bomb survivors and high-dose therapy patients) and excludes relevant lower dose and dose rate data. These data include (a) the extensive dosimetric documentation from nuclear power reactor and military personnel, (b) lower dose imaging data, and (c) environmental data. The BEIR VII report notes that these types of studies were evaluated, but not incorporated into the analysis. Failure to include these lower dose data provides an inherent bias and overestimates the risk of low levels of ionizing radiation.

2. BEIR VII incorporates a dose and dose rate effectiveness factor (DDREF) for low linear energy transfer data. A range of DDREF values of 1.1 to 2.3 were considered, and a value of 1.5 was deemed to be appropriate (*3*). The DDREF value is applied for doses below 1 Sv, and a mathematic discontinuity in the *linear curve* is created by reducing the slope of the dose–response curve (effects vs. dose) by a factor of the reciprocal of the DDREF below 1 Sv (*3*). The use of the DDREF is a tacit admission of the fallacy of the LNT approach that is a fundamental underpinning of BEIR VII. There would be no need to create an artificial DDREF factor if the LNT model were correct. Other dose cutoff values can be defined that further serve to challenge the LNT approach. For example, Siegel, Pennington, and Sacks (*4*) credibly demonstrate the fallacy of the LNT hypothesis as applied to medical imaging. Siegel et al. (*4*) note that credible evidence of imaging-related carcinogenic risk at low absorbed dose (<100 mGy) is nonexistent. A 100 mGy, 1 Sv, or discontinuity at another value adds support to challenge the credibility of the LNT approach.
3. The most recent report of the Radiation Effects Research Foundation (RERF) (*5*) notes a definite curvature in the data that further serves to challenge the LNT approach. RERF report 14 (*5*) updated the RERF report 13 (*6*) results and noted that formal dose-threshold analysis indicated no threshold; that is, zero dose was the best estimate of the threshold. However, Ozasa et al. note that: "Although the linear model provided the best fit in the full dose range, statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy ($\theta = 0.81$, $P = 0.02$) (Tables 6 and 7). The curvature over the 0–2-Gy range has become stronger over time, going from $\theta = 0.20$ for the period 1950–1985 to 0.81 for 1950–2003, and has become significant with longer observation (Table 7)." In the preceding quote, θ is the curvature of the fit, and P is the statistical significance (likelihood test). The reader should recall that RERF report 13 (*6*) was a significant basis for establishing the credibility of the LNT hypothesis in the BEIR VII report (*3*).
4. Although the evaluation of DNA and its robust repair mechanisms are important, risk is best formulated as the integrated challenge to an organism. The effects of adaptive response, human immune system repair and mitigation, apoptosis, and other inherent protective functions also influence the final risk. Focusing solely on DNA repair is only one aspect for formulating a risk estimation model.

The BEIR VII report and Duncan et al. do not consider the aforementioned 4 factors that serve to challenge the LNT approach. As such, this letter supports the contentions of Siegel et al. (*2*) and encourages future BEIR reports to incorporate the challenges offered by these authors to improve future reports. In addition, the updated RERF report 14 data and low-dose and dose rate data should be incorporated into future BEIR reports to provide the best scientific assessment of the risk of ionizing radiation.

ACKNOWLEDGMENT

I acknowledge Dr. Ozasa, who kindly supplied raw data from RERF report 14 (*5*) that were used to independently verify curvature in the dose–response curve noted in argument 3 above.

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Published online Aug. 2, 2018.
DOI: 10.2967/jnumed.118.217604

Mechanistic Insights Into Why Radiation Dose Matters? It Matters Most Because of Adaptive Responses at Low Radiation Doses

TO THE EDITOR: In their Invited Perspective, Duncan et al. (*1*) continue a defense of the linear no-threshold (LNT) model for low-dose radiation (LDR) but do not respond to Siegel et al. (*2*) regarding important issues within the Biologic Effects of Ionizing Radiation (BEIR) VII report. This usually means that the authors concur with those contents, or do not find them objectionable. Here are 2 concerns:

1. Both Siegel et al. (*2*) and the National Research Council (*3*) agree that at low doses in the range of 0−100mSv, there are no data supporting the LNT model. BEIR VII uses data to support the LNT model (*4,5*) down to about 20 mSv, but Siegel et al. demonstrate the BEIR VII effort shows the failure of the LNT model in the 0- to 100-mSv range. Duncan et al.'s (*1*) nonresponse to Siegel et al. (*2*) seems a tacit admission of BEIR VII's failure to make a valid claim for linearity in the "low-dose range" of 0–100 mSv.
2. Siegel et al. (*2*) emphasize "at relatively low doses, there is still uncertainty as to whether there is an association between radiation and disease, and if there is an association, there is uncertainty about whether it is causal or not" (*3*). Duncan et al. (*1*) ignore this observation, which is key to their claims about the risks of low-dose CT scans.

More recent understandings of mutations disclose a substantial number of spontaneous, endogenous double-strand breaks (DSBs) (EDSBs), and further studies of the close fidelity of DSB repairs between EDSBs and radiation-induced DSBs (RIDSBs) for low doses/dose rates (as with CT scans) demonstrate that there can be no identifiable, increased CT-induced cancer risk compared with the background risk from spontaneous EDSBs in the whole body. This results from the body's adaptive responses to LDR.

Many CT scans produce doses less than 10 mSv, most are less than 20 mSv, and all are low in the LDR range. For a typical, low-dose CT scan covering 10% of the body, current literature shows that such low doses affect only DNA in a small fraction of cells in the target mass/volume. The RIDSBs from those are only about 3 in 1 million of the spontaneous EDSBs occurring in the body over the same time. Un- or misrepaired RIDSBs from higher doses are about 0.001% of the un- or misrepaired EDSBs in the body over the same time. For an essentially equal repair fidelity of RIDSBs and EDSBs, as discussed previously (*6*), un- or misrepaired RIDSBs are only about 0.0003% of un- or misrepaired EDSBs in the body over the same time. Further, all un- or misrepaired DSBs still require other low-probability events (which are also addressed by adaptive response) to arrive at some cancerous prelude.

Finally, the U.S. government has recently reported that cancer incidence declined by about 1%/y, and cancer mortality declined by about 1.6%/y over recent years, whereas CT usage has expanded, in support of increasing early detection and decreasing cancer mortality. Duncan et al. (*1*) repeat the words that "a threshold requires processes that leave no cells harboring DNA mutations" (*3*). Contradictorily, Duncan et al. (*1*) then cite how DNA errors of EDSB repair can lead to inactivating tumor suppression genes through premalignant lesions. These are obviously background, spontaneous DNA events, and with large contributions of EDSBs harboring DNA mutations, the fallacy of the quotation (*3*) is apparent: large, spontaneous, EDSB backgrounds exist in the body due to its metabolism, environments, and other factors; thresholds exist because LDR stimulates adaptive responses to remove IRDSBs and EDSB backgrounds, an enhanced dose response that reduces the body's inventory of potential cancer precursors.

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Published online Jul. 20, 2018.
DOI: 10.2967/jnumed.118.217984

Radiation Dose Does Indeed Matter: Proof That Invalidates The Linear No-Threshold Model

TO THE EDITOR: In their Invited Perspective (*1*), Duncan et al. "respectfully disagree" with our commentary challenging the Biologic Effects of Ionizing Radiation (BEIR) VII report conclusions (*2*). In it, we demonstrate point by point *and without speculation* that the BEIR committee's conclusions are contradicted even by their own selected evidence. Choosing to ignore the evidence presented, Duncan et al., emphasizing facts that we show to be irrelevant, proclaim their unwavering *belief* in the correctness of BEIR VII's conclusion that the linear no-threshold (LNT) model is valid. Since BEIR VII is a frequently cited source on the legitimacy of the LNT model, a solution to this controversy is crucial.

Duncan et al. repeat arguments made in their previous letter that we have already refuted (*3*). They ignore our refutations that demonstrate the need for reassessment of BEIR VII. In this brief response, we focus on 2 misconceptions [emphasis ours]:

1. ". . .a threshold [for cancer causation] requires processes that leave *no* cells harboring DNA mutations."
2. LNT "remains the best, and certainly the most *conservative*, means of estimating the risk of exposing humans to varied levels of ionizing radiation."

The existence of a threshold for radiation exposure does *not* require that *all* cells with mutations be completely repaired or removed, leaving no cells with mutations. All that is required is that *fewer* such cells be left with mutations after radiation exposure than before, *once sufficient time is allowed for repair and removal processes to take place—usually less than 24 h.* This *decrease* in the baseline mutation rate is the essence of hormesis.

Duncan et al. grant that endogenous processes cause mutations whether radiation—beyond the omnipresent natural background radiation—is present or not. Mutations occur continually throughout our bodies, so the baseline from which radiation operates is not zero mutations, yet some 60% of us never develop clinical cancer. This must indicate there are processes that repair or *remove* cells in which DNA damage could theoretically lead to cancer, a fact that is demonstrated by hundreds of studies (*4,5*). Thus, unrepaired and misrepaired mutations, along with double-strand breaks that exist in the absence of or after low-dose exposure, are *not* sufficient for the development of clinical cancer.

The claim of colinearity across dose ranges characterized by different biologic responses dissociates mathematics from its putative referent in reality. The well-established linearity of the dose response to higher-dose acute exposures (>100 mSv), as noted by Duncan et al. and undisputed by us, is irrelevant to the claim of linearity at lower doses, let alone to the existence or absence of a threshold. Furthermore, there is no credible evidence *at lower doses* of either