most promising for further research, at least for the near future, was based on various considerations. A major decision factor was the potential for contribution toward possible improvement of radiation protection policies and practices. Other considerations included the likelihood that the research would be successful, based on our current understanding of the problem, and the level of resources likely to be available for its support. Recognizing that the basis for such judgment cannot be totally rigorous and objective, the following research areas were determined most likely to produce useful results. The order of discussion is not intended to represent a prioritized ranking.

Low-dose radiological effects on the immune system

It has long been known that massive doses of radiation inhibit function of the immune system in humans and other mammals. However, recent evidence has shown that low-dose radiation can also affect immune response. These effects can be either inhibitory or stimulatory in nature, depending on the dose range and the affected part of the immune system. For example, it has been demonstrated that T-lymphocytes in mice proliferate under prolonged exposures to low-dose γ radiation, as described in Makinodan and James' workshop paper. There is also some evidence that low-dose radiation can stimulate production of antigens. Other evidence indicates low-dose radiation damage to lymphocytes under certain conditions, but those conditions have not been well characterized, nor do we understand whether these effects are mediated centrally or on the lymphatic tissues themselves.

Mechanisms of DNA damage and repair

Carcinogenic/mutagenic agents such as radiation are believed to exhibit their effects by interaction with cellular DNA. Mechanisms for such interactions are poorly understood, although, from a theoretical basis, the relative rates at which DNA damage occurs vs. the rate of DNA repair is critical to the health of the affected organism. It would be important to develop methods to identify and measure specific forms of DNA damage, to identify factors affecting the efficiency of DNA repair, and to develop our knowledge of the critical balance of DNA damage/repair rates on carcinogenicity and general health.

Improved methods of mutation "marking"

In recent years, there have been major advances in methods for detection of somatic mutations and chromosome aberrations. Past efforts toward quantitative estimation of radiation risk have been hampered by significant uncertainties in radiation dosimetry. The ability to measure mutations such as glycophorin A in specific genes can provide us with a direct means of biological dosimetry. Improvement in methods of mutation marking, such as "chromosome painting" methods (see Discussion section by Mendelsohn) could result in significant improvements and sensitivity in radiation dosimetry and risk evaluation.

Efficacy of extrapolation

Low-dose radiation effects are not discernible by direct observation. For obvious ethical reasons, human effects cannot be determined from experimental observation. Therefore, radiation effects in humans are estimated via extrapolation from either historically observed effects of high-dose exposures (e.g., Ra dial workers, Hiroshima/Nagasaki victims, etc.) or experimentally observed effects of animal exposures. These extrapolation processes have been the subject of serious question. Inquiry is needed of whether, and under what conditions, extrapolation may be considered a valid procedure, and when it might produce misleading results.

Hormesis

In recent years, considerable literature has been published indicating the occurrence of certain low-dose radiation effects that may be of a beneficial nature. In 1985, a conference was held with the objective of reviewing and assessing evidence related to hormesis. (See the May 1987 issue of *Health Physics* for the proceedings.) Although this evidence was not found to be conclusive, it appeared that several possible hormetic effects of low-dose radiation were worthy of further investigation. These included nonspecific extension of longevity, stimulating effects on immune response systems, and increased resistance to harmful effects of subsequent radiation exposures. Research is needed that will characterize conditions under which these stimulatory effects are manifested, as well as to explore the underlying mechanisms of their production.

Host factors

Exposure to a given type and quantity of radiation can produce effects of varying nature and severity depending on the species of organism and tissue system exposed. There can also be a significant range of radiosensitivity between individuals of the same species. Clearly, there are certain intrinsic factors within the host organism that affect the nature and severity of consequences of radiation exposure. Some known host factors include age and rate of cell division. However, it is likely that there are several other less understood or unknown host factors (possibly diet, drugs, enzymes, hormones) that may, under certain conditions, affect radiosensitivity. Improving our understanding of these factors and how they operate could contribute to our ability to minimize harmful effects of radiation.

Multiple biological response

Ionizing radiation is known to produce effects within the cell, but is also known to produce effects on neuroendocrine regulatory mechanisms. Several studies to date have focused on radiation effects on DNA and the resultant somatic and genetic radiobiological consequences. Existing evidence indicates that radiation also affects other biological systems, including hormone and enzyme production, immune response, and neurological systems. I

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Guest Editorial

WHAT IS HORMESIS AND WHY HAVEN'T WE HEARD ABOUT IT BEFORE?

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Abstract—Low doses of ionizing radiation are widely believed to produce effects similar to those observed at high doses; only the incidence (i.e. risk) varies with dose. Furthermore, it is assumed that effects other than those observed at high doses will not occur at low doses. Yet there have been frequent reports in the literature of "anomalies" at low doses—effects unrelated to and unpredictable from the high-dose exposure experiences. These have been referred to as "hormetic" effects. These effects have their parallel with other hormetic effects seen with many other agents generally considered toxic. It is postulated that hormesis has previously received scant attention because it conflicts with the conventional radiation science paradigm.

INTRODUCTION

MOST people (and perhaps even most scientists) think of scientific knowledge as progressing monotonically toward an ultimately perfect state of knowledge. This view of science ignores the existence of what Thomas Kuhn (Ku70) calls "paradigms"—interlocking sets of assumptions regarding the operation of complex systems. These paradigms, he says, channel scientific attention and effort in certain specified and acceptable directions, with the result that observations which fail to fit the paradigm are ignored or suppressed. Kuhn says:

> "Normal science, the activity in which most scientists inevitably spend almost all their time, is predicated on the assumption that the scientific community knows what the world is like. Much of the success of the enterprise derives from the community's willingness to defend that assumption, if necessary, at considerable cost. Normal science, for example, often suppresses fundamental novelties because they are necessarily subversive of its basic commitments."

In common with other sciences, environmental sciences have their paradigms too. In part, the paradigm states that biological observations at high doses can be used to predict effects at low doses. Because significant effects can be detected only at high doses, and because most biological systems are overwhelmed at high doses, harmful effects consistently occur. Thus our assessment of the influence of most environmental agents at low doses is strongly colored by the poisonous consequences of high-dose exposures.

Another element of the paradigm is the assumed relationship of each disease to some specific environmental agent. Just as it is assumed that each infectious disease is the result of exposure to some specific pathogen (the "germ theory"), so too is it assumed that each of our "modern" diseases is the result of exposure to some specific agent compound or organism. Toxicology, then, becomes a Holmesian hunt for culprits.

We cling to this paradigm despite the fact it is generally contrary to experience ("common sense"); nothing is all bad or all good. In general, biological responses are far too rich in their complexity to be described in terms of a single function. If one examines dose-response curves for naturally occurring agents such as vitamins, sunlight or hormones, qualitatively different phenomena are observed at different exposure levels; manifestly, several different mechanisms are operating. Often the optimal level for human health is that found at or near physiological or naturally occurring levels; either an excess or a deficit produces harm. That is to say, the presence of the agent in physiological concentrations is beneficial.

Some recent publications illustrate my assertion that fidelity to our paradigm blinds us to beneficial effects of exposures to environmental agents. Haseman reviewed all of the 2-y cancer bioassay feeding studies conducted in Fisher 344 rats in the National Toxicology Program (Ha83). There was a total of 25 studies, each with a control and two exposure levels. Many of the agents tested are now regulated as carcinogens. Dr. Haseman's analysis of the data revealed that there were as many significant decreases in organ-specific cancers as there were increases. On the basis of these studies, it would have been equally logical to focus on the significant deficits of some site specific cancers, with the conclusion that the agents are useful in protection against cancer.

Haseman also found that the exposed animals had

statistically greater survival in these studies than did the control animals. The significance test (Wilcoxon) was positive for males at the .05% level and for females at the .01% level. Because of the paradigm, we took note only of cancer increases, not of the decreases or increased life span.

These observations are not unique. Weinberg and Storer have reviewed several examples of what they call "ambiguous carcinogens," i.e. agents which change the site-specific appearance of cancer without increasing the overall risk of the disease. Among these are dioxins, DDT and ionizing radiation (We85).

Why has this not been observed before? The likely reason is that the common paradigm suggests that environmental or dietary carcinogens increase cancer; it excludes the possibility that chemicals protect against cancer or increase survival. We discard such data and concentrate on data related to the causation of disease. We design experiments in which we look for increases in disease (the germ theory) and we ignore decreases which occur as anomalies or "outliers," even though they have the same degree of statistical significance; we are blind to them—they are not part of our paradigm.

THE RADIATION PARADIGM

What is our radiation effects paradigm? It is a subset of the environmental paradigm described above. Put very simply, it states that (1) radiation exposure is harmful; (2) radiation exposure is harmful at all dose levels; and (3) there are no effects at low doses which cannot be predicted from effects noted at high-dose levels.

There has been little dissent from this view. Just as biblical or Talmudic scholars argue incessantly over minute details of dogma without ever questioning the fundamental assumptions, radiation scientists argue about the shape of the dose-response curve and the absolute levels of risk but never question the triad of assumptions described above. One searches in vain through studies of low-level radiation (LLR) effects conducted by various prestigious committees for even a mention of possible stimulatory effects (hormesis).

RADIATION HORMESIS: WHAT IS IT?

The term hormesis has not been widely used, at least in the radiation community. According to Stebbing, 'hormesis' was coined in a 1942 publication to describe the stimulation of fungi by a naturally occurring antibiotic which at higher concentrations suppresses fungal growth (St82). Although such stimulatory effects cannot be demonstrated for all substances, the phenomenon has been shown for many agents, both naturally occurring as well as synthetic. Stebbing suggests that hormesis may be the result of regulatory overcorrections by biosynthetic control mechanisms to low levels of inhibitory challenge, resulting in growth that is greater than normal.

I believe that the term need not be limited to growth stimulation but may well be applied to any physiological effect which occurs at low doses and which cannot be anticipated by extrapolating from toxic effects noted at high doses. The term will be better defined when those effects, if any, are identified and their mechanisms understood.

But what are "low doses?" There is some controversy about this. Some would insist that only exposures in the range of background radiation be considered "low." I see no reason to specify rigid limits. We are searching for effects other than those widely recognized to occur at high doses. Presumably, these other effects (I shall describe them below) are relatively weak and will not be demonstrable in the presence of the toxic effects of high-dose radiation. If and when mechanisms become clear, hormetic phenomena will be characterized in terms of the dose-response characteristics of those phenomena and the need to define "low doses" will disappear.

For some, the definition of hormesis implies benefits. My own opinion is that such value-laden terms are best avoided and that we should restrict ourselves to investigating and understanding these phenomena without attribution of benefit or harm. To do otherwise only further politicizes radiation science. "Benefits" are often in the eyes of the beholder. For example, increased fertility in the human female may be a benefit to some but not to others, an advantage at one stage of life but not at others.

There is still another point which I should like to make. If non-toxic or stimulatory effects do occur at low doses, such effects need not exclude the coexistence of toxic effects at low doses; they might coexist. Furthermore, they might interact in a manner which is impossible to predict; in some individuals one of those effects might predominate, while in others the other effect might predominate.

I have no difficulty in accepting the existence of an agent which simultaneously creates a hazard and a benefit. A number of agents are associated with both effects. Nickel and Cr, for example, are necessary to nutrition yet are known carcinogens (Fu80; Ni74; Ki85; Me69). Female sex hormones are also carcinogenic at high doses (Ki59).

CHALLENGING THE PARADIGM

Returning to Kuhn, he notes that when sufficient evidence accumulates which is inconsistent or in conflict with the conventional paradigm, the obsolete paradigm will be abandoned and replaced by another which better explains the available facts. The evolution from the old to the new paradigm is often associated with considerable acrimony between those who want to retain the old and those who advocate the new. The history of science is full of such disputes: Galileo was tried by the Inquisition and narrowly escaped with his life. In the last century, the role of bacteria in the causation of disease was vigorously resisted.

How do we test the radiation paradigm? I would suggest that there are two tests. One is plausibility: a comparison of the paradigmatic assumptions with our knowledge of biology generally. I have already expressed an

opinion on this matter; the great majority of natural agents do not behave in a linear fashion.

A second and more important test is the existence of observations which cannot be explained on the basis of the radiation paradigm. How substantial is the evidence of phenomena at low doses which deviates from the conventional triad of mutagenesis-carcinogenesis-teratogenesis?

POSSIBLE HORMETIC EFFECTS OF LOW-LEVEL RADIATION

These are commonly considered to be possible hormetic outcomes of low-level radiation exposure: (1) increased longevity, (2) increased growth and fertility of both plant or animal organisms, and (3) a reduction in cancer frequency.

Some years ago, Lorenz conducted experiments in which he found that animals exposed to doses of radiation only slightly above background actually survived longer than the control or unexposed animals (Lo50). Although the result has been replicated in other species and in other laboratories, its significance has been in some doubt, partly because it could not be consistently replicated and partly because there was no obvious mechanism demonstrated. Congdon reviews the Lorenz work in this issue of *Health Physics* (Co87).

A second area of radiation hormesis is the stimulation of growth and fertility. For several decades there have been reports in the literature which demonstrate that LLR can produce a stimulatory effect. Luckey has provided an important review of the subject (Lu82). Reports of radiation stimulation of growth first appeared in 1907. There are also many reports of increased fertility. One recent example is a study by Canadian workers suggesting an increase in fertility and survival of trout embryos fertilized with irradiated sperm (Ne73; Fig. 1). Newcombe's interpretation of increased survivability of these irradiated embryos was as follows:

> "More unexpected was the finding of an analogous "beneficial" effect of the lower doses to sperm, on the survival of embryos after they had been formed. This implies a lingering influence, which is known to extend over many cell generations and over at least the first half of the period of development of the egg. It is therefore difficult to imagine a likely mechanism which does not involve the genetic materials of the irradiated sperm cell. If the genetic materials of the germ cell are involved, it follows, at least over this range of doses, that for certain hereditary effects of radiation the response curve must be non-linear and the "benefit" must predominate over the "harm" where the dose is sufficiently low."

The third area which is sometimes considered to demonstrate a hormetic effect is protection against cancer.

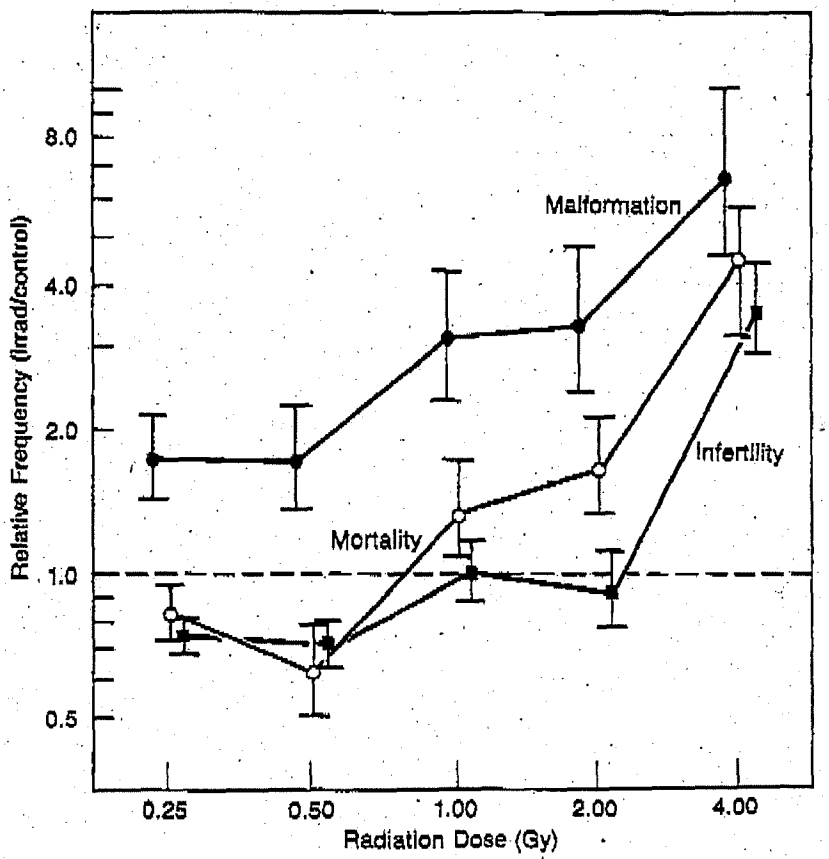

Fig. 1. Frequencies of different end points following irradiation of trout sperm.

Two hypothetical situations should be distinguished. In one, cancers expected (on the basis of linear extrapolation) as a result of radiation exposure fail to appear, suggesting a threshold. Bone cancers among painters of radium watch dials have most often been discussed as demonstrating a threshold (Ro84). Is this hormesis? According to my suggested definition (effects which cannot be extrapolated from high-dose exposures), it is not hormesis; it would simply mean that the dose-response relationship is other than linear. One caution is in order here, and that is that judgments regarding the influence of low doses of radiation on cancer induction (or reduction) be made only when complete data on the exposed population are available. As was noted earlier, investigators who are testing a hypothesis regarding cancer induction in one organ system may neglect cancer reduction in another organ system. For example, Storer has noted that radiation-induced leukemias in mice occur at the expense of reticulum cell sarcomas. As a result, there is no increase in total cancer frequency until the dose rises above 100 rad (1 Gy) (We85). In studies of radiation-induced cancer, it may be advisable to examine longevity of the exposed animal population; as noted by Haseman above, longevity may be influenced differently than carcinogenesis. If both carcinogenesis and longevity were increased, would hormesis be present?

Other observations have been made which suggest that organisms exposed to low-dose radiation adapt to that exposure. In one case, cell populations exposed to radiation increase cell production in response to increased cell killing. Is this hormesis? My view would be that it is, since germinal cells are (indirectly) stimulated to proliferate. Others might disagree.

MECHANISMS

If convincing evidence did appear of stimulation following exposure to low-dose radiation, one might reasonably ask whether under these conditions radiation was acting as a non-specific stressor (as Stebbing suggests in St82) or whether the organisms were responding favorably to increased access to a necessary nutrient. The answer will not be easily obtained. Although one can shield against cosmic and terrestrial radiation, it is almost impossible to provide a diet free of radioactive materials. Most research, then, is not the result of observations at artificially low levels of radiation, but rather is directed to observations of effects in biological materials which result from moderate increases of exposure above background. Th implication is that if physiological effects result fron moderately increased levels of exposure, then it would b plausible to assume that reduced levels of natural exposur might be detrimental. Planel, who has worked in this are for many years, reports on this work in this issue of *Healt Physics* (Pl87).

One possible mechanism of radiation hormesis involves the immune system, that complexity of cells and serum factors which is increasingly being found to participate in protecting us against infectious diseases, cancer and many chronic diseases, including heart disease and diabetes. Early in the study of ionizing radiation, it was recognized that the immune system is particularly radiosensitive. I am particularly intrigued with the possibility that if hormesis does exist, stimulation of the immune system could mediate such effects. Studies of radiation effects on the immune system during the 1950s and 1960s were voluminous (Le62; An76). In the interval, understanding of the immune system has progressed remarkably. It would seem to be timely to apply some of these more sophisticated techniques to an examination of the response of the immune system to low-level radiation exposures.

In the introduction to this paper, I quoted Dr. Kuhn (Ku70). The quotation ended with the following: "Normal science," he said, "often suppresses fundamental novelties because they are necessarily subversive of its basic commitments."

That, however, was not the conclusion of Dr. Kuhn's statement. He added: "Nevertheless, so long as those commitments retain an element of the arbitrary, the very nature of normal research ensures that novelty shall not be suppressed for very long."

Like Prof. Kuhn, I too am confident that in spite of the power of existing paradigms to produce conformity and inhibit innovation, the force of scientific inquiry will eventually result in the replacement of obsolete models. Focusing attention on the possibility of stimulatory effects of low dose radiation will result in either confirmation or rejection of our radiation paradigm. If stimulatory effects are found to exist, the radiation paradigm will be revised and both science and public health policy will benefit. If no such effects are found, we will have had the opportunity to validate the assumptions which underlie the radiation paradigm. To avoid consideration of hormesis altogether will only strengthen smugness.

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