LNT THEORY: A CREDIBLE MIDDLE GROUND?

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Abstract: This presentation will summarize pros and cons of the debate which has been proceeding in the radiation protection community concerning the 'correctness' of the linear-no-threshold (LNT) theory. We shall summarize in general terms the discussions at three recent international meetings where the topic has been discussed: IAEA/WHO meeting in Seville (November 1997) on Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control; the Pacific Basin Nuclear Conference (Banff, May 1998); and the American Statistical Association (San Diego, June 1998) "Radiation and Health" meeting, this year on the topic Radiation effects at low doses. The issues are complex. Specific impressions will be provided from each meeting on how the debate is proceeding, and some general conclusions drawn.

INTRODUCTION & SUMMARY OF POSITIONS

The following two paragraphs summarize the main arguments in the debate about the appropriateness of the LNT theory for radiation risk assessment, and serve to provide context for our summary remarks on meetings where the "LNT or not LNT—that is the question" issue has been debated.

The anti-LNT side, as evidence that risk at low doses has been overestimated, cite: *DNA repair* capability as a powerful force eliminating potentially dangerous damage initially formed following deposition of radiation energy; possible *hormetic effects* of ionizing radiation, whereby a radiation exposure may result in overall benefits (for "all causes" of cancer-initiating or cancer-promoting events) offsetting or outweighing any small, associated ionizing radiation-specific detriment; and *protective effects* of low dose exposure, inferred from observations of standard mortality ratios (SMRs) of less than one for cancer in populations living in or occupationally exposed to enhanced radiation and from experiments ("adaptive response") with cultured cells. As well, they point to: the 'small number' of radiation-induced DNA damage events compared with those which occur spontaneously, which means that insults from ionizing radiation add but little to the totality of DNA damage; the multistage nature of the radiocarcinogenic process, which means that several 'hits' are required; and inequities with the collective dose concept, especially in relation to costs for protection.

Supporters of LNT cite: the indisputably linear nature of low dose damage at the DNA level, especially for genetic changes; evidence that even a single track has a finite, non-zero probability of inducing a complex lesion which is inherently difficult to repair; that DNA repair seems not ever to be "100%" effective (induced genetic changes are evidence of this); and the ever-firmer evidence of excess fatal cancers (and, increasingly, of other adverse effects on health) from acute exposures, even for fairly low doses. LNT'ers recognize the inability of epidemiological studies on relatively small populations ever to provide sufficient information at low doses to answer the LNT question one way or the other, owing to statistical limitations, but they also note that in some cases where the background is very low—for example, on studies with children or on those exposed *in utero*—a significantly elevated risk can be identified at very low doses, even at 10 mSv. This side points out that the uniqueness of some of the damage (*i.e.*, double-strand breaks) induced by ionizing radiation, compared with that from other carcinogens or to 'spontaneous' damage, makes comparison of 'relative numbers' moot, and agrees that the collective dose concept should not be used for predicting long-term effects but point to its usefulness

as a tool for making radiation protection decisions. (Guidance has in fact been provided by international committees against misuses of the collective dose concept across vast strata of individual doses without some form of discounting the implied detriment.) Supporters of LNT also note: that radiation just provides an 'extra push' to steps in carcinogenesis which proceed anyway for other reasons, thereby implying linearity with any dose; confusion between "the lowest dose at which a statistically significant increased risk is seen" and what guidance is reasonable at doses lower than this; and that high costs mandated for radiation protection are not due to LNT *per se* but rather to the "dread" factor .

Proponents of these two sides in the LNT debate tend to be largely from within the radiation protection community, and sometimes forget that a third constituency exists, which is very active. This third side is not represented in the summary arguments above, and constitutes those who believe (and provide some defensible arguments in support) that radiation risks have been under-estimated, including those for low doses and low dose rates. Recent developments, including the phenomenon of *genomic instability*, bolster their case. This group may well have the ear of media and politicians, and represent the public, to a greater extent than the radiation protection community envisages.

THE "SEVILLE CONFERENCE"

The World Health Organization (WHO) and International Atomic Energy Agency (IAEA) held a conference in Seville, Spain (in November 1997) on **Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control**. The conference was held with the intention of taking stock of new advances in molecular genetics and cellular biology and of new epidemiological findings, to see what implications these might have for regulations in radiological protection. The meeting certainly provided a good overview of the main research areas that support radiation protection and of the approaches taken and issues that arise in regulatory practice. But we feel that more time could have been devoted to discussion of the controversy over whether the linear-no-threshold (LNT) theory is an appropriate model for what is happening biologically compared to its being a basis for regulation: these are distinct issues, something that is often missed. In the LNT debate there seems to be a tendency for some proponents on both sides to take it as self-evident that their particular views are correct. While strong arguments and rebuttals could often have been made to misinterpretations or misrepresentations, they were not; this is unfortunate, as the debate is sufficiently complex that we need to identify and agree upon just what issues are important and which lines of debate can be dispensed with. We had the sense that views by some on both sides of the debate are captured in the quotation of Werfel's with which we opened our oral presentation:

"For those who believe, no explanation is necessary,
while for those who do not believe, no explanation is possible."

A consequence is that one can expect to hear some reports so widely variant that one may wonder if everybody attended the same meeting. The LNT debate will not advance, and will not be resolved, as long as we have "two solitudes"; worse, we may find our debate co-opted by those in the third constituency, who maintain that radiation risks are in fact greater than present radiation protection regulations allow for.

As unbiased an assessment as is reasonably achievable is needed of the strengths and weaknesses of both sides of the debate. This is especially important as many persons don't have the

background or the knowledge to judge expertly for themselves the validity of various claims. One of the factors in risk communication which is most apt to lead to concern and uncertainty is "apparent disagreement among experts". If we proceed by emphasizing too much the uncertainties inherent in risk estimates, especially for low doses, we run a concomitant risk of appearing to outsiders to diminish the very real strengths of radiation protection principles and practices.

In *molecular mechanisms of radiation effects*, there is renewed speculation about the significance of genomic instability (GI), whereby cells accumulate mutations at accelerated rates or at times long after exposure. The significance of these events to radiogenic cancer was only speculative at the time of this meeting. There is evidence that radiation can give rise to GI. The belief is that radiogenic cancers progress in the same way as spontaneous cancers; molecular evidence supports the monoclonal origin of cancer—that almost all cancers are the progeny of a single cell that underwent a first mutation and subsequently accumulated others. Cancer does not appear to progress by the "domino effect" suggested by the GI hypothesis.

There is evidence that a single alpha transit through a cell can cause the kind of damage thought to be important in cancer initiation (double strand breaks in DNA together with complex accompanying molecular damage). Mutations which resulted (usually large deletions, compared to the small deletions usually found to be characteristic of spontaneous mutations) clearly seemed to follow the linear relationship between dose and effect.

Ecological epidemiological studies are of very limited value because they cannot address "confounding" at the individual level, which is the only level at which it can properly be addressed. Ecological studies are not going to shed light on mechanisms and models. Ecological studies are most useful as "hypothesis generators". Thus while an ecological study of lung cancer and radon levels in various US counties can ostensibly address the question of the LNT hypothesis, it fails because regional-level data on possible confounders—cigarette smoking, for example, a major factor in lung cancer—cannot be used to correct for cancers which are a phenomenon at the level of the individual.

The phenomenon of *adaptive response* has been demonstrated for priming doses in the range 5-100 mSv, with radiation resistance being induced for challenge (i.e., subsequent) doses in the range of 0.5 - 3 Gy. The adaptation persists for a few days; it is reduced by repair inhibitors and by protein synthesis inhibitors. It is not clear what the implications are for survival and cancer in whole animals. Adaptation has not been found in all biological systems, or in all donors; genetic disposition is likely to be an important variable. *There is no evidence of its influence on radiogenic cancer induction.* There is a window for any adapting dose that is narrow in time and value. Small increments in doses distributed randomly would have a low probability of hitting this window. Several epidemiologists noted that the doses received by nuclear industry workers in what are relevant periods were below the values of priming doses observed for the phenomenon, and were not, in any event, followed by large, challenge doses. It wasn't clear therefore, whether an adaptive response would be relevant to risk assessment or to radiation protection.

The overall conclusion was that adaptive response is relatively reproducible, is a laboratory phenomenon for which the best evidence is at the cellular level, and that well-defined experimental conditions are needed for it to be observed. There is a dependence on the cell system and genetic disposition. The mechanisms are not well understood. It has not been

demonstrated as affecting radiogenic cancer. There is a need to discover more about the evolutionary development of repair. Now, the practical significance is not clear.

Hope is growing that it may be possible in future to identify a *genetic fingerprint* of radiogenic change. The majority of radiation-induced changes in DNA are large deletions, often extending to adjacent genomic regions. In contrast, about one-half of spontaneous changes are small (point mutations), the remainder representing both small and large deletions, the latter being mostly within the gene proper.

A point to bear in mind when one hears claims of "*genetic effects* in persons exposed to enhanced radiation" is that the genes in most experimental systems are non-essential for survival or are in genomic regions which can be deleted without loss of viability. A mutation rate obtained from such systems cannot be applied to all disease-causing processes in man.

In the sessions on *epidemiology*, several speakers disagreed with statements that it is impossible to learn about low doses from epidemiology: difficult maybe, but not impossible. Epidemiology is the study of the distribution and determinants of disease in actual human populations: a point often insufficiently appreciated is that as epidemiology is conducted on humans, we don't have to extrapolate from rats, mice or cells in culture. It is necessarily observational rather than experimental.

Detecting effects from 1 cGy would require one million people in the study population. Such study population sizes are never available, whether for nuclear industry workers or residents in high natural background areas. Therefore negative results don't mean there is no effect but quite likely that we couldn't identify it.

Epidemiologists acknowledge that for radiation risks of societal concern (low doses at low dose rates) we have so far been unable to quantify (either to establish or deny) risk adequately. The study by the International Agency for Research on Cancer of mortality from cancer in nuclear industry workers actually yielded a slightly negative estimate for radiogenic solid cancer, but its upper confidence interval was also consistent with risk being even higher than in the Japanese A-bomb survivor study. New cohorts have been identified, and studies are in progress, that may address this low dose/low dose-rate question better. These are mainly from the former Soviet Union, and include Chernobyl (both the clean-up workers and people who resided in the vicinity), the Mayak reprocessing plant workers, residents along the Techa River, Kazakstan nuclear test site residents, and further studies of aircrew (where the vexing problem is who should be a control, comparison group).

In a session on *radiobiological issues in the application of epidemiological evidence*, it was noted that when ICRP decided to link risk estimates to dose limits, it embarked on a course unlikely to ever be reversed. Prior to the study of the Japanese cohort, most of the data available for risk assessment involved exposures which were large and non-uniform. In contrast, the data from Hiroshima and Nagasaki were more uniform and offered the possibility of detecting risk at lower doses. The most recent update of cancer mortality in the A-bomb survivors by the Radiation Effects Research Foundation (RERF) was able to show elevated risk down to about 50 mSv (though this point is still debated, and the question of to what degree excess cancers in the cohort may be related to neutrons perhaps remains), and a second powerful study—that of fetal irradiation—shows significant excess risk at 10 mSv. The non-threshold model certainly does have an observational basis.

While studies of irradiated animals generally provide curvilinear responses, the RERF workers contend a linear response fits better (others would say, "at least as well"). ICRP used this linear model, and then applied a DDREF = 2 for low dose, low dose-rate, exposures. There has been criticism of this 2-step procedure from both sides: one side points out that while the first step is quantitatively-based, the extension changes this; and the other side says that the DDREF mandated by ICRP should be larger. (For leukemia, which has a linear-quadratic dose dependence, the cross-over dose of about 1 Gy corresponds roughly to a DDREF = 2.) The ICRP maintains that a value of 2 is the largest factor compatible with the A-bomb population data for solid tumors but still fully compatible with the leukemia data.

There is a lot of concern about the results of distance-dependent discrepancies in thermal neutrons at Hiroshima. Committees deliberating this have yet to make a decision, but it appears the Straume estimates should not be taken at face value. While there are likely going to be changes announced in doses, this will likely be to increase the gamma doses by only some 10-12%. And if neutron doses were revised upwards, the largest effect would be at small doses; this is because the 'correction factor' becomes larger as distance from the hypocentre increases.

To a claim that "LNT is obviously false, there is overwhelming evidence from both humans and animals, and that insufficient radiation is killing hundreds of thousands each year [this inferred from a study of cancer SMR's <1 in ARW's, with the implication that they were protected from cancer by their occupational radiation]", there was little agreement, but incredulous disagreement, voiced. The idea that we should all receive "safe radiation supplementation" of 10-100 mSv each year was a very hard sell.

The Chief of Epidemiology at the Radiation Effects Research Foundation in Hiroshima remarked that it is unfair and misleading to characterize the RERF's *life-span study* (LSS) of the Japanese bomb survivors as a high-dose study, because it is in fact one of the largest low-dose cohorts in the world, exceeded (in person-Sv) only by the IARC study for doses of 0.2 Sv and below. (But, it certainly is a high dose-rate study.) The LSS results support a linear dose response for mortality from solid cancer. Moreover, in tests about linearity, they do not provide any strong evidence against linearity. There is some evidence of a somewhat lower slope at low doses in the cancer incidence data, i.e., a possible linear-quadratic fit, but this is similar to what the application of a DDREF in radiation protection recognizes.

What is agreed is that the LSS results do not provide direct data on low dose/low dose-rate exposure. The cohorts likely to be valuable in this regard are: the next IARC pooled worker study; the Mayak Workers; the Techa River residents; and residents in the East Urals Radioactive Trace (from the 1957 Kystym accident). These had been identified earlier in this meeting in the same context. Doses for persons in these cohorts have been appreciable. The Mayak facility had about 8000 workers who received some 2 Gy exposure annually during 1948-53. For the Techa River cohort, the doses were fairly high (marrow doses average 1 Gy within the first 70 km downstream) but delivered at low dose rate (over about three years, then they were evacuated). Thus the cohort (about 28,000 persons, about 60% women) has high statistical power, a long time for follow-up (for effects to develop) but chronic exposure. They provide a good opportunity to learn about low dose rate risks.

Studies of *prenatal exposure and childhood cancer* were extensively reviewed. A dose of 10 mSv to the fetus is associated with a relative risk of 1.4 for childhood cancer. (Note: although 10

mSv thus adds 40% to childhood cancer risk, this is a small risk in absolute terms. The normal rate is 1 cancer in 600 for age 0-15; 10 mSv exposure makes this only 1.4 in 600). Any threshold of greater than 5 mGy can be conclusively ruled out by the data. Possible objections to causality were addressed and refuted. For the strongest of these dissensions—that children irradiated *in utero* from the A-bombs do not show comparable risk of leukemia, though solid cancer risk increased—the explanation was thought to be that a few cases were missed because follow-up did not commence till 1950.

Some studies from Nagasaki School of Medicine, in which it was claimed that there were significantly fewer non-cancer deaths at low doses in A-bomb survivors, were discussed. Life expectancy was claimed to be prolonged by five years for males who received 31-100 cGy, but not for females. It was noted that there are some problems with this Nagasaki cohort, because they are self-selected, and may not be representative of the full cohort. The Swedish representative to UNSCEAR, a prominent epidemiologist (and recently elected Chairman of UNSCEAR), disagreed most emphatically with the claim of increased longevity: he remarked that the Nagasaki University study included mortality data only from 1970 on, thereby excluding or censoring all deaths which occurred prior, and that the Nagasaki University researchers had no idea how mortality before 1970 affected their results.

(The reader should keep in mind that the discussions in this section relate to low-LET radiation. What the situation is for high-LET radiation, especially at low dose rates, is uncertain.)

A concluding **Round Table on Regulatory Control and Scientific Research** yielded useful discussion points:

(1) More information on the response to radiation of whole organisms was needed since studies with cells and tissues did not tell the whole story.
(2) Molecular biology would soon provide the way to distinguish radiogenic cancers from spontaneous ones.
(3) A contribution of epidemiology is that it has indicated we are not underestimating radiation risks.
(4) There is no reason to conclude that the response to low doses of radiation at the DNA level is other than linear. The non-threshold linear model remained the most appropriate for regulation. But it can lead (and has led) to absurd decisions when the insignificance of low values of nominal risk was not understood.
(5) Dose estimates over populations at low doses are not good predictors of health effects. Collective dose should therefore not be used for predicting detriment; it is just a planning tool.
(6) Public involvement is important in establishing what are tolerable risks.
(7) Different circumstances would lead to different levels of acceptable risk.
(8) Radiation protection standards are fairly uniform around the world, despite 100-fold disparities in GNP. Is this right?
(9) The three ICRP principles can helpfully be supplemented by others, notably: precautionary, substitution (e.g., ultra sound for X-rays), fair distribution of risks to public and workers, medical ethics, professional ethics, and the protection of nature.
(10) So-called educated people can have quite incorrect notions on radioactivity; effort is needed to correct this.

THE "PACIFIC BASIN NUCLEAR CONFERENCE"

At The Pacific Basin Nuclear Conference (PBNC; May 1998) in Banff, Alberta, a full session and a panel discussion were specifically devoted to low dose issues. As well, some speakers in other sessions provided related material. Many of the issues and discussion points were similar to those in other fora (including the foregoing), although certain areas were addressed in greater detail. Two such areas relate to costs for radiation protection and to the possibility of radiation-related hormetic effects; these are selected for expanded discussion here.

There was general agreement that the costs mandated for radiation protection seem excessive. Untoward costs arise because of a perception that radiation risks may somehow be different from other risks, and because the public seems willing to pay (or have the industry pay) unseemly high costs to reduce exposures further. "Willingness to pay" as a societal index of course presumes that an adequate knowledge base exists among those polled to make this sort of assessment.

These are sometimes termed "opportunity costs". Health protection resources deployed where they provide no real health benefit represent opportunities lost. An ethical dilemma therefore arises if resources are 'wasted', as they are if little or no discernible health benefits accrue. (Since resources in society are not limitless, 'wasting' them carries a negative health benefit because they are not available to spend in areas where identifiable and validated returns might be obtained.) In this view, it is unethical for the radiation protection community to "go along" with ever lower and more costly ratcheting-downwards of radiation protection regulations because these reductions are not warranted by cost-benefit considerations and justifying this by a belief that 'the next reduction should surely assuage the public' is not sustainable. While the ethical principle seems to add a moral imperative and perhaps some urgency to the debate, it detracts from what is and should remain a scientific issue.

The *de minimis* or "below regulatory concern" (BRC) approaches advanced by various regulatory jurisdictions seek to provide the sort of cut-off value which anti-LNT proponents advocate. There are two problems with the concept. First, the *de minimis* "threshold values" are generally much lower than what threshold advocates feel should be in place and are more judgements of triviality of risk rather than indications of a real threshold. Second, these enacting agencies fail in the task of sufficiently "selling" or defending even this limited application (one that is eminently defensible on cost-effectiveness grounds) of what is equivalent to a practical threshold concept.

The point has been made that persons occupationally exposed to low-level radiation receive their exposures in a way so that, should an adaptive response exist, a low "inducing exposure" may have no benefit because a subsequent, "challenge exposure" (sufficiently large to make the inducing dose beneficial) is unlikely to occur within the necessary, short interval. This line of argument does not hold, however, if the low dose inducing exposure induces a true hormetic effect: if the causal chain of cancer attributable to 'spontaneous' causes is interfered with, then the initial radiation could theoretically lead to an overall benefit which outweighs the radiation detriment. (In other words, what one loses in terms of direct radiation causation is more than made up by reduced rates of cancer from other agents, whatever they may be.) This is certainly a theoretical possibility; the challenge is to show whether an adaptive response, or radiation hormesis, exists in the way in which people live their lives as opposed to in a model, laboratory situation.

AMERICAN STATISTICAL ASSOCIATION 13TH CONFERENCE ON RADIATION AND HEALTH

These conferences on Radiation and Health by the American Statistical Association (ASA), held at generally two year intervals, provide an opportunity to discuss both qualitative and quantitative aspects of radiation health research in a multidisciplinary setting. These ASA gatherings also serve to provide an "early glimpse" at new findings which impact on radiation risk assessment and on how effectively we manage risk. The subject of this year's gathering (San Diego, California; 1998 June 14-17) was certainly topical, reflecting the current debate about **"Radiation effects at low doses"**.

This conference represented the professionals—both epidemiologists and radiobiologists—who provide the data and models on which out nominal probability coefficients for radiation risk are decided. There was a strong emphasis on hard data, and on arguing from it directly, and fortunately little of rhetoric and "what ifs".

To the "low dose epidemiologists", as a group, the current debate concerning the appropriateness of the linear-no threshold theory was almost a non-issue. Rather, they are concentrating on the tools and data which will lead to direct estimates of low-dose risks. They think that epidemiology can provide the answers. But there was a palpable feeling that they did not as a group think there was much substantive data against linearity.

The meeting opened with a debate on the topic "*Epidemiological studies are useful in addressing radiation health effects at low doses*". Arguing for the ***pro*** side was Geoffrey Howe of Columbia University; Charles Land of the US National Cancer Institute argued for the ***con***.

Basically Howe was arguing that low dose (LD) epidemiological studies were important even if these didn't provide useful risk coefficients *per se*. If the confidence intervals can be made fairly narrow, the studies can provide assurance that if there is any risk (and there may not be), the risk is not large. In other words, such studies can credibly exclude the type and magnitude of risk one hears expressed by anti-nuclear activists. Howe's message was "Don't ignore the importance of the issue of reassurance. " Although certain LD studies may indeed have little power to reject the null hypothesis that no risk exists, they can have substantial power to reject the hypothesis that a high risk exists. One example cited was that people say and believe that "the population that lives around Hanford has a high rate of thyroid cancer"—doing the actual study showed that it isn't so.

The problem with doing only high dose (HD) studies, according to Howe, is that you have to then extrapolate to all sorts of LD occupational exposure situations, and the risk studies have to model or account for all sorts of other factors which contribute to the endpoint. The great advantage of LD studies is thus that *the groups studied are the actual ones you want information on*. LD studies are thus valuable additions to making extrapolations from HD studies. LD and HD studies are complementary: it's a very powerful result when you measure risks directly in the population you're concerned with, and can demonstrate they're consistent with [not higher than] extrapolations from HD studies.

Land, for the *con* side, felt that the only proper place for study of populations exposed to LD is to provide a contrast to HD studies. LD studies have a poor signal-to-noise ratio: you don't get much information because the assessment endpoint is dominated by variations in baseline. Too often data below about 15 cGy, say, are compatible with everything—they're just not informative. He felt, in contrast, that HD studies have a lot to say about what happens at LD. Another difficulty is that at LD, even small confounders can be very important, and since uncertainties tend to lower the apparent relative risk (RR) estimate, perhaps some of the "reassuring" LD studies Howe refers to are falsely reassuring. Land pointed out that in epidemiological studies, the width of the 95% confidence intervals is driven by essentially D/N [dose divided by number of subjects at that dose], and therefore that the power for rejecting the null hypothesis is a function of $D\sqrt{N}$ for small D. This means that for constant statistical power, a decrease in D from one level to another requires an increase in N by the ratio $(D_1/D_0)^2$, which means *e.g.* that a ten thousand-fold larger sample size is required if D decreases by a factor of one hundred.

A vote by show-of-hands was held at the conclusion of the debate. The vote was overwhelmingly for the *pro* (Howe's) side.

There was a session on *The links between radiobiology and radiation epidemiology: Can radiation epidemiologists and radiobiologists help each other?* This explored whether inputs from radiobiology or genetic epidemiology could be used to augment the present purely empirical (descriptive) epidemiological approaches. This could aid our ability to determine which cancers may be radiogenic, or to extrapolate more credibly to effects likely at low doses. One problem concerns our models—for example, how we extrapolate from animals to humans. The Armitage-Doll model, for example, 'illuminates' some of the fundamental differences between human and rodent carcinogenesis which have been plaguing us for generations in regard to risk assessment judgments. Humans have about one thousand-times more stem cell targets than mice, and about thirty-five-times the lifespan, together comprising a 35,000-fold disparity between mice and men. Why don't human beings all get cancer, early? Why is it so easy to transform mouse cells in culture, and so hard to transform human cells? It seems that the human cells have more degrees of protection: the slope *n* of an Armitage-Doll plot for mice is three less than for humans. The question of import is, what are the extra hits in humans required for?

The data on indoor radon are increasingly indicating a significant excess lung cancer risk proportionately associated with dose; the correlations seem to improve when methods of assessing historical exposure are employed for dosimetry.

Perhaps the most interesting session was on *New paradigms for low-dose radiation response*. Genomic instability (GI), the delayed appearance of effects, is a growing issue. There seems to be a good rationale for considering chromosomal changes after ionizing radiation to be an example of GI. Looking at a representative sample of cellular metaphase "populations" at only one instant after clonal expansion may be misleading us. GI is seen in a large number of cell types from different species. GI is a frequent event if you study clones surviving X-ray exposure. So also are transformation and reduced plating efficiency. These high frequencies suggest either a large target size or multiple targets, and that GI is not a mutation. Are we "turning on" with radiation the genes that interfere with stability or are we turning off the genes that control stability? The biggest question may be whether a ***mutator phenotype*** is associated with GI. It appears that this may be the case. Other speakers presented evidence that the relationship between GI and cancer induction is, in fact, now clearly established.

On the biological side, a new ***trigger paradigm*** seems to be emerging wherein the biological effects of radiation can be seen in cells which have not been "hit" by radiation. (In 1992, for example, Little's group at Harvard showed that following alpha-particle exposure there were more cells showing elevated sister-chromatid exchanges or SCE's [2-3 times as many] than had actually been traversed by alpha particles.)

We have changing paradigms in radiobiology. Initially there was **target theory**, a nearly mechanical theory. This model did not accommodate cellular recovery, and it was difficult to incorporate the complexity of DNA structure into target theory. It did, however, stimulate an understanding of the chemical nature of "hits", and fostered a search for the biological nature of targets critical to cell survival.

Next came the **repair paradigm**, which acknowledged that radiation-damaged cells "fight for survival". It stimulated an understanding of the nature of recovery, now nearly synonymous with DNA repair. But repair provided no direct explanation for numerous other radiation effects, *e.g.*, apoptosis, bystander effects, 'adaptive response' and hormesis.

What seems to be emerging now is the **trigger paradigm,** whereby the effects of radiation appear through their stimulation of cellular processes. This effect is not restricted to "protective" processes but is manifested for damage effects as well.

A bystander effect is a radiation-induced effect produced in a cell that had not absorbed any radiation dose. A bystander effect, by virtue of how it is observed, is essentially a low dose phenomenon: it doesn't mean that the same effect isn't observed at high dose, just that you can't see it because of a 'saturation effect'. The idea arose that perhaps radiation triggers a biological process that can cause damage as well as one(s) that may enhance repair. It might be noted that for years there has been a rich literature, mostly ignored, on *clastogenic factors*, which appear to represent the same phenomenon.

The comment was made that far from being a panacea, the trigger paradigm is a nightmare for radiobiologists. A low dose, for example, may have a hormetic effect or induce genomic instability.

There is thus both a positive and a negative side to triggered effects. It appears that on the negative side there is DNA damage, mutator phenotype and genomic instability "down the line". In the past few years, what the anti-LNT'ers have touted are the putative positive effects, but this can be offset by the "dark side" of triggered responses: the late biological effects of radiation do not necessarily arise only in cells that have sustained direct DNA damage: they also arise in non-hit cells, as a biologically-mediated result of cellular response to that damage. The existence of genomic instability means that by concentrating only on effects immediately apparent in irradiated cells, radiobiologists may be missing mechanistically a major part of the story.

EVEN IF A THRESHOLD WAS PROVED, WOULD IT CHANGE THINGS OPERATIONALLY?

A distinction has to be made between the *science* and the *practice* of radiation protection. If it could be established that there was some sort of threshold for radiation detriment, even if only in a limited subset of individuals, would it substantially change the way we do things operationally? We wouldn't likely be able to discriminate between workers in either direction—for example, expose to significant levels only those persons who are likely to have a threshold in 'their' radiation response. It therefore wouldn't likely change the way we manage worker exposures. This is because we would not know, for the group as a whole, what the actual ultimate influence on biological state will be for any particular small increment in dose. We know only the bounds of the likely influence. Radiation protection practices—and radiation risk estimates—apply to populations. Risk applies to individuals. Certainly substantial uncertainty exists in our risk estimates; we are aware of this already.

If a threshold existed, moreover, any posited threshold may well be smaller that the age-and sex-specific variations in susceptibility we have already identified. We don't apply even this existing information to radiation protection; if we did, we would only expose older workers to radiation.

In any population the effects on individuals of small additions in the day-to-day radiation doses will vary, depending *inter alia* on the individuals' genetic make-up and the spatial and temporal distributions of cellular doses. Eventually, a combination of sufficiently large doses and dose rate to a population, from natural background, medical and other man-made sources, could result in a deleterious biological response in some individuals. Since we do not possess a detailed accounting of any individual's complete personal dose history, nor of their genetic make up, nor of their individual cellular responsiveness to radiation at any particular time, then (given the multitude of factors influencing radiation response) there is only one practical and equitable way to proceed: to associate with increments of radiation dose from man-made sources (or any other) some finite (non-zero) probability of advancing an individual (whose position in the distribution we do not know) towards a deleterious biological response. *The only reasonable assumption for a hypothetical individual somewhere in the distribution is that the bigger the dose, the proportionately bigger the likelihood of an advance towards an effect.*

This is no different in practice than what we do now. Thus the only conceivable advantage to proving that a threshold exists might be in relation to public perception. We think that this 'benefit' is oversold. Given failure to succeed at a far less onerous task—that of setting radiation risks in perspective with other risks—"proving" the existence of a threshold would not be the panacea that some anticipate it would be for improved public support.

THE PATH FORWARD: FINDING COMMON GROUND

This 'internal' epistemological debate is dividing us and may hurt the credibility of radiation protection. It behooves us to emphasize instead that solid and common ground we can identify, and to go forward from there.

One aspect of "problems with LNT theory"--excessive costs for protection against radiation versus other risks to human health--may be addressable within the present radiation protection system. The issue is that the attention given to low doses of radiation is excessively high *even if the LNT-based risk*

coefficients were to be correct. (If LNT is not correct, the discrepancy simply becomes more marked.) This is common ground on which both sides in the debate can coalesce. This is the issue we have to continue to address and rectify. The "cost of a theoretical cancer death prevented" is out-of-whack. Public misperception, or whatever else leads to this misperception is to blame for this—not LNT *per se*. To be effective, it is the perception issue that has to be addressed.

Another common ground is to be found in a consensus from a growing, scientifically-defensible body of evidence which indicates that **at sufficiently low dose rates the risks of radiation exposure are demonstrably less than presently allowed for**. The LNT debate, and the way in which we interpret scientific results, may be advanced if we change our present thinking (and how we design experiments) from focusing on the physical aspect of dose and recognize the importance of the rate at which damage is inputted. (Biological protection mechanisms are most apt to function effectively if not overwhelmed by having to deal with a large amount of DNA damage essentially all-at-once.) This in essence is the *dose and dose-rate effectiveness factor* (DDREF) already incorporated into the ICRP nominal probability coefficients for occupational and public radiation risk. Reducing uncertainty *vis-à-vis* the low dose/low dose-rate situation would materially advance risk assessment and perhaps support public acceptance of trivial exposures.

These or any other "ways forward" will not happen by wishing it so, or by acrimonious debate within the radiation protection community. Rhetoric will not help; credible data will. The challenge to both sides is to provide a sufficiently coherent body of evidence to be accepted by regulators, risk assessors and the public alike, which supports this new view.

Until we have the needed coherent body of evidence, the most credible alternative for regulators is to maintain reliance on the simplest form of the "precautionary principle"—the LNT theory. It is also, in fact, the best defence we presently have against the excesses of the "third constituency". Holding to LNT is, at the present state of evidence on this very complex topic, a credible middle ground between the extremes of hormesis on one side and of claims for supralinearity (in various guises) on the other.