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Radiation Hormesis: Incredible or Inevitable?

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It has long been recognized that exposure to low levels of toxic chemicals could have beneficial effects, such as increased resistance to related chemicals or stimulation of growth or development. The notion of radiation hormesis, that exposure to low levels of ionizing radiation could produce beneficial effects, developed seriously in the late 1950's, and was, to most radiation scientists, incredible. This was due in part to the then prevailing ideas of radiobiological mechanisms, in part to the sweeping generalizations made by the leading proponents of the radiation hormesis concept, and in part to the many failures to confirm reports of beneficial effects. More recent understanding of the mechanisms of radiation damage and repair, and discoveries of induction of gene expression by radiation and other genotoxic agents [the adaptive response] make it seem inevitable that *under suitable conditions*, irradiation will produce beneficial effects.

The term hormesis generally implies a beneficial effect of exposure to a toxic agent, but the term has also been described as a stimulatory effect or, in a striving for objectivity, as a response to low levels which could not be predicted from the effects of high levels of such an agent. Most writings in the field do not discuss the obverse situation: toxic effects at high levels of substances hailed as beneficial at lower levels! The notion of chemical hormesis was widely accepted as the Arndt-Schultz Law, but in recent years has come into disuse, if not active rejection, at least in part because of concerns about effects of environmental pollution. The subject of chemical hormesis and its history has been reviewed in masterly fashion (Calabrese and Baldwin, 2000a). The notion of radiation hormesis is much more recent, and the debate over its existence much more acrimonious and therefore, perhaps, more interesting. I shall discuss current notions of radiation hormesis and their development from a historical perspective, partly to account for some of the acrimony, partly to create a model for some types of scientific progress, and partly to permit my airing of some personal prejudices.

Some Pertinent Aspects of the First 55 Years of Radiation Science

The need for quantitative methodology

In 1895, W. Roentgen, Professor of Physics at the University of Wurtzburg, discovered that Crookes tubes, already common tools in physics laboratories, emitted some form of electromagnetic radiation which could affect photographic media. The mechanism for this effect was not clear, and in testing one theory of the photoreaction a French chemist, H. Becquerel, discovered radioactivity. Shortly afterwards, the Curies discovered and isolated radium. These discoveries were exciting to the general populace – and to entrepreneurs – as well as to the world of science, and soon there were advertisements for sale of thorium and other radioactive materials, for treatment of various human ills, including sexual impotence in elderly men! In 1906 two French physicians recognized as radiotherapy specialists enunciated the Law of Bergonie and Tribondeau, that the radiosensitivity of a tissue is proportional to its proliferative activity and inversely proportional to its degree of differentiation. This law guided radiation oncologists for the next 50 years.

Radiotherapy [and radiation research] were hampered by the lack of reliable dosimetry and of a rational dose unit. The unit used in the clinic was the SED, the skin erythema dose, or the minimum exposure to produce reddening of the skin [usually, on the radiologist's arm] within 48 hours. Aside from the poor physics and the variability in radiosensitivity of the skin of different radiologists, by the early 1920's it was apparent that chronic exposure to moderate X-ray doses was causing a high incidence of cancer among the radiologists.

General public interest in radiation science waned, but became highly emotional, particularly in the United States, when the plight of the radium dial painters was publicized. Major manufacturers gave subcontracts to small businesses to prepare radium-painted dials for

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clocks and watches. Most of the employees were women in their 20's or late teens. They used small brushes, moistening them on their lips to have fine points for the free-hand painting. Much of the paint would be absorbed into the women's bodies, with the radium, chemically similar to calcium, winding up in the jaws and other bones. Bone cancer occurred with extremely high incidence! Again, it was clear that prolonged exposure to moderately high radiation doses caused high rates of cancer!

Quantification of dose

In 1926 there were 2 related events: 1) An international commission agreed on an X-ray *exposure* unit, the roentgen, R, defined as the amount of radiation producing 1 electrostatic unit of charge in 0.001293 grams [i.e., 1 cubic centimeter] of dry air. This amounts to absorption of 83 to 97 ergs/gram, depending on whether the absorber is air, water, soft tissue, or bone. [When it was decided, after World War II, to develop a unit of *absorbed* dose, the **rad** was defined as absorption of 100 ergs/gram. More recently the SI system, with the Joule as the basic unit of energy and the kg as basic unit of mass, a new unit of dose, the gray, was defined as absorption of 1 J/kg, which = 100 rad.] 2) An American physicist, John Victoreen, developed a condenser meter to measure the number of ions [and, thence, of roentgens] produced within the known volume of air in the dosimeter.

Development of target theory

With a readily and reliably measurable unit now available, some physicists began to perform radiation experiments on simple biological materials, chiefly enzymes [the only molecules whose activity or "survival" which could be scored at this time] and on bacteria. Radiation-survival curves for these molecules were exponential, like radioactive decay curves, without any threshold or shoulder, suggesting that a single critical event [a "hit"] in the right place [the "target"] was sufficient to inactivate the molecule or bacterium. By assuming, logically, that the "hit" was a cluster of ionizations, and applying Poisson considerations [that is, an average of one hit per target produced e^{-1} or 37% survival] the researcher could estimate the size of the critical target. For a variety of enzymes, the target size calculated was approximately the molecular weight, suggesting that a hit anywhere within the molecule was sufficient to inactivate the entire molecule, a perfectly reasonable concept. Comparable studies and reasoning with bacteria, however, led to target-size estimates much larger than known for any molecule, but much smaller than the cell. Nevertheless, an English biophysicist, Douglas Lea (1947) and a pair of investigators (Timofeeff-Ressovsky and Zimmer) in Germany almost simultaneously published books on Target Theory as applied to cells, the core notion being that *within each cell there is a critical target—a volume or an organelle—within which a single hit is necessary and sufficient to inactivate the entire cell.* Most biologists could not accept that notion, because they could not conceive of any such critical entity within the cell. Note, at that time the critical role of DNA had not yet been recognized, and bacteria were not credited with having nuclear material!

Despite the misgivings of most biologists, Target Theory was a very good theory, in that it accounted for most of the pertinent facts known at the time, and, more importantly, it made predictions which were amenable to experimental test.

These predictions were:

1) Densely ionizing radiation would be less effective, because of energy wasted: far more than one cluster of ionizations would be deposited in the target.
2) External or environmental factors would have little or no influence.
3) There could be no repair of damaged targets.

During the 1950's, each of these predictions was proven incorrect, but many of the concepts of target theory remain useful today.

The legacy of World War II

Target Theory was developed, primarily in Great Britain and in Germany, just prior to World War II. During the war, little radiation science was performed in either of these countries. The United States, however, largely out of fear that Germany was preparing atomic weaponry, mounted a large "Atom Bomb Project" with supporting research on whole animal and genetic responses to acute radiation exposure. After the war there was widespread euphoria, both in the general population and in the scientific community, not only about the political future, but about the benefits which would accrue to mankind from the availability of cheap, safe, and plentiful atomic power. Atomic energy was considered so important by the United States government that the Congress established a "joint committee" [that is, one composed of members of both houses, the Senate and the House of Representatives] on atomic energy. There were some in the general populace who were terrified of any radiation, but they were not taken seriously. There were some in the scientific community, however, who did not argue that radiation was necessarily unsafe but, rather, that we did not have enough information to judge whether or not occupational exposure to fairly low doses posed any hazard. One of the most influential of these was a biophysicist, Egon Lorenz, who had worked at the Manhattan [atomic bomb] Project during the war, and who held appointments in both the National Cancer Institute and the AEC [Atomic Energy Commission] Argonne National Laboratory. Lorenz appeared before the Joint Committee, and convinced them to fund a

[for that time] extremely large research program to follow the entire life spans of mice, rats, and guinea pigs exposed to sublethal doses: 100 or 200 R at one time, or a few R/day, 5 days/week, to mimic possible exposure in the work-place. The preliminary results of the Lorenz project suggested that the rodents exposed to low doses had shorter life expectancies than their controls, but the differences were rarely, if ever, statistically significant. Deaths in a laboratory animal population are distributed over a very long time period, so the standard error of mean survival time is very large. Before he could compile more experimental data or apply more sophisticated statistical procedures, Lorenz himself passed away. This left the AEC in a quandary: Should they search for outstanding personnel to take over and continue this very expensive program, or conclude that there were no important data coming from it and end its support? In short, they needed a thorough and objective analysis of the Lorenz findings. To perform this task, they called upon George Sacher, a mathematically-gifted and erudite young biologist at the Argonne Laboratory. Sacher, too, was frustrated by the lack of statistically significant differences. He either knew, or learned from his extensive reading, about the Gompertz function in human longevity studies. [Benjamin Gompertz was not a biologist, but an insurance actuary]. In 1825 Gompertz had pointed out that the age-specific mortality rate, R, in various human populations increased exponentially as a function of age, beginning about the time of puberty:

$$R = R_p e^{kt}$$

Sacher applied the formula to the Lorenz data, confirming that life tables of laboratory animals also followed Gompertzian kinetics. Actually, Simms (1946), a biochemist at Columbia University's medical school, had "rediscovered" the Gompertz function, showing that it applied to many different specific causes of death in humans; using a few sets of data published by earlier workers, Simms also suggested that it applied to rats and to *Drosophila*! This type of analysis is now a common tool in experimental gerontology. More directly pertinent to the Lorenz project: Gompertz plots for animals irradiated acutely at young ages were shifted up [to the left], as if the radiation had added an increment of age. Some of the groups first irradiated late in life showed small shifts to the right, however; the slopes of the exponential portions were essentially unchanged. The slopes for chronically [5 days/week] exposed animals were increased, as if the aging process was being steadily accelerated. Most of Sacher's work first appeared in Argonne Laboratory reports, not readily available to investigators outside the radiation science community; Sacher, like Lorenz, was particularly interested in the effects in chronically exposed animals, and most of his pertinent publications in the open literature focussed on these. But results similar to Sacher's for singly-exposed animals were found in the large studies of mice exposed in the atom bomb tests (Upton et al., 1960) and in smaller studies with rats (Jones and Kimeldorf, (1964).

Consequences of the Lorenz-Sacher Study

The subdiscipline of experimental gerontology

The demonstration of significant life shortening in the fashion of induced aging was very exciting to radiation biophysicists and other physical scientists, and attracted investigators trained in mathematically rigorous disciplines. Sacher himself became a distinguished gerontologist, serving as president of the American Gerontological Society, and was for many years the North American editor for the journal Experimental Gerontology. Howard Curtis, a biophysicist, stepped down from the directorship of the Biology Division in the AEC's Brookhaven Laboratory to set up a large gerontology research unit there, and later wrote an exceptionally readable textbook of gerontology (Curtis, 1966). Bernard Strehler, a biophysicist previously known for ultra-violet light studies and work on bacteriophage, became a full-time gerontologist and long-time editor-in-chief of the journal Mechanisms of Aging and Development. These developments were initiated by the belief that radiation induced aging, and could be as powerful a tool for gerontology as it was for genetics. Interest in gerontology among biophysicists continued, however, even after it became evident that virtually all of the life-shortening effects of radiation were attributable to early induction of cancer (Walburg, 1975).

Does radiation accelerate aging in Drosophila and other insects?

It was obviously attractive to examine the effect of radiation on longevity of *Drosophila*. There was a potential complication, however. Radiation induces acute lethality in mammals in a matter of weeks, a small fraction of their normal life-span; death is clearly the result of events following killing of the proliferative cells of the intestinal lining (high doses) or of the proliferative hemopoietic cells (moderate doses). In most adult insects, somatic cell proliferative activity is limited to the regenerative nidi of the mesenteron, and there is considerable evidence (Ducoff, 1972) that radiation-induced death of beetles and most other adult insects is the eventual result of cytocidal effects in these cells. But in adult Diptera, including *Drosophila*, there is no somatic cell renewal; these insects appear very radioresistant, and simply die off more rapidly, without a clear period of acute mortality, after high radiation doses. Several investigators, including Sacher (1963) did measure Drosophila longevity after low radiation doses, found that life span increased, and abandoned that approach. One group, however, conducted more detailed studies, and noted that the

increase occurred in the females, but not in the males (Lamb, 1965). The female flies, even when not mated, lay eggs, and it was found that the irradiation inhibited egg-laying; apparently the irradiated female had proteins and/or energy sources which would otherwise have been expended in egg-laying available for her own somatic tissues, and so lived longer! [In a later review, Lamb (1978) cited and discussed other investigators who either supported or argued against this explanation.] Another possible explanation, however, was suggested by the observation (Baxter and Blair, 1969) that young Drosophila exposed to low doses of ionizing radiation became resistant [overrecovery] to later high-dose challenge! Subsequently, Bhatnagar et al. (1965) working with house flies, noted that sexually-segregated males lived longer after irradiation. Both Rockstein's group (Rockstein, 1956) and Sohal's (Ragland and Sohal, 1973; Allen and Sohal, 1982), in a series of papers, correlated wing abrasion and loss with aging in male flies, and noted that wing loss was increased with mating or other physical activity, but was reduced after irradiation. Patterson (1957) had noted that resistance, *usually* by female flies which had mated previously, but *sometimes by males*, to males seeking mating, often led to wing damage or loss. Thus, physical and mating (including homosexual rape) activity were reduced after irradiation, and this probably explained the longevity enhancement!

Radiation hormesis: the concept

We have noted that the Gompertz curve of some of the Lorenz-Sacher groups [mostly those exposed acutely at fairly advanced ages] was shifted to the right, or down; that is, they appeared to have *gained* life expectancy. This phenomenon caught the attention of a biochemist, T. D. Luckey, who had been involved in the early studies indicating that incorporation of antibiotics into the diets of young chicks enhanced their growth and development. So here was another inhibitory agent, ionizing radiation, enhancing viability! Luckey did painstaking searches of the literature, and found many hundreds of published papers in which authors had reported explicitly, or their data seemed to suggest, radiation effects which were beneficial or stimulatory. He published (1980) a large informative volume on *Radiation Hormesis*, as well as many journal articles.

Luckey did not simply describe examples of beneficial effects. He argued that life had evolved in an environment which included radiation, and that radiation was essential to life. He also argued that benefits of irradiation were a law of nature! The idea that cells could benefit from irradiation was not compatible with target theory, and so had important implications for basic radiation science. The idea also had political and economic implications. Development of nuclear power was often opposed as too greatly risking people to radiation exposure or as a threat to the environment; but if low-dose exposure is beneficial.. On the other hand, if cells may benefit from some radiation exposure, radiotherapy protocols would have to be reassessed. And perhaps crops could benefit from irradiation; a Soviet scientist, A. Kuzin, became a leading investigator in this area.

Scientific shortcomings of the hormesis concept

Although there were hundreds of reports of stimulatory or apparently beneficial effects of radiation, many did not include adequate statistical analysis (Miller and Miller, 1987) or could not be repeated by other workers. An early study of stimulatory effects in plants (Skok et al., 1965) dismissed the effect as being too small to matter. About the only "hormetic" phenomenon confirmed in various laboratories and for many species was the radiation-enhanced longevity of adult insects. [Probably the earliest report of such enhanced longevity was that of Davey (1919), using the flour beetle, *Tribolium confusum.* Davey (1917) first studied beetle lethality following higher doses, and, reviewing much of the published work on animals other than man, suggested that radiation might resemble drugs in that low doses could be stimulatory, moderate doses produce a destructive effect after a latent period, and high doses produce instant destruction.] If enhanced longevity was the result of inhibited reproductive activity or behavior, however, it was not biologically beneficial. Among the stimulatory effects cited was increased potassium extrusion; but cells take in K^+ against a concentration gradient, and K^+ extrusion is generally considered an indicator of membrane damage! Classifying radiation as a law of nature made the concept even less acceptable, since its occurrence was rarely verifiable; furthermore, if a phenomenon is a law of nature there is little incentive to seek a mechanism!

A personal perspective

In 1961 I began to use insects, particularly *T. confusum* and *T. castaneum*, as the experimental tools in my radiobiological research. I wanted to use insects because of their previously mentioned lack of dependence on somatic cell proliferation, and chose flour beetles because their nutritional requirements were known and so, like some nematode worms, they could be grown on defined media. I hoped (naively) that I would be able to learn which metabolic pathways were involved in recovery from radiation damage and, possibly, in the aging process. I soon found a paper (Cork, 1957) reporting that irradiating newly emerged adult flour beetles [a physicist, he wrote of *newly-hatched individuals*, but correspondence with one of his associates confirmed that he had meant *newly-eclosed*]. Neither Cork nor Davey separated the sexes. Using *T. castaneum*, I found (Ducoff, 1975) that irra-

diation markedly increased mean life expectancy in sexually-segregated adults of both sexes. There was little or no increase in maximum life span, but great reduction or delay in early mortality. This pattern has been reported, or is seen in published data, for several insect species and by various authors. Being familiar with the publications on *Musca* and on *Drosophila*, I did not regard the effect as necessarily beneficial, and so I avoided (or evaded) the hormesis controversy. This left me free to worry about mechanism!

The usual manifestations cited for chemical hormesis are induction [by low doses of a chemical] of resistance to later challenge by the inducing chemical or by similarly-acting chemicals, or increased rates of growth or development, but not enhanced longevity. Could radiation induce resistance to subsequent irradiation? After Elkind and Sutton (1959) demonstrated that cells could repair damage by ionizing radiation, numerous investigations at the molecular level showed that many radiation-induced DNA lesions are eliminated by excision-repair processes similar to those acting on UV-induced lesions. It was recognized that, at least in bacteria, there was an UV-inducible repair process [SOS-repair] for DNA lesions produced by UV radiation. More pertinently, desmids exposed to low doses of ionizing radiation developed radioresistance (Howard and Cowie, 1976). Would induced radioresistance affect longevity of insects not deliberately irradiated? Hart and Setlow (1974) measured the UDS [unscheduled DNA synthesis, a manifestation of excision repair] by fibroblasts taken from various mammals [from shrews to elephants] and found remarkable correlation between UDS following standard UV exposure and the mean lifespan of the species, but there was no influence by the age of the donor. Furthermore, they pointed out that many endogenously generated chemicals, such as reactive oxygen entities, produce DNA lesions similar to those produced by radiations. Thus, it appeared logical that low dose irradiation might induce greater capability to repair metabolism-caused DNA damage, thereby enhancing longevity. But if so, why do insects benefit consistently, whereas mammals do not?

Noting that Hart and Setlow had found no influence of donor age on UDS activity in fibroblasts, I postulated (Ducoff, 1976) that the [recognized] DNA damages which occurred during replication maintained repair activity at a genetically-determined high level, but that repair capability would decline over time in terminally-differentiated tissues, and accumulated lesions would interfere with gene transcription and, therefore, with adaptation to stresses. Thus, in mammals and other organisms highly dependent on cell proliferation, even low radiation doses would primarily be detrimental, but in organisms like insects, composed primarily of postmitotic cells, radiation-induced increases in repair capability would lead to benefits from retardation of age-related decline in ability to adapt.

The advantage of this concept was that it might be tested experimentally: If we could identify some stressors to which resistance declined with age, radiation exposure of young adults should retard the age-related decline in resistance. We did find that adult flour beetles became steadily more sensitive to hyperbaric oxygen (Lee and Ducoff, 1983) and to heat, and that beetles which had been irradiated were more resistant to these stresses (Lee and Ducoff, 1984; Ducoff and Lee, 1984). The problem was that stress resistance in the irradiated beetles was considerably greater than in the young controls, so the effect was not simply a retardation of aging! The probable explanation was found in two publications from other groups: Krueger and Walker (1984) found that germicidal UV light stimulated *E. coli* to synthesize heat stress proteins, recognized as the basis for heat-induced heat resistance, and Mitchel and Morrison (1984) reported that UV or ionizing radiation induced development of heat resistance in yeast. Suddenly, there appeared to be a possible mechanism not only for radiation enhancement of insect longevity (Ducoff, 1986), but for many types of radiation hormesis.

The Adaptive Response - Is Hormesis Inevitable?

Why apparently beneficial responses now seem inevitable

Studies with yeast led to an estimate (Ruby and Szostic, 1985) that there were some 80 genes inducible by damage to DNA, and by no means were they all known to be involved in DNA repair! Extensive work on mammalian cells (reviewed by Fornace, 1992; Fornace et al., 1992) showed that many damage-induced genes are associated with growth responses, some stimulatory and some negative.

Perhaps the most influential report in this field was an investigation by Sheldon Wolff, a highly regarded cytogeneticist, and his colleagues (Olivieri et al., 1984) who reported that prior treatment with very low doses of tritium led to an adaptive response in human lymphocytes subsequently challenged with X-rays, and Wolff et al. (1988) gave further evidence that low X-ray doses also rendered the cells refractory to X-ray induction of chromosome aberrations. Subsequent work by this group (Youngblom et al., 1989) showed that the effect was inhibited by cycloheximide, indicating that induction of radiation resistance required protein synthesis. There is now widespread agreement that DNA damage, induced by any of a number of agents, can induce expression of numerous genes including not only those for DNA repair but also some genes for resistance to stresses by prevention, such as binding heavy metals, and some of as yet unknown function. For example, UV irradiation induces synthesis of metallothioneins, the -SH proteins known to protect against heavy metal toxicity (Fornace et al., 1988). Not

all damaging agents produce the same array of expressed genes, however. Woloschak and Chang-Liu (1990) have shown that even different forms of ionizing radiation elicit different arrays! These considerations have led to the concept of the *adaptive response*. It is interesting to recall that a brief exposure to high temperature was found (Maynard Smith, 1958) to enhance longevity of *Drosophila*!

Why, then, were hormetic effects so frequently denied?

My answer is at least partially speculative, and Calabrese and Baldwin (2000b) express a very different view. The early advocates rushed into publication on the basis of few experiments and, often, as pointed out by Miller and Miller (1987) with inadequate or no statistical analysis. Also, induction of stress-resistance proteins provides no benefit in short-term experiments, unless the system is subjected to external stresses; skeptical investigators who tested reports of better growth, development, or survival were extremely careful to control external factors such as temperature, pH, solvent purity, etc., so benefits, if any, were minimal. Luckey himself (1980, p. 49) commented *The effect is usually magnified by unfavorable conditions*. I have already noted that in our own work on insect longevity, the irradiation primarily reduced early mortality, making the survivorship curves more rectangular; clearly, our conditions [and those of most laboratory experiments with insects] are far from ideal!

Does radiation hormesis require that risk assessment be greatly altered?

Clearly, we do not have enough knowledge to make quantitative estimates of how much radiation exposure might be beneficial, rather than detrimental. The amount and the profile of gene expression induced varies not only with the type of radiation, but with the stage of the cell cycle exposed. The time interval between exposure and induction is usually a matter of several hours; the duration of the induction is rarely measured but appears to be somewhat longer. Would a low dose have to be repeated regularly for long-term benefit in a long-lived creature like *H. sapiens?*

The qualitative problem is even more disturbing. The breadth of the adaptive response spectrum—that is, the variety of stress genes induced—is matched by the breadth of the spectrum of inducing agents. How does low dose radiation exposure interact with low dose exposure to other environmental inducers? I am not aware of any studies designed to examine such interactions, although many reports indicate that increasing the size of the "low radiation dose" has little or no greater inducing effect. Would there be synergism, additivity, or antagonism if inducing doses of radiation and of heat or heavy metals were administered at the same time?

Conclusion

We have seen that the "modern era" of radiation hormesis study began with Sacher's analysis of the Lorenz rodent data. It is fitting to conclude this review with Sacher's (1963) concluding remarks in his paper reporting increased longevity in irradiated *D. melanogaster*, written long before there was any concept of a molecular basis for the phenomenon. He had noted a reduction in variability of mean after-survival between replicates of the irradiated samples, and he attributed both the reduction of variability and the improved survival to a reduction in the effectiveness of a deleterious environmental variable:

> *It cannot be determined whether this reduced effectiveness results from an inactivation of the environmental factor or from an increase in resistance induced in the flies by the radiation exposure.*

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