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RADIATION, ECOLOGY AND THE INVALID LNT MODEL: THE EVOLUTIONARY IMPERATIVE

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□ Metabolic and energetic efficiency, and hence fitness of organisms to survive, should be maximal in their habitats. This tenet of evolutionary biology invalidates the linear-no-threshold (LNT) model for the risk consequences of environmental agents. Hormesis in response to selection for maximum metabolic and energetic efficiency, or minimum metabolic imbalance, to adapt to a stressed world dominated by oxidative stress should therefore be universal. Radiation hormetic zones extending substantially beyond common background levels, can be explained by metabolic interactions among multiple abiotic stresses. Demographic and experimental data are mainly in accord with this expectation. Therefore, non-linearity becomes the primary model for assessing risks from low-dose ionizing radiation. This is the evolutionary imperative upon which risk assessment for radiation should be based.

Keywords: adaptation, background radiation, Chernobyl, ecology, environmental stress, evolutionary expectation, hormesis, LNT model, metabolic efficiency, oxidative stress, radiation

BACKGROUND RADIATION VARIATIONS

Exposure to ionizing radiation has always been part of the environment on Earth. Life apparently evolved spontaneously from basic chemicals formed by reactions largely initiated by ionizing radiation from the sun. When life commenced on Earth around three and a half billion years ago, the natural level of radiation was up to five times higher than today.

Everyone is exposed to background ionizing radiation in the environment from outer space, the sun, terrestrial rocks, the soil, buildings, the air that we breathe, the food we eat, and from human and animal bodies. Using a standard measure of the effects of radiation in terms of milliSieverts (mSv) per year, these exposures from natural sources total around 2.15 mSv each year at around sea level. Smaller components from man-made sources principally from medical procedures (around 0.30 mSv per year), and a minor component (around 0.05 mSv per year) from other sources including consumer products and fall-out, bring the total to around 2.5mSv per year. Doses from man-made sources therefore

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amount to substantially less than 20% of natural exposures. In summary, the average dose rates due to natural and man-made background ionizing radiation in industrial countries in mSv per year are:

Background radiations of natural origin	
Naturally occurring radioelements in the soil, rocks etc.	0.40
Radon, thoron, and their short lived decay products	1.20
Cosmic radiation at sea level	0.25
Radionuclides inside the human body, mainly potassium-40	0.30
Man-made sources	
Medical procedures, mainly X-rays	0.30
Other man-made sources (consumer products, air travel,fall-out etc.)	0.05

giving a total of around 2.5 mSv per yer at sea level (Lowenthal and Airey, 2001)

Background radiation of natural origin can be substantially higher than those around sea level. The two major sources of variation upwards are height above sea level and diverse geological backgrounds. Background radiation can shift upwards by a factor of three or more in populations with increasing altitude as found in the Rocky Mountains regions of USA. Populations numbering several millions are exposed to background radiation in the range of 3 to 8 mSv per year and much higher for some smaller groups, when exposed to geological structures rich in uranium, thorium and their decay products.

Some areas of the world, called high background radiation areas (HBRAs), have extremely high levels of background radiation. A field of medical geology has emerged defined by the International Commission of Geological Sciences for Environment Planning as the science dealing with the influence of ordinary environmental factors on the geographical distribution of health problems in humans and animals.

Dissanayake (2005) has published many research papers in medical geology. In a recent essay in the American journal Science, he writes:

> Extreme HBRAs are found in Guarapari (Brazil), southwest France, Ramsar (Iran), parts of China, and the Kerala coast (India). In certain beaches in Brazil, monazite sand deposits are abundant. The external radiation levels on these black beach sands range up to nearly 400 times the normal background level in the United States. The Brazilian coastal sands have several radioactive minerals, among them monazite, zircon, thorianite, and niobate-tanalate.
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> In India, along the 570-km-long coastline of Kerala, there are major deposits of monazite-rich mineral sands with very high natural radiation. The monazite deposits are larger than those in Brazil, and the dose from external radiation is, on average, similar to those reported in Brazil.

Ramsar, a city in northern Iran, has one of the highest natural-radiation levels in the world. In some locations at Ramsar, the radiation level is 55 to 200 times higher than the background level.

The most interesting feature in all these cases is that the people living in these HBRAs do not appear to suffer any adverse health effects as a result of their high exposures to radiation. On the contrary, in some cases the individuals living in these HBRAs appear to be even healthier and to live longer than those living in control areas that are not classified as HBRAs. These phenomena pose many intriguing questions for medical geologists.

THE RADIATION-EXPOSURE PARADOX

Although more critical data are needed, the apparent health-promoting consequences of HBRAs are paradoxical and are frequently disputed. Definitive studies of outlier populations such as HBRAs require enormous sample sizes to differentiate between populations exposed to differing radiation levels. Even when negative correlations occur between dose and cancer incidence in these demographic studies, there is always the problem of whether correlation implies causation. For example, Cohen (1995) found a highly significant negative association between mean radon exposure and lung mortality across US counties. Cohen and his colleagues explored many possible explanations including variations in smoking prevalence, errors in the radon data, coincidental properties of data sets, and confounding by socioeconomic factors, but none of these led to substantial reductions in the effect. In spite of extensive efforts, the negative correlation between radiation exposure and lung cancer rate therefore remained. Consequently "there is no evidence in this analysis that low-level radiation causes cancer, and there is at least some evidence that it may protect against cancer."

On the other hand, the commonly assumed model for radiation protection is the linear- no-threshold (LNT) model, which assumes a direct linear extrapolation from the deleterious health effects of radiation at high doses to the very small doses in our background. The contrasting model of negative associations between low exposures and health consequences giving non-linearity (i.e. a U shaped curve) is referred to as hormesis. Non-linearity is typically manifested by reduced cancer incidence and increased longevity at low radiation exposures. This is to be expected since organisms evolve over time to be fittest in the environments in which they live, that is exposed to background radiation. This fundamental tenet of evolutionary biology shows that the LNT model is a biological impossibility (Parsons, 1990, 2000,2003). In accord with this reality, radiation hormesis has been demonstrated on numerous times in controlled experiments in organisms ranging from microorganisms to mice (eg Luckey, 1991; Calabrese and Baldwin, 2000).

Furthermore, the multiplicity of environmental agents to which we are exposed on Earth interact metabolically, so that the LNT model breaks down to include the exposures of geological outliers including HBRAs as explained in detail in the next section. Therefore the hormetic zone apparently extends to exposures substantially in excess of those at sea-level (Parsons, 2003, 2005).

Some French scientists recently carried out a comprehensive assessment of the evidence for and against the LNT model. In an excellent report "Dose-Effect Relationships and Estimation of the Carcinogenic Effects of Low Doses of Ionizing Radiation," published by the French Academies of Medicine and Science, Tubiana *et al.* (2005) concluded that the LNT model for human data defaults at doses less than 100 mSv, and even more so at extremely low doses less than 10 mSv. Positive health consequences of low exposures to ionizing radiation are implied compared with the LNT model. Such positive health or fitness deviations from the LNT model are a manifestation of radiation hormesis.

In preparing the French report, the authors note the very real difficulties in obtaining accurate estimates from demographic data. They emphasize that hundreds of thousands of subjects need to be included and monitored for a sufficiently long time, but that "below 20 mSv generally encountered within the context of radioprotection, epidemiology can neither confirm nor refute the existence of an increased incidence of cancer."

The French report is based upon an analysis of a range of populations including the survivors of the Hiroshima and Nagasaki bombs, people involved in the clean up following the Chernobyl accident, nuclear industry workers, and radiologists and radiology technicians. Even airline flight crews are included where the French report concludes:

> Airline flight crews receiving exposures of 1.5 to 6 mSv per year have been studied. No increase in the total number of cancers or of cancers in the most radiosensitive organs has been detected in 44,000 members of flight crews or in 2,749 Canadian pilots. An excess of melanomas was observed in these populations, and this can be explained by their more frequent exposure to the sun.

A potentially safe exposure range substantially above those recommended by the International Commission of Radiation Protection (ICRP) emerges from the French report. The lack of deleterious consequences from background exposures in HBRAs, plus the evidence for hormesis, appears consistent with a limit to the safe range in the region of 50 - 100 mSv per year for the general population. Therefore, the limit of 1 mSv per year recommended by the ICRP appears absurd in view of these estimates. From this descent into fantasy based upon the demonstrably invalid LNT model, spurious estimates of risks follow.

A consequence of these spuriously inflated risk estimates is media hysteria based upon radiophobia (Parsons, 1999) for the Chernobyl accident and exposure to depleted uranium. In the case of Chernobyl, a recent report of the Chernobyl Forum (2005) made up of eight UN specialized agencies, has shown that the Chernobyl incident was not catastrophic and not nearly as substantial as had at first been feared. Even so, one prediction of the Forum is that eventually an extra 4,000 may eventually die from cancer. This speculative upper limit is based upon the LNT assumption. In any case, such a predicted number cannot be verified, and equally, it is difficult to falsify. Most importantly, any hormetic model would necessarily imply substantial reductions below the estimated 4,000 deaths, almost certainly closer to zero than to 4,000.

WHY IS THE LNT MODEL INVALID BEYOND BACKGROUND EXPOSURES?

On evolutionary grounds, organisms tend to become increasingly adapted to their habitats. While fitness is characteristically assessed at the organismic level for a range of traits such as fecundity, survival and longevity, energy provides a more fundamental foundation for fitness (eg Van Valen, 1976; Watt, 1986; Parsons, 2005). A tendency towards increased energetic efficiency of organisms in their habitats therefore represents an adaptive process which translates into increased fitness, however measured. That is, a basic measure of fitness in a stressed world is energetic efficiency in the face of multiple environmental hazards, including ionizing radiation.

In this context, stress is an energy drain and can be expressed by a loss of fitness. Consequently, stress is an environmental change or probe that targets energy carriers so that energetic efficiency is reduced. Any increase in stress will disturb the energy balance between input and output that organisms build up in their habitats. More generally, the second law of thermodynamics requires that any process underway in a system universally degrades the energy in that system. Stress therefore reduces energy flow until a critical threshold is reached where cells and hence organisms can no longer survive. Based upon this reductionist approach, the availability of energy and its interaction with stress underlie fitness, and hence can determine limits to adaptation in populations of the past and present (Parsons, 2005).

Variation in the severity of an environmental stress gives a non-linear fitness continuum. Considering temperature, fitness should be maximal at intermediate temperatures between the extremes of heat and cold. Physiologically, this expectation is manifested by low metabolic rates at intermediate temperatures. For example in fasting rats, minimum heat production and maximum survival occur around the intermediate temperatures of 28-29°C (Kleiber, 1961; Blaxter, 1989). This and other exam-

ples show that biological systems are the most stable and energy dissipation is low in the thermal neutral zone, which is a region of high energetic efficiency and hence high fitness (Zotin, 1990).

Since fitness in relation to stress level is non-linear, the LNT model often assumed between the level of an environmental agent and its biological and health consequences is invalid, since all environmental agents have energetic costs (Parsons, 2003, 2005). The term hormesis can be used to describe the maxima especially for agents that are exceedingly toxic at high exposures. Radiation hormesis becomes merely a case study of a general ecological and evolutionary expectation for all environmental agents.

An array of mild stresses including cold, heat, physical activity, irradiation and caloric restriction can induce longevity extensions (Calabrese and Baldwin, 2000; Rattan, 2004). One metabolic consequence of such hormetic exposures to mild stress is the production of "heat shock" or "stress" proteins, hsps. However, this adaptive process can incur a cost, since Hercus *et al.* (2003) increased life span of *Drosophila melanogaster* by repeated exposure to mild heat stress but fecundity fell. Sørensen *et al.* (2003) argue that the expressed hsps level in each species and population is a balance between benefits (resistance to stresses) and costs (negative effects on growth, development rate, fecundity etc.). Fitness maxima of hormetic zones therefore should reflect tradeoffs among various metabolic components all directed towards the maximization of energetic efficiency.

Radiation hormesis is commonly observed in experimental organisms and in man at exposures substantially exceeding background radiation levels. Assume that energetic and metabolic reserves such as hsps are built up to counter the wide array of stresses, especially climatic, to which all organisms are exposed in natural habitats. Such adaptive responses could provide protection from low-level to moderate stresses such as ionizing radiation at non-catastrophic levels but at higher levels than common background (Parsons, 2003). That is, the hormetic response becomes part of a general stress response involving hsps and other metabolic adaptations across stress levels and environmental agents (Hercus *et al.,* 2003). Fitness interactions for combinations of stresses should therefore ameliorate the effects of individual stresses in isolation. Therefore the hormetic model can be extended to multiple environmental agents. Cross-protection among various environmental agents could then occur, so that hormesis depends upon the energetic consequences of the totality of interacting environmental stresses of natural habitats. Hormesis therefore is an expression of high energetic and metabolic efficiency and hence high fitness that evolve in response to single and multiple environmental agents where energetic costs are not excessive. This generalization is consistent with the lack of deleterious

consequences of life in HBRAs, and to negative associations between radiation exposure and cancer incidence, which only change to positive when exposures become extreme.

OXIDATIVE STRESS, METABOLIC BALANCE AND ADAPTATION

Recent attention given to oxidative stress in natural populations will now be considered in the light of the above energetic and metabolic efficiency arguments.

The free radical theory of aging, based on the premise that a single common process is responsible for aging and death of all living beings, is a convenient starting point. Life apparently evolved spontaneously from basic chemicals formed by free radical reactions largely initiated by ionizing radiation from the sun. Under the free radical theory, the process of aging is determined by the sum of the deleterious free radicals occurring continuously throughout the cells and tissues of organisms. Free radicals, however incited, are proposed to underlie the progressive deterioration of biological systems over time due to their innate ability to produce change. In particular, oxygen is combined with enzymatically degraded food products to produce energy during tissue respiration at the mitochondria. A number of reactive oxygen species, ROS, are generated during this process. A wide range of cellular molecules including membrane lipids, proteins and DNA, can be attacked and seriously damaged by ROS. These free radicals therefore generate oxidative stress so reducing fitness and accelerating aging (see Arking, 1998).

Genetically-determined resistance to a variety of stresses in many species, including yeast, nematodes and *Drosophila,* is strongly correlated with longevity. Multiple-stress screening including oxidative stress, is an effective procedure for identifying longevity genes (Wang *et al.,* 2004). Similar patterns of gene expression characterize aging and oxidative stress in *D.melanogaster*, suggesting that the primary or operative feature is oxidative-stress resistance (Arking, 1998). Individuals with the potential for a long life should therefore carry genes for resistance to ROS, which are an inevitable consequence of life in a world rich in oxygen (Hekimi and Guarente, 2003).

In *D. melanogaster,* the stresses tested include temperature extremes, desiccation, anoxia and ionizing radiation. Recently, three ecological stresses (aridity, high temperature, solar radiation) which differentiate the north and south facing slopes of Evolution Canyon in Israel have been reduced to oxidative stress responses in field collected yeast, *Saccharomyces cerevisiae* (Miyazaki *et al.,* 2003), as anticipated from temperature-stress experiments in *D. melanogaster* (Nevo *et al.,*1998).

Physical stresses in natural populations therefore appear reducible to oxidative stress responses, deriving from the universality of ROS. Oxidative stress responses are therefore critical in the adaptation of nat-

ural populations, so that survival becomes a function of the efficiency of handling such stress over time. For example, oxidative stress is lower in healthy centenarians than in other aged subjects (Paolisso *et al.,*1998).

One of the most radioresistant organisms on Earth is the red-pigmented bacterium, *Deinococcus radiodurans,* which is resistant to other physical stresses including ultraviolet radiation, hydrogen peroxide, heat, desiccation and a variety of toxins. Genes protective against radiation stress are therefore protective against other stresses. For example, antioxidants can protect against both X-irradiation and oxygen poisoning in mice (Lane, 2002).

Damage from increased oxidative stress can be related to an imbalance between free-radical production and antioxidant protection. While this imbalance strengthens as radiation exposure increases, it should be minimal where fitness is highest in hormetic zones in accord with evolutionary expectations. A range of physical stresses should increase this imbalance, but metabolic interactions among stresses should adaptively ameliorate the consequences of individual stresses so providing metabolic protection. A significant consequence is radiation hormesis for exposures substantially in excess of common background exposures.

Radiation hormesis therefore becomes a manifestation of minimum metabolic imbalance. Analogously considering nutrition, excessive diets elevate the production of ROS implying increased metabolic imbalance, so giving a non-linear relationship and hence nutritional hormesis. In any case in the hormetic zone of caloric restriction, metabolic rate is less and stress resistance is higher than under excessive diets, implying a region of high metabolic balance (Nesse and Williams, 1994; Lane, 2002).

Radiation hormesis can be viewed as the summation of interdependent and complex adaptations involving ROS, antioxidants, heat shock proteins, DNA repair processes, and so on. More generally, complex metabolic processes at the molecular, genetic, chromosomal, cellular, physiological and immunological levels are interdependent, and have been considered in the hormetic context by increasing numbers of authors (eg. Pollycove and Feinendegen, 2001; Feinendegen 2005; Feinendegen and Neumann, 2005; Tubiana *et al.*,2005). Hormetic deviations from the LNT model follow, manifested by high fitness at the whole organism level typically measured by longevity and survival, and in demographic data by reduced cancer incidence. The biosystem therefore responds to ionizing radiation so efficiently in the hormetic zone that the risk of mortality from cancer should fall and life span should increase due to protective metabolic processes, apparently reducible to the evolutionary consequences of oxidative stress.

CONCLUSION: THE EVOLUTIONARY EXPECTATION INVALIDATES THE LNT MODEL

The invalid LNT premise has been documented in over 5,000 examples of physical/chemical agents (Calabrese and Baldwin, 2003). Scattered observations back to the early part of last century are even suggestive of hormesis in bacteria for uranium salts, and in the last decade a low-dose hormetic response to depleted uranium in grass has been reported (Buchanan and Fulmer1930; Meyer *et al.*,1998). More information would assist, but uranium is a constituent of most rocks and the sea, giving an evolutionary expectation of uranium hormesis. It is not surprising that Gerber *et al.* (1999) concluded: "We suggest that hormesis may be almost universal for substances normally present throughout geological time."

Habitats provide the ecological theatre for assessing the LNT model. Adaptation towards high energetic and metabolic efficiency, that is fitness, to counter the metabolic consequences of the stresses from single and multiple environmental agents should occur over time. This evolutionary process is expected to lead to non-linear continua for fitness for all agents including ionizing radiation. In the specific example of radiation, hormesis extends to exposures substantially in excess of background due to interactions between the metabolic effects of an array of abiotic stresses to which organisms are exposed in their habitats.

Non-linearity should therefore be the primary hypothesis against which any data set is tested. Indeed, Calabrese has said "I actually think that there should be a paradigm shift and that the hormetic model should be the default model." This quote comes from Hadley (2003), one of the few commentators who has considered the need to emphasize evolutionary inputs in attempting to understand hormetic zones. She emphasizes the underlying evolutionary process of selection for metabolic efficiency to adapt to a stressed world, which immediately predicts the universality of hormesis for all environmental agents. This is a present-day version of the often repeated Dobzhanky (1973) dictum that "Nothing makes sense in biology except in the sense of evolution." In conclusion, non-linearity is the fundamental model for assessing the risks from low-dose radiation.

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