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THE NEW RADIOBIOLOGY: RETURNING TO OUR ROOTS

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□ In 2005, two expert advisory bodies examined the evidence on the effects of low doses of ionizing radiation. The U.S. National Research Council concluded that current scientific evidence is consistent with the linear no-threshold dose-response relationship (NRCNA 2005) while the French National Academies of Science and Medicine concluded the opposite (Aurengo *et al.* 2005). These contradictory conclusions may stem in part from an emphasis on epidemiological data (a "top down" approach) versus an emphasis on biological mechanisms (a "bottom up" approach). In this paper, the strengths and limitations of the top down and bottom up approaches are discussed, and proposals for strengthening and reconciling them are suggested. The past seven years since these two reports were published have yielded increasing evidence of nonlinear responses of biological systems to low radiation doses delivered at low dose-rates. This growing body of evidence is casting ever more doubt on the extrapolation of risks observed at high doses and dose-rates to estimate risks associated with typical environmental and occupational exposures. This paper compares current evidence on low dose, low dose-rate effects against objective criteria of causation. Finally, some questions for a post-LNT world are posed.

Key terms: linear no-threshold hypothesis, hormesis, cancer

INTRODUCTION

> "In the space of one hundred and seventy-six years the Lower Mississippi has shortened itself two hundred and forty-two miles. That is an average of a trifle over one mile and a third per year. Therefore, any calm person, who is not blind or idiotic, can see that in the Old Oolitic Silurian Period, just a million years ago next November, the Lower Mississippi River was upwards of one million three hundred thousand miles long, and stuck out over the Gulf of Mexico like a fishing-rod. And by the same token any person can see that seven hundred and forty-two years from now the Lower Mississippi will be only a mile and three-quarters long, and Cairo and New Orleans will have joined their streets together, and be plodding comfortably along under a single mayor and a mutual board of aldermen. There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact."
>
> —Mark Twain - Life on the Mississippi (Twain 1883)

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Current radiation protection philosophy is based on the linear no-threshold (LNT) theory. This theory postulates that any dose of ionizing radiation, no matter how small, causes a finite increase in cancer risk. The LNT theory does not predict any qualitative differences in effects between low doses delivered at low dose-rates (LDDR) and high doses delivered at high dose-rates (HDDR), it does not allow for the possibility that LDDR may decrease risks, and it does not account for nonlinear modifiers of risk. While a majority of radiation scientists believe a threshold model more accurately describes LDDR risks than the LNT model (Silva *et al.* 2007; Jenkins-Smith *et al.* 2009), the opinions expressed by expert advisory bodies are divided. Based in part on epidemiological evidence, the U.S. National Research Council's BEIR VII Committee concluded, "…current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans" (NRCNA 2005). On the other hand, based in part on radiobiological evidence, the French National Academies of Science and Medicine concluded, "…it is not justified to use the linear no-threshold relationship to assess the carcinogenic risk of low doses observations made for doses from 0.2 to 5 Sv since for the same dose increment the biological effectiveness varies as a function of total dose and dose rate" (Aurengo *et al.* 2005).

Other authors have written authoritative histories of how the LNT came to be the current foundation of radiation protection philosophy (Taylor 1980; Kathren 1996; Jones 2005; Calabrese 2009), and it is not the purpose of this paper to recount the details of this history. The important point to note for the current discussion is that the LNT theory has not always enjoyed the dominant status that it has today. Indeed, during the first three decades of radiation regulation, protection standards were based on the philosophy that there was a threshold dose which must be exceeded to induce harmful effects. It was only in the years after World War II that a no-threshold assumption began to take hold. The shift from a threshold based view of LDDR effects to a LNT view has been controversial from the very beginning. This change in regulatory philosophy was due in part to a variety of non-scientific influences (Taylor 1980), and to the advocacy of the LNT theory by H. J. Muller and other like-minded geneticists, in spite of evidence contradicting low dose linearity (Calabrese 2011, 2012). Over the years the topic of biological effects and risks of low doses of ionizing radiation, and how these should be calculated, has developed into the longest running debate in the radiation sciences.

This paper examines the current insights from radiation biology and epidemiology, in particular the body of research from these fields focusing on the biological effects of occupationally and environmentally rele-

vant doses of radiation (*i.e.* typically LDDR). This body of research is critically evaluated against the criteria of causation laid out in a seminal and highly influential classic paper from occupational medicine (Hill 1965) that describes how causation may be differentiated from association when determining the relationship, if any, between environmental factors (*e.g.* ionizing radiation), and disease (*e.g.* cancer).

RETURNING TO OUR SCIENTIFIC ROOTS

The starting assumption, or null hypothesis, in epidemiological (or biological) studies is that there is no association between the putative causative agent (*e.g.* exposure to ionizing radiation) and the observed effect (*e.g.* cancer) (Rothman *et al.* 1998). Should the evidence prove sufficient to reject the null hypothesis in favor of an alternative hypothesis (*e.g.* radiation exposure increases the incidence of cancer in linear proportion to dose), the alternative is accepted in place of the null. It can and has been argued that the lack of an observed association in epidemiological studies between radiation and cancer, especially in populations exposed to LDDR, should not be interpreted as evidence that such an association does not in fact exist (UNSCEAR 2000; Preston *et al.* 2003; ICRP 2005). It is certainly true that one can never conclude that there is absolutely no association, because it can always be argued that a vanishingly weak association may exist but be so small in magnitude that it is undetectable, especially in studies with limited statistical power. However, it is scientifically unsound to extend this argument as the basis for a presumption that carcinogenic risk is increased by LDDR radiation exposure, even at doses and dose-rates far below where such risks have actually been observed, simply because an absolute absence of any association whatsoever cannot be demonstrated. This line of reasoning inappropriately shifts the burden of proof to the null hypothesis (no effect), and creates a well-known logical fallacy (Walton 1999) because it is impossible to prove a negative assertion. To assert that LDDR increases cancer risk simply because it is impossible to prove that it does not is an untestable argument, and therefore it is contrary to accepted scientific method (Popper 1959). The burden of proof is appropriately placed on the alternative hypotheses predicted by the LNT theory. The same burden of proof must be borne by any other alternative hypotheses *e.g.* hormesis, supra-linearity, *etc.*

Advocating *for* any particular alternative hypothesis and defending it against challenges is diametrically opposed to the scientific method. Rather, the responsibility of scientists is to vigorously attempt to *disprove* hypotheses predicted by particular theories. It is only by failing to disprove the hypotheses of a given theory after repeated attempts that it gains some measure of credibility. It is worth remembering that no theo-

ry – whether it is hormesis, LNT, or any other – can ever be proved. It can only fail to be disproved (Popper 1959).

HILL'S CRITERIA OF CAUSATION

In 1965, Sir Austin Bradford Hill delivered an address to the British Royal Society of Medicine's newly formed Section of Occupational Medicine (Hill 1965). The purpose of Hill's address was to address the questions,

1. "How in the first place do we detect these relationships between sickness, injury and conditions of work"?
2. "How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized"?
3. "…we see that in the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?"

Hill proceeded to lay out several criteria by which causation could be distinguished from simple associations between factors in the occupational environment and adverse health impacts. The current paper evaluates the body of evidence related to LDDR and carcinogenesis against Hill's criteria. Hill was careful to note that he was describing a weight-of-the-evidence approach, stating,

> "Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (Hill 1965)

Before proceeding with this evaluation, it is worth discussing some of the underlying premises. First, an evaluation via Hill's criteria of whether or not LDDR causes cancer presupposes that an *association* between LDDR and cancer has been observed. This is a very debatable supposition. While very few scientists would argue against an association between

HDDR exposures and increases in cancer risk, there is a growing body of radiobiological evidence that the biological mechanisms initiated in response to LDDR are qualitatively different than those initiated in response to HDDR (Amundson *et al.* 2003; Ulsh 2010; Neumaier *et al.* 2012). This calls into question the logic of treating LDDR as a lesser degree of HDDR, and extrapolating from HDDR effects which can be observed, to predict effects of LDDR which are not in evidence. To proceed with the current evaluation, suffice it to say that at least a few epidemiological studies claim to observe an association between LDDR and cancer. Given these claims, how strong is the evidence that LDDR *causes* cancer? This is the subject of the current paper.

1. STRENGTH

The first of Hill's criteria is the strength of the association. Stronger associations (*i.e.* larger effects per unit dose) are more convincing than weaker ones. Though some have claimed adverse health risks from acute doses as low as 10 mGy (Brenner *et al.* 2003), the general consensus is that the lowest dose at which increases in cancer risk are consistently observed is approximately 50-100 mGy for acute doses, and 100 mGy for chronic exposures (HPS 2010). Given that the annual background dose-rate in the United States is approximately 6.2 mSv (NCRP 2009), this means that chronic doses even 16 times higher than background fail to cause an observable increase in cancer risk.

As an example, consider the most widely cited study of a radiation exposed population, the Life Span Study (LSS) of the survivors of the atomic bombings in Japan. Studies of this cohort form much of the basis for contemporary radiation standards. Among the 105,427 Japanese survivors of the atomic bombings of Hiroshima and Nagasaki studied in the LSS, there were 17,488 solid cancers as of 1998 (Preston *et al.* 2007). This compares with an expectation of 16,595 solid cancers in the absence of radiation exposure in this population, yielding an excess of 893 solid cancers which the authors attributed to radiation exposure. Roughly speaking, this is an overall excess of $(893/16{,}595) \approx 5\%$ in this population. Compare this with the health impact of smoking. According to the U.S. Surgeon General, smoking causes 443,000 deaths in the United States each year (Benjamin 2010). That means 20% of the total number of deaths occurring in the U.S. each year are attributable to cigarette smoking. This comparison is presented here simply to demonstrate that ionizing radiation, even at high doses and dose-rates, is a relatively weak carcinogen.

2. CONSISTENCY

This criterion is generally defined by Hill as repeatability, or generality. Associations are more convincing if they have been observed on

numerous occasions, under different circumstances, and by numerous researchers. Ionizing radiation is one of the most exhaustively studied and easily measured carcinogens, and thousands of studies of occupational and environmental exposure situations have been conducted. Findings on LDDR exposures and cancer risk have consistently failed to show an association with cancer, with a few claimed exceptions. Only a few epidemiological studies have claimed to observe an association between LDDR and increased cancer risk *e.g.* (Cardis *et al.* 2005; Krestinina *et al.* 2005).

Extrapolation from higher doses to estimate low doses is employed because epidemiological studies of occupational cohorts exposed to ionizing radiation frequently reveal cancer rates that are *below* those of the general population, and/or no dose-response relationship is observed when exposed workers are compared to unexposed workers in the same cohort. This is almost always axiomatically attributed to the healthy worker effect (Monson 1986), without any consideration of plausible alternative hypotheses (*e.g.* radiation hormesis) (Fornalski *et al.* 2010). This is a discussion for another paper.

The most parsimonious explanation for the rarity of epidemiological observations of a change in risk at low doses is that LDDR has no effect on risk. Alternatively, this may simply reflect a lack of power to detect effects at low doses and dose rates, even if such effects exist. The inability to distinguish between these two alternatives is a fundamental limitation of the top-down, epidemiological approach (Land 1980; Brenner *et al.* 2003). Accounting for confounding factors (*e.g.* smoking, excessive alcohol consumption, obesity, etc.) can also be challenging. The result is that epidemiological approaches are limited in their ability to provide support for one hypothesis of LDDR risks (*e.g.* LNT) and exclude competing alternative hypotheses (*e.g.* threshold, hormetic, or supra-linear dose responses) at the environmental and occupational doses and dose-rates with which we are typically concerned. Furthermore, most epidemiological studies are designed to detect only increases in risk, and they ignore the possibility of radiation-induced suppression of cancer in spite of a wealth of biological evidence to suggest this as a possibility. These design characteristics include reporting excess relative risk (ERR) which does not account for risk decrements, assigning individuals exposed to low, possibly protective doses as the control group (which artificially inflates risk estimates), discarding significant fractions of the received dose (*i.e* lagging), even though this is inconsistent with the LNT theory, binning doses over wide intervals [which camouflages departures from linearity (Scott 2011)], and including only recorded external dose when subjects were potentially exposed to doses from internally deposited radionuclides as well, or vice versa (*e.g.* almost all uranium miner studies). These limitations must be balanced against the inherent strength of epi-

demiological studies - they directly observe the endpoint of interest (*i.e.* frequency of cancer, or some other health effect in exposed human populations), and no extrapolation from putative surrogate endpoints of risk (*e.g.* chromosome aberrations or mutations) is required. However, it is worth noting that some biological studies show that LDDR delays the onset of cancer, rather than changing the frequency of cancer *e.g.* (Mitchel *et al.* 1999), and most radiation epidemiology studies do not explicitly look for this effect.

To get a more complete picture of the effects of LDDR, we must turn to radiation biology to fill in some of the missing pieces. While radiation epidemiology focuses on the top of the biological hierarchy (*i.e.* human populations), radiation biology studies take a bottom-up approach, typically focusing on lower levels of biological organization – from biologically relevant molecules (*e.g.* DNA) to individual organisms (*e.g.* mice). The fundamental strengths of this approach are that exquisite control of potential confounding factors can be exercised and high precision and power to detect small effects can be achieved. These strengths must be balanced against the fundamental limitation of radiation biological approaches – relating surrogate endpoints (*e.g.* DNA double strand breaks, chromosome aberrations, mutations, DNA repair foci, *etc.*) to effects we really care about (*e.g.* cancer) is not straightforward. Extrapolating risks from species typically studied in the laboratory (*e.g.* mice, rats, *etc.*) to humans adds another layer of uncertainty (NCRP 2005).

Radiation biological studies have frequently observed non-linear dose-response relationships between LDDR and various biological endpoints. So how general are these nonlinear phenomena? If they are "boutique" phenomena *i.e.* they are only observed in very specific and unrealistic situations created in the laboratory, then they are likely to have limited applicability to real-world situations. On the other hand, if they are widely observed in various species, in response to various stressors, and under different conditions, the case for causation would be bolstered. Consider, for example, adaptive responses. This phenomenon has been observed in algae (Boreham *et al.* 1993), yeast (Boreham *et al.* 1994), insects (Schappi-Buchi 1994), frogs (Audette-Stuart *et al.* 2011), mice (Mitchel *et al.* 1999; Mitchel *et al.* 2002; Boreham *et al.* 2006; Day *et al.* 2007; Singh *et al.* 2011), rabbits (Liu *et al.* 1992; Cai *et al.* 1996; Flores *et al.* 1996), cows (Flores *et al.* 1996), deer (Ulsh *et al.* 2004), fish (Smith *et al.* 2011) and humans (Broome *et al.* 2002).

The generality of hormesis has also been questioned (Thayer *et al.* 2005), based in part on the frequency of this dose-response phenomenon, and a putative assumption that such responses are universally beneficial. The more than 1250 references cited in (Luckey 1980), the more than 1000 references cited in (Luckey 1991), and other broad evaluations

of the frequency of hormetic dose-responses (Calabrese *et al.* 2006) offer a certain level of confidence that this is a widely observed phenomenon. Hormesis has been observed in disparate fields including toxicology, biomedical sciences, and psychology, in addition to radiation biology (Calabrese 2008). Radiation hormesis is typically observed over an acute dose range spanning roughly a few mGy up to several tens of mGy, and up to a few hundreds of mGy for low dose-rates, depending on the endpoint considered. On the other hand, a linear dose-response is typically observed at higher acute doses – from several tens of mGy up to a few hundred mGy. While HDDR exposures indisputably increase cancer risk, LDDR exposures consistently fail to do so even at doses 5-10 times background, and LDDR frequently decreases the frequency of surrogate endpoints associated with carcinogenesis.

3. SPECIFICITY

The importance of this particular criterion should not be overestimated. As Hill stated, "…if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence". The question is, are there unique, specific effects that appear to be associated with the putative causative agent?

While the relationship between radiation and cancer is not as specific as, for example, asbestos and mesothelioma – there are many other causes of cancer - there is a well-established relationship between HDDR and some (but not all) forms of cancer. Comprehensive reviews of the association between ionizing radiation exposure and various site-specific cancers have been published (Boice *et al.* 2006; UNSCEAR 2006; Mettler *et al.* 2008), and there is reasonable consensus that some forms of cancer are associated with ionizing radiation exposure, particularly HDDR, and others are not. There is consistent or strong evidence of an association between HDDR and cancers of the female breast, colon, esophagus, leukemia (excluding chronic lymphocytic leukemia), liver, lung, ovary, salivary gland, stomach, and urinary bladder. On the other hand, there is little or no consistent evidence of an association between HDDR and chronic lymphocytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma or cancers of the gall bladder, larynx, male genitalia, oral cavity, pancreas, pharynx, prostate, skin (squamous cell carcinoma and malignant melanoma), small intestine, and uterus. The evidence for radiogenicity of bone and kidney cancers is limited to high doses characteristic of radiotherapy and injection of bone-seeking a emitters. There is little evidence suggesting a relationship at low to moderate doses typical of the occupational or environmental exposures. In the case of brain cancer, there is evidence of radiogenicity only for benign tumors, especially meningioma and neurilemmoma. There is little evidence of an

association between ionizing radiation exposure and malignant brain tumors. There is little evidence of radiogenicity of rectal cancer at low to moderate environmental or occupational doses. The evidence for an association is stronger at very high doses (tens of Gy). The evidence for radiogenicity of basal cell carcinoma (BCC) of the skin is more complicated. There is strong evidence of an association between basal cell carcinoma and ionizing radiation exposure received at young ages. The strength of association with exposures declines with increasing age. The evidence of radiogenicity of thyroid cancer is similarly limited largely to populations exposed as children. In summary, while there is evidence of associations between HDDR and some specific forms of cancer, the same cannot be said of LDDR exposures.

4. TEMPORALITY

Is the observed effect preceded in time by exposure to the putative causative agent? Hill notes that this criterion might be especially important in diseases of slow development. If essence, this criterion deals with identifying whether the environmental factor of interest is the cause of the adverse health effects, or the result. It is certainly the case that HDDR causes subsequent peaks in cancer incidence years after the exposure occurred (*e.g.* in the Japanese survivors of the atomic bombs), and this speaks directly to the temporality criterion. One obvious application of this criterion would be in evaluating evidence from medically exposed cohorts *e.g.* is any subsequent increase in cancer incidence a result of the medical exposure, or does an underlying susceptibility to cancer make medical exposure more likely. It is less obvious how any health effect might make LDDR exposure more likely, therefore this criterion would not seem to be particularly informative for this situation.

5. BIOLOGICAL GRADIENT

Hill asserts that demonstration of a dose-response relationship, particularly a simple relationship (*e.g.* a linear, no-threshold) greatly adds to the weight of the evidence in favor of a causative relationship. The problem, as discussed throughout this paper, is that LDDR exposures appear to elicit qualitatively distinct responses from those associated with HDDR. Very low doses of radiation exhibit nonlinear dose-responses. One of the defenses of the LNT theory is that it is simple. But simplicity at the expense of realism is no bargain. While a simple, LNT dose-response would be more convenient and would strengthen the case for LDDR causation of cancer, LDDR exposures in fact appear to result in complex and nonlinear responses.

6. PLAUSIBILITY

Causation is more convincingly indicated when observed associations *e.g.* in epidemiology studies, are consistent with biological knowledge. Hill cautions that this criterion cannot be demanded as a condition of causation, as a lack of a plausible explanation may simply reflect the shortcomings of the state of biological knowledge. But this criterion represents one of the most significant challenges to the LNT model. The LNT theory is predicated on the notion that since radiation damages cells in a fashion linearly dependent on dose, subsequent carcinogenesis should also be linearly dependent on dose (NCRP 2001). However, this theory takes no account of intervening biological mechanisms for maintaining homeostasis, many of which have been shown to be nonlinear with dose. As evidence continues to accumulate that biological responses to LDDR are nonlinear, the plausibility of the LNT theory continues to erode.

7. COHERENCE

Interpretation of epidemiological data should not conflict with the known natural history of the disease in question. For example, the rise in lung cancer rates with the smoking rate supported the conclusion of a causative relationship. Due in no small part to the effectiveness of a safety culture in nuclear and radiation applications, HDDR is generally limited to very discrete situations (*e.g.* radiotherapy, nuclear warfare, etc.). It would be difficult to determine the concordance between cancer rates in general, and HDDR exposures in particular since only small, discrete segments of the population are exposed to HDDR. On the other hand, population exposures to generally low-dose, but high dose-rate exposures in medical applications is increasing (NCRP 2009), and there is much debate about the risks, if any, that this poses (Scott *et al.* 2008; Brenner *et al.* 2011). It will be very informative to see whether or not an increase in cancer frequency - predicted by the LNT theory – actually materializes as a result of increased medical exposures among the general population. The lack of such an increase would seem to put the LNT theory at odds with the coherence criterion.

8. EXPERIMENT

Experimental evidence greatly strengthens the case for causation. There is a solid body of experimental evidence showing that HDDR, but not LDDR, increases the frequency of several experimental endpoints thought to be involved in the chain of events leading to eventual carcinogenesis. The frequency of chromosome aberrations as measured by chromosome painting techniques is clearly increased by doses of 1 Gy or higher delivered at high dose-rates (1.3 Gy min^{-1}) (Loucas *et al.* 2001).

Even at these high doses and dose-rates, nonlinear dose-response curves were observed. However, while this endpoint shows great promise, improvements in technique would enhance its utility for detecting LDDR effects (Tucker 2008). Studies of cell transformation reveal that HDDR (doses greater than 100-200 mGy delivered at dose-rates of 30-3000 mGy min^{-1}) increases transformation frequency, while LDDR reduces transformation frequency below spontaneous levels *i.e.* this model system follows a typical hormetic dose-response curve (Redpath 2006; Redpath *et al.* 2007; Elmore *et al.* 2008). Radiation-induced mutations have also been shown to follow nonlinear, hormetic dose-response models (Kelsey *et al.* 1991; Zeng *et al.* 2006; Day *et al.* 2007). Cells exposed to LDDR frequently undergo apoptosis, and LDDR also induces apoptosis in spontaneously damaged cells (Bauer 2007), suggesting a hormetic mechanism. A variety of immune system parameters associated with cancer suppression are improved by LDDR, providing another hormetic mechanism (Nowosielska *et al.* 2006; Liu 2007). These are just a few examples of recent radiobiological evidence that is increasingly inconsistent with the LNT theory, and frequently reveal threshold or hormetic responses to LDDR exposures. Reviews of additional examples have been published by many authors (Cohen 2008; Scott 2008a; Averbeck 2009; Tubiana *et al.* 2009; Sanders 2010; Ulsh 2010).

9. ANALOGY

The analogy criterion suggests that the weight of the evidence for causation is strengthened if other agents have been identified that induce a response similar to that observed following exposure to the agent in question. There are many other chemical and physical agents that induce an adaptive response and/or nonlinear dose-responses similar to that observed following LDDR exposure. Chemically-induced effects frequently follow a hormetic or threshold dose-response (Calabrese *et al.* 2006; Calabrese *et al.* 2008; Calabrese *et al.* 2011). Hyperthermia also induces an adaptive response similar to that induced by LDDR (Boreham *et al.* 1997). Exposure to low levels of some metals induces a radioadaptive response (Cai *et al.* 1996; Cai *et al.* 2000; Cai *et al.* 2004), as does exposure to low levels of hydrogen peroxide (Dominguez *et al.* 1993; Flores *et al.* 1996). Indeed, in studies with study designs capable of detecting it, hormesis is a relatively commonly encountered dose-response relationship across diverse environmental agents (Calabrese 2009), while low-dose linearity is rarely observed but rather is frequently an artifact of extrapolation from high doses to low.

STRONG INFERENCE

By combining the insights from top-down, epidemiology approaches and bottom-up, biology approaches, a more complete picture of LDDR

effects based on the total weight of the combined evidence can be gained (Clarke 1999). Hill's criteria (Hill 1965) provide an objective and organized framework for evaluating the weight of the evidence on cancer causation by LDDR. This evaluation has revealed that the case for LDDR causation of cancer fail to satisfy these objective criteria, while hormesis and threshold models have a much more compelling weight of the evidence behind them.

In his seminal 1964 article, Platt observed that some fields of science were advancing rapidly, while others seemed to stagnate (Platt 1964). He attributed the success of certain fields (*e.g.* particle physics and molecular biology) to the rigorous strategy of testing multiple hypotheses, and iteratively designing experiments to exclude particular hypotheses – a strategy he referred to as "strong inference". On the other hand, the lack of progress in other fields was a result of failure to continuously and iteratively test hypotheses and a retreat to the tedium of repeating similar experiments over and over again without any thought to advancing the state of the knowledge.

Unfortunately, the LDDR debate frequently devolves into warring camps of scientists advocating particular hypotheses (*e.g.* LNT, threshold, or hormesis), and accusations of selective data interpretation fly from all sides. Advocacy of particular theories has inappropriately supplanted healthy scientific skepticism, hypothesis testing, and robust application of the scientific method. The main purposes of this paper were to evaluate the current state of knowledge on LDDR effects, to issue a call for a return to "strong inference" (Platt 1964) and an abandonment of advocacy of particular theories of LDDR effects by the scientific community. Indeed, advocating any theory, instead of vigorously attempting to disprove it, is contrary to the scientific method and leads inevitably to the stalemate and acrimony that characterizes the current state of LDDR sciences. It is time to move beyond the LNT debate.

QUESTIONS FOR A POST-LNT ERA

Once a consensus that biological responses to LDDR are nonlinear is widely acknowledged, the scientific community can refocus on more productive avenues of inquiry instead of devoting its collective efforts and resources on trying to make nonlinear data fit LNT theory. Some questions that could be addressed include:

1) What is the relevance to organism and population level effects of the *in vitro* nonlinear phenomena (*e.g.* induced hyper-radiosensitivity, genomic instability, bystander effects, adaptive response) that appear to dominate biological responses to low dose, low dose-rate exposures?

2) How general are *in vitro* nonlinear phenomena? Are there conditions (*e.g.* exposure protocols, cell lines, cell cycle status, etc.) where these phenomena are not observed?
3) Do nonlinear factors such as bystander effects and induced genomic instability increase or decrease cancer risk? Or is the situation even more complex than this question suggests? How relevant are these phenomena in *in vivo*?
4) Are alternative dose-responses (*e.g.* threshold, hormetic, supra-linear, etc.) inconsistent with epidemiological studies of populations exposed to low dose, low dose-rate exposures? If epidemiological studies lack the statistical power to select one alternative hypothesis and exclude plausible competing hypotheses, then the null hypothesis stands (*e.g.* no detectable effects). If this is the case, over what range of doses and dose-rates are effects ("positive" or "negative") observed? How consistent are these ranges across different endpoints, cell-types, tissues, and organisms?
5) Epidemiological practices such as dose-lagging, where doses received for a period immediately prior to the diagnosis of cancer are disregarded, should be re-examined in light of current mechanistic knowledge. Lagging has been justified on the basis of observations that cancers tended to appear in waves some years after discrete, acute exposures (*e.g.* in the LSS cohort). But does lagging make sense in the context of LDDR, where activation of various biological defense mechanisms is the norm in the hours following exposure or even while chronic exposure is still occurring? Throwing away dose tends to inflate estimates of risk per unit dose, and to obscure the existence of thresholds.
6) What interactions (*e.g.* synergism, antagonism, etc.), if any, occur between LDDR radiation and other common environmental stressors (*e.g.* hyperthermia, heavy metals, organic toxicants, etc.)?
7) There is some suggestion that LDDR can actually prevent lung cancer among high risk groups (Scott 2008b; Scott *et al.* 2009). There is also evidence that LDDR can improve cancer control rates (Sakamoto *et al.* 1997). The prophylactic effect of LDDR could have clinical significance, and should be investigated.
8) There is also evidence that radon can inhibit inflammation (Franke *et al.* 2000; Kataoka *et al.* 2012), and protect against hepatic and renal damage (Kataoka *et al.* 2011). The clinical efficacy of radon therapy for such conditions should be considered against a realistic and accurate (*i.e.* not derived from extrapolation of HDDR exposures) assessment of any risks from the radon exposures involved in such treatments.
9) What radiation protection strategies make sense in a post-LNT world?

These are just a few of the relevant questions we could be addressing if we collectively decided not to cling to increasingly dubious and outdated theories of linearity. Explicit experiments designed to narrow the field of plausible alternative hypotheses should be designed and rigorously tested. Moving beyond the LNT debate promises to open exciting and productive avenues of scientific research and provide defensible strategies for the protection of workers, the public, and the environment.

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