Are Radiation-Induced Effects Hormetic?

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The original definition of the once obsolete word hormesis came to us from pharmacology, and meant a stimulation brought about by a low-level exposure to a substance that was toxic at high levels. In recent times, however, the word has been resurrected and the definition has been modified to refer not only to a stimulatory effect but also to a beneficial effect. In other words, hormesis now connotes a value judgment whereby a low dose of a noxious substance is supposedly good.

Although one cannot deny that hormetic effects can occur with pharmacological agents, the situation is much less clear with ionizing radiations, which produce random lesions within cells. The amount of energy deposited by low doses of radiation is just too small to bring about the physiological effects that could lead to stimulation. The reason for this, of course, is that Avogadro's number is so large that, even though the molar concentration of, say, an enzyme in a cell is small, the cell still will have a very large number of identical molecules necessary to carry out its proper metabolic function, which thus will not be affected by the destruction of a small percentage of the molecules. Consequently, to account for the effects of low-level radiation, it has been necessary to look for a system within the cell that not only is sensitive to radiation, but also is capable of magnifying an individual lesion so that it can have a physiological effect. The genetic apparatus, the genes and chromosomes in the nucleus, represents just such a target for radiation. Radiation can induce mutations, occasionally by inducing some random base changes, but mainly by breaking chromosomes, which then can result in the broken pieces being deleted or rearranged, and these effects can have a profound influence on the cell.

The usual experiment on the genetic effects of ionizing radiations, however, has shown that the effects induced, rather than being hormetic with a beneficial effect, are deleterious (*1*). This has been shown in innumerable experiments in mutation in which it has been found that radiation-induced mutations themselves, unlike spontaneous ones, are, indeed, usually deleterious. That this should be so is not surprising, in that all living organisms are the result of eons of evolution in which they have been selected to fit their proper ecological niches. Any random mutational change then would be expected to change this fine balance and decrease fitness. With ionizing radiation, in which most of the induced mutations are deletions, this is even more likely.

The question of hormesis after somatic irradiation is even more problematical, in that the deleterious effects of radiation would be different in each cell and, somehow, in the absence of strong selection (these are low doses after all) the effects would have to be translated into a *repeatable* beneficial effect for the whole organism.

The field of hormesis is replete with sporadic reports of unrepeatable beneficial effects being brought about by irradiation. Perhaps the greatest profusion of these reports came out of the Soviet Union in the late 1940s to early 1950s, in the era of Lysenko, during which there was a severe repression of modern Mendelian genetics. For reasons of political ideology whereby the state could change the environment and thus ameliorate man's (and other organisms') condition, the whole basis of modern genetics was suppressed. During that time, numerous reports appeared in which plants changed morphology, matured faster, grew bigger, and so on, if they had been irradiated. Unfortunately, when these experiments were repeated with proper scientific controls outside of the Lysenkoist sphere, the results were not found to be reproducible in any systematic way (*2*).

Although these theoretical and observational reasons speak against any hormetic effects of low-level radiation, recent experiments raise some questions regarding the possibility that, under some conditions at least, repeatable effects might be found. Among these is the observation that under *strong* selective pressure, bacteria appear to respond to a change in their environment with the production of new mutations related to the change (*3*). This observation, which on the surface smacks of Lamarckism, might have a more conventional interpretation that involves a general error-prone DNA repair with a concomitant selection of only those mutants that are capable of coping with the selective environment (*4*).

The other experiments consist of the repeatable adaptation of human lymphocytes (*5–10*) and V79 Chinese hamster cells (*11*) to low-level radiations from tritiated thymidine or x-rays, which then makes the cells less susceptible to the induction of chromosomal damage by subsequent high doses of x-rays. This phenomenon lasts for up to three cell cycles after the cells have been preexposed to doses of as little as one-half rad (0.5 cGy). The response is induced by radiation and other agents, such as alkylating agents, bleomycin, or oxidative radicals, that produce breaks in DNA, and is negated by the inhibition of poly(ADP-ribosyl)ation, which itself is induced by DNA breaks. This adaptive response has been attributed to the induction of a hitherto unknown chromosomal break repair mechanism that, if in place when the cells are subsequently exposed to high doses of radiation, can repair much of the initial damage and leave the cells with only approximately one-half as much cytogenetic damage as expected. The response has also been found to take 4 to 6 hours after the preexposure to become fully operational, and it can be inhibited by the protein synthesis inhibitor, cycloheximide, if it is present for this 4- to 6-hour period. Presumably, the enzymes necessary for the repair are being synthesized at this time and, indeed, two-dimensional gel analysis of protein extracts from lym-

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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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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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