RADIATION HORMESIS: CHALLENGING LNT THEORY VIA ECOLOGICAL AND EVOLUTIONARY CONSIDERATIONS

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Abstract—Ecological and evolutionary considerations suggest that radiation hormesis is made up of two underlying components. The first (a) is background radiation hormesis based upon the background exposure to which all organisms are subjected throughout evolutionary time. The second and much larger component (b) is stress-derived radiation hormesis arising as a protective mechanism derived from metabolic adaptation to environmental stresses throughout evolutionary time especially from climate-based extremes. Since (b) >> (a), hormesis for ionizing radiation becomes an evolutionary expectation at exposures substantially exceeding background. This biological model renders linear no-threshold theory invalid. Accumulating evidence from experimental organisms ranging from protozoa to rodents, and from demographic studies on humans, is consistent with this interpretation. Although hormesis is not universally accepted, the model presented can be subjected to hypothesis-based empirical investigations in a range of organisms. At this stage, however, two consequences follow from this evolutionary model: (1) hormesis does not connote a value judgement usually expressed as a benefit; and (2) there is an emerging and increasingly convincing case for reviewing and relaxing some recommended radiation protection exposure levels in the low range.
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INTRODUCTION: BACKGROUND HORMESIS

MOSSMAN (2001) asks "Is the evidence enough to warrant abandonment of the linear no-threshold (LNT) theory in favor of hormesis as a basis for radiation protection?" In posing this query, he notes the substantial support for radiation hormesis in animal and cell studies. Demographic analyses make human data much more difficult to interpret, but consistency with hormesis is accumulating. Mossman (2001) surmises that "Hormesis proponents have failed to define clearly the phenomenon or

develop a consensus of how hormesis should be quantified." My aim in this Forum is to put forward a model directed towards the amelioration of this unsatisfactory situation and briefly to consider its implications. In the interests of simplicity I assume the validity of hormesis as a phenomenon rather than reiterate numerous discussions on this issue (see for example Mossman 2001).

The model is based upon the ecological point that all organisms exist in habitats subjected to a multiplicity of environmental agents that become increasingly stressful towards extremes. The range of environmental agents for which hormesis has been documented includes heavy metals, pesticides, antibiotics, essential trace elements, and ionizing radiation. All are stressful at high exposures and give hormetic zones at low exposures. Such deviations from the LNT model are the norm and are not exceptional (Calabrese and Baldwin 1999). A unifying biological interpretation applicable to all agents comes from measures used to assess hormesis since they are components of Darwinian fitness, including growth, longevity, fecundity and general survival. A central tenet of the field of evolutionary biology, rarely considered in the context of health physics and toxicology, is that in a given environment natural selection favors maximum fitness of organisms. Hormetic zones should therefore occur under the environments in which organisms most commonly exist in their natural habitats. Examples include temperature variability, hydrological circumstances, and ethanol usage and tolerance as well as hormesis for ethanol derivatives such as acetic acid and acetaldehyde (Parsons 1992, 2001). Such ecological considerations are fundamental since the environment is the ultimate key to understanding evolutionary change.

Hormetic agents are predominantly normal or background constituents of habitats including various metals that are exceedingly toxic at high concentrations. In particular, background hormesis may be almost universal for substances present through geological time, such as mercury (Gerber et al. 1999). *Exactly parallel arguments apply to exposures of organisms to background ionizing radiation* (Parsons 1990). These exposures are mainly in the range 2.5–4.0 mSv y^{-1}, but in certain geological outliers in various parts of the world exposures can substantially exceed ten times this range (Luxin et al. 1997).

Rapidly accumulating examples of radiation hormesis occur from studies on experimental organisms ranging from protozoans to mammals. For example, in

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protozoans lower fitness was found close to zero radiation in a lead shielding device than at somewhat higher exposure levels including background (Planel et al. 1987). Furthermore, this hormetic effect can be induced artificially within the lead shielding device by adding appropriate radionuclides. Apart from such experiments on microorganisms, there are probably no other reliable experimental data at around background exposures. Furthermore, human demographic data are insufficiently precise for the detection of effects at such low exposures.

On the other hand, in many and perhaps most examples, radiation hormesis occurs at exposures that exceed background to levels that are substantially above exposures from geological outliers (where no radiation-induced deleterious effects have been detected). A recent study of the life span of mice measured the survival time for 50% of mouse populations, which was 22.6% higher than the controls following trials with exposure of 70 and 140 mSv y^{-1} of radiation (Caratero et al. 1998). This is consistent with experimental exposures of 100–800 mSv, which increased fitness measured by longevity in mice and rats by at least 20% (Luckey 1991). Depleted-uranium induced hormesis in plants is another example (Meyer et al. 1998). Furthermore, there are claims for radiation hormesis from A-bomb survivors at exposures exceeding 500 mSv (Mine et al. 1990; Kondo 1993). Can hormesis at these apparently stressful exposures be explained?

STRESS-DERIVED HORMESIS

In the process of adapting to a multiplicity of environmental agents, hormetic zones occur together with heat shock proteins (hsps). Since hsps occur and respond adaptively to environmental stress (Coleman et al. 1995), the hormetic response is part of a generalized stress response (Smith-Sonneborn 1993; Minois 2000). In natural populations, hsps levels reflect evolutionary adaptation to relatively rare periods of extreme stress—especially temperature perturbations from climatic variation. Metabolic reserves should then evolve that are available to provide protection from the array of lesser and milder background environmental agents to which organisms are continuously exposed including ionizing radiation. Metabolic protection could therefore underlie radiation hormesis at exposure levels substantially exceeding background. This would be an evolutionary expectation irrespective of the organism considered, since life itself evolved in inhospitable environments. In other words, if a case for radiation hormesis exists in various invertebrate and vertebrate taxa at similar whole-of-life exposures, it would be applicable to humans as a first approximation. In a parallel way, DNA repair mechanisms are universal irrespective of taxa, and in fact form one of the underlying molecular mechanisms proposed for hormesis (Wolff 1996).

Taking into account the universality of stressful environments, radiation hormesis has two components (Parsons 1999, 2000a): (a) *background radiation hormesis* from the direct adaptation of organisms to their habitats; and (b) *stress-derived radiation hormesis*, which derives from metabolic reserves evolving from and maintained as an adaptation to extremes of environmental stresses through evolutionary time. The exposure under (b) is far greater than under (a) by two orders of magnitude or more in many situations since background radiation is mainly below 10 mSv y^{-1}.

Under this model radiation hormesis is predominantly an evolutionary adaptation deriving from the metabolic consequences of environmental stresses of which radiation is a relatively small component. Furthermore, high fitness in the hormetic zone implies high metabolic efficiency in the face of interacting multiple stresses. A non-linear association of exposure to stress and fitness emerges which is incompatible with LNT theory based on biophysical principles. More generally, metabolic adaptations at the molecular, genetic, chromosomal, cellular, physiological, and immunological levels come together and interact to give hormetic deviations from the LNT model as discussed by Pollycove (1995) for ionizing radiation. The consequence of this scenario is enhanced biosystem efficiency with positive health effects of individuals subjected to radiation exposures within hormetic zones (Pollycove 1998). Therefore, the biosystem should respond to hormetic exposures to radiation to function so effectively that the risk of mortality and cancer should fall and life span should increase due to various interacting metabolic processes.

All environmental agents can be incorporated into this model of non-linear fitness continuums, assuming that selection for high metabolic and energetic efficiency is part of the process of the evolutionary adaptation of organisms to their habitats. For temperature, fitness tends to be maximal under the relatively benign fluctuations that characterize most habitats (Parsons 1992). However, the need to adapt to rare periods of extreme temperature foreshadows the existence of metabolic reserves that can underlie hormesis for correlated traits including radiation. Furthermore, the increase of hsps with distance from the hormetic zone indicates common underlying metabolic processes (Minois 2000). Radiation hormesis therefore can be predominantly regarded to be a second order effect deriving from the array of stresses of natural habitats, especially from the climate defined in the broadest sense.

A conundrum for many, which has been debated extensively, is the finding of a highly significant negative association of radon exposure and mortality among U.S. counties (Cohen 1995). This negative regression is counterintuitive based upon simplistic LNT models. It is not therefore surprising that this conclusion has been the subject of much debate, especially the underlying epidemiological methods (see Cohen 1998a and b for responses to some of these comments especially on ecological aspects). However, assuming stress-derived hormesis, the hormetic zone should extend to radiation exposures substantially above those experienced in the most extreme of these counties. Data on radiation dose and health effects from regions of high natural radiation

in China and elsewhere give results tending toward the same direction. For instance, the main outcome has been less cancer mortality in high background areas, but the differences are not significant (Luxin et al. 1997). However, Cohen's (1995) results do suggest that an important question is the radiation exposure at which hormesis is maximal. Below the maximum, a positive association is expected between exposure and fitness, that is a negative association between exposure and mortality. Above the maximum, conventional LNT theory should progressively take over with increasing exposure. It can be inferred from published data (Luckey 1991, 1999; Goraczko 2000) that the maximum should substantially exceed the exposure level of geological outliers.

The establishment of the maximum would appear to be directly relevant for suggestions concerning the possible health "benefits" of radiation supplementation that are now beginning to appear [see van Wyngaarden and Pauwels (1995) for a useful discussion of this issue]. Experimental studies on continuous low-dose gamma irradiation in rodents such as those of Caratero et al. (1998) may be particularly apt for investigating the exposure range of hormetic zones and their maxima. Similarly, rapidly breeding organisms such as the protozoan *Paramecium tetraurelia*, in which Planel et al. (1987) found hormesis for growth under gamma radiation at very low chronic exposures, could play a pivotal role in such investigations and form an exemplar for demographic studies especially in relation to debates on Cohen's (1995) data.

However, in contrast to many claims (e.g., Luckey 1999), it is not possible to view hormesis as a special phenomenon, benefit or low-dose stimulatory effect. These features of hormetic zones directly arise from the evolution of high metabolic efficiency to accommodate the array of stresses to which all organisms are exposed (Parsons 2000b, 2001). In these zones, the metabolic costs from stresses should be low. Furthermore, the occurrence of correlations among abiotic stresses as shown by the induction of hsps, indicates that stresses and stress levels to which populations are not normally exposed can be incorporated into the same hormetic paradigm. Consequently, radiation hormesis can occur at exposures substantially exceeding those of natural habitats, so providing an ecological and evolutionary basis for the benefits frequently claimed for radiation. This approach provides an underlying model for "benefits" across all levels of biological organization from molecules to organisms. In summary, hormesis does not connote a value judgement whereby a low exposure to a noxious agent is supposedly good (Wolff 1989), since it is an evolutionary expectation applicable to all organisms. Differing modes of thinking concerning hormesis are therefore implied, even though the consequences for health are generally equivalent.

In summary from the model proposed in this Forum, *hormesis is an expression of high fitness and high metabolic efficiency that evolves in response to single and multiple environmental agents in a low stress and low metabolic-cost habitat*. This definition applies not only to ionizing radiation but to all environmental agents, including other forms of radiation such as ultraviolet for which hormesis has been recorded (Stevens et al. 1998).

CONCLUSION

Investigations of hormetic effects require substantial empirical investigations based upon unambiguous hypotheses that can be accepted or rejected, so that the robustness of any proposed model, including the one outlined here, can be rigorously tested. Many remain doubtful of the existence of hormesis especially for ionizing radiation because of a lack of biological models. Following Yalow (1989), for too long has there been acceptance of "the radiation phobia which is based on the concept that any amount of ionizing radiation delivered at any rate is hazardous to human health." Based upon the dictum of Dobzhansky (1973) that "Nothing in biology makes sense except in the light of evolution," here I present a model of hormesis based upon the adaptation of organisms to stressful environments through evolutionary time, which can be tested empirically. This is a reductionist approach that renders LNT theory invalid for all environmental agents including radiation. Assuming that hormetic deviations from LNT expectations extend beyond the radiation exposures of geological outliers, a persuasive case is becoming established for the development of modifications of radiation exposure levels used for protection purposes especially in the low range. In this way, a softening of existing regulations to deal with phantom risks from low-level radiation would ameliorate some financial burdens now imposed on society. However, this is a topic well beyond the scope of this Forum, which is devoted to the presentation of a model for the expectation that hormetic zones exist for all environmental agents. For ionizing radiation, the hormetic zone is expected to occur for exposures substantially beyond those of the most extreme of geological outliers.

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