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INTRODUCTION

Despite the nearly universal adoption of the linear nonthreshold dose response model (LNT) as the primary basis for radiation protection standards for the past half century, the LNT remains highly controversial and a contentious topic of discussion among health physicists, radiation biologists, and other radiological scientists. Indeed, it has been pointed out that the LNT has assumed the status of a paradigm, synonymous with an ideal, standard, or paragon or perhaps to some, a sacred cow.[1] Reduced to its very basics, the LNT postulates that every increment of ionizing radiation dose, however small, carries with it a commensurate increase in the chance or risk that the exposed individual will suffer some undesirable radiation effect, and that the risk thus incurred is directly proportional or linearly related to the dose. The specific effects are termed "stochastic," which has been defined as "of a random or statistical nature."[2] Stochastic or probabilistic effects of radiation may occur as a result of low doses and are generally taken to be cancers (including leukemias) and genetic defects in the progeny. The severity of these radiation-induced stochastic effects, should they occur, are independent of the dose that produced them; thus, even though the likelihood or probability of an occurrence may be small to negligible, any and all manifestations of a radiation induced stochastic effect will have equal severity.

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1. Ronald L. Kathren, *Pathway to a Paradigm: The Linear Nonthreshold Dose-Response Model in Historical Context*, 70 J. Health Physics 376, 376-390 (1996).

2. Intl. Comm. on Radiological Protection, *1990 Recommendations of the International Commission on Radiological Protection*, 21 Annals of the ICRP 1-201 (nos. 1-3 1991).

By contrast, higher doses of radiation are known to produce characteristic somatic or deterministic effects including erythema, epilation, sterility, diminution of blood cell counts, cataracts and, in very high exposures, acute and chronic radiation syndromes. Such frank biological effects are nonstochastic in nature (in fact, they were at one time termed "nonstochastic effects") and will always be manifested once a particular minimum dose – i.e., a "threshold" – has been received. The severity of the effect is related to the dose. Below the threshold dose there will be no demonstrable effect; as the dose increases beyond the threshold, so does the severity of the effect, or the degree of harm.

It bears repeating that the LNT is specifically applicable to the so-called stochastic effects of cancer and genetic defects in the progeny, and refers only to low doses and presumably low dose rates of ionizing radiation. What constitutes a low dose is open to interpretation. Many authors and publications simply use the term "low dose" without definition or further explanation. Indeed, there is disagreement among radiological health scientists as to just what constitutes a "low dose." This is evident from the numerous radioepidemiologic studies that have been carried out over the years, and the application of the LNT down to doses that are fractions of the natural background radiation levels. The authoritative International Commission in Radiological Protection (ICRP) Publication 60, *1990 Recommendations of the International Commission in Radiological Protection,* indicates that stochastic effects occur at ". . .doses well below the thresholds for deterministic effects,"[3] and that for most tissues (Paragraph 58), severe effects are unlikely at dose rates less than about 0.5 Gy (Gray) y^{-1}.[4] The ICRP report further lists thresholds for various deterministic effects. The lowest threshold so listed is for temporary sterility in the male, given as a single acute dose to the testes of 0.15 Gy. Generally, however, the term low dose, as applied to radiation induced stochastic effects, is taken to be in the neighborhood of 0.1 Gy (10 rad) above the natural background dose acquired by an individual. In a recent report, the National Council on Radiation Protection and Measurements (NCRP) published human studies of cancer risks from "low radiation doses," including in their range doses of several tens of Gy and noting that almost all risk coefficients for stochastic effects have been obtained from individuals whose doses have exceeded 0.1 Gy,[5] and, most recently concluded, perhaps somewhat equivo-

3. Intl. Comm. on Radiological Protection, *Individual Monitoring for Intakes of Radionuclides by Workers: Design and Interpretation*, 19 Annals of the ICRP 21 (nos. 1-3 1990).

4. Intl. Comm. on Radiological Protection, *supra* n. 2, at 1-201.

5. Natl. Council on Radiation Protection and Measurements, *Principles and Application of Collective Dose in Radiation Protection*, Rpt. 121 (Natl. Council on Radiation Protection and Measurements 1995).

cally, that the exact shape of the dose response relationship for radiation induced carcinogenesis in humans at doses below about 0.05 to 0.1 Sv (Seivert) is not known but that there is sufficient experimental evidence to suggest that a threshold is unlikely to exist.[6] This, coupled with several recent Position Statements by the Health Physics Society and the international conference "Bridging Radiation Policy and Science," which pointedly noted that for lifetime doses below 10 rem (equivalent to 0.1 Gy for low Linear Energy Transfer (LET) radiation) stochastic effects are negligible or nonexistent, might by implication suggest that this level might serve as the boundary for what defines low dose. Although it should be noted that a case could be made for defining the 0.1 Gy dose level as either the upper or lower boundary for low dose.[7] At least one investigator has proposed in a recent paper examining whether low-level ionizing radiation causes cancer that the upper limit for low dose be specified as 0.1 Gy.[8]

The purpose of the above discussion is to illustrate the underlying controversy and confusion that surrounds the LNT today, as well to underscore the lack of precision that sometimes accompanies the arguments of both the proponents and opponents of the LNT. Given that the LNT is a low dose phenomenon, there needs to at least be consensus on what is low dose, and such a consensus needs also to include consideration of other relevant and important factors such as the dose rate and specific stochastic end point (i.e., type of cancer or mutation). With this as a backdrop, the historical development and gyrations that led to the LNT as it is currently applied (or, some would say, misapplied) in radiological protection can be examined in the context of current scientific thinking with respect to radiation effects. It is not the purpose of this paper to endorse any particular position or to take sides but rather to present the story in a factual and fair-minded manner. Hopefully, what follows will successfully achieve this goal. Thus, this paper will briefly review the scientific bases and supporting studies that led to the development and acceptance of the LNT in health physics. It will briefly touch on such topics as hormesis and other studies, such as the classic work of the late Robley Evans, that clearly demonstrate a threshold and nonlinear response for certain stochastic effects such as osteogenic sarcoma, along with the plethora of studies that suggest or have been interpreted to indicate that for at least some end

6. Natl. Council on Radiation Protection and Measurements, *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation,* Rpt. 136 (Natl. Council on Radiation Protection and Measurements 2002).

7. Kenneth L. Mossman et al., Final Rpt. of Bridging Radiation Policy and Sci. Intl. Conf. (Health Physics Socy. Dec. 31, 2000).

8. Ronald L. Kathren, *Does Low-Level Ionizing Radiation Cause Cancer?* Radiation Protection for Our Natl. Priorities 130-138 (Am. Nuclear Socy. 2000).

points (i.e., cancers), response to ionizing radiation is consistent with the LNT model.

EARLY OBSERVATIONS OF RADIATION CARCINOGENESIS

Although the stochastic nature of radiation carcinogenesis was not uncovered for several decades, the possible association between radiation exposure and cancer was pointed out as early as 1902, only a scant six years after the twin discoveries of x-rays and radioactivity by Roentgen and Becquerel, by German physician A. Frieben based on his observation of a carcinoma on the dorsum of the hand in a worker in a factory producing x-ray tubes.[9] That same year, Pittsburgh radiologist George Coffin Johnson identified keratotic patches on the hands of a surgeon who had acquired a large x-ray exposure resulting from x-ray exposure as "precancerous patches" based on his histological study.[10] Other reports of an association between radiation exposure and cancer soon followed in medical and scientific literature; in 1907, Porter and White[11] characterized eleven fatal cases of radiation-related cancers in humans, and by 1911 at least ninety-four cases of apparent x-ray-induced skin carcinoma in man – all in patients treated with x-rays for lupus (twenty-four), in practicing radiologists or x-ray technicians (twenty-six), and the remainder (twenty-four) in technical personnel working with x-rays – were documented, an average of about six per year.[12] By 1915, only twenty years after the discovery of x-rays, radiation carcinogenicity had been well identified and was a generally accepted phenomenon associated with excessive exposure. Still, by 1950, however, only 200 cases of x-ray-induced skin carcinoma had been reported, for an incidence rate of only 2.5 per year for the subsequent four decades despite considerably increased usage and opportunity for exposure.[13] Given the increased usage and numbers of users of x-rays, this diminution in incidence was, at least in part, attributable to improved protection practices, although decreased reporting is also likely responsible in part, as the phenomenon was no longer novel.

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9. A. Frieben, *Demonstration eines Cancroids des rechten Handrückens, das sich nach langdaurnder Eirwirkung von Röntgenstrahlen entwickelt hatte*, 6 Fortschritte Gebiete Röntgenstrahlen 106, 106-111 (1902).

10. G. C. Johnson, *Philadelphia Medical Journal*, in M. H. Kassabian, *Electrotherapeutics and Rontgen Rays* arch 8-15, 406 (J. B. Lippincott Co. 1907).

11. C. A. Porter & C. J. White, *Multiple Carcinomata following Chronic X-ray Dermatitis*, 46 Annals of Surgery 649, 649-671 (1907).

12. Otto Hesse, *Symptamologie, Pathogenese and Therapie des Röntgenkarzinoms* (J. A. Barth 1911).

13. Frederich Ellinger, *Medical Radiation Biology* 150n. (Charles C. Thomas 1957).

From his evaluation of the ninety-four cases, Hesse found that the interval between exposure and the diagnosis or recognition of the skin carcinoma ranged from four to fourteen years with a mean of nine years.[14] If there had been a radiation-induced dermatitis, the interval between the dermatitis and the diagnosis of the malignancy was considerably shorter, ranging from one to eleven years, and averaging four to five years. This was evidently the first observation of the effect of dose on latency, for a higher dose would be expected in those who manifested frank dermatitis. In 1915, still long before the stochastic nature of radiogenic cancer had been elucidated, British physician Hector Colwell and his physicist colleague Sydney Russ concluded that chronic low level x-ray exposure was in fact carcinogenic, presciently describing the process thusly: "The significant fact, therefore, is that repeated small doses of soft x-rays, when applied to human tissues, produce gradual changes therein, which may cause such tissues to develop malignant features."[15]

But the prevailing view at the time and for some decades thereafter was that frank damage, as would be the case with high exposures producing acute effects, was a necessary precursor to radiation-induced malignancy, and thus radiation carcinogenesis was essentially a high dose phenomenon. The concept that low doses of radiation might be harmful was slow to develop. Indeed, for at least three decades following the discovery of x-rays and radioactivity, many radiologists and other physicians and biologists believed that small doses of radiation, and in particular radon and radium emanations, were not only unharmful, but might in fact be beneficial. Some cited as justification the Arndt-Schulz Law, which had been formulated in the late nineteenth century prior to the discovery of x-rays and radioactivity, and which postulates that small doses of drugs produce a stimulatory effect, while larger doses would produce increasingly deleterious effects. This is, of course, the basis for homeopathic drug therapy and analogous to, if not an actual statement of, the more contemporaneous concept of radiation hormesis.

Observations of potential long term effects on the blood significantly influenced radiation protection during the first half of the twentieth century, and were indeed to play a central role in the development of the earliest protection strategies. The focus of attention was the diminution in blood counts – a deterministic effect – but the reverse in the form of leukemia was also observed. In 1911, radiation exposure was postulated as

14. Hesse, *supra* n. 12.

15. Hector A. Colwell & Sydney Russ, *Radium, X-rays and the Living Cell* 283 (G. Bell and Sons 1915).

the cause of four cases of lymphatic leukemia observed in radiologists.[16] This pioneering and highly prescient work was far overshadowed by other studies largely concerned with depression of red and white cell counts, and although several studies did indicate an increase in monocytes, little attention was directed towards the possibility that radiation was in fact leukemogenic until the 1940s, spurred by the suggestion that it was in 1941 by Paul Henshaw of the National Cancer Institute.[17] In 1944, Henshaw, in collaboration with J. W. Hawkins, reported that the leukemia incidence in physicians was 1.7 times that of the adult male population and attributed this increase to radiation exposure.[18]

THE TOLERANCE DOSE AS THE BASIS FOR RADIATION PROTECTION PHILOSOPHY

For at least the first thirty years subsequent to the discoveries of x-rays and radioactivity, there was little if any indication, let alone scientific support, for the notion that biological response to radiation was a linear function of dose. Similarly, the prevailing wisdom was that, much like sunburn, a threshold or minimum dose was required to provoke a biological response. And, much like sunburn, the effects resulting from exceeding this threshold dose were reversible. Indeed, the earliest considerations of radiation effects and protection were built on the principle that the various tissues of the body could withstand a specific level of radiation without apparent ill effect – a so-called tolerance dose which was considered to be that level of radiation to which an individual could be continuously exposed without demonstrable ill effect. Demonstrable ill effect or harm was considered solely in terms of what are now known as deterministic effects such as a clinical manifestation of radiation effects – diminution of blood counts, skin erythema, or epilation among them.

Since there was little if any precedent in medicine for the manifestation of effects at long times after exposure to a toxic or hazardous agent (i.e., a latency or incubation period of years to decades), it was not unreasonable for physicians and others to assume from the outset that untoward effects from exposure to radiation would be no different. Overexposure to toxic chemical agents or hazardous physical agents generally resulted in an

16. N. Von Jagie et al., *Blutebefunde bei Rontgenstrahlen*, 48 Berl. Klin. Wochschr. 1220, 1220-1222 (1911); Colwell & Russ, *supra* n. 15, at 66ff.

17. Paul S. Henshaw, *Biologic Significance of the Tolerance Dose in X-ray and Radium Protection*, 1 J. Natl. Cancer Inst. 789, 789-805 (1941).

18. Paul S. Henshaw & J.W. Hawkins, *Incidence of Leukemia in Physicians*, 4 J. Natl. Cancer Inst. 339, 339-346 (1944).

acute phase of illness followed by recovery or death; the idea of an effect manifesting itself in some fraction, but by no means all, of those exposed to a particular level years or even decades later was by and large outside of the thinking of the day. Thus, the concept of a tolerance dose – a dose of radiation to which an individual could be exposed to without any ill effect – was clearly a logical conclusion, particularly in view of the fact that the concept of stochastic effects with long latency periods had not been articulated. Indeed, sufficient time had to pass before long-term effects with latency periods of years to decades could even be observed. Thus, it is not surprising that what was likely the first statement of a true dose limit, proposed by physicist Arthur Mutscheller at the 1924 meeting of the American Roentgen Ray Society, was based on a tolerance dose, the foundation for which was the skin erythema dose (SED), the minimum quantity of x-ray dosage that would produce a reddening of the skin.[19] The SED is by no means exact, but is, among other things, primarily a function of radiation quality, dose rate, and the specific response of the individual. Mutscheller thus prudently set his proposed limit as 1/100 of the SED in a thirty-day period, from measurements of radiation levels in well-run x-ray installations. From these measurements, he estimated the monthly radiation to personnel and, since none had suffered any apparent ill effect, developed from this his recommended exposure limit, which roughly corresponded to a modern day whole body dose of about 700 mSv/year.

It is important to note that implicit in the concept of tolerance dose is the notion of recovery (or repair) from any clinical effects. Again, this concept was in keeping with the state of medical knowledge of the day. And, once recovery from the acute phase was achieved, the tolerance dose clock, so to speak, was reset. Thus, if acute somatic effects were observed, restriction from radiation work until recovery occurred was all that was necessary.

The concept of a permissible radiation exposure limit with a tolerance dose as its basis was well received by the medical and scientific community. The influential British physicist G. W. C. Kaye adopted the tolerance dose as the basis for his proposed safety limits and efforts were made, albeit sporadic and not always systematic, to better quantify the tolerance dose and establish its scientific basis.[20] Lauriston Taylor, who recently celebrated his 100th birthday and was one of the original members of predecessor of both the NCRP and ICRP, recalled of efforts by three prominent early investigators independently working to establish a quanti-

19. Arthur Mutscheller, *Physical Standards of Protection Against Roentgen Ray Dangers*, 13 Am. J. Roentgenology 65, 65-69 (1925).

20. G. W. C. Kaye, *Roentgenology* 68-82 (Paul B. Hoeber 1928).

tative level for tolerance dose: ". . .no one of these people, or anybody else, claimed that they had ever detected any injury due to radiation at levels above this one-hundredth of an erythema dose per month."[21] His observation is well supported by the literature of the day, as exemplified by an examination of the potential radiation risks to roentgenologists carried out by Barclay and Cox, who made measurements under actual operating conditions and failed to detect any ill effect in either of the two workers they followed.[22] One worker received a substantial dose by modern standards, estimated as a daily dose of about 70% of the limit proposed by Mutscheller over a time period of six years, or about 3 Sv. The Barclay-Cox study was but one of several that lent support to the concept of a threshold or tolerance dose below, which untoward effects did not occur. In retrospect, such studies were badly flawed, typically extrapolating broadly from results obtained with only a few individuals.

RADIATION MUTAGENICITY AND RECOGNITION OF THE LNT

Certainly one of the most significant radiobiological discoveries was made in 1927 by American geneticist Herman J. Muller who, in experiments with the fruit fly *Drosophila melanogaster,* demonstrated that exposure to x-rays could produce genetic mutations in the progeny.[23] Even of greater significance, Muller found that the mutation rate was linear with dose. Muller's observation of the mutagenicity of x-rays was quickly confirmed by Weinstein[24] and shortly thereafter, mutations induced in plants by x-rays[25] and in somatic cells[26] led to the conclusion that x-ray mutagenicity was generic and species independent, and hence likely applicable to humans as well. Subsequent studies established that the induced mutation rate was independent of dose rate, and a single hit process with no threshold, and cumulative over a lifetime.[27] Thus, it was

21. Lauriston S. Taylor, *Reminiscences about the Early Days of Organized Radiation Protection*, in *Health Physics: A Backward Glance* 109, 109-122 (Ronald L. Kathren & P. L. Ziemer eds., Pergamon Press 1980).

22. A. E. Barclay & S. Cox, *Radiation Risks of the Roentgenologist*, 19 Am. J. Roengenology Radium Therapy & Nuclear Med. 551, 551-558 (1928).

23. Herman J. Muller, *Artificial Transmutation of the Gene*, 66 Science 84, 84-87 (1928).

24. A. Weinstein, *The Production of Mutations and Rearrangements of Genes by X-rays*, 67 Science 376, 376-377 (1928).

25. L.J. Stadler, *Genetic Effects of X-rays in Maize*, 14 Proc. Natl. Acad. Sci. 69, 69-75 (1928).

26. J. T. Patterson, *The Effects of X-rays in Producing Mutations in Somatic Cells of Drosophila Melanogaster,* 68 Science 41, 41-42 (1928); N. W. Timofeev-Ressovsky, *The Effects of X-rays in Producing Somatic Genovariations of a Definite Locus in Different Directions in* Drosophila melanogaste*,* 63 Am. Naturalist 118, 118-122 (1929).

27. C. P. Oliver, *An Analysis of Varying the Duration of X-ray Treatment on the Frequency of Mutations*, 61 Zeitschr. Indukt. Abstammungst. 447, 447 (1932) in F. Ellinger, *Medical Radiation*

from observations of x-ray-induced mutagenicity in plants and lower animals that the first observations and understanding of an LNT dose response were made. Additional cellular studies revealed the existence of x-ray-induced somatic mutations, offering a plausible explanation for the observed apparent carcinogenicity of ionizing radiations and the long latency period associated with the production of cancer.

During World War II, systematic and extensive radiobiological studies were carried forth. These were, in large measure, devoted to study of obvious clinical manifestations, with a primary purpose being validation and refinement of the basic radiation protection philosophy and criteria, which were, in turn, based on the concept of tolerance dose.[28] There were some quite unexpected and highly surprising results, including an apparent hormetic effect by Lorenz and his coworkers[29] who observed that mice exposed to 0.11 R per day, approximately the accepted tolerance dose in the 1940s, outlived control animals. This observation, although replicated, has never been satisfactorily explained. From a human standpoint, clinical laboratory studies were carried out *en mass* on the workforce but failed to show indications of potential long-term low-level effects.[30] However, the population was followed for only a few years during the war, an insufficient period to observe long term effects from low-level exposure. Thus, at the conclusion of World War II, a full half-century after the discovery of x-rays and radioactivity and nearly two decades after the observations of the LNT for genetic mutations, radiation protection philosophy remained firmly grounded in the tolerance dose. Two basic criteria underlay the tolerance dose concept: 1) that there was a threshold dose that needed to be exceeded if any effects were to occur; and 2) complete recovery from radiation effects was possible, thereby precluding long term effects if the threshold level had not been reached. But the observations of Muller and other geneticists were inconsistent with the tolerance dose concept and indicated biological response at low doses was both linear and without a threshold, a rather bold new idea that was

Biology 62, 62 (Charles C. Thomas ed., 1957); N. W. Timofeev-Ressovsky et al., *Uber die Natur der Genmutation und der Genstrukture, Nach. Gesellschaft Wissenschaften* 189, 189-245 (1935); D. E. Uphoff & C. Stern, *The Genetic Effects of Low Intensity Radiation*, 100 Science 609, 609-611 (1949).

28. Simeon T. Cantril, *Biological Bases for Maximum Permissible Exposures*, in *Industrial Medicine on the Plutonium Project* 36, 36-74 (McGraw-Hill 1951); J.J. Nickson, *Protective Measures for Personnel*, in *Industrial Medicine on the Plutonium Project* 75-112 (McGraw-Hill 1951).

29. Egon Lorenz et al., *Long-Term Effects of Acute and Chronic Irradiation in Mice, Survival and Tumor Incidence Following Chronic Irradiation of 0.11 r per day*, 15 J. Natl. Cancer Inst. 1049, 1049-1058 (1955).

30. Leon O. Jacobson & E. K. Marks, *Clinical Laboratory Examination of Plutonium Project Personnel*, in *Industrial Medicine on the Plutonium Project* 113, 113-139 (McGraw-Hill 1951); Leon O. Jacobson et al., *Hematological Effects of Ionizing Radiations*, in *Industrial Medicine on the Plutonium Project* 140, 140-196 (McGraw-Hill 1951); Lorenz et al., *supra* n. 29, at 1049-1058.

emerging and which would shape the direction of radiation effects research as well as radiation protection philosophy in the coming years.

FROM TOLERANCE DOSE TO LNT

The late 1940s saw the beginning of what was to be a rather rapid and significant switch from the tolerance dose to the LNT as the basis for radiation protection standards setting and risk assessment. The great appeal of the LNT model lay in its mathematical simplicity and in its judicious or prudent representation of an upper limit for risk in the low dose region. The principal scientific foundation lay in the studies of radiation-induced genetic changes by Muller and others some two decades earlier, which were indicative of a nonthreshold linear response. Although somatic effects had only been observed at high doses, the presumption was that what was likely the case for genetic effects also applied to somatic effects, and that straight-line extrapolation of the dose-response curve through the low dose domain to the origin was appropriate. Underlying this extrapolation was the belief that the true risk in the region would actually lie somewhere between zero and the upper limit, as defined by the location of the extrapolated line, and hence the extrapolation was really a statement of the upper limit of risk in the low dose region of the dose-response curve – the very region of interest from a protection standpoint and the very region in which dose-response data were not available. There was clearly no intention to reject any other shape of dose response curve, or to deny the possible existence of a threshold or zero response below some specific dose. The linear nonthreshold extrapolation was originally selected largely for its mathematical simplicity and its perceived conservatism, a fact that has by and large been forgotten or at least lost sight of over the years.

The shift from tolerance dose to the LNT model as the basis for radiation protection proceeded rapidly. NCRP Report No. 17, published in 1954, introduced the concept of the *maximum permissible dose* (MPD) in lieu of the tolerance dose in the United States, and the British followed suit the following year.[31] Underlying the MPD was the concept of acceptable risk, and hence a nonthreshold model, the basis for which were the now two-decade-old observations of dose-response linearity for genetic mutations, which, for protection purposes, was applied to somatic mutations as well. An unstated influence on the recommendations was a growing realization of the potential worldwide genetic consequences of small doses of

31. Natl. Council on Radiation Protection and Measurements, *Permissible Dose from External Sources of Ionizing Radiation*, Rpt. 17 (Natl. Council on Radiation Protection and Measurement 1954).

radiation to large populations from atmospheric nuclear weapons tests, about fifty of which were announced during the approximately five-year period (1949-54) that NCRP Report 17 was in preparation.

The real impetus for the LNT came from the first report of the United Nations Scientific Committee on the Effects of Radiation (UNSCEAR). In this important consensus document, numerical estimates of radiation-induced effects were made using both the LNT model and a threshold model. In briefly summarizing what was known about low-level radiation effects up to that time, UNSCEAR equivocated, noting:

> Present knowledge concerning long-term effects and their correlation with the amount of radiation received does not permit us to evaluate with any precision Article I. The possible consequence to man of exposure to low radiation levels. Many effects of radiation are delayed; often they cannot be distinguished from other agents; many will develop once a threshold dose has been exceeded; some may be cumulative and others not; and individuals in large populations, or particular groups such as children and foetuses may have special sensitivity. These facts render it very difficult to accumulate reliable information about the correlation between small doses and their effects either in individuals or in large populations.[32]

However, with respect to leukemia, which had been observed in the Japanese atomic bomb survivors, UNSCEAR concluded that both the threshold hypothesis model and the LNT hypothesis corresponding to a single hit with no repair somatic mutation model had equal validity, a contention that was disputed by the Committee on Pathologic Effects of Atomic Radiation of the National Academy of Sciences/National Research Council which straightforwardly stated that "a considerable body of experimental evidence" favored nonlinearity, and hence presumably a threshold, and urged that nonlinear relationships be given greater heed.[33]

The following year, the newly created U.S. Federal Radiation Council (FRC) published its first report, supporting the concept of the LNT extrapolation of the dose response curve down to the low dose region, noting that application of the LNT would provide the upper limit of risk for a given dose in the region of extrapolation and would hence be conservative for radiation protection applications, an important qualifying statement that

32. U. N. Sci. Comm. on the Effects of Atomic Radiation, *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation,* U. N. General Assembly, 13th Sess. 42 (no. 17 supp. 1958).

33. Natl. Acad. of Sci. Natl. Research Council Comm. on Pathologic Effects of Atomic Radiation, *A Commentary on the Report of the United Nations Scientific Committee on the Effects of Atomic Radiation* 647 (Natl. Acad. of Sci. Natl. Research Council 1959).

would be lost over the years.[34] At approximately the same time, the Joint Committee on Atomic Energy (JCAE) of the U.S. Congress held extensive hearings on the effects of potential problems of low-level long-term radiation effects from fallout, which greatly influenced the thinking of both the scientific community and the general public. The hearings began in 1957 with an inquiry into the nature of radioactive fallout and its effects on people and included testimony from recognized and highly regarded scientific experts relating to both the LNT hypothesis and threshold dose, as well as the concept of an acceptable level of exposure as expressed via the MPD.[35] Although the expert testimony generally supported a linear response for genetic effects, it did not support the use of the LNT to characterize the dose response to low levels of ionizing radiation. The upshot of the hearings was that the JCAE concluded that continued nuclear weapons testing in the atmosphere represented a hazard to the population of the world, but left unresolved the question of whether there was in fact a threshold or "safe" level for exposure, below which such effects as leukemia, bone cancer, or life shortening would not occur.

In another round of hearings in 1959, the JCAE attempted to gain the answer to the shape of the dose response curve.[36] Once again, the question remained unresolved but there was clearly a tilt towards the applicability of the LNT, at least for genetic effects. Taking note of the lack of experimental evidence regarding low dose somatic effects and supporting no specific model, the JCAE cited testimony by Karl Z. Morgan, then Director of the Health Physics Division at Oak Ridge National Laboratory and an acknowledged leader in the field, who stated that only certain types of effects, including genetic mutations, leukemogenesis, and life shortening were without a threshold.[37] The Committee was strongly influenced by the testimony of Edward B. Lewis, a prominent geneticist and a professor at the California Institute of Technology, who made a strong case for the linear hypothesis as the basis for protection standards, and conceptually put forth what is the current regulatory and radiation protection concept of As Low As Reasonably Achievable (ALARA).[38] Throughout the 1960s, the JCAE considered the problems of worker protection standards and compensation, as well as revisiting fallout from weapons tests and carrying out

34. F. Radiation Council, *Background Material for the Development of Radiation Protection Standards*, Rpt. 1 (F. Radiation Council 1960).

35. Jt. Comm. on Atomic Energy, *Hearings on the Nature of Radioactive Fallout and Its Effects on Man* (Govt. Printing Off. May 27-29, 1957 and June 3-7, 1957).

36. Jt. Comm. on Atomic Energy, *Hearings on Fallout from Nuclear Weapons Tests* (Govt. Printing Off. May 5-8, 1959).

37. *Id*. at 19.

38. Jt. Comm. on Atomic Energy, *Selected Materials on Radiation Protection Criteria and Standards: Their Basis and Use* 404-407 (Govt. Printing Off. May 1960).

hearings related to the radiological hazards associated with mining, moving subtly closer to an LNT or proportionality hypothesis for low level long term effects with each succeeding series of hearings.

In 1962, the second UNSCEAR report appeared, reaffirming what had been put forth in the 1958 report.[39] Although noting that the available data were insufficient to make absolute risk estimates, the UNSCEAR used the LNT to calculate risks from various sources of radiation exposure, offering as partial justification the argument of the mathematical simplicity and conservatism of the LNT model. In subsequent reports, the UNSCEAR declared that the extrapolated linear curve marked the upper limit of the estimate of risk for a given dose, a concept also put forth by the ICRP in 1966.[40]

Up until at least the middle 1960s, the LNT was generally considered by the scientific community, as evidenced by the UNSCEAR reports as well as the JCAE hearings, and reports of the ICRP, FRC and other bodies, as an upper limit risk estimate and hence a conservative or err-on-the-side-of-safety approach to the establishment of radiation protection standards. That the shape of the dose-response curve for low level irradiation might in fact differ from linearity or have a threshold seemed to be rather beside the point, for use of the LNT as the basis for radiation protection standards inherently assured that the risk of a given exposure would never exceed and likely be much lower than those estimated by application of the LNT.

Continuing worldwide concern over the potential long-term effects of nuclear weapons test fallout was an instrumental force in the creation and signing of the Nuclear Test Ban Treaty in 1962. The Treaty banned atmospheric nuclear weapons testing but permitted underground testing for both military and civilian application so long as no radioactivity from the test was detectable beyond the borders of the country carrying out the testing. But nuclear weapons and explosives were but one part of a larger picture; the nuclear genie had a peaceful side as well, and optimistic plans for widespread peaceful nuclear electric generation as well as widespread diagnostic uses of radionuclides and Project Plowshare which proposed applications of nuclear explosives for construction of roads, harbors and similar projects requiring large excavations, led to increasing concern regarding long term low level radiation effects. Even though genetic effects

39. U. N. Sci. Comm. on the Effects of Atomic Radiation, *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation,* U. N. General Assembly 17th Sess. (no. 16 supp. 1962).

40. U. N. Sci. Comm. on the Effects of Atomic Radiation, *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation,* U. N. General Assembly 19th Sess. (no. 14 supp. 1964); Intl. Comm. on Radiation Protection and Measurements, *Recommendations of the International Commission on Radiological Protection* 9 (adopted Sept. 17, 1965) (Pergamon Press 1966).

had not been demonstrated in human populations, it was generally accepted within the scientific community that there was in fact no threshold for genetic effects, and a growing suspicion that this was true for carcinogenesis as well. This was certainly the theme of the 1956 Biological Effects of Atomic Radiation (BEAR) Committee and British Medical Research Council reports.[41] The mission of the BEAR Committee – a high level and highly influential scientific advisory committee with several expert subcommittees – was to examine problems related to radiation protection, including the shape of the low dose response curve. In its blue and white covered, five-centimeter-thick report, the BEAR Committee introduced an important departure from previous radiation protection practice, introducing the concept of regulation of population doses based on genetic risk, and ultimately genetic dose, to future generations.[42]

SOLIDIFICATION OF THE LNT: THE 1970S

It was perhaps during the decade of the 1970s that the LNT became fully entrenched as an integral part of radiation protection philosophy and standards. In the 1970s, the interest in worldwide fallout and associated radiation effects diminished, brought about in part by the cessation of atmospheric nuclear testing. However, interest in low-level radiation effects remained keen. At the start of the decade, the NCRP published a well-received comprehensive report, which put forth recommended dose limits for workers and the general population based on the fundamental assumption that the most important radiation health effects do not have a threshold and that radiation exposures should be kept to lowest practicable level.[43] This was tempered by the NCRP's observation that extrapolation of high dose-high dose rate response curves would not provide realistic estimates of actual risks from low level low LET radiation, but would rather overstate the risks.

The BEAR Committee, having apparently completed its mission, disbanded and was replaced by the NAS/NRC Committee on the Biological Effects of Ionizing Radiations (BEIR), funded by the U.S. Environmental Protection Agency. BEIR issued its first report in 1972, a comprehensive review of the literature relating to low-level radiation effects and evalua-

41. Natl. Acad. of Sci. Natl. Research Council, *The Biological Effects of Atomic Radiation. A Report to the Public,* (Natl. Acad. of Sci. Natl. Research Council 1956); British Med. Research Council, *The Hazards to Man of Nuclear and Allied Radiations* (Her Majesty's Stationary Off. 1956).

42. Natl. Acad. of Sci. Natl. Research Council, *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation* 5 (Natl. Acad. Press 1972).

43. Natl. Council on Radiation Protection and Measurements, *Basic Radiation Protection Criteria*, Rpt. 39 (Natl. Council on Radiation Protection and Measurements 1971).

tion of risk assessment methodology to the time of its publication. The issue of the shape of the dose response curve at low doses was discussed in considerable depth, and essentially sidestepped, but BEIR I did support the use of the LNT on pragmatic, but not necessarily scientific, grounds. It stated "Although experimental evidence indicates that the dose-effect relationship for x rays and gamma rays may not be a linear function that is invariant with dose and dose rate, the use of a non-linear hypothesis for estimating risks in support of public policy on radiation would be impractical in the present state of knowledge. . ." It further stated that "use of linear extrapolation . . . may be justified on pragmatic grounds as a basis for risk estimation."[44]

Also in 1972, the U.S. Atomic Energy Commission (AEC) issued revised regulations pertinent to the construction and operation of nuclear power facilities; Appendix I to Title 10, U.S. Code Federal Regulations Part 50 incorporated for the first time the concept of "as low as practicable" (ALAP, now known as ALARA) into regulations. The ALAP/ALARA concept considered dose reduction on both an individual and collective basis and considers the risk from a given low level exposure to be the same whether delivered to a single individual or spread out over many individuals; for example, a dose of 100 mrem to a single individual would produce in that individual the same risk of developing cancer as would the collective risk from a dose of 1 mrem to 100 individuals. Therefore the ALAP/ALARA concept implicitly assumes an LNT dose-response. Thus, the single year 1972 saw a rather significant shift in acceptance and applicability of the LNT to radiation protection.

There was not, however, unanimity of opinion among the learned scientific bodies with respect to broad and essentially unrestricted application of LNT. In contrast, perhaps, to the BEIR I report, the 1972 UNSCEAR report was not so accepting of the general applicability of the LNT to low level radiation response, stating:

> Estimates of risk per unit dose derived from epidemiological investigations are valid only for the doses at which they have been estimated and they can be applied to a range of doses only if there is a linear relationship between dose and incidence since extrapolations beyond that range may lead to gross errors.[45]

The clear implication is that for some low level effects, response may not be linear; it also leaves open the door to the possibility of a threshold.

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44. Natl. Acad. of Sci. Natl. Research Council, *supra* n. 42, at 89.

45. U. N. Sci. Comm. on the Effects of Atomic Radiation, *Ionizing Radiation: Levels and Effects,* Sales No. E.72 IX.7, ISBN 92-1-142143-8, 403 (U. N. 1972).

It is of interest to note that this same theme was repeated more than two decades later by the NCRP in its report on collective dose,[46] which, while allowing for the presumption of an LNT response for both carcinogenesis and genetic mutations, nonetheless felt constrained to recommend that the application of the linear dose-response be limited to those areas of the curve for which actual data exist.[47] A similar concern was also expressed in mid-decade by the NCRP, which revisited and confirmed its 1971 report.[48]

Another, and perhaps most significant, conceptual change with respect to radiation protection practice was put forth in 1977, when the ICRP discarded the old Maximum Permissible Dose system with its underlying bases in favor of a new risk-based system of radiation protection based on three considerations: justification of practices; optimization of doses; and limitations of individual risks and presented this new system in its Publication 26.[49] More significantly, carcinogenesis was defined as a stochastic (now termed nondeterministic) effect, and the new system represented a complete departure from the concept of a threshold. The impact of this novel concept electrified the radiation protection community. In developing estimates of stochastic risks to specific tissues, the ICRP derived weighting factors for specific tissues based on the carcinogenic risk of radiation exposure and then used these to calculate a new dose quantity – the effective dose equivalent. The effective dose equivalent was the summation of the weighted combination of doses to specific tissues and organs from internal irradiation, along with doses to the whole body from external irradiation. The result was the effective dose equivalent, a single numerical value that was an expression of the total stochastic risk of radiation exposure – partial body irradiation as well as whole body irradiation – in terms of the equivalent risk of whole body irradiation.[50] Over the years, the ICRP system has been refined and expanded upon by both the ICRP[51]

46. Natl. Council on Radiation Protection and Measurements, *supra* n. 5.

47. *Id*.

48. Natl. Council on Radiation Protection and Measurements, *Review of the Current State of Radiation Protection Philosophy*, Rpt. 43 (Natl. Council on Radiation Protection and Measurements 1975).

49. Intl. Comm. on Radiological Protection, *Recommendations of the International Commission on Radiological Protection*, 26 Annals of the ICRP 1 (no. 3 1977).

50. *Id*.

51. *Id*.; Intl. Comm. on Radiological Protection, *Limits for Intakes of Radionuclides by Workers,* ICRP Publication 30, (Oxford: Pergamon Press 1978-80); *see also* various numbers in *Annals of the ICRP* 2(3/4), 4(3/4), 5, 6(2/3), 7, 8(1-3) 1978-80; Intl. Comm. on Radiological Protection, *Individual Monitoring for Intakes of Radionuclides by Workers: Design and Interpretation*, 54 Annals of the ICRP 19 (nos. 1-3 1990); Intl. Comm. on Radiological Protection, *supra* n. 2, at 1-201.

as well as the NCRP[52] and ultimately adopted into regulations by American regulatory bodies including the Environmental Protection Agency,[53] Department of Energy,[54] and United States Nuclear Regulatory Commission.[55]

Although basically recommending the same permissible exposure limit of 50 mSv (5 rem) annually for occupational exposure, the new ICRP system represented a sharp departure from past practice and was met with resistance, particularly in the United States. There was considerable and often time contentious argument within the operational health physics community regarding the new risk-based proposed ICRP dose limitation system. One particular objection related to the ICRP recommendation to prospectively assign the entire dose incurred over fifty years from an intake of radioactivity to the year of intake. This recommendation imposed additional restrictions on permissible limits for intake of long-lived bone seeking alpha emitters such as isotopes of Pu and Am, and was particularly objectionable to some health physicists who were involved with the protection aspects of these nuclides. Significantly, the basic objection was not to the risk-based concept, *per se*, but rather with the administrative problems of implementation of the new system and, to some extent, resistance to change.

The ICRP system introduced the fatal accident rate in so-called safe industries as a measure of acceptable risk from radiation exposure – an important and highly significant step, it provided a perspective as well as a means of comparison of radiation risks with those associated with other human endeavor. The new ICRP system also defined and differentiated between stochastic and nonstochastic (now nondeterministic and deterministic) risks, and thus quite appropriately retained the threshold concept where it clearly applied, namely to so-called nonstochastic risks such as radiation-induced lenticular opacities and skin changes. It thus left open the door to applying the threshold concept to specific stochastic effects, if indicated by experimental data.

52. Natl. Council on Radiation Protection and Measurements, *Recommendations on Limits for Exposure to Ionizing Radiation,* Rpt. 93 (Natl. Council on Radiation Protection and Measurements 1987).

53. 52 Fed. Reg. 2822, 2822-2834 (January 27, 1987).

54. U. S. Dept. of Energy, *Radiation Protection for Occupational Workers*, Order 5480.11 (Dec. 21, 1988).

55. 56 Fed. Reg. 23360, 23360-23474 (May 21, 1994).

THE LNT AS A PARADIGM

The late 1970s saw the application of the LNT to widespread prediction of what were euphemistically termed health effects in studies of the effects of anthropogenic environmental radiation, some of which predicted as few as a few dozen effects of a specific kind over periods as long as 10,000 years in the entire world population. By 1980, the LNT was well on its way towards being established as a paradigm or even a fundamental principle of radiation biology.[56] Heavily reliant on the emerging data and results from the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, both the NCRP[57] and ICRP,[58] expanded and enlarged the risk based system originally put forth by the ICRP in 1977, utilizing the LNT dose-response model as the basis for their recommendations. In addition to providing bases for establishing a dose limit, ICRP Publication 60, the successor to the pioneering 1977 Publication 26, developed a new risk projection model using a multiattribute approach for weighing risk, considering such factors as lifetime risk of fatality, loss of life expectancy, and age-related mortality and morbidity considerations for both fatal and nonfatal somatic and hereditable effects. The concept of a Dose Rate Effectiveness Factor (DREF), applicable to low LET radiations and in large measure based on the time required to repair single strand breaks in DNA, was introduced and recommended for application at doses below 200 mGy or dose rates of less than 100 mGy per hour.[59]

Perhaps the most comprehensive and certainly highly influential ongoing review and evaluation of the scientific literature with respect to low-level response to radiation has been undertaken by the BEIR Committee, which issued its first report on the effects of low level radiation in 1972.[60] This report was published without incident and generally well received by the scientific community. The BEIR Committee consensus and indeed its collegiality came apart with the publication of the so-called BEIR III report. The original version of BEIR III was released in May 1979, but distribution was quickly halted because of disagreement among members of what was supposed to have been a consensus committee over the shape of the dose response curve. In the transmittal letter that accompanied the final version of the report, which was not published until July 1980, more than a year later, Philip Handler, President of the National Academy of

56. Kathren, *supra* n. 1, at 376-390.
57. Natl. Council on Radiation Protection and Measurements, *supra* n. 52.
58. Intl. Comm. on Radiological Protection, *supra* n. 51.
59. Intl. Comm. on Radiological Protection, *supra* n. 2, at 19.
60. Natl. Acad. of Sci. Natl. Research Council, *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation* (Natl. Acad. Press 1972).

Sciences, noted with refreshing candor in his cover letter to the funding agency that the report "has had a troubled history" and that two members of the Committee had found it impossible to endorse the report.[61] The final revised report attempted to present a balanced consensus viewpoint and, by and large, adopted the linear-quadratic model for cancer induction. And, in what may well be an unprecedented action, the final version included statements by the two dissenting Committee members, one by BEIR Committee chairman Edward P. Radford in support of the LNT and the other by Harald H. Rossi who espoused the pure quadratic form of the dose response curve. Radford provided a detailed twenty-five-page argument in favor of the LNT, buttressed with thirty-five references from the scientific reviewed literature. By contrast, Rossi's dissent was only six pages in length, without references. The final report of the Committee actually presented a range of dose-response models for solid tumor induction by low-level radiation, ultimately expressing a preference for a linear-quadratic model, although also putting forth the caveat that the available data were insufficiently conclusive to definitively decide on a model.

BEIR III stated that it was likely undeterminable if dose rates at environmental levels, i.e., on the order of 1 mGy per year (effective doses from radon were not included), were detrimental to people and further concluded that the available data did not support an increased risk of carcinogenesis at low dose rates from low LET radiations. The Committee also recognized that differing human genotypes as well as age differences may alter the carcinogenic risk associated with a specific dose. For certain developmental effects from irradiation *in utero*, based on a multi-target/multi-hit theory, a threshold was considered likely. Significantly, although it examined various curvilinear models, the Committee agreed that the LNT model still provided the best fit to the observations of genetic effects, extrapolating these effects from animal studies even though genetic effects had never been observed in human populations. But although these and the other important conclusions were subscribed to, or at least accepted by, twenty-one of the twenty-three members of the Committee, the contentious argument within the Committee and the poles apart minority opinions and non-acceptance of the report by two of its members, one of whom was the Chairman, served to fuel further dissent both within the radiological community and among interested lay persons and interveners; for some, battle lines had clearly been drawn.

The contentious BEIR III report was updated in 1990 by BEIR V, which once again was devoted to a comprehensive review of scientific

61. Natl. Acad. of Sci. Natl. Research Council, *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: BEIR III*, iii (Natl. Acad. Press 1980).

knowledge relating to the broad topic of health effects from low-level exposure to ionizing radiation, and which provoked a swell of controversy, criticism and concern within the radiological community upon its publication, largely because of its increased risk estimates for both solid tumors and leukemia, and by the unequivocal advocacy of the LNT as the best model for induction of solid tumors by low level radiation.[62] The BEIR V risk estimates for solid tumors following a short period of irradiation were calculated by an LNT response model and were about threefold times greater than those previously estimated in BEIR III. Also introduced was the Dose Rate Effectiveness Factor, which modified or reduced the lifetime risk, perhaps by a factor of two or more, of a specific dose if delivered over a protracted period of weeks or longer. In sharp contrast to BEIR III, there was no equivocation over the shape of the dose-response curve; BEIR V concluded that the available human data for solid tumors were best fit by a linear dose response relationship. For leukemias, the Committee stated that the available data were best fit by a linear-quadratic curve and the resultant risk calculations estimated the radiogenic leukemia risk to be about four times greater than put forth in BEIR III. From examination of the Japanese atomic bombing survivors, the Committee concluded that irradiation *in utero* resulted in children with diminished intelligence test scores and performance in school, noting that the degree of impairment was related to dose and was greater if delivered early in the gestation period. The Committee again noted the lack of human data to verify estimates of genetic effects, generally confirming previous estimates of genetic risk in humans and the applicability of previous extrapolations from animal data, while at the same time observing that review of the human data showed less evidence of inherited radiation-induced defects than was previously estimated from the animal data. As of this writing (January 2003), the BEIR VII report dealing with low-level radiation effects is still in preparation, but even so has not been free of conflict and controversy. One well-qualified and highly respected member of the Committee was summarily removed from the Committee, which has been accused of politicizing the process and stacking the deck in favor of a particular desired result, i.e., the support and application of the LNT.

Alternating with the BEIR III and BEIR V reports, which dealt with low-level radiation effects generally, were BEIR IV[63] and BEIR VI[64] published in 1988 and 1999, respectively. The 602-page BEIR IV report was a

62. *Id.*

63. Natl. Acad. of Sci. Natl. Research Council, *Health Risks of Radon and Other Internally Deposited Alpha-Emitters: BEIR IV* (Natl. Acad. Press 1988).

64. Natl. Acad. of Sci. Natl. Research Council, *Health Effects of Exposure to Radon: BEIR VI* (Natl. Acad. Press 1999).

comprehensive treatise on the health risks of radon and other internally deposited alpha emitting radionuclides known to produce health effects.[65] For mathematical simplicity, the Committee characterized radiation-induced lung cancer in terms of a modified relative risk model, which included consideration of both time since exposure and age at risk. Although the LNT figured prominently in the risk determinations BEIR IV, there was no out and endorsement of any one particular dose-response model. Different endpoints were characterized by different dose response functions, including along with the LNT, linear quadratic along with a number of specific suggestions for further epidemiologic and other studies with an eye towards more clearly revealing the shape of the long term low dose response curve. Based on mechanistic considerations, BEIR VI "chose to use a linear relationship between risk and low doses of radon progeny without a threshold"[66] and fully endorsed the LNT as applicable to carcinogenesis from low doses of radon, explicitly stating, "linearity is thus a reasonable assumption with the implication of no threshold in dose."[67]

Over the past two decades or so, the experiences of other learned bodies concerned with low-level radiation risks, such as UNSCEAR,[68] the ICRP, and the NCRP, mirror to a great extent the BEIR Committee. Most recently, NCRP Publication 136 concluded on the basis of recent studies describing the so-called "bystander effect" – the influence of a struck or hit cell on its unirradiated neighbors – that there could be a linear response until all cells were hit. More significantly, it stated that "the majority of biological dosimetry studies . . . provide broad support for a linear response at low-dose levels."[69] Thus, over the past quarter century, a more or less consistent radiation protection philosophy has evolved, based largely on the LNT and incorporating the principle that any exposure to ionizing radiation, however small, carries with it a commensurate risk of a long-term effect, and that radiation exposures must therefore be kept as low as reasonably achievable below the numerical limits established as radiation protection standards. ALARA has become a fundamental principle of radiation protection practice, and implicitly embodies the LNT. The

65. Natl. Acad. of Sci. Natl. Research Council, *supra* n. 63

66. Natl. Acad. of Sci. Natl. Research Council, *supra* n. 64, at 88.

67. *Id*. at 66.

68. U. N. Sci. Comm. on the Effects of Atomic Radiation, *Sources, Effects and Risks of Ionizing Radiation,* Sales No. E.88 IX.7, ISBN 92-1-142143-8 (U. N. 1988); U. N. Sci. Comm. on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation,* Sales No. E.94 IX.2 (U. N. 1993); U. N. Sci. Comm. on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation,* Sales No. E.94 IX.7, ISBN 92-1-142211-6 (U. N. 1994).

69. Natl. Council on Radiation Protection and Measurements, *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation,* Rpt. 136, 77 (Natl. Council on Radiation Protection and Measurements 2002).

LNT itself has gone from consideration as an upper limit bound of risk to the more or less general belief that this model is indeed scientifically correct, a view so strongly held that attempts by regulatory bodies to incorporate minimum levels – so-called *de minimis*, below regulatory concern, or the negligible individual risk level of the NCRP – have been abandoned. Some experts even go so far as to suggest that the LNT model may even understate the risk of low-level radiation exposure. Now, after slightly more than a century of experience with ionizing radiation, the shape of the dose-response curve at low dose levels is still unknown but the LNT dose-response model for carcinogenesis has gained considerable currency and indeed is solidly entrenched as the basis for radiation protection standards and risk analysis.

SOME COMMENTS ON HUMAN DATA SUPPORT OF LNT

Humankind has beneficially used and experimented with ionizing radiation for more than a century, and it would seem that in this span of time, sufficient human data would have become available such that human response to low doses of ionizing radiation would be known with a fair, if not high, degree of assurance. However, unlike animal studies, which can be designed to study various end points under controlled conditions, human data suffer from many weaknesses. Studies of low-level radiation response in human populations is generally accomplished by epidemiologic and related studies of exposed populations, but such studies are subject to a number of weaknesses including low statistical power, population biases, dosimetry uncertainties, errors of diagnosis, healthy worker effect, changes in the cohort, and other confounders including genetics, diet and nutritional factors, medical or environmental radiation exposures, socio-economic status, and even investigator bias.[70]

Still, despite numerous and oft times significant limitations, radioepidemiologic studies have lent or have been interpreted to lend considerable support to the LNT. Studies of radiation workers have been particularly controversial and contentiously criticized, frequently on methodological grounds. Long-term low-level radiological exposure effects that have been documented or thought to occur in human populations include both leukemia and solid tumors, life shortening, development or teratogenic effects on the developing fetus, increased leukemia among children irradiated *in utero,* and possible adverse immunologic effects. On the other side of the coin, judging by the numbers of scientific papers reporting the phenome-

70. Kathren, *supra* n. 8, at 130-138.

non, there appears to be abundant evidence of a low-level radiation-induced stimulatory effect, which may result in an increased life span or reduced incidence of chronic disease such as cancer. Controversial and perhaps as it may be, hormesis it still needs to be considered as a possibility when evaluating low-level radiation dose response, if for no other reason than scientific objectivity and completeness.

Reference to some of the more relevant publications from the voluminous scientific literature relating to low-level radiation response in humans is important in providing insights into the general acceptance of the LNT for radiation protection purposes. Leukemia is arguably the best known and most widely studied stochastic effect and thus might serve as the exemplar for the difficulties associated with human studies of the association of low-level radiation exposure and stochastic effects generally. However, although there is ample evidence from both human and animal study to reliably conclude that certain types of leukemia are in fact radiation related, the shape and dimensions of the dose response curve are still not well established, even though the consensus seems to be that the shape is linear-quadratic.[71] And, the shape let alone other parameters and constants of the leukemia dose-response curve are unlikely to fit other carcinogenic effects.

Although a LNT dose response is not inconsistent with data from several tens of radioepidemiologic studies of leukemia in humans, it is nonetheless not possible to draw definitive conclusions with respect to whether very low dose or fractionated exposures do in fact carry significant leukemia risks, and whether the LNT dose-response model in fact applies to leukemogenesis. In a relatively recent case control study of persons exposed to weapons test fallout, Stevens et al.[72] found indication of possible leukemogenesis at low doses. Other studies in populations exposed to fallout or diagnostic radiation have been negative or marginally positive.[73] Comparison studies in China of stable populations resident in high and low background areas have likewise failed to show an association between leu-

71. Natl. Acad. of Sci. Natl. Research Council, *Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V* (Natl. Acad. Press 1990); Natl. Acad. of Sci. Natl. Research Council, *supra* n. 64; Natl. Council on Radiation Protection and Measurements, *supra* n. 69.

72. W. Stevens et al., *Leukemia in Utah and Radioactive Fallout from the Nevada Test Site*, 264 J. Am. Med. Assn. 585, 585-591 (1990).

73. R. Gibson et al., *Irradiation in the Epidemiology of Leukemia Among Adults*, 48 J. Natl. Cancer Inst. 301, 301-311 (1972); F. Gunz, & H. Atkinson, *Medical Radiations and Leukaemia: A Retrospective Survey*, 1 British Med. J. 389, 389-393 (1964); A. Linos et al., *Low-Dose Radiation and Leukemia*, 302 New England J. Med. 1101, 1101-1105 (1980); S. Preston-Martin et al., *Diagnostic Radiography as a Risk Factor for Chronic Myeloid and Monocytic Leukaemia (CML)*, 59 British J. Cancer 639, 639-644 (1989); Alice M. Stewart et al., *Malignant Disease in Childhood and Diagnostic Irradiation*, ii in utero, Lancet 447, 447-448 (1958).

kemia and low-level exposure,[74] as have follow up studies in patients treated for hyperthyroidism with radioiodine.[75] But other studies in groups with protracted or low doses at least imply an association between leukemia and low dose irradiation.[76] And, suggestive of a threshold are studies of x-ray workers and radiologists in which there is an apparent association between leukemia and high doses, but studies of persons with lower doses have not shown such an effect.[77] Perhaps the most definitive results have come from the Japanese atomic bomb survivors, by far the largest and most extensively studied cohort. In this group, there was elevated leukemia incidence peaking at five to six years post exposure along with an excess of a number of solid tumors correlated with dose.[78] Despite this apparently solid and generally accepted evidence for a low-level leukemogenic effect, a few critics have pointed to genetic population biases and the fact that this was a war-time population stripped of young healthy males with borderline nutrition as reasons for doubting, if not actually rejecting, these findings, as well as the observation by Kondo[79] that at doses estimated to be in the range of 10 to 90 mSv, there was in fact a lower leukemia death rate among survivors.

At first glance, comparison of the health experience of radiation workers to that of their occupational cohorts or siblings would appear to offer the greatest promise of validating the LNT hypothesis. Of the several dozen studies done to date, significant excess leukemia mortality in radiation workers has been observed in only one. Meta-analysis of the data from several studies has been carried out by several investigators and is currently under way by the International Agency for Research on Cancer, without definitive results. In one such study, by Gilbert et al.,[80] positive

74. L. Wei, *Health Survey in High Background Radiation Areas in China*, 209 Science 877, 877 (1980).

75. D.A. Hoffman et al., *Cancer Incidence Following Treatment of Hyperthyroidism*, 11 Intl. J. Epidemiology 218, 218-224 (1982); L. Holm et al., *Cancer Risk after Iodine 131 Therapy for Hyperthyroidism*, 83 J. Natl. Cancer Inst. 1072, 1072 (1991).

76. F. Davis et al., *Cancer Mortality after Multiple Fluoroscopic Examinations of the Chest*, 78 J. Natl. Cancer Inst. 45, 45-652 (1987); R. F. Spengler et al., *Cancer Mortality Following Cardiac Catheterization: A Preliminary Follow-up Study on 4, 891 Irradiated Children*, 71 Pediatrics 235, 235-239 (1983).

77. John D. Boice, Jr. et al., *Diagnostic X-ray Procedures and Risk of Leukemia, Lymphoma, and Multiple Myeloma*, 265 J. Am. Med. Assn. 1290, 1290-1294 (1991); S. Jablon & R. Miller, *Army Technologists: 29-Year Follow Up for Cause of Death*, 126 Radiology 877, 877-879 (1978).

78. H. Kato & Y. Shimizu, *Cancer Mortality Risk Among A-Bomb Survivors*, in *Health Effects of Atomic Radiation* 225-236 (Proc. of Japan-USSR Symposium on Radiation effects Research June 25-29, 1990).

79. S. Kondo, *Rational Risk Estimation in Relation to Atomic Bomb Radiation*, 31 J. Radiation Research 174, 174-188 (1990).

80. Ethel S. Gilbert et al., *Updated Analyses of Combined Mortality Data for Workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant*, 136 Radiation Research 408, 408-421 (1993).

risk estimates were indicated, but the wide confidence intervals do not preclude the possibility of no association. In their meta-analysis of seven studies, Wilkinson and Dreyer[81] concluded that low-level irradiation resulted in an elevated risk from leukemia, but again, this study has been criticized on methodological grounds.[82] Thus, despite the large number of studies, the data or the analytical procedures are inadequate to validate the LNT, or to establish the existence of a threshold, or to otherwise characterize the shape of the dose response curve with a high degree of confidence. The problem is further exacerbated by the latency period, which is thought to be variable for different types of leukemia[83] and possibly by infection, which may be a confounder.[84]

The failure of human studies of radiation-induced leukemia to conclusively demonstrate the LNT is mirrored by studies of other stochastic effects in human populations. By and large, the results of such studies are consistent with the LNT, but none have provided compelling validation. Indeed, there is some strong evidence, largely ignored, to the contrary. In particular the data from the radium dial painters show clear evidence of both a threshold and nonlinearity for osteosarcomas and the study itself arguably has fewer problems and greater credibility than the typical radioepidemiological study.[85] Osteosarcoma was completely absent in dial painters whose skeletal dose was less than 10 Gy; as the skeletal dose was increased, the fraction of dial painters developing osteosarcoma rose steeply and then leveled off at about 28%, never exceeding this incidence no matter how high the dose.

As has been noted above, contemporary radiation protection practice is firmly grounded on the LNT model of long-term low-level carcinogenic risk, with effects at low doses determined largely from epidemiologic studies and extrapolation from high dose studies. The epidemiologic basis, however, is less than definitive as has been pointed out by epidemiologists themselves. In critiquing the epidemiologic basis for the linear hypothesis, Gilbert[86] and Land,[87] both highly respected radioepidemiologists, have identified what they consider to be significant problems associated with

81. Gregg S. Wilkinson & N. A. Dreyer, *Leukemia Among Nuclear Workers with Protracted Exposure to Low-Dose Ionizing Radiation*, 2 Epidemiology 305, 305-309 (1991).

82. Ethel S. Gilbert, *Leukemia Among Nuclear Workers*, 3 Epidemiology 275, 275-276 (1992).

83. Natl. Acad. of Sci. Natl. Research Council, *supra* n. 71.

84. L. J. Kinlan et al., *Evidence from Population Mixing in British New Towns 1946-85 of an Infective Basis for Childhood Leukaemia*, 336 Lancet 577, 577-582 (1990).

85. Robley D. Evans, *Radium in Man*, 27 J. Health Physics 497, 497-510 (1974).

86. Ethel S. Gilbert, *Studies of Workers Exposed to Low Doses of External Radiation*, 6 Occupational Med.: State of the Art Reviews 665, 665-680 (1991).

87. Charles E. Land, *Low Dose Extrapolation, Time Following Exposure and Transport between Populations*, in O. F. Nygaard & J. F. Lett, *Advances in Radiation Biology, Effects of Low Dose and Dose Rate Reduction* 259-272 (Vol. 16, Academic Press 1993).

application of radioepidemiologic studies. On the other hand, epidemiologic studies in the former Soviet Union are providing evidence of hitherto unreported and perhaps even unsuspected low-level effects and much shorter latency periods for the development of cancers than heretofore suspected.[88]

Thus, in brief summary, the evidence for the existence or lack of the LNT in human populations is anything but clear-cut. As has been recently pointed out by the NCRP,[89] the human data typically are consistent with the LNT but do not strongly support its existence. One possible explanation may be that the dose response for each specific stochastic end point is different, and that not all dose response curves are of the LNT type. For some effects, notably osteosarcoma in the radium dial painters, evidence of a threshold is strong, as has been pointed out by Evans and his coworkers.[90] But these results may not, in fact, be inconsistent with the LNT for carcinogenesis if the possibility of an *effective threshold*, determined by dose, dose rate, and other factors, which determine the latency period, is assumed. If the latency period for tumor expression following low-level exposure exceeds the remaining life span, or death occurs from other unrelated causes, there is obviously no effect, and hence an effective threshold. This concept is buttressed by the work of Raabe,[91] whose three dimensional analysis of dose-rate, time and response, suggest that there is no significant difference in the shape of dose response curves for radiation induced cancer, widely accepted as a stochastic (nonderministic) effect, and for radiation induced non-neoplastic tissue injury, a deterministic effect.

As the second century of human experience with x-rays and radioactivity progresses, so too will our understanding of the complexities of human response to low-level radiation. For the present, and for the foreseeable future, however, our radiation protection standards and efforts will remain strongly anchored to the LNT dose response for low-level radiation carcinogenesis.

88. L. N. Astakhova et al., *The Status of the Thyroid System and the Peculiarities of its Pathology Formation in Children and Teenagers Affected by Iodine Radionuclides due to the Chernobyl Accident* 190-193 (Proc. of Japan-USSR Symposium on Radiation effects Research June 25-29, 1990); M. M. Kossenko & M. O. Degteva, *Cancer Mortality and Radiation Risk Evaluation for the Techa River Population*, 142 Science Total Env. 73, 73-89 (1994).

89. Natl. Council on Radiation Protection and Measurements, *supra* n. 5; Natl. Council on Radiation Protection and Measurements, *supra* n. 69.

90. Evans, *supra* n. 85, at 497-510.

91. Otto G. Raabe, *Three-Dimensional Models of Risk from Internally Deposited Radionuclides*, in *Internal Radiation Dosimetry* 633, 633-656 (Otto G. Raabe, Medical Physics Publishing Co. 1994).