Policy Forum

On Radiation, Paradigms, and Hormesis

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Three lines of inquiry have recently raised the surprising possibility that very low doses of ionizing radiation may not be harmful after all or may even have net benefits, a phenomenon known as hormesis. Many studies (but not all) show that laboratory animals exposed to low doses of radiation outlive unexposed animals (*1*). How could this happen? DNA damage occurs commonly as a result of normal metabolic processes as well as from exposure to environmental mutagens. Whether the outcome is harmful depends on the dynamic balance between damage and repair processes. A net benefit can result when protective responses to low-grade exposure more than compensate for the harmful effects of the radiation. For example, a major cause of radiation injury at high doses is thought to result from the production of free radicals. Feinendegen *et al.* have shown that free radical scavengers increase after low-dose radiation, possibly to a greater extent than that necessary to neutralize the radicals produced by the radiation (*2*). This increased production of scavengers might increase cell defenses against free radicals that result from exposure to other environmental mutagens or those produced by normal oxidative metabolism.

In other work, Wolff and colleagues have found evidence that DNA repair may be enhanced by low doses of radiation (*3*). This suggests another means of protection, namely, that radiation-exposed DNA may be more readily repaired after subsequent exposures to mutagens. One study demonstrates that enhanced DNA repair exists in workers occupationally exposed to radiation (*4*).

Third, radiation-induced cell death stimulates cell reproduction as a homeostatic mechanism that maintains cell compartment size. Accordingly, Kondo has suggested another possible response to low-level stimulation, namely, that immune cell production may be enhanced by low-dose radiation (*5*). Evidence for increased numbers of lymphocytes in laboratory animals after exposure to low-dose radiation has been presented by several investigators (*6–8*). Whether this immune enhancement results from direct effects on lymphatic tissues or through stimulation of central neuroendocrine regulatory mechanisms deserves investigation.

Epidemiological studies of human populations exposed to relatively low doses of ionizing radiation have not shown the existence or absence of low-dose effects. For example, the studies of populations living in areas of high natural background radiation have not shown any increase in adverse health effects (*9*). In the absence of observable effects, it has nevertheless been assumed that low-level exposures produce the same harmful effects as those seen at high levels of exposure, but with lower frequency. This assumption has become the accepted radiation paradigm, justified on the basis of prudence, and on certain laboratory observations of mutagenic effects of ionizing radiation at relatively low doses. Beginning in the 1950s, fear of genetic effects, together with the associated "target theory" of radiation injury, have continued to dominate radiation protection thinking. As a result, substantial efforts are made to reduce or avoid small exposures, even exceedingly small exposures, to workers and members of the public.

In more recent years, accumulated experience has tended to reduce fears of the mutagenic effects of low-dose ionizing radiation. Direct observations of mutagenesis in human populations have shown humans to be one-fourth as sensitive as expected from previous indirect estimates based on rodent studies. Furthermore, although some findings are suggestive, genetic studies of survivors of the atomic bombings have failed to produce statistically significant findings (*10*). Finally, while radiation damage to DNA was once thought to be irreparable, and radiation uniquely dangerous, we now know such damage from a great variety of agents to be common. We also now recognize the remarkable efficacy of DNA repair mechanisms (*11*). Because of these protective mechanisms, DNA appears not to be fragile, but highly resilient.

An alternative model in which low-level radiation is not harmful, but could under certain circumstances produce net benefits, is plausible. The stimulatory effect of low doses of a wide variety of chemical agents on the growth of organisms had been noted by Hugo Arndt and Rudolph Schultz, German biologists, in the 19th century. They considered the phenomenon to be universal. More recently, these earlier observations have been extended to include increased longevity of animals exposed to low doses of agents toxic at high doses (*12*). In 1940, the term "hormesis" was coined to describe this stimulatory effect. In 1979, Luckey collected some 1200 references supporting the existence of hormetic effects from exposure to low doses of radiation (*13*). Much of this literature was reviewed at a conference held in Oakland, California, in August of 1985 (*14*). The proceedings of a second recent conference on low-dose radiation and the immune system are also available (*15*). At neither of these meetings was a consensus reached regarding the existence of hormetic effects; however, there does appear to be a movement away from an attitude of general skepticism to one of a new willingness to consider the evidence.

Although it may be premature to revise public health policy on the basis of the newer observations cited above, it would seem prudent that the scientific community reexamine the paradigm. Failure to examine a stimulatory response to low-dose radiation could result in neglect of important biological and possibly clinically important information regarding immune function.

Finally, further research to resolve uncertainty about the health effects of low-dose radiation would provide improved guidance for public health policy on very low-dose radiation. This is especially important when, for example, literally tens of billions of dollars are

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carbonyl (2ClZ); Trp, formyl; His, 2, 4-dinitrophenyl (DNP); Arg, tosyl; Thr, benzyl, and Tyr, bromobenzyloxycarbonyl (BrZ). Machine-assisted assembly of the protected 99-residue peptide chain was carried out by stepwise addition of amino acids to the resin-bound carboxyl terminal residue (*18*), and took 3.3 days. Protection of Nα side chains with *tert*-butyloxycarbonyl (Nα Boc chemistry) was used, in combination with highly optimized synthetic protocols specifically developed for the preparation of long polypeptide chains (*19*). Side chain protecting groups were removed and the peptide chain cleaved from the resin with a modified S_N2–S_N1 treatment with strong acid (*20*) after prior removal of the N^{α}-Boc, His (DNP), and Trp (formyl) groups to prevent side reactions. The resulting crude polypeptide product was dissolved in 6*M* guanidine·HCl (GuHCl) buffered to *p*H 7.0 and was worked up by gel filtration (G50, in 6*M* GuHCl), followed by semipreparative reversed-phase HPLC (0.1 percent trifluroacetic acid versus acetonitrile). The purified polypeptide was dissolved in 6*M* GuHCl, 25 m*M* phosphate, *p*H 7.0 at a concentration of 200 μg/ml and was folded by slow dialysis versus decreasing concentrations of GuHCl, to the final 25 m*M* phosphate-buffered to *p*H 7.0, 10 percent glycerol, and concentrated in a Centriprep 10/Centricon 10 to ~3 mg/ml.
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24. The protein sample was dialyzed against 50 m*M* sodium cacodylate buffer, *p*H 7.0, 0.1*M* NaCl and subsequently concentrated slightly by dialyzing against 12.5 percent (w/v) polyethylene glycol 14,000 in the same buffer to compensate for the increase in volume during removal of glycerol. Droplets (10 to 25 μl) were sealed over 1-ml reservoirs containing 10 to 30 percent ammonium sulfate. The total amount of refolded protein used in this study was ~1 mg. Crystals were shaped as tetragonal bipyramids and usually appeared after 5 to 7 days and reached their maximum size (0.35 mm) within another week.
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37. Abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
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being sought by one federal program alone for the purpose of reducing exposure to low levels of radiation and chemical wastes on the basis of largely hypothetical health risks (*16*).

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phocytes exposed to 1 cGy of x-rays shows that certain proteins are absent in all control cultures, but are reproducibly present in all irradiated cultures. These proteins represent excellent candidates for being the induced enzymes needed for the repair of the cytogenetic damage.

Nevertheless, the fact that a protein (enzyme) involved in repair can be induced by very low doses of radiation does not necessarily mean that these doses are in and of themselves "good" or hormetic. Several new proteins were found to have been induced, which indicates that the metabolism of the cells had been changed. Some of these proteins might have a metabolic effect of their own, and could possibly lead to a cascade effect whereby subsequent metabolic steps unrelated to the induced repair would be altered. To call this beneficial would be premature, indeed.

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