Special Submission

PATHWAY TO A PARADIGM: THE LINEAR NONTHRESHOLD DOSE-RESPONSE MODEL IN HISTORICAL CONTEXT: THE AMERICAN ACADEMY OF HEALTH PHYSICS 1995 RADIOLOGY CENTENNIAL HARTMAN ORATION

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Abstract—**This paper traces the evolution of the linear nonthreshold dose-response model and its acceptance as a paradigm in radiation protection practice and risk analysis. Deterministic effects such as skin burns and even deep tissue trauma were associated with excessive exposure to x rays shortly after their discovery, and carcinogenicity was observed as early as 1902. Still, it was not until 1925 that the first protective limits were suggested. For three decades these limits were based on the concept of a tolerance dose which, if not exceeded, would result in no demonstrable harm to the individual and implicitly assumed a threshold dose below which radiation effects would be absent. After World War II, largely because of genetic concerns related to atmospheric weapons testing, radiation protection dose limits were expressed in terms of a risk based maximum permissible dose which clearly implied no threshold. The 1927 discovery by Muller of x-ray induced genetic mutations in fruit flies, linear with dose and with no apparent threshold, was an important underpinning of the standards. The linear nonthreshold dose-response model was originally used to provide an upper limit estimate of the risk, with zero being the lower limit, of low level irradiation since the dose-response curve could not be determined at low dose levels. Evidence to the contrary such as hormesis and the classic studies of the radium dial painters notwithstanding, the linear nonthreshold model gained greater acceptance and in the centennial year of the discovery of x rays stands as a paradigm although serious questions are beginning to be raised regarding its general applicability. The work includes a brief digression describing the work of x-ray protection pioneer William Rollins and concludes with a recommendation for application of a *de minimis* dose level in radiation protection.**
Health Phys. 70(5):621–635; 1996

Key words: dose assessment; x rays; radiation risk; safety standards

INTRODUCTION

It is but a few months short of a full century since Wilhelm Conrad Roentgen made a most insightful discovery, a discovery which has led to many changes in our understanding of the world and to numerous beneficial applications for mankind. As we look back over the century since this great discovery, we readily will recognize that the gift of x rays is a two sided one, and that our noble profession of health physics exists because the benefits of that discovery cannot be realized without the payment of some price in the form of detriment. Indeed, it is precisely because of the two sided nature of this discovery that the profession of health physics has evolved.

A central aspect of the profession of health physics is to establish practical scientifically based radiation protection standards with the worthy aim of minimizing the detriment while at the same time enhancing the benefits derived from x rays and other sources of ionizing and nonionizing radiation. For at least four decades, more than the professional lifetimes of virtually all current practitioners of health physics, the fundamental underpinning of these standards has been the linear nonthreshold dose-response model. Briefly articulated, the model states that any exposure to ionizing radiation, no matter how small, carries with it a commensurate risk of detriment (i.e., a fatal cancer or adverse genetic effect), with the risk being proportional to the dose accumulated. Professionally, although aware of other mathematical characterizations of dose-response, most of us engaged in the practice of health physics have known of nothing other than the linear nonthreshold model as the basis for the dose limits, risk evaluations, and other protective measures, at least insofar as the regulatory aspects of our work has been concerned. The model has assumed the status of a paradigm which, according to the dictionary, is synonymous with an ideal, a standard, a paragon or a touchstone.

The pathway to this paradigm will be the theme of this presentation. Thus, this paper will briefly review the scientific bases and supporting studies that led to the development and acceptance of the linear nonthreshold model for low level radiation effects, emphasizing studies carried out in human populations. It will include consideration of observations and studies such as hormesis and the clear threshold for certain stochastic effects such as osteogenic sarcoma in the radium dial painters that do not support the linear nonthreshold model, as well

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(*Manuscript received* 4 *August* 1995; *accepted* 6 *January* 1996)
0017-9078/96/$3.00/0

as the plethora of studies that do. It concludes with a brief examination of the contemporary application of risk assessment in radiation protection practice and closes with the recommendation that to better fulfill the central goal of the profession of health physics, consideration should be given to incorporation of a *de minimis* basis or philosophy for operational radiation protection and for application to risk assessment of low level radiation effects.

IN THE BEGINNING: THE FIRST DECADE

The pathway begins, as it necessarily must, with the twin discoveries of x rays and radioactivity, made only a few months apart a few years before the close of the nineteenth century. In November 1895, German physicist Wilhelm Konrad Röntgen recognized that an energized evacuated Crookes tube was emitting a penetrating form of radiation and so discovered x rays. The following March, French physicist Henri Becquerel observed the blackening of a photographic plate on which an ore of uranium had been placed and correctly deduced the existence of a penetrating form of radiation similar to x rays.

Few discoveries have excited the world, both scientific and lay alike, as did the discoveries of x rays and radioactivity, and a period of intensive study of these new phenomena began. Thus it was only a matter of weeks after the discovery by Röntgen that reports of deleterious biological effects attributable to the x rays began to appear. The first of these appeared as brief news items describing eye irritation associated with the use of x rays and fluorescent screens reported independently in two separate brief news items by two Americans, Thomas Alva Edison and William J. Morton in the 5 March 1896, issue of the British journal *Nature* (Edison 1896; Morton 1896) incorrectly attributing these effects to x-ray exposure (Kathren 1962). About the same time, H. Marcuse, a German physician, associated injury to the skin—dermatitis and loss of hair—with exposure to x rays in the first of what was to become a long inventory of articles in the medical and scientific literature describing what were clearly acute and hence deterministic effects manifested in the form of dermatitis, epilation, and erythema with deeper tissue trauma in the more extreme cases (Marcuse 1896).

Not surprisingly, the initial observations in humans as well as studies of the effects of x rays (the great interest in radioactivity was to come a few years later after the publication of the doctoral dissertation of Marie Curie in 1903) were related to deterministic effects. By the turn of the century, a scant five years after the discovery of x rays, the fact that excessive exposure to x rays would result in a variety of acute effects from high level exposure was by and large recognized and accepted by the scientific and medical community. A minority, including some prominent medical experts, remained unconvinced that skin burns and other acute deterministic effects observed in some patients were in fact attributable to their exposure to radiation, offering alternative explanations. But within another few years, virtually all accepted the incontrovertible fact, likely aided in this conclusion by a spate of successful malpractice lawsuits brought by those who had suffered such effects (Kathren 1962). Yet to be recognized and studied, however, were long term non-deterministic or stochastic effects and the effects of chronic low level exposure.

INTERLUDE: WILLIAM ROLLINS AND THE ORIGINS OF HEALTH PHYSICS

It is most fitting that this centennial celebration and the joint meeting of the American Academy of Health Physics, the Health Physics Society, and the American Association of Physicists in Medicine is held in the city of Boston, for it is this city that was home to William Herbert Rollins. Rollins was born in Charlestown, Massachusetts, in 1852, and was raised in the Boston suburb of Lawrence where he apprenticed to a local dentist for three years before graduating in 1873 at the age of 21 from the Harvard University dental school. Subsequently, and while engaged in his practice of dentistry, Rollins also earned a medical degree from Harvard but never was to practice that profession.

An apparently shy and reticent man with a penchant for working with his hands, dentistry was more suited to Rollins. When he learned of x rays, like so many others of the day, he quickly began his studies—all personally and privately funded—of this newly discovered form of radiant energy. Within months of the discovery, he devised a number of new applications and significant improvements to the primitive x-ray tubes of the day. His first publication, in July of 1896, described a "cryptoscope"—basically a fluoroscope for intraoral radiographic examinations, which innovatively featured leaded glass over the fluorescent screen which Rollins, some years later was to assert was designed to protect the eyes of the operator from radiation (Kathren 1964). His second publication, a month later, observed the value of x rays in dentistry and described the intraoral use of celluloid films rather than glass plates for intraoral radiography (Rollins 1896). An interesting invention, described in 1899, was the "Seehear," basically a combination of a fluoroscope and stethoscope which enabled the radiologist to hear the sounds from the heart and lungs as he was visualizing them.

From the beginnings of his investigations into the nature of x rays, Rollins was apparently concerned with the potential hazards of x rays and protection from the same. He devised collimating diaphragms and leaded tube housings, perhaps as much to improve radiographic image quality as for protection, but it was clear that x-ray protection was an important aspect of his work. In 1901–2, he published a series of brief notes in the *Boston Medical and Surgical Journal* describing a series of straightforward experiments in which he exposed guinea pigs to x rays and observed the results. Primitive, crude, and, certainly by today's standards, unsophisticated and

perhaps even childlike in design and execution, these papers nonetheless rank as classics of radiation biology and radiation protection. The first was quite simply titled "X-light Kills" (Rollins 1901a). In the terse and unpolished style that characterized his writing, Rollins used only 261 words in the *Boston Medical and Surgical Journal*, dated 14 February 1901, to describe an experiment in which he exposed two guinea pigs to x rays two hours per day, noting how one died on the eighth day of the experiment and the other on the eleventh without external manifestation of trauma or pathology. Skin burns, heretofore always associated with excessive x ray exposure, were not noted. This simple experiment was apparently the first in which it was shown that acute x-ray exposures could kill the higher forms of life. His reason for brevity was given in these sage words which have modern application as well: Rollins noted that "many details . . . are not given, remembering how many hours of sunlight have been lost through being obliged to read long papers" (Rollins 1901a). The brief article, however, included three protective precautions recommended to users of x rays: radio-opaque glasses, shielded tube housings, and limiting exposure of the patient to the region of interest.

In the next issue of the *Boston Medical and Surgical Journal*, Rollins (1901b) described the results of exposing a pregnant guinea pig to x rays, noting the death of the fetus and expressing concern about exposing pregnant women for pelvimetry or routine x-ray examinations. Decades were to pass before routine radiography of pregnant women was halted, and then largely as a result of the classic epidemiologic investigation of Stewart and coworkers (1958) which linked x rays *in utero* to leukemia in childhood. In a third note, Rollins described the lack of effects of his control animals and offered a suggestion that was ahead of his time, based on his observations of the exposed animals: that the demonstrated deep tissue effects that he had observed might prove valuable in treatment of inoperable cancers, an application first attempted two years later by Chicago radiologist Nicholas Senn who favorably treated leukemia with splenic irradiation (Senn 1903).

A subsequent paper described still more studies with guinea pigs exposed to external x-ray fields, and included a brief history of the theories of x-ray burns. It also included tabulation of the daily weights of the exposed animals and controls, showing a drop for the former prior to their death, and concluded with a lament of the inability of Rollins to interest a pathologist in examining the tissues from his dead animals and the words "it is hoped some clear-eyed observer will realize here is a new field where useful original work can be done" (Rollins 1902a) The final paper in the series summarized additional conclusions primarily related to x-ray therapy which Rollins derived from his guinea pig experiments and included the recommendation for protective purposes using only very soft x rays for superficial therapy and maintaining a large tube-to-skin distance for deep therapy (Rollins 1902b).

Rollins' contributions to x-ray protection alone were numerous and often decades ahead of their adoption. He was an early proponent of collimation and nonradiable x-ray tube housings and even designed a method of testing the efficacy of the latter, using timed fogging of a photographic plate as a quantitative measure of leakage. He applied the general principles of protection derived from x rays to radium (1902), recommended leaded goggles be worn by fluoroscopists (1902), and suggested reduction of patient exposure in fluoroscopy through the use of pulses or bursts of x rays rather than a continuous beam (1903). By the time he privately published the compendium of his works entitled *Notes on X-Light* (Rollins preferred the term 'X-light' to x rays or Roentgen rays feeling it was more descriptive and recognized the electromagnetic nature of the rays) in 1904, he had elucidated all of the fundamental principles of radiation protection, some of which would not be implemented for decades. His researches were all self financed, carried out as a hobby, and his numerous inventions and innovations were freely given to all without hinderance of patent or copyright or hint of monetary gain or personal acclaim. He was a devoted husband and left his entire estate to the Smithsonian Institution for the establishment of the William and Herbert Rollins Fund, after previously, and again with great prescience, donating land he owned near Wellfleet, Massachusetts, for the establishment of a wildlife preserve. This obscure Bostonian who flourished a century ago was a man of great character and ability. In this centennial year of the x ray, he well deserves remembrance and recognition for his pioneering contributions to x-ray science and engineering generally, and especially to health physics. It is he who truly merits the title of Father of Health Physics.

TOWARD DEVELOPMENT OF A RADIATION PROTECTION PHILOSOPHY: THE EARLY YEARS

For the first three decades after the discovery of x-rays and radioactivity, there was no indication, let alone support, for the idea that biological response—even a specific biological response—to radiation was a linear function of dose. Recognition of the carcinogenic, and hence longer term effects, of radiation exposure was first made in 1902 by Frieben based on his observation of a carcinoma on the hand in a worker in a factory producing x-ray tubes (Frieben 1902). Over the next several years, reports of a number of x ray induced malignancies, including fatalities, appeared in the literature, along with experimental studies with animals in which both skin carcinomas and sarcomas were induced by x-ray exposure. By 1911 at least 94 cases of apparent x ray induced skin carcinoma in humans were documented in the literature, an average of six per year since the discovery (Hesse 1911). By midcentury, only a total of 200 cases of x ray induced skin carcinoma had been reported (Ellinger 1957) for an incidence rate of only 2.5 per year for the subsequent four decades despite consid-

erably increased usage and opportunity for exposure. Protection practices clearly contributed to this improvement, although a part of the apparent slowing in cases may have come from decreased reporting since the phenomenon was no longer novel.

From evaluation of these first 94 cases, Hesse (1911) found that the interval between exposure and the diagnosis or recognition of the skin carcinoma averaged 9 y (range, 4 to 14 y), with the interval between an acute radiation induced dermatitis and diagnosis of the malignancy averaging 4 to 5 y (range, 1 to 11 y). This was a clear demonstration of the dependency of the latency period on dose, for the dose to those with dermatitis was likely greater than that to those who did not develop dermatitis, or in the latter cases the doses were fractionated. A few years later, the carcinogenic potential of chronic low level x-ray exposure was clearly stated by British physician Hector Colwell and his physicist colleague Sydney Russ in what may well have been the first text book of radiobiology (Colwell and Russ 1915): "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."

However, well into the first century after the discovery of ionizing radiation, the prevailing view regarding induction of malignancy by x rays was that it was necessary for actual damage (as would be the case with high exposures producing acute effects) to occur in order to ultimately lead to malignancy. And, at least in the early years of the twentieth century, many subscribed to the premise that small doses of radiation might in fact be beneficial, some citing as justification the Arndt-Schulz Law. The Arndt-Schulz Law, which applied to drugs and served as an important underpinning of homeopathy, was formulated in the late nineteenth century prior to the discovery of x rays and radioactivity and theorizes that small doses produce a stimulatory effect, while larger doses would produce increasingly deleterious effects. This is, of course, analogous to, if not an actual statement of, the more contemporary concept of radiation hormesis. The belief that small doses of radium or radium emanation (i.e., radon) was salutary was held by many reputable physicians through at least the first quarter of the twentieth century.

It was, however, the observations of potential long term effects on the blood that greatly influenced radiation protection in those early decades following the discovery of x rays and radioactivity. As early as 1911, a cause and effect relationship was postulated in four cases of lymphatic leukemia observed in radiologists (Colwell and Russ 1934). Minor blood changes, including leukopenia in radiologists, were described the following year, and, although such effects were not noted by all investigators, there was a growing awareness, perhaps subconscious to some extent, that continued low level irradiation at levels considered to be within the range of safety might produce adverse effects in the long term. This was buttressed by the deaths of a number of prominent radiation workers, including the redoubtable Marie Curie in 1934, from aplastic anemia and other causes attributable to their radiation exposure (Henshaw 1941). It was thus effects on the blood—deterministic effects, specifically—that served as the basis for early protection standards and for longer term sequelae of irradiation.

THE TOLERANCE DOSE AND THE STATUS OF RADIATION PROTECTION PHILOSOPHY: 1925

The earliest considerations of radiation effects and protection were built on the principle that a certain specific level of radiation can be incurred by various tissues without apparent ill effect. This in turn logically led to the concept of a "tolerance dose." More completely and precisely, the tolerance dose 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, of course, was considered in terms of what are now known as deterministic effects; risk (or more appropriately recognition of the hazard) was thus characterized in terms of a clinical manifestation of radiation effects such as a diminution in the circulating leukocyte count. The tolerance dose thus served as the basis for what was likely the first statement of a dose limit, determined as a fraction of the skin erythema dose, which was put forth by Arthur Mutscheller at the 1924 meeting of the American Roentgen Ray Society (Mutscheller 1925). It was a concept that served as the basis for radiation protection standards—i.e., dose limits—for the subsequent three decades.

In general, and as applied to early protection limits, the tolerance dose was based on a fraction of the so-called erythema dose, i.e., the dose required to produce a perceptible reddening of the skin. Since the erythema dose is by no means an exact quantity, dependent as it is on radiation quality, dose rate, and the specific response of the individual, the tolerance dose was also by no means an exact quantity. Mutscheller's original recommended level corresponds to a whole body dose of about 700 mSv y^{-1} and was derived from calculations of anticipated exposures in well run x-ray installations. Levels proposed by others within the next several years were, typically, roughly equivalent to a whole body equivalent dose in modern units of 250 to 500 mSv annually; an annual level considerably in excess of what is now considered as low dose in radiation protection practice.

There was considerable scientific and anecdotal support for the concept of tolerance dose. One of the few still living health physicists professionally active in the early days of the tolerance dose, Lauriston Taylor, in discussing efforts by three prominent early investigators independently working to establish a quantitative level for tolerance dose, observed "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" (Taylor 1980). There was, in fact, supporting evidence in the literature. Bar-

clay and Cox (1928) examined radiation risks to roentgenologists, making measurements under actual operating conditions.

They failed to detect any ill effect in either of the two workers they followed, one of whom they estimated was exposed to a daily dose of 0.007 unit skin dose (i.e., erythema dose) for 6 y, a dose rate 30% lower than that proposed by Mutscheller and equivalent to about 500 mSv annually in modern terms over a time period of 6 y. Similar findings were reported by other investigators, buttressing the idea that low level effects did not occur. A major failing of these studies was that they involved only a few individuals and were perhaps ingenuous in assuming that if effects were not seen in one or a few individuals exposed to relatively low level, such effects would be absent in all individuals so exposed.

The tolerance dose was thus effectively a statement of threshold in which was clearly implicit the idea of recovery (or repair) from any subclinical acute effects with denial of the possibility of long term low level effects. Such was the state of radiation risk philosophy a full three decades after the discovery of x rays and radioactivity.

WATERSHED: H. J. MULLER AND THE FRUIT FLIES

In 1927, American geneticist Herman J. Muller made a highly significant discovery which was to win for him a Nobel Prize and to exert perhaps the single most significant influence on radiation protection philosophy some twenty years later and for at least the next half century after that. In experiments with the fruit fly *Drosophila melanogaster,* Muller demonstrated that exposure to x rays could result in the mutations, and that the mutation rate was linear with dose (Muller 1928). Muller's extraordinary observation of the mutagenicity of x rays was quickly confirmed by Weinstein (1928) and shortly thereafter mutations were induced in plants by x rays (Stadler 1928) and in somatic cells (Patterson 1928; Timofeev-Ressovsky 1929), lending support to the idea that x-ray induced mutations were generic and species independent. Studies in the 1930's established that the induced mutation rate was independent of dose rate, and, perhaps most significantly, that mutation was a single hit process with no threshold, and that the mutagenic effect of radiation is cumulative over a lifetime (Oliver 1932; Timofeev-Ressovsky 1935; Uphoff and Stern 1949; Spencer and Stern 1954). Moreover, of perhaps even greater significant than genetic mutations, was the existence of x-ray induced somatic mutations, which offered a plausible explanation for the carcinogenicity of ionizing radiations and also was consistent with the long latency period associated with the production of cancer.

RADIATION PROTECTION PHILOSOPHY AND PRACTICE: 1925–1945

The two decades between 1925 and 1945 have been dubbed "The Era of Progress" and were a period when radiation protection emerged as a science in its own right (Kathren and Ziemer 1980). These years saw the formation of such protection oriented bodies as the International X-ray and Radium Protection Committee (1928), predecessor of the International Commission on Radiological Protection (ICRP), and the U.S. Advisory Committee on X-Ray and Radium Protection (1929), the direct forerunner of the modern National Council on Radiation Protection and Measurements (NCRP). During this 20 year span, these bodies, as well as the League of Nations, various national governments, and individual investigators were to promulgate radiation protection standards, all having as their underlying basis the concept of a tolerance dose.

In 1931, the American body put forth a tolerance dose of 0.2 R d^{-1}, and the international group did likewise in 1934. Subsequently, in 1936, the American body reduced its value to 0.1 R d^{-1}, largely as a result of changes in the assumptions and calculational method. The recommended maximum exposure level was further reduced to 0.02 R d^{-1} in 1941, a level that corresponds almost exactly with the 50 mSv limit almost universally accepted for regulatory purposes today, more than a half century later. (Note: In the 1930's, dose was expressed in units of the roentgen, symbolized by R, which, for photon radiations, are roughly numerically equivalent to cSv). Also in 1931, the League of Nations put forth a tolerance dose limit of 1×10^{-5} R s^{-1}, based on an exposure of 8 h per day 300 d per year (Wintz and Rump 1931), which corresponds to about 860 mSv in modern terms. Significantly, and perhaps presciently, they noted that it was impossible to exactly determine a dose incapable of damaging cells, or "exercising any stimulating action," and thus wrote in terms of a so-called harmless dose which would result in no effect detectable by clinical examination (Wintz and Rump 1931), in effect leaving the door open at least a crack for effects determined or inferred from radioepidemiologic studies of human populations.

It was in the Manhattan District of World War II that systematic and extensive study was made of radiobiological phenomena to establish radiation protection criteria and standards. In large measure, the radiobiological studies in animals were devoted to deterministic effects, i.e., obvious clinical manifestations, with a major purpose being verification of the basic protection philosophy and criteria which were in turn based on the concept of tolerance dose (Cantril 1951; Nickson 1951). In some instances, results were quite unexpected and highly surprising. Lorenz and his coworkers (1954, 1955) observed that mice exposed to 0.11 R d^{-1}, approximately the accepted tolerance dose in the 1940's, outlived control animals, an observation that has never been satisfactorily explained. Clinical laboratory studies, carried out *en mass* on the workforce, failed to yield indications of potential long term low level effects (Jacobson and Marks 1951; Jacobson et al. 1951), although clearly the population was not followed for a

sufficiently long period thus obviating the detection of possible long term effects from low level exposure.

At the conclusion of World War II, fully a half century after the discovery of x rays and radioactivity, radiation protection philosophy was firmly grounded in the tolerance dose concept. To be sure, the concept of tolerance dose was not inconsistent with the idea of late or long term effects of irradiation, for indeed such effects had been demonstrated at least three to four decades previously, but only with what would today be considered high level doses. The generally prevailing belief underlying the tolerance dose was that there was a threshold dose that needed to be exceeded if any effects—early or late—were to occur. And, for many, implicit in the prevalent belief was the idea that complete recovery from radiation effects was possible, thereby precluding long term effects if the threshold level had not been reached.

However, the seeds of possible long term low dose effects had been sown by the work of Muller and other geneticists, already described briefly above, which raised serious questions regarding the existence of a threshold and the validity of the tolerance dose concept, and seemed to indicate biological response at low doses was both linear and time independent. This new idea would shape the direction of radiation effects research as well as radiation protection philosophy in the coming years.

THE GROUNDWORK IS LAID: 1945–1970

After World War II, the pathway takes a significant turn away from the tolerance dose directly towards the linear nonthreshold dose-response model and becomes more of a two lane highway than the leisurely pleasant and relaxed country lane it once had been. In the late 1940's, scientific interest in the applicability of the linear nonthreshold model for somatic effects was kindled, and the model began to be applied in radiation protection risk assessment methodology. Usage was gradually refined over a period of perhaps 15 or 20 years with special reference to the potential long term health effects from atmospheric nuclear weapons testing. Regrettably, political or ideological considerations were not absent in the choice and refinement of the low dose-risk assessment model for this and other purposes, and sometimes took precedence over strictly scientific considerations.

To a great extent the choice of the linear nonthreshold model was dictated by its mathematical simplicity and its judicious or prudent representation of an upper limit for risk in the low dose region. Its principal scientific foundation lay in the studies of radiation induced genetic changes observed by Muller and others some two decades earlier in the fruit fly *Drosophila melanogaster*, which were indicative of a nonthreshold linear response. The presumption was that what was likely the case for genetic effects also applied to somatic effects, and although somatic effects had only been observed at high doses, straight line extrapolation of the dose-response curve could be readily made down through the low dose domain to the origin.

Implicit in the early consideration of the linear nonthreshold extrapolation of the dose-response curve was the concept that the true risk in the region of extrapolation—i.e., the low dose region where effect had not been observed—would lie somewhere between zero and the upper limit, as defined by the location of the extrapolated line. This was not a denial of any other shape for the curve, nor even of the existence of a threshold. Rather the threshold—zero response if you prefer—was included in the range of values or effects from a given dose in the region of extrapolation. Perhaps what has in fact been forgotten or at least lost sight of over the years is that the original representation of the linear nonthreshold extrapolation of the dose-response curve into the low dose region in which there were no empirical data was actually couched in terms of a range of values or responses for any given dose, *with the extrapolated line itself providing the upper limit of the range of response at any given dose.*

Historically, the shift to the linear nonthreshold model and the refinement with respect to its interpretation came about relatively rapidly. In the fall of 1954, the NCRP put forth its new recommendations on permissible dose from external sources of radiation in its Report No. 17, originally published as National Bureau of Standards Handbook 17 (NCRP 1954), and the British did likewise the following year. In place of the tolerance dose, Report No. 17 introduced the concept of the *maximum permissible dose* (MPD). Implicit in the MPD was the idea of acceptable risk, and hence a nonthreshold model, the basis for which were the observations of linearity in genetic mutations in *Drosophila melanogaster* which, for protection purposes, were assumed to also apply to somatic mutations. There was also unstated concern about genetic mutations as well, for during the approximately five year period that NCRP Report 17 was in preparation (1949–54), there were about 50 announced atmospheric weapons tests and a growing realization of the potential genetic consequences of even small doses to large (i.e., in this case worldwide) populations.

Less than five years after the historic NCRP report, the first report of the United Nations Scientific Committee on the Effects of Radiation was published (UNSCEAR 1958). Some credence was given to the linear nonthreshold model, which was used along with a threshold model to make numerical estimates of effects. The UNSCEAR report included what is basically a brief summary of the state-of-the-art with respect to low level radiation effects, a statement that today, nearly four decades later, still rings true:

> "Present knowledge concerning long-term effects and their correlation with the amount of radiation received does not permit us to evaluate with any precision 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." (UNSCEAR 1958, p. 41)

It is of interest to note that this statement clearly identified the existence of a threshold and further noted, in contradistinction to the current applications, that some effects may in fact not be cumulative.

With respect to leukemogenesis, which had already been unequivocally observed in the Japanese atomic bomb survivors, UNSCEAR concluded that both the threshold hypothesis model and the linear nonthreshold hypothesis corresponding to a single hit with no repair somatic mutation model had equal validity. This contention 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 (NAS/NRC 1959). The following year, the short-lived U.S. Federal Radiation Council (FRC), which had been created only the year before, published its initial report in which it reiterated the original concept of the linear nonthreshold extrapolation, noting that the model merely provided the upper limit of risk for a given dose in the region of extrapolation (U.S. FRC 1960).

During this same time frame, the scientific questions were perhaps at once both illuminated and obscured by the extensive hearings of the Joint Committee on Atomic Energy of the U.S. Congress. The hearings focused attention on the potential problems of low level long term radiation effects, and greatly influenced the thinking of both the scientific community and the general public. The Congressional hearings began in 1957 with an inquiry into the nature of radioactive fallout and its effects on people (JCAE 1957). The Committee heard testimony from scientific experts relating to both the linear nonthreshold hypothesis and threshold dose, as well as the concept of an acceptable level of exposure as expressed via the MPD. Although accepting proportionality for genetic effects, the bulk of the expert testimony did not favor a proportional—i.e., linear nonthreshold hypothesis—for low level long term somatic effects. The Committee, while recognizing that the shape of the curve was not well known, concluded, among other things, that continued nuclear weapons testing in the atmosphere at the level of the previous five years 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.

An attempt was made by the Committee to answer that very question in its 1959 hearings (JCAE 1959). Again, the question remained unresolved, but the final Committee summary report, while pointing to the lack of experimental evidence regarding low level somatic effects and still equivocating with respect to the specific low level model that applied, quoted testimony by Karl Z. Morgan to the effect that only certain types of effects, including genetic mutations, leukemogenesis, and life shortening were without a threshold (JCAE 1959). Also highly influential in the hearings and in the Committee's subsequent consideration of radiation protection standards was testimony by Edward B. Lewis, a biology professor at the California Institute of Technology, who made a strong case for the linear hypothesis as the basis for protection standards, and indeed conceptually put forth what is the current regulatory and radiation protection concept of As Low As Reasonably Achievable (ALARA) (JCAE 1960). Subsequently, throughout the 1960's, the JCAE considered the problems of worker protection standards and compensation, as well as revisiting fallout from weapons tests and carrying out hearings related to the radiological hazards associated with mining, moving subtly closer to a linear nonthreshold or proportionality hypothesis for low level long term effects with each succeeding series of hearings.

The next report of the UNSCEAR was issued in 1962. It, as well as subsequent reports in 1964 and 1972, reaffirmed its 1958 report and used the linear dose-response relationship to compute risks from various sources of radiation, offering as partial justification the argument of the mathematical simplicity and conservatism of the linear nonthreshold model (UNSCEAR 1962). The report (UNSCEAR 1962) further noted that the available data were insufficient to make absolute risk estimates. Again, in its 1964 and 1966 reports, 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 (UNSCEAR 1964; ICRP 1966).

To a considerable extent, concern over the low level long term effects of radiation led to the treaty banning atmospheric nuclear weapons in 1962. Optimistic plans for nuclear electric generation, however, aroused increasing concern regarding long term low level radiation effects. It was generally accepted within the scientific community that there was no threshold for genetic effects, even though such effects had never been demonstrated in human populations, including the survivors of the atomic bombings of Japan. However, there was still not common acceptance of the applicability of the linear nonthreshold dose response curve to somatic mutations or effects. In 1964, the NAS/NRC, acting on a request from the FRC, established an advisory committee—the so-called BEAR (Biological Effects of Atomic Radiation) Committee—to look into problems related to radiation protection, including the shape of the low dose response curve. In an important departure from previous practice, this highly influential committee introduced the concept of regulation of population doses based on genetic risk (and ultimately genetic dose) to future generations (NAS/NRC 1972).

THE 1970'S: THE PATHWAY TURNS INTO A SUPERHIGHWAY

The change in direction that had begun after World War II continued, but at ever increasing speed. Indeed, the pathway, to continue with the metaphor, was rapidly becoming a six lane superhighway, laden with high speed vehicles, each representative of a scientific or technical paper in the literature. The BEAR Committee subsequently gave way to the NAS/NRC Committee on the Biological Effects of Ionizing Radiations (BEIR), which issued its first report in 1972. This initial BEIR report, as do later BEIR reports, provides a comprehensive review of the literature relating to low level radiation effects and evaluation of risk assessment methodology to the time of its publication. Although sidestepping the issue of the shape of the dose response curve at low doses, BEIR I nonetheless put forth absolute risk values for various nondeterministic (i.e., carcinogenic) effects derived primarily from linear extrapolation of the data for the Japanese atomic bomb survivors as well as other exposed groups which at the least, clearly implied there was no threshold with respect to low dose response (NAS/NRC 1972).

Another major shift to the linear nonthreshold dose-response model also took place in 1972. In that year, the U.S. Atomic Energy Commission (AEC), forerunner of the current U.S. Nuclear Regulatory Commission (U.S. NRC), incorporated the concept of "as low as practicable" (now known as ALARA) into its regulations. Implicit in the ALARA concept is the linear nonthreshold dose-response. Thus, in perhaps the single year 1972, the situation had changed, and changed dramatically.

The 1970's also saw another major conceptual change with respect to radiation protection practice. In 1977, the ICRP adopted 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 in its Publication 26 (ICRP 1977). In developing estimates of nondeterministic (stochastic was the term in use at that time, and basically referred to carcinogenic risk) risks to specific tissues, a number of tissue weighting factors were derived and these were then used in calculating a new dose quantity—the effective dose equivalent. The effective dose equivalent was a weighted combination of doses to various parts of the body (such as organ doses from internal irradiation) with doses to the whole body from external irradiation. The resultant single numerical expression of effective dose equivalent expressed the total nondeterministic (i.e., stochastic) risk of radiation exposure—partial body irradiation as well as whole body irradiation—in terms of the equivalent risk of whole body irradiation (ICRP 1977). The system has been basically adopted, and refined and expanded upon not only by ICRP (ICRP 1977, 1979, 1990, 1991) but also by NCRP (1987) and various American regulatory bodies including the EPA (U.S. EPA 1987), DOE (U.S. DOE 1988) and U.S. NRC (1991).

Although basically recommending the same permissible exposure limit of 50 mSv annually for occupational exposure, from the standpoint of applied radiation protection the new ICRP system represented a sharp departure from past practice. In the United States in particular, contentious argument went on within the operational health physics community regarding the assignment of the entire 50 dose commitment from an intake of radioactivity to the year of intake, an idea particularly objectionable to some members of the health physics community who were involved with the protection aspects of long-lived bone seeking alpha emitters (e.g., plutonium and americium isotopes). The basic problem, it seemed, lay not with 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. More significantly, carcinogenesis was defined as a stochastic (now nondeterministic) effect, and the new system represented a complete departure from the concept of a threshold.

The fatal accident rate in so-called safe industries was introduced as a measure of acceptable risk. This was an important step in that it provided a perspective as well as a means of comparison of radiation risks with those associated with other human endeavors. The ICRP 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—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.

THE HUMAN EXPERIENCE

While animal studies provide insights into possible long term low level effects of irradiation in humans, it is human epidemiologic and related studies that provide, at least in theory, the most relevant data regarding long term effects of low level radiation applicable to the setting of radiation protection standards. Indeed, despite significant limitations, radioepidemiologic studies have played a major role in the acceptance of the linear nonthreshold paradigm. The nature and small size of the populations available, the existence of background levels of the effects being observed, and the vagaries of the dosimetry on which such studies are based are but three of the uncertainties in such studies that make it intrinsically difficult to assess the shape of the dose response curve or the level of risk.

A major intrinsic limiting factor of radioepidemiologic studies relates to population size. In small study populations, there are likely to be few effects, and the incidence of radiation induced effects may be overshadowed or swamped out by the natural frequency or incidence of whatever is chosen for study in the population. The ability to distinguish between the natural incidence and a radiation induced effect is a function of

both size of the study population and dose, decreasing exponentially as the dose is reduced. Thus, to distinguish between effects that have a small likelihood of occurrence and the natural incidence, the requisite population size may be prohibitively large if the dose is small. Radioepidemiologic studies of radiation workers have been particularly controversial and contentiously criticized, frequently on methodological grounds. However, the largest and most extensively studied cohort, the Japanese atomic bomb survivors, showed a clear and indisputable elevation in leukemia incidence peaking at 5–6 y post exposure and elevated incidence of a number of solid tumors correlated with dose (Kato and Shimizu 1990), although it has been noted 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 (Kondo 1990).

Long term low level effects either documented or believed to occur in human populations include radiation induced leukemia and solid tumors, life shortening, and effects on the fetus. In addition, there is evidence for radiation hormesis, or stimulation, which may produce life lengthening or reduced incidence of disease including cancer, and possible adverse immunologic effects.

Leukemia has been perhaps the most widely studied nondeterministic effect, and there is ample evidence both in humans and animals to make indisputable the conclusion that certain types of leukemia are in fact radiation induced. However, the shape of the dose response curve or the resultant models for prediction of risk from low level exposure are as yet not well established (NAS/NRC 1990). Independent evaluation of approximately four dozen epidemiologic studies dating back to 1962 reveals equivocal results with respect to whether low dose or fractionated exposures do in fact carry significant leukemia risks and certainly raise the question of whether the linear nonthreshold dose-response model is applicable to leukemogenesis. A recent case control study of persons exposed to weapons test fallout (Stevens et al. 1990) was indicative of a possible low level leukemogenesis but other studies in populations exposed to fallout or diagnostic radiation have been negative or marginally positive (Gibson et al. 1972; Gunz and Atkinson 1964; Linos et al. 1980; Preston-Martin et al. 1989; Stewart et al. 1962). Studies in China comparing populations in high and low background areas have likewise failed to show an association between leukemia and low level exposure (Wei 1980), as have followup studies in patients treated for hyperthyroidism with radioiodine (Hoffman et al. 1982; Holm et al. 1991). On the other hand, other studies with protracted or low doses have at least implied a positive association (Davis et al. 1987; Spengler et al. 1983). Excess leukemia has been associated with exposure in radiologists or x-ray workers with high doses, but studies of persons with lower doses have not shown such an effect (Boice et al. 1991; Jablon and Miller 1978).

Studies of radiation workers in the nuclear industries would seem to offer the greatest promise of determining the shape of response curve at low doses and specifically whether the linear nonthreshold hypothesis is valid. However, because only a small fraction of the cohort has recorded occupational exposures significantly greater than background, the statistical power of such studies is greatly reduced.

Nonetheless it is significant to note that in only one study has a significant excess leukemia mortality in the workforce been observed. Combined analyses of the data from several studies have been carried out by several investigators and is currently under way by the International Agency for Research on Cancer. Again, results have not been unequivocal. For example, Gilbert et al. (1993) obtained positive risk estimates from their meta-analyses but the wide confidence intervals do not exclude the possibility of no risk, or define the shape of the low dose response curve. In their meta-analysis of seven studies, Wilkinson and Dreyer (1991) claimed evidence of elevated risk from leukemia, but again, this study has been criticized on methodological grounds (Gilbert 1992). In short, despite the large number of studies, the data are simply not adequate to characterize the shape of the dose response curve with exactitude. Moreover, the latency period is known to differ for different types of leukemia and appears to be dependent upon the age of irradiation NAS/NRC (1990), and at least one paper has suggested infection as a confounder and cause of leukemia in populations around nuclear sites (Kinlan et al. 1990).

Other studies of human populations have done little to clarify and define the shape of the low level dose-response curve. Although many, if not most, studies are consistent with the linear nonthreshold dose-response paradigm, none have provided unequivocal validation. Indeed, the studies of the radium dial painters provide compelling evidence to the contrary, at least for osteosarcomas, where Evans and his coworkers (1972) have shown clear evidence of a threshold. Thus, the evidence from both animal and human studies, if taken as a whole, is not clear cut and can be used to support a number of dose response curves for both mutagenesis and carcinogenesis in both humans and animals at low doses and dose rates. In general, however, the studies do not support a threshold model, although a notable exception appears to be osteogenic sarcoma for which there is clear evidence of a threshold in both humans and animals.

Further confounding and confusing the characterization of the low dose response curve have been reports of an apparent hormetic or beneficial stimulatory effect of low level radiation in humans. The basic premise underlying hormesis is similar conceptually to homeopathy, specifying that while large doses may be harmful, small doses are stimulatory, and thus may lead to improved functioning of the immune system and to other beneficial effects. T. D. Luckey has documented a large and impressive body of literature—much of it peer reviewed—in support of the hormesis thesis, including apparently valid interpretations of human epidemiologic studies, including those of the Japanese atomic bomb survivors (Luckey 1991). Certainly the reduced inci-

dence of certain types of cancers in groups with low level radiation exposure, as has been reported in numerous radioepidemiology studies, can be cited as supporting evidence for hormesis, although an argument could also be made that these are simply statistical artifacts. A number of beneficial effects have been associated with low level exposure, including enhanced growth and development, resistance to infection and other immune system improvements, lowered incidence of cancer, and longer lifespan (Luckey 1983, 1991; Mine et al. 1990).

Although hormesis presents to some an attractive alternative to the conventional dose response evaluations of low level radiation effects, it has received scant attention in the conventional radiation risk evaluation process. Indeed, it is by and large ignored or even rejected out of hand as going against conventional wisdom by many otherwise independent radiation scientists. Certainly, for some, hormesis—the suggestion that low levels of radiation exposure may be beneficial—is not a "politically correct" viewpoint. However, recent publications of UNSCEAR provide new insights with respect to hormesis, which can be explained in terms of a cellular adaptive response mechanism to low levels of radiation (UNSCEAR 1993; 1994)

CONTEMPORARY TIMES (1980–1995)

The trailblazing groundwork put forth in ICRP Publication 26 was expanded upon by both the NCRP in its Report No. 91 (1987) and in ICRP Publication 60 (1990), which might be considered the second generation or direct descendent of the 1977 Publication 26. Both reports rely heavily on the emerging data and results from the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki and utilize the linear nonthreshold dose-response model as the basis for their recommendations. In addition to providing the bases for establishing a dose limit, Publication 60 put forth a new risk projection model and an in depth discussion of their proposed new approach to taking Relative Biological Effectiveness into account. A multiattribute approach was used by the ICRP in weighing risk, considering such factors as lifetime risk of fatality, loss of life expectancy, and both age related mortality and morbidity considerations for both fatal and nonfatal somatic and hereditable effects. Both the ICRP and NCRP put forth values and specific guidance for application 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. The ICRP recommended application of the DREF at doses below 200 mGy or dose rates of less than 100 mGy h^{-1} (ICRP 1991).

Since the 1960's, there have been numerous reports of low level radiation effects in both humans and animals, and a complete, or even near complete, review or listing of the literature is virtually impossible. Perhaps the most comprehensive review and evaluation of the scientific literature has been undertaken by the BEIR committee, but even that prestigious and expert group has not been unanimous in its interpretations or without disagreement. The so-called BEIR-III report, originally released in May 1979, was subsequently withdrawn and revised because of dissention among members of the Committee with respect to the shape of the dose response curve. When finally published in 1980, the BEIR III report included two "minority" opinions as well as presenting the consensus of the rest of the Committee with respect to the shape of the dose response curve. The Committee by and large adopted the linear-quadratic model for cancer induction; the two dissenting members took very different viewpoints, one adopting the linear model, the other a pure quadratic model (NAS/NRC 1980).

The BEIR III committee made a number of important observations in what was their final report. They observed that it was likely undeterminable whether dose rates at environmental levels, i.e., on the order of 100 mrad (1 mGy) per year, 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 confer different degrees of risk with respect to carcinogenesis for a specific dose. The likelihood of a threshold for certain developmental effects from irradiation *in utero* was accepted based on a multitarget multi hit theory. And, with respect to genetic effects, although curvilinear models were examined, the BEIR Committee agreed that the linear nonthreshold model still provided the best fit to the observations of genetic effects, extrapolating these effects from animal studies.

The BEIR Committee has published two reports since the 1980 BEIR III. BEIR IV, published in 1988, was specific to the health risks of radon and other internally deposited radionuclides (NAS/NRC 1988). Although recognizing the importance of age, for mathematical simplicity the Committee chose a relative risk model to characterize radiation induced lung cancer, for, unlike the absolute risk model, this model did not require a complex power function to take age into account and required few variables to characterize the observations of lung cancer in the miner cohort. Perhaps most significantly, the Committee made a number of specific suggestions for further epidemiologic and other studies that might more clearly reveal the shape of the long term low dose response curve.

The most recent report, BEIR V (NAS/NRC 1990), once again considered the broad topic of health effects from low level exposure to ionizing radiation. 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 There was, however, a change with respect to the calculation of somatic effects, which were determined with a linear no-threshold model modified in some cases for dose rate effects. Also introduced was the Dose Rate Effectiveness

Factor (DREF) 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.

The experiences of other learned bodies concerned with low level radiation risks, such as UNSCEAR and the ICRP, mirror to a great extent the BEIR Committee. Together, the actions of these bodies have led to a more or less consistent radiation philosophy of the past two decades, one that is based on 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.

To a great extent, the acceptance of this paradigm has been influenced by regulatory bodies and by the general public. The public has become increasingly fearful of radiation effects and demands ever increasing guarantees of safety and even zero risk. Unlike scientific bodies, which deliberate in private and among themselves, in the setting of standards for protection against radiation regulatory bodies must hold hearings and obtain public comment. Testimony and comments from the public are thus a driving force behind radiation protection regulations and standards, and have contributed greatly to the widespread current acceptance of the linear nonthreshold model and the belief that this model is indeed correct, and may even understate the risk of low level radiation exposure. So strongly held is this view that attempts by regulatory bodies to incorporate minimum levels—so-called *de minimis*, below regulatory concern (BRC), or the negligible individual risk level (NIRL) of the NCRP—have been abandoned. From the 1970's, risk evaluations of nuclear operations, and in particular nuclear waste disposal, have largely been based on the linear nonthreshold model and the assumption that any dose, no matter how small, carries with it some risk. Total risk is thus estimated by summation of individual risks, and has been carried to the extend of including even a large number of vanishingly small individual risks in the computation. A strong case could be made for truncation of very small doses in such risk evaluations, but given the wide spectrum of opinion and belief with respect to low level long term radiation effects, even among the so-called radiation protection "establishment," and despite nearly a century of experience with ionizing radiation, induction of long term effects such as cancer by low level exposures remains a controversial and often highly emotionally charged question that cannot be answered with any reasonable degree of certainty or scientific consensus.

INTO THE SECOND CENTURY

As the first century following the discovery of x rays and radioactivity draws to a close, the shape of the dose-response curve at low dose levels is still unknown, but the linear nonthreshold dose-response model continues to serve as the basis for radiation protection standards and risk analysis, as has been the case for about the past half century. Contemporary radiation protection practice is firmly and seemingly unswervingly based upon the linear nonthreshold model of long term low level risk, with effects at low doses determined largely from epidemiologic studies and extrapolation from high dose studies. The epidemiologic basis is less than solid; Land (1993), in a critique of the epidemiologic basis for the linear hypothesis, has clearly elucidated some of the significant problems associated with application of such studies to the problem, as has Gilbert (1991) in a review of low level external radiation studies. So too is the basis for extrapolations from high dose studies, which are sometimes done in total disregard of a clear and obvious threshold for the effect under consideration, the unequivocal threshold for osteosarcoma in the radium dial painters notwithstanding.

On the other hand, a number of recent papers indicate that the Chernobyl accident and other radiation releases in the Former Soviet Union are beginning to yield firm epidemiologic evidence of hitherto unreported and perhaps even unsuspected low level effects and much shorter latency periods for the development of cancers than heretofore suspected (Astakhova et al. 1993; Kossenko and Degteva 1994). It is thus important to consider all observations of low level radiation effects in an appropriate perspective, without preconceptions, and to bear in mind that the linear nonthreshold hypothesis is just that—a hypothesis.

For the near term at least, the linear nonthreshold model for low level long term effects coupled with ALARA is likely to remain the current philosophy and practice in applied radiation protection. It is a conservative, mathematically simple, and satisfying philosophy and perhaps with even a touch of Occam's razor. Recently, however, there has been increasing unrest in the radiation protection community as well as among other scientists with respect to the validity of the linear nonthreshold dose-response paradigm. In a provocative article, Peterson (1993) devised a tabular representation to characterize what he calls the distortion of the linear, nonthreshold dose-effect assumption, tracing it from an assumption in which every dose is postulated to have an associated risk of ill health, through various steps until the final one in which it is stated unequivocally that radiation has a linear dose response relationship and that all radiation exposure is unsafe.

Exhaustive studies and analyses by Cohen (1995) of the relationship between environmental radon concentrations and lung cancer have actually and consistently shown not only that the linear nonthreshold dose-response curve does not apply, but strongly suggest radiation hormesis. A recent Health Physics Society *Newsletter* (May 1995) exemplifies the concern and increasing frustration with the apparent obsequious application of the paradigm to radiation protection. And, in its 1994 report, UNSCEAR has devoted considerable attention to the possibility of a cellular adaptive response

to low level radiation in humans, but notes that at present no conclusions can be drawn regarding its effects in human populations (UNSCEAR 1994).

While many observations of radiation effects are not inconsistent with linear extrapolation to low dose, there are a number of effects for which linear extrapolation is obviously inappropriate and incorrect. It is a preposterous and even arrogant denial of valid scientific observations to assume that the linear nonthreshold response is the only, or even the best, characterization of human response to low level radiation exposure. Clearly, some effects exhibit a threshold, as has been pointed out by Evans and his coworkers for osteogenic sarcoma in the dial painters (Evans, Keane and Shanahan 1972).

And, for others, there may be an effective threshold, determined by dose, dose rate, and other factors which determine the latency period. If the latency period exceeds the life span, there is obviously no effect, and hence a threshold.

Recently Raabe (1994) has put forth three dimensional models of risk which lends strong and perhaps even conclusive support to the effective threshold concept put forth by Evans and his coworkers in 1972. His 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 (nondeterministic) effect, and for radiation induced non-neoplastic tissue injury, a deterministic effect. Raabe's methodology clearly supports the concept of an effective threshold and should be applied to other radiation effects to determine for which effective thresholds exist.

Logically it would seem that if low level radiation effects, whether positive or negative, were significant in human populations, these would have been identified long before now. Human response to low level radiation exposure is clearly highly complex, and despite a plethora of scientific publications pertinent to the problem, the prescient statement from the UNSCEAR report of nearly four decades ago is still germane. The recent recommendations of the ICRP (1991) represent a reasonable and serious attempt to apply existing knowledge within the framework of a practical protection schema which can readily be adapted to incorporation of such factors as dose rate effectiveness (which is not single valued, but rather likely to be a smooth continuous function), LET, age dependency of a specific risk, and the expected variety of dose response curves for various specific effects into a single equation which could then be solved to obtain a dose for a predetermined acceptable risk level.

Human response to radiation exposure needs to include consideration of many factors, such as latency period and dose rate, whose influence on response is not well known. The data clearly show that the dose response curves for various endpoints are different. When taken as a whole, the sum total of all the various human responses to radiation exposure can be depicted quite well by the familiar Gompertzian or sigmoidal curve (Fig. 1), which provides a rather satisfying characterization of human

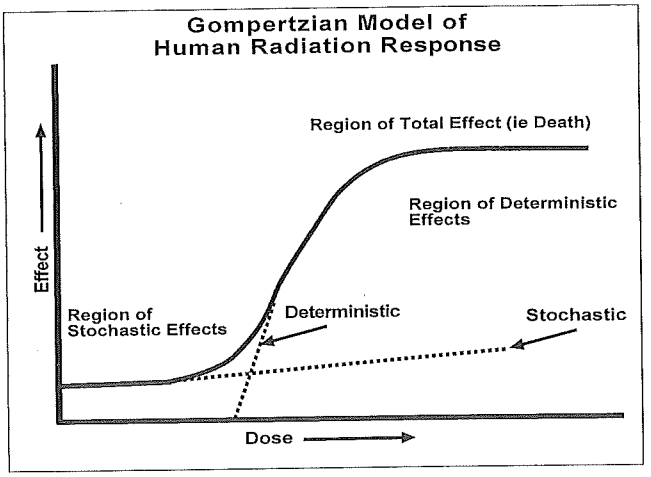

Fig. 1. Stylized human radiation dose-response curve.

radiation response that fits quite well with our existing state of knowledge. The Gompertzian model can readily be divided into two response functions, one representing the deterministic effects and the other the nondeterministic or stochastic effects. This portion of the curve can be drawn to include a threshold, or perhaps an effective or practical threshold, and can incorporate and accommodate a linear response as well.

The current schema propose no lower limit on dose, and thus radiation protection seem not only to fly in the face of practicality, but also appear incompatible with the principle of optimization and ALARA. Given the present state of knowledge, it is not unreasonable to apply the practical or effective threshold concept in low level radiation risk estimation and to incorporate this concept into regulatory and other radiation protection standards, as has been proposed for the past twenty or so years by a number of authors in terms of so-called *de minimis*, NIRL, or BRC levels for regulatory purposes. Recognizing the danger of predictions, I nonetheless am convinced that early in the second century of x rays and radioactivity such levels will become *de rigueur* in radiation protection practice, and that new models of low level radiation response, more in keeping with the scientific observations and the philosophy of optimization will be devised and applied to protection of people and the environment from the effects of radiation exposure. To do otherwise would be an abrogation of our responsibilities to the public and of our ethics as scientists.

Acknowledgements—Selection as a Hartman Orator provided the impetus to prepare this paper and author is indebted to the American Academy of Health Physics for that honor, and to the Radiology Centennial, Inc. for its creation and support of the Hartman Orator and Medalist program.

REFERENCES

Astakhova, L. N.; Davydova, E. V.; Dardynskaya, I. V.; Zelenko, S. M.; Drozd, V. M.; Kobzev, V. F.; Poverenny, A.

M.; Dubovtsov, A. M.; Zhukovskaya, I. V.; Polyanskaya, O. N.; Khmara, I. M.; Arinchin, A. N.; Anychtenko, S. L. The status of the thyroid system and the pecularities of its pathology formation in children and teenagers affected by iodine radionuclides due to the Chernobyl accident. In: Kobayashi, S.; Uchiyama, M. and Matsudaira, H., eds. Health effects of atomic radiation—Hiroshima-Nagasaki, Lucky Dragon, Techa River and Chernobyl, Proceedings of Japan-USSR Symposium on Radiation Effects Research, June 25–29, 1990, National Institute of Radiological Sciences: Tokyo, 1990, 190–193.

Barclay, A. E.; S. Cox. Radiation risks of the roentgenologist. Amer. J. Roengenol. Radium Ther. 19:551–558; 1928.

Boice, J. D., Jr.; Morin, M.; Glass, A.; Friedman, G.; Stovall, M.; Hoover, R.; Fraumeni, J. F., Jr. Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. J. Am. Med. Assn. 265:1290–1294; 1991.

Cantril, S. T. Biological bases for maximum permissible exposures. In: Industrial medicine on the Plutonium Project. New York: McGraw-Hill; 1951: 36–74.

Cohen, B. L. Test of the linear no-threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys. 68:157–174; 1995.

Colwell, H. A.; Russ, S. Radium, x rays and the living cell. London: G. Bell and Sons; 1915.

Davis, F.; Boice, J. D., Jr.; Kelsey, J.; Monson, R. Cancer mortality after multiple fluoroscopic examinations of the chest. J. Nat. Cancer Inst. 78:45–652; 1987.

Edison, T. A. Notes. Nature 53:421; 1896.

Ellinger, F. Medical radiation biology. Springfield: Charles C. Thomas; 1957.

Evans, R. D.; Keane, A. T.; Shanahan, M. M. Radiological effects in man of long-term skeletal alpha-irradiation. In: Stover, B. J. and Jee, W. S. S., eds. Radiobiology of plutonium, Salt Lake City: The J. W. Press, 1972, 431–468.

Federal Radiation Council (FRC). Background material for the development of radiation protection standards. Washington, DC: Federal Radiation Council; Report No. 1; 1960.

Frieben, A. Demonstration eines Cancroids des rechten Handrückens, das sich nach langdaurnder Eirwirkung von Röntgenstrahlen entwickelt hatte. Fortschritte Gebiete Röntgenstrahlen 6:106–111; 1902. (In German).

Gibson, R.; Graham, S.; Lilienfeld, A.; Schuman, L.; Dowd, J.; Levin, M. Irradiation in the epidemiology of leukemia among adults. J. Nat. Cancer Inst. 48:301–311; 1972.

Gilbert, E. S. Studies of workers exposed to low doses of external radiation. Occupational Medicine: State of the Art Reviews 6:665–680; 1991.

Gilbert, E. S. Leukemia among nuclear workers. Epidemiology 3:275–6; 1992.

Gilbert, E. S.; Cragle, D. L.; Wiggs, L. D. Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant. Radiation Res. 136:408–421; 1993.

Gunz, F.; Atkinson, H. Medical radiations and leukaemia. A retrospective survey. Brit. Med. J. 1:389–393; 1964.

Henshaw, P. S. Biologic significance of the tolerance dose in x ray and radium protection. J. Nat. Cancer Inst. 1:789–805; 1941.

Hesse, O. Symptamologie, pathogenese and therapie des röntgenkarzinoms. Leipzig: J. A. Barth; 1911.

Hoffman, D. A.; McConahey, W.; Fraumeni, J. F., Jr.; Kurland, L. Cancer incidence following treatment of hyperthyroidism. Int. J. Epidemiol. 11:218–224; 1982.

Holm, L. E.; Dahlqvist, I.; Israelsson, A.; Lundell, G. Cancer risk after iodine 131 therapy for hyperthyroidism. J. Natl. Cancer Inst. 83:1072; 1991.

International Commission on Radiological Protection (ICRP). *The Evaluation of Risks from Radiation*, ICRP Publication 8, Oxford: Pergamon Press, 1966.

International Commission on Radiological Protection. Recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press; ICRP Publication 26; Ann. ICRP 1(3); 1977.

International Commission on Radiological Protection. Limits for intakes of radionuclides by workers. Oxford: Pergamon Press; ICRP Publication 30; Ann. ICRP 2(3/4): 1–116; 1979.

International Commission on Radiological Protection. Individual monitoring for intakes of radionuclides by workers: Design and interpretation. Oxford: Pergamon Press; ICRP Publication 54; Ann. ICRP 19(1–3); 1990.

International Commission on Radiological Protection. 1990 Recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press; Ann. ICRP 21(1–3):1–201; 1991.

Jablon, S.; Miller, R. Army technologists: 29-year follow up for cause of death Radiology 126:877–879; 1978.

Jacobson, L. O.; Marks, E. K. Clinical laboratory examination of plutonium project personnel. In: R. S. Stone, ed. Industrial medicine on the plutonium project. New York: McGraw-Hill; 1951: 113–139.

Jacobson, L. O.; Marks, E. K.; Lorenz, E. Hematological effects of ionizing radiations. In: Stone, R. S., ed. Industrial medicine on the plutonium project. New York: McGraw-Hill; 1951: 140–196.

Joint Committee on Atomic Energy of the Congress of the United States. Hearings on the nature of radioactive fallout and its effects on man. 2 vols. plus summary. Washington, DC: Government Printing Office; 1957.

Joint Committee on Atomic Energy of the Congress of the United States. Hearings on fallout from nuclear weapons tests. 3 vols. plus summary. Washington, DC: Government Printing Office; 1959.

Joint Committee on Atomic Energy of the Congress of the United States. Selected materials on radiation protection criteria and standards: Their basis and use. Washington, DC: Government Printing Office; 1960.

Kathren, R. L. Early x-ray protection in the United States. Health Phys. 8:503–511; 1962.

Kathren, R. L. William Herbert Rollins (1852–1929): X-ray protection pioneer. Bull. His. Med. Allied Sci. XIX:287–294; 1964.

Kathren, R. L.; Ziemer, P.L. Introduction: The first fifty years of radiation protection—A brief sketch. In: Kathren, R. L. and Ziemer, P. L. eds. Health physics: A backward glance. New York: Pergamon Press; 1980: 1–9.

Kato, H.; Shimizu, Y. In: Kobayashi, S.; Uchiyama, M. and Matsudaira, H., eds. Health effects of atomic radiation—Hiroshima-Nagasaki, Lucky Dragon, Techa River and Chernobyl, Proceedings of Japan-USSR Symposium on Radiation Effects Research, June 25–29, 1990, National Institute of Radiological Sciences: Tokyo, 1990, 225–236.

Kinlan, L. J.; Clarke, K.; Hudson, C. Evidence from population mixing in British new towns 1946–85 of an infective basis for childhood leukaemia. Lancet 336:577–582; 1990.

Kondo, S. Rational risk estimation in relation to atomic bomb radiation. J. Radiat. Res. 31:174–188; 1990.

Kossenko, M. M.; Degteva, M. O. Cancer mortality and radiation risk evaluation for the Techa River population. Sci. Total Environ. 142:73–89; 1994.

Land, C. E. Low dose extrapolation, time following exposure and transport between populations. In: O. F. Nygaard and J. F. Lett, eds. Advances in radiation biology. Effects of low dose and dose rate reduction. Vol. 16. San Diego: Academic Press; 1993: 259–272.

Linos, A.; Gray, J.; Orvis, A.; Kyle, R.; O'Fallon, M.; Kurland, L. Low-dose radiation and leukemia. New Engl. J. Med. 302:1101–1105; 1980.

Lorenz, E. L.; Jacobson, L. O.; Heston, W. E.; Shimkin, M.; Eschenbrenner, A. B.; Deringer, M. K.; Doniger, J.; Schweisthal, R. Effects of long-continued total body gamma irradiation on mice, guinea pigs, and rabbits. III. Effect on life span, weight, blood picture and carcinogenesis and the role of the intensity of radiation. In: Zirkle, R. E., ed. *Biological effects of external x and gamma radiation*, New York: McGraw-Hill, 1954, 24–148.

Lorenz, E.; Hollcroft, J. W.; Miller, E.; Congdon, C. C.; Schweisthal, R. Long-term effects of acute and chronic irradiation in mice. I. Survival and tumor incidence following chronic irradiation of 0.11 r per day. J. Nat. Canc. Inst. 15:1049–1058; 1955.

Luckey, T. D. Physiological benefits from low levels of ionizing radiation. Health Phys. 43:771–790; 1983.

Luckey, T. D. Radiation hormesis. Boca Raton: CRC Press; 1991.

Marcuse, W. Nachtrag zu dem Fall von Dermatitis und Alopecie nach Durchleuchtungsversuchen mit Röntgenstrahlen. Deutsche Med. Wochschr. 21:681; 1896. (In German).

Morton, W. J. Notes. Nature 53:421; 1896.

Muller, H. J. Artificial transmutation of the gene. Science 66:84–87; 1928.

Mutscheller, A. Physical standards of protection against Roentgen ray dangers. Am. J. Roentgenol. 13:65–69; 1925.

National Academy of Sciences/National Research Council Committee on Pathologic Effects of Atomic Radiation. A commentary on the Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. Washington, DC: National Academy of Sciences/National Research Council; NAS/NRC Publication 647; 1959.

National Academy of Sciences/National Research Council. The effects on populations of exposure to low levels of ionizing radiation. Washington, DC: National Academy Press; 1972.

National Academy of Sciences/National Research Council. The effects on populations of exposure to low levels of ionizing radiation: BEIR III. Washington, DC: National Academy Press; 1980.

National Academy of Sciences/National Research Council. Health effects of exposure to low levels of ionizing radiation: BEIR V. Washington, DC: National Academy Press; 1990.

National Council on Radiation Protection and Measurements. Permissible dose from external sources of ionizing radiation. Washington, DC: U.S. Department of Commerce; NCRP Report No. 17; U.S. National Bureau of Standards Handbook 59; 1954.

National Council on Radiation Protection and Measurements. Review of the current status of radiation protection philosophy. Bethesda: NCRP; NCRP Report No. 43; 1978.

National Council on Radiation Protection and Measurements. Influence of dose and its distribution in time on dose-response relationships for low-let radiations. Bethesda: NCRP; NCRP Report No. 64; 1980.

National Council on Radiation Protection and Measurements. Recommendations on limits for exposure to ionizing radiation. Bethesda: NCRP; NCRP Report No. 93; 1987.

National Council on Radiation Protection and Measurements. The relative biological effectiveness of radiations of different quality. Bethesda: NCRP; NCRP Report No. 104; 1990.

Nickson, J. J. Protective measures for personnel. In: Industrial medicine on the plutonium project. New York: McGraw-Hill; 1951: 75–112.

Oliver, C. P. An analysis of the effect of varying the duration of x ray treatment on the frequency of mutations, *Zeitschr. Indukt. Abstammungsl.*, 61:447, 1932; cited in Ellinger, F. *Medical radiation biology*, Springfield: Charles C. Thomas, 1957, 62.

Patterson, J. T. The effects of x rays in producing mutations in somatic cells of drosophila melanogaster. Science 68:41–42; 1928.

Peterson, H. T., Jr. Public aversion to environmental releases of small quantities of radioactive materials. In: Kathren, R. L.; Denham, D. H.; Salmon, K., eds. Environmental health physics, proceedings of the Twenty-Sixth Midyear Topical Meeting of the Health Physics Society. Richland, WA: Research Enterprises Publishing Segment; 1993: 255–262.

Preston-Martin, S.; Thomas, D.; Yu, M.; Henderson, B. Diagnostic radiography as a risk factor for chronic myeloid and monocytic leukaemia (CML). Brit. J. Cancer 59:639–644; 1989.

Raabe, O. G. Three-dimensional models of risk from internally deposited radionuclides. In: O. G. Raabe, ed. Internal radiation dosimetry. Madison, WI: Medical Physics Publishing Co.; 1994: 633–656.

Rollins, W. An oral camera for Röntgen photography. Internat. Dent. J. 17:49T; 1896.

Rollins, W. X-light kills. Bost. Med. Surg. J. 144:173; 1901a.

Rollins, W. Notes on x-light. Bost. Med. Surg. J. 144:221, 1901b.

Rollins, W. Vacuum tube burns. Bost. Med. Surg. J. 146:39; 1902a.

Rollins, W. Some conclusions from experiments with guinea pigs which are of importance in the treatment of disease by x-light. Bost. Med. Surg. J. 146:430–2; 1902b.

Senn, N. A case of splenomedullary leukemia successfully treated by the use of the Roentgen ray. Med. Rec. 64:281–3; 1903.

Spencer, W. P.; Stern, C. Experiments on the validity of the linear relation of mutation frequency to x-ray dose in Drosophila melanogaster. In: Blair, H. A., ed. BIological effects of radiation, New York: McGraw-Hill, 1954, 153–193.

Spengler, R. F.; Cook, D.; Clarke, E.; Olley, P.; Newman, A. Cancer mortality following cardiac catheterization: A preliminary follow-up study on 4,891 irradiated children. Pediatrics 71:235–239; 1983.

Stadler, L. J. Genetic effects of x rays in maize. Proc. Nat. Acad. Sci. 14:69–75; 1928.

Stevens, W.; Thomas, D.; Lyon, J.; Till, J.; Kerber, R.; Simon, S.; Lioyd, R.; Elghany, N.; Preston-Martin, S. Leukemia in Utah and radioactive fallout from the Nevada Test Site. J. Am. Med. Assoc. 264:585–591; 1990.

Stewart, A. M.; Webb, J.; Giles, D.; Hewitt, D. Malignant disease in childhood and diagnostic irradiation in utero. Lancet ii:447–448; 1958.

Stewart, A. M.; Pennybacker, W.; Barber, R. Adult leukaemias and diagnostic x rays. Brit. Med. J. 2:882–890; 1962.

Taylor, L. S. Reminiscences about the early days of organized radiation protection. In: Kathren, R. L.; Ziemer, P. L., eds. Health physics: A backward glance. New York: Pergamon Press; 1980: 109–122.

Timofeev-Ressovsky, N. W. The effects of x-rays in producing somatic genovariations of a definite locus in different directions in drosophila melanogaster. Amer. Naturalist 63:118–122; 1929.

Timofeeff-Ressovsky, N. W.; Zimmer, R. G.; Delbruck M. Uber die Natur der Genmutation und der Genstructure, *Nach. Gesellschaft Wissenschaften* (Gottingen), 1935, 189–245. (In German).

United Nations Scientific Committee on the Effects of Atomic Radiation. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. New York: United Nations; General Assembly Official Records; Thirteenth Session Supplement No. 17 (A/3838); 1958.

United Nations Scientific Committee on the Effects of Atomic Radiation. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. New York: United Nations; General Assembly Official Records; Nineteenth Session Supplement No. 14 (A/5814); 1964.

United Nations Scientific Committee on the Effects of Atomic Radiation. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. New York: United Nations; General Assembly Official Records; Seventeenth Session Supplement No. 16 (A/5216); 1962.

United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, effects and risks of ionizing radiation. New York: United Nations Publications; 1988.

United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York: United Nations Publications; 1993.

United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York: United Nations Publications; 1994.

United States Department of Energy. Radiation protection for occupational workers. Washington, DC: U.S. Department of Energy; 1988.

United States Environmental Protection Agency. Radiation protection guidance to Federal agencies for occupational exposure. Federal Register 52:2822–2834; 1987.

United States Nuclear Regulatory Commission. Standards for Protection Against Radiation. Federal Register 56:23360–23474; 1991.

Uphoff, D. E.; Stern, C. The genetic effects of low intensity radiation. Science 100:609–611; 1949.

Weinstein, A. The production of mutations and rearrangements of genes by x rays. Science 67:376–77; 1928.

Wei, L. Health survey in high background radiation areas in China. Science 209:877; 1980.

Wilkinson, G. S.; Dreyer, N. A. Leukemia among nuclear workers with protracted exposure to low-dose ionizing radiation. Epidemiology 2:305–309; 1991.

Wintz, H.; Rump, W. Protective measures against dangers resulting from the use of radium, Roentgen and ultra-violet rays. Geneva: League of Nations; Official Publication C. H. 1054; 1931.