are no effects at low doses which cannot be predicted from the deleterious effects noted at high dose levels.

The acceptance of this paradigm is explicit in the estimates of cancer deaths attributed by various scientific organizations and individuals to radiation exposure resulting from low dose radiation. An example is the radioepidemiological tables of the National Institutes of Health which predict cancers at all levels of radiation exposure, without consideration of a threshold (*Ad Hoc* Committee, 1985).

Controversy regarding the health effects of exposure to low dose radiation (LDR) does exist in the radiation community, but the controversy is confined to rather limited issues; just as biblical or Talmudic scholars argue incessantly over minute details of dogma without questioning fundamental assumptions, radiation scientists argue the shape of the dose–response curve, but rarely question the triad of assumptions described above. The possible existence of the possible beneficial effects of LDR, i.e. hormesis, for example, is never mentioned in authoritative reviews such as those of the National Academy of Sciences BEIR committee.

These assumptions cited above are not unique to ionizing radiations; toxicologists generally accept similar assumptions regarding chemical exposures. Indeed, regulatory practices generally assume that all agents (with the exception of nutritional agents) are harmful at all doses.

Environmental agents rarely produce a linear response in biological systems. Whether it be sunlight, vitamins, or alcohol, there are qualitatively different responses at low and high doses, with high doses being usually harmful and low doses often being beneficial. This is not only true of naturally occurring agents, as in the examples just cited, but with synthetic agents as well (see below).

Indeed, examples of agents which are *only* harmful are difficult to find. Stebbing points out that of all dose response curves (Fig. 1), curve A, characteristic of an agent which *only* produces harm, is relatively uncommon, and when such a response is exhibited, one may question whether the experiment had been adequately designed to expose an hormetic curve (Stebbing, 1982).

HORMESIS—WHAT IS IT?

A 17th century reference to the concept now known as hormesis is to be found in the writings of Paracelsus, who stated that "what makes a man ill also cures him." He also wrote that "the poison is not in the substance, but in the dose."

In the 19th century, Hugo Schulz proposed that, depending on the magnitude of a stimulus, it could either enhance or diminish physiological activity (Schulz, 1888). Later, another German biologist, Rudolph Arndt, wrote, "If genuinely weak stimuli promote the vital activity of organs and organisms, a poison, when administered in a sufficiently reduced amount, must exert not a harmful effect but rather a beneficial effect on the substrate of its influence."

Ultimately, what came to be called the Arndt–Schulz "Law" was promulgated. This law states that "weak stimuli accelerate vital activity, medium ones promote it, strong ones inhibit it, and very strong ones snuff it out."

The term "hormesis" is of relatively recent origin. According to Luckey, hormesis was first used in a 1942 publication to describe the stimulation of fungal growth by low concentrations of a naturally

occurring antibiotic substance found in tree bark which at higher concentrations suppresses fungal growth. Luckey's book on radiation hormesis deservedly receives credit for establishing interest in radiation hormesis (Luckey, 1980, 1982).

The evidence that a wide variety of synthetic and naturally occurring agents are stimulatory at low doses is now overwhelming. Calabrese and his colleagues have collected evidence of stimulation (of some form) from exposure to the following agents: (1) chloroform (5 studies); (2) essential trace elements (5 studies); (3) pesticides (9 studies); (4) heavy metals (13 studies); (5) polychlorinated biphenyls (3 studies); (6) antibiotics (8 studies); (7) hydrocarbons (4 studies); (8) alcohols and oleates (4 studies); (9) miscellaneous (14 studies).

Among the miscellaneous group of agents are radionuclides such as Co-60 (Calabrese *et al.*, 1987). In addition to a large number of agents which can produce stimulation, the number of biologic species which respond to such agents is also very large (Stebbing, 1982): (1) bacteria; (2) yeasts and other fungi; (3) protozoa; (4) cell culture; (5) multicellular invertebrates; (6) invertebrate larvae; (7) vertebrates.

In spite of this contrary evidence, the assumption of harm from exposure to environmental agents at all exposure levels is widely accepted, but is probably more firmly entrenched in public thinking and in regulatory decision-making for radiation than for any chemical agent. One reason for this was the early identification of a linear relationship between radiation exposure dose and mutation rates. Early in the history of radiation biology, the genetic effects of radiation exposure were of greater concern than were somatic effects. When Müller and others identified a linear response of drosophila to radiation, that dose–response relationship was imputed for all effects.

Secondly, in the 1940s there was proposed a theory which suggested that the radiobiological effects were due to radiation "bullets" hitting a genetic target. It was also believed at the time that cellular DNA was extremely stable, and that any damage, such as that resulting from exposure to such radiation bullets, would leave irreparable harm. As described below, we now know that DNA is under constant attack by a number of mutagenic agents, both environmental and also those resulting from metabolic processes, and that the cell has a number of enzymes which are able to repair and maintain the integrity of the DNA (Kirkwood, 1989).

HORMETIC EFFECTS OF LOW LEVEL RADIATION IN COMPLEX ORGANISMS

Several biological effects in whole organisms are considered as possible hormetic effects of LDR. They are: (1) increased longevity; (2) a reduction in cancer frequency; (3) increased growth and fertility of both plant or animal organisms.

Longevity

A number of reports suggest that small continuous doses of radiation prolong life. This has been shown for instance, in drosophila (Sacher, 1963) as well as in marine organisms (Strehler, 1977).

Considerable evidence of longevity hormesis also exists in mammals. Some years ago, Lorenz conducted experiments in which we found that animals exposed to doses of radiation above background actually survived longer than the unexposed animals (Lorenz *et al.*, 1955). Although the result has been replicated in other species and in other laboratories, the significance of this result has been in some doubt, partly because it could not be consistently replicated, and partly because there was no obvious mechanism demonstrated. The Lorenz work has recently been reviewed (Congdon, 1987).

In addition to life prolongation from low doses of radiation, it has also been demonstrated that shielding from background radioactivity will reduce the lifespan of drosophila as well as several other species (Plane and Geiss, 1973).

Radiation resembles several other chemical agents in its ability to prolong survival at very low exposure levels. Haseman has analyzed data from carcinogenesis testing studies showing that in animals exposed to test agents, many of which were shown to carcinogenic, there was a significant increase lifespan of the exposed animals, in comparison with the unexposed animals (Haseman, 1983).

Boxenbaum and his colleagues have also collected data from a number of studies demonstrating increased survival of animals chronically exposed to agents, such as procaine, normally thought to be harmful (Boxenbaum *et al.*, 1985–6).

In addition to observations in laboratory animals, there are some provocative observations in humans. One such data set is the work of Sir Richard Doll who has studied mortality among British radiologists. Matanoski has also reported a deficit in mortality among radiologists, particularly radiologists below the age of 55, after which mortality rates rise above those of other physicians (Matanoski, 1987).

Cancer frequency

The most thoroughly studied consequence of radiation exposure is an increased risk of cancer. Multiple studies on exposed human populations as well as in laboratory animals make it clear beyond any doubt that exposure to high doses of radiation increases the risk of cancer. Whether exposures in the range of occupational doses, i.e. less than 5 rad per year, are carcinogenic or not is a matter of controversy. Estimates of cancer risk at these low levels of exposure are drawn from high dose experiences (particularly Japanese studies) by the use of mathematical m These estimates are quite unstable, varying b factor of five, and do not exclude zero (Jablon, 1988).

Nevertheless, direct observations of populations exposed to low doses of radiation often show a

reduction in the rates of expected cancer. For example, in his recent review of four such studies, Mole finds standardized mortality ratios (S.M.R.s) of 75, 95, 85 and 78 (Mole, 1987). These differences from expected values are highly significant statistically. The general explanations for the low frequency of cancer in such studies is the so-called "healthy worker" effect, i.e. the assumed health advantage of employed populations when compared with unselected national populations. However, there are other reasons to believe that a real protective effect of low levels of radiation against cancer may be operating. Some examples:

—cancer rates among atomic bomb survivors who received the lowest doses of radiation, i.e. between 1 and 9 rad, appear to demonstrate a significant deficit of cancer in comparison with the unexposed surviving populations of the two Japanese cities (Fremlin, 1987).

—populations living around nuclear installations in Great Britain have recently been studied because of the concern that exposures which result from proximity to such facilities increases cancer. In fact, the study showed that, although childhood leukemia rates were inexplicably higher than among those living more distally, overall cancer rates were lower than expected (Forman *et al.*, 1987).

—in studies of cancer rates among populations living in geographic areas where background radiation is higher than normal, cancer rates tend to show an inverse relationship with background radiation; the higher the background radiation, the lower the cancer rates. Such studies have been conducted in China (Wei *et al.*, 1986), in India (Nambi and Soman, 1987) and in the United States (Frigerio *et al.*, 1973).

Fertility, growth and reproduction

A third area of radiation hormesis is the stimulation of growth and fertility in both plants and animals. There have been for several decades reports in the literature which demonstrate that LDR can produce a stimulatory effect. Luckey has provided an important review of this literature (Luckey, 1980). Miller has recently reviewed the plant literature (Miller, 1987) and concludes that this effect may be the result of killing of the terminal meristemic tissues, resulting in the increased growth of flowers and fruits. There are also many reports of increased fertility following LDR. One recent example is a study by Canadian workers suggesting an increase in fertility and survival of trout embryos fertilized with irradiated sperm (Newcombe, 1973).

Newcombe's interpretation of increased survivability of these irradiated embryos was as follows:

> "More unexpected was the finding of an analogous 'beneficial' effect of the lower doses to sperm, on the survival of embryos after they had been formed. This implies a lingering influence, which is known to extend over many cell generations and over at least the first half of the period of development of the egg. It is therefore difficult to imagine a likely mechanism which does not involve the genetic materials of the irradiated sperm cell. If the genetic materials of the germ cell are involved, it follows, at least over this range of doses, that for certain hereditary effects of radiation the response curve must be nonlinear and the 'benefit' must predominate over the 'harm' where the dose is sufficiently low."

MECHANISMS

If hormesis is a generalized phenomenon, then an explanatory theory should provide a basis for understanding the underlying mechanism; i.e. how does it work? Two different mechanisms have been proposed; one relates to the cellular response to potential injury, and the second, to "cell-replacement repair", or "altruistic cell suicide".

Response to sub-lethal cell injury

Simply stated, radiation effects are thought to result from several different mechanisms; the first relates to the production of oxygen radicals, and the second to damage to DNA. Both of these mechanisms can be used to explain protective effects of low doses of radiation.

A free radical is any chemical species that contains one or more unpaired electrons, i.e. electrons present singly in atomic or molecular orbitals. Examples are superoxide, hydrogen peroxide, and hydroxyl. In high concentration, free radicals are thought to produce tissue damage, through interactions with fatty acids in cell membranes, and with DNA. Some diseases are thought to result from excessive exposure to free radicals (Halliwell, 1987). Such has been the conventional wisdom ("free radical formation is bad").

Recent studies now suggest, however, that low concentrations of free radicals may be beneficial and even necessary to cell growth, as shown by several investigators (Murrell *et al.*, 1989; Cerutti *et al.*, 1989 and Sohal *et al.*, 1989).

Protection against the effects of free radicals provided by a number of antioxidants, including the enzyme, superoxide dysmutase, and certain metal ions. Reactions amongst these agents, oxidants and antioxidants, are complex, and are just being explored. The extent of tissue damage is the result of the balance between the free radicals generated and the antioxidant protective defense system.

These observations suggest a possible explanation for protection resulting from LDR or other agents which produce free radicals; if radiation stimulates the synthesis of antioxidants (an "up-regulation"), then the net result could be a general increase in protection against oxidants. Ludwig Feinendegen and Victor Bond, working at the Julich Nuclear Research Center, have shown that one such

antioxidant, thymidine kinase, is increased by LDR (Feinendegen, 1987).

A second possible protective mechanism is suggested by the observations on the efficiency of DNA repair mechanisms. Wolfe and co-workers have observed that extremely low exposures to ionizing radiations apparently "up-regulate" the repair process, resulting in an increased resistance of cells treated in this manner to be subsequent high-dose exposures. That such a phenomenon might also operate in humans is suggested by the observation of Austrian workers (Tuschl *et al.*, 1980). They have noted that persons employed in radium mines used for therapy have increased DNA repair efficiencies.

Altruistic cell suicide

In 1906, Bergonie and Tribondeau noted that the effectiveness of radiation is greatest on those cells which are most primitive and are most actively reproducing. Why should this be so? Sohei Kondo has suggested that, since DNA replication is rarely perfect, the effect of DNA damage would be greatest in cells which frequently reproduce since in such tissues the effects of deleterious damage would rapidly result in amplification of induced errors (Kondo, 1988). The surest way of preventing these errors in replicating cells then, would be for "altruistic suicide" or programed death of these injured cells. Such a strategy might also explain death rather than implantation of injured fetuses. Through means which are not entirely understood, the death of cells stimulates the proliferation of primitive stem cells. There is considerable evidence that this stimulation "up-regulates" the reproductive process, that is, results in a greater rate of cell production than would have occurred in the absence of cell destruction (Fabrikant, 1987).

One means through which altruistic cell suicide could enhance the health of mammalian species involves the immune system, that complex system of cells and serum factors which is increasingly being found to participate in responses to not only infectious diseases, but also to cancer and many of the chronic diseases including heart disease and diabetes.

Effects of LDR on the immune system

Early in the study of ionizing radiation, it was recognized that the immune system is particularly radiosensitive to high doses, but it was also recognized early on that low doses of radiation enhanced immunity. In the early literature, experimentation was largely directed towards the effects of LDR on resistance to bacterial infection in laboratory animals as well as in man. For example, in a review of the literature reported in 1951, Taliaferro noted a number of reports in which experimental animals could be shown to be more resistant to infection with bacteria (Taliaferro, 1951). He concluded that "small amounts of X-rays, often administered locally, sometimes enhance antibody formation and the immunity of experimental animals to nonliving antigens and certain infections. This conclusion has also been reached with respect to a wide range of infections in man but may not be justified in all cases because of inadequate controls." Unfortunately, research on the effects of LDR on immunity largely ended before a sophisticated understanding of the immune system existed.

In more recent decades, experimental attention has been directed towards the role of radiation enhanced immunity on resistance to transplanted tumors. What now appears to be demonstrated is that the suppressor T-cells are more sensitive to radiation than are effector T-cells. Therefore, if the radiation expososure is appropriately timed and in small dose, there is an enhanced immune response which results in a suppression of transplanted tumor cell growth in animals (Anderson *et al.*, 1988). There is also at least one report which suggests that small doses of radiation may inhibit the growth of advanced lymphomas in human patients (Chaffey *et al.*, 1976).

CONCLUSIONS

In closing, I should like to emphasize that I am not arguing that the case for hormesis requires that low doses of radiation *always* be beneficial. Indeed, if nontoxic or stimulatory effects do occur at low doses, such effects need not exclude the co-existence of toxic effects at low doses; both might co-exist. Furthermore, they might interact in a manner which is impossible to predict, and in some individuals, one of these might predominate while in another, the other effect could predominate.

I have no difficulty in accepting the existence of an agent which simultaneously creates a hazard and a benefit. We have several examples of agents which are associated with both effects. Nickel, chromium and selenium are three examples of agents which are necessary to nutrition and are known carcinogens. So too are the thyroid and the female sex hormones.

What is the future of hormesis, a concept which is viewed as a novelty, as being outside of normal conventional wisdom? In his book, *The Structure of Scientific Revolutions*, Thomas Kuhn (1970) says; "Normal science often suppresses fundamental novelties because they are necessarily subversive of its basic commitments. . . . Nevertheless, so long as those commitments retain an element of the arbitrary, the very nature of normal research ensures that novelty shall not be suppressed for very long." Like Professor Kuhn, I too have confidence that if radiation hormesis exists, that in spite of the powerful influence of the radiation paradigm, the truth shall eventually prevail. If the absence of stimulatory or hormetic effects should be confirmed and the paradigm thus strengthened, we will have gained in that comparisons with alterfiative models will have strengthened our awareness of our underlying assumptions. If hormesis is confirmed, we will have improved the robustness of our radiation model.

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ADMINISTRATIVE SESSION

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Cognizant Member: J. Garrick
Cognizant Staff Member: R. Summers

ADMINISTRATIVE SESSION

- AGENDA -

		Presentation Time
I.	Introduction - Dr. Garrick	5 min.
II.	Conclusions of March 26, 1996 Meeting - Letters, Reports, etc. - Need for further Subcommittee Meetings on March 26th topics	30 min.
III.	Future Meetings - Need - Suggested Topics	30 min.
IV.	Charter and Protocol for Joint Subcommittee	25 min.

ADMINISTRATIVE SESSION

- STATUS REPORT -

Draft Protocol

A draft Protocol was sent to each Subcommittee member on February 29, 1996, for comment. Comments were received from three members: Dr. Steindler, Dr. Kress, and Dr. Powers.

Suggested changes were as follows:

Dr. Kress:

Dr. Kress recommended [page 4] that the Chairmanship of the Subcommittee alternate annually and that Dr. Garrick remain the Chairman during the first year. He also recommended that membership not change depending on the subjects to be discussed.

Dr. Powers:

Dr. Powers recommended [page 5] that the Subcommittee devote some time at its first meetings to strategic planning to include issues that do not now appear but may arise in the near future. He did not have substantive changes to the draft Protocol.

Dr. Steindler:

Dr. Steindler's comments [page 6] began by suggesting that such a formal documents may not be needed. He made several other suggestions about the signature for letters, which by-laws would govern, etc. and concluded that the experience of the first meeting would be valuable in making some of these decisions.

Topics for Future Meetings

Members were asked for suggestions for topics for future meetings. The following topics have been suggested:

1. Risk Harmonization
2. Probabilistic Risk Assessment
3. Expert Judgment
4. Rebaselining/Strategic Planning (the NRC initiative)
5. Excess Weapons Plutonium Disposition, as waste or fuel

Dr. Powers suggested [page 5] that new issues be determined by devoting some time at the Subcommittee's first meetings to strategic planning, to identify issues that do not now appear but may arise in the near future.

DRAFT PROTOCOL FOR JOINT ACRS/ACNW SUBCOMMITTEE

PURPOSE

The purpose of the Joint Subcommittee is to review a limited number of topics that are, or could be, of interest to both the ACRS and the ACNW, thus avoiding dual reviews and conserving NRC staff and Committee resources. The Joint Subcommittee will also review subjects that could benefit from the combined expertise of members from both Committees.

It is anticipated that the Joint Subcommittee will consider issues under discussion or development at NRC sufficiently in advance to influence the direction of those issues.

The proposed Protocol for the Joint ACRS/ACNW Subcommittee is as follows:

I. Chairmanship

~~The Co-Chairmen are Dr. Thomas S. Kress, Chairman, ACRS, and Dr. B. John Garrick, Vice Chairman, ACNW. The first meeting will be chaired by Dr. Garrick. Subsequent meetings, if any, will be chaired alternately by Dr. Kress and Dr. Garrick.~~

II. Membership

Members of the Subcommittee, in addition to Drs. Kress and Garrick, are: Dr. Robert L. Seale, Dr. Dana Powers, and Dr. William Shack (ACRS), and Dr. Martin Steindler (ACNW). Members are expected to set the dates and agendas for meetings and to determine subjects for review by the Subcommittee and for referral to the Full Committees. ~~Membership on the Subcommittee is subject to change depending on the subjects to be discussed.~~

Other Members of both Committees are invited to attend Subcommittee meetings and to participate fully in all discussions and draft letter-writing activities. Members of both Committees are invited to suggest topics for Subcommittee review.

III. Staff

The Nuclear Reactors Branch, the Nuclear Waste Branch, and the Operations Support Branch will work together as a team to support the Joint Subcommittee. The staff for the first Joint Subcommittee meeting will consist of R. Summers, N. Dudley, and M. Larson. R. Summers, Operations Support Branch, will be responsible for drafting Federal Register notices, scheduling and coordinating the meetings, publishing agendas, and ensuring that status reports, minutes, draft letters, and other documentation are

II. Chairmanship

The chairmanship of the subcommittee will alternate annually between ACNW and ACRS. The first year

To: Roxanne Summer

Dana A. Powers

From: Dana A. Powers

Subject: **Protocol for the Joint ACRS/ACNW Subcommittee**

I have examined the draft protocol you prepared for the meetings of the joint ACRS/ACNW Subcommittee and I have no substantive comments on the draft. In my work with the U.S.Department of Energy, I am part of a team that is again trying to rewrite the rules for dealing with radioactive wastes from the defense programs. Our current approach is to adopt a performance base for any revised rule. A major issue we face is the definition of incidental waste that NRC will adopt when it considers regulation of Department of Energy repositories. In view of the ongoing interest in external regulation of the Department of Energy, possibly by the NRC, it would appear useful if the joint Subcommittee could devote some time in its first meetings to strategic planning to include issues that do not now appear but may arise in the near future.

FAX COVER SHEET

PRIORITY: HIGH/MEDIUM/ROUTINE DATE: 3/1/96
TIME: 12:15AM
PAGES INCLUDING COVER: 1

TO: Roxanne Summers @ FAX 301 415 5422
ACNW T2 E5 X7371

FROM: MARTIN J. STEINDLER Phone (H) 708 241 3750@
Phone (O) 708 252 4314+
Fax (O) 708 252 5528+
FAX.....(H) 708 241 3750#

MESSAGE:

Concerning your fax on the Protocol for the joint ACNW/ACRS meeting:

-I find it hard to believe that we need such a formal document for a session between groups that are suposed to work for the same Commissioners.

-Re item V: If the operation of the subcommittee is such as to involve both committees or members thereof, why not foward to the Commission a letter signed by both the the co-chairs? Is it likely that consensus will be too difficult to attain? How can the members of the Committee NOT writing the letter provide compelling input to the advice given to the Commission? I wonder if all letters should not be joint letters.

-It sounds as though the members will review topics and not the entire subcommittee. Is this right? It should not be.

-In light of DOE and NRC activities on excess weapons plutonium disposition and the fact that this stuff is supposed to be waste or fuel, should this not be a topic for the subcommittee?

-Since the ACNW is outvoted, should not there be some provision for 'protection of the minority'? Also, do Roberts Rules of Order apply? Are the ACNW by-laws governing or are the ACRS by laws governing? (or does any of this matter)

-Let's see how it goes before we cast this in concrete.

@Address is 1524 Chicago Ave, Downers Grove IL 60515-3450. Fax number is the same as the phone number. (See below at #)

+ Address is Argonne National Laboratory, Chemical Technology Division, Building 205, Argonne, IL 60439-4837
e-mail address: steindler@cmt.anl.gov

#No unattended reception. Call and talk to us before sending.

DRAFT PROTOCOL FOR JOINT ACRS/ACNW SUBCOMMITTEE

PURPOSE

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completed on schedule. After the Subcommittee determines the subjects for review, a team member will become responsible for each subject. Each team member will prepare agenda items, coordinate presentations, and draft minutes of the subjects for which they are responsible.

IV. Topics for Review

Members and staff of both Full Committees may propose topics for Joint Subcommittee consideration, but Members of the Joint Subcommittee will make the final decision on topics for its review. Suggested topics include, but are not limited to: spent fuel storage, health effects of low-level radiation, decommissioning, and risk-based regulations, including the use of PRA and expert judgment. The Co-Chairmen will decide which Members and staff will be assigned responsibility for each topic. Several memoranda are available for guidance in this process.

V. Letter Writing

When the Subcommittee determines that a topic on the agenda should be the subject of a letter to the Commission, its members will generally refer the matter either to the ACRS or to the ACNW. In rare cases, a joint letter may be preferred. A draft letter will be prepared by the Subcommittee Member(s) assigned to the subject. The drafts will initially be reviewed by the Subcommittee, prior to going to the full Committee(s). Members of one Full Committee may participate fully in the letter-writing process of the other Full Committee on a topic referred by the Subcommittee, but they may not vote on the final letter.

VI. Agenda

The Agendas will be prepared by the Staff Team, based on guidance from the Subcommittee Co-Chairmen.

VI. Minutes

R. Summers will be the Technical Secretary for the Joint Subcommittee and will be the person responsible for producing the final Minutes. Staff Team members will prepare draft minutes for portions of the agenda assigned to them. Minutes will be certified by the Co-Chairman who chaired the meeting.