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HORMESIS AND NURTURE WITH IONIZING RADIATION

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A. INTRODUCTION

"From the evidence of various experimenters, it is apparent that considerable more investigation will be required to determine what the physiologic effects of X-rays are, or even whether any such effects are produced by them at all. The testimony on this subject is very conflicting, even taking only that of the highest authorities." (Anon.1896)

Hormesis is the stimulation from low doses of any agent. This broadened concept came from Southam and Erlich (1942) who used it for a microbial toxicant. Hormesis is equivalent to older terms which convey a more limited or similar meaning, the Arndt-Schultz law is one example. Nurture is the sum of environmental effects upon an organism; it includes essential agents, as oxygen, nutrients and gravity, and nonessential agents such as starlight and helium (Fig. .1).

FIGURE .1. NATURE AND NURTURE. Each individual is a composite of his genetic potential, his nature, which directs his ontogenetic development according to the impact of his total environment, his nurture, from conception to death.

Ionizing radiation is a component of our nurture. Many radioactive elements are in our bodies, food, air, clothes, homes, furniture, tools and machines; such information abounds in texts and articles about background radiation. Note that unless otherwise stated the radiation is exposure to X or gamma rays. Hormesis with ionizing radiation has been noted throughout this century and has recently been reviewed generally (Luckey, 1980, 1982,1983), in immunity (Luckey, 1981) and as the expression of an essential agent for protozoa (Luckey, 1986). This review will emphasize radiation hormesis in cancer induction and mortality.

FIGURE .2 DOSE-RESPONSE MODELS FOR IONIZING RADIATION. The three major dose-response models for the effects of ionizing radiation are the linear model, the lower curve which has several variations, the threshold model, and the hormesis model where the curve passes through the threshold, the zero equivalent point (ZEP).

The three major models for the effects of different amounts of ionizing radiation upon organisms is presented in figure .2.

The lower line represents any of the linear models which suggest that all radiation is harmful. No variation of this model allows a threshold, a point at which there is no difference between the

irradiated and control organisms. The horizontal line indicates that a threshold has been established with low doses of ionizing radiation. The threshold model indicates no difference between lightly irradiated and control organisms. The latest BEIR report (BEIR 1980) accepted the threshold model for all physiologic functions except mutation and cancer induction. The hormesis model projects diametrically opposite responses to high and low doses of ionizing radiation. The hormesis model provides a "point" threshold, the zero equivalent point (ZEP), and decreases the significance of any of the non-threshold models.

This review provides a brief summary of the effects of low doses of ionizing radiation in bacteria, plants and invertebrates. A brief overview of radiation hormesis invertebrate growth, reproduction, and resistance is background for radiation hormesis with cancer. The evidence of radiation hormesis in cancer induction and mortality will be examined in more detail to show that major studies provide little evidence of any non-threshold model for cancer incidence and mortality following low dose irradiation. The evidence that low levels of ionizing radiation provide greater health and increased average longevity raises vital questions. Is ionizing radiation essential for optimum physiologic performance? for life?

When studied with microbes this question was answered in the affirmative. The positive microbic results combined with extensive evidence for radiation hormesis in animals and humans suggest the need for changed attitudes, recommendations and practices in government, industry, medicine and public health regarding ionizing radiation. Discussion of the consequences of these concepts includes evaluation of the scientific data, new areas for critical research, public health implications, and a peek into the quagmire of the provision of a set of recommended allowances for increased background levels of ionizing radiation.

B. RADIATION HORMESIS IN PHYSIOLOGIC FUNCTIONS

I. BACTERIA

As early as 1896 X-rays were found to kill bacteria (Schrader,1896) and soon bacterial growth was found to be increased by exposure to low doses of X-rays (Atkinson,1898). Protozoan growth and survival were increased by low levels of radium (Venenzaini,1904; Zuelzer,1905; Richet,1905). Gager(1908) found that fermentation was doubled by appropriate exposures of yeast to radium rays. Uranium salts were reported to stimulate yeast (Kayser,1912) and bacterial growth (Agulhon and Sazerac, 1912). These early reports have been amply confirmed and summarized (Luckey,1980,1987). One example is illustrated in figure .3 (Seuberling,1970). Note the consistency in these two experiments which were performed two years apart.

FIGURE .3. EFFECT OF A SINGLE DOSE OF X-RAY IRRADIATION UPON EUGLENA GROWTH. The rate of growth, cell division, of Euglena gracilis is given on the ordinate as % of control growth. The cultures were illuminated at 25oC for 24 hours. The abscissa indicates the doses at 3.5 krad/min (Seuberling,1970).

II. PLANTS

There are well over a thousand references regarding radiation hormesis with plants in the reviews of Berezina and Kaushanskii (1975), Kuzin (1977), Simon (1977) and Luckey (1980). Excellent work at the Hannover Institute of Radiation Botany provided good examples of radiation hormesis in plants (Fig. .4). The experiments with strawberries provide reliable results where the use of clones precluded genetic variability (Fendrick and Glubrecht,1972). The experiments with duckweed, a small two leafed plant which floats on water, give an easily repeatable experiment with consistent results (Feldman,1971).

FIGURE .4 RADIATION HORMESIS IN PLANTS.
.4A X IRRADIATION OF STRAWBERRY CLONES. Exposure of young strawberry plants, Senga precosa, increased early and total yield, ordinate, when irradiated with one dose of X-rays (Fendrick and Glubrecht, 1972).

.4B X-RAYS STIMULATE GROWTH OF Lemna minor. The irradiated plants weighed more than controls with 6 hours of light at 26oC. The ordinate is % of control and the abscissa indicates the acute dose administered at the start of the experiment (Feldman,1971).

Endpoints studied with plants include amount and time of germination, pollen tube growth, root growth and development, stem and leaf growth, branching, number and timing of flowers, and yield at harvest. The harvest may be measured as total plants, total grain, fruit or vegetable, yield per unit of land, uniformity of harvest, timing of harvest, and nutritive value of the product. Zelles (1978) records the increased growth of the vegetative nucleus, the generative nucleus and the cytoplasm

within a single cell, the pine tree pollen. He noted that exposure had to be completed within 100 sec to be effective.

Russia (Kuzin,1977) and Hungary (Simon,1977) have commercial ventures using mobile irradiators for seeds. However, formidable variables seem to have precluded general commercial acceptance and large scale use on farms in the western part of the world. The variables include both exogenous variables, such as dose rate, total dose,type of radiation and several environmental factors, and endogenous factors such as water content, maturation, storage and strain. Results are generally more readily obtained under suboptimum conditions. Temperature change immediately following irradiation seems to be a synergistic factor. Timing of the exposure within the photoperiod was found to be very important in the example given; irradiation early in the light cycle had the greatest effect. Many of the experimental papers involve continuous irradiation of whole plant, the green portion,the growing tip or the roots. Another problem has been interpretation using lumped data; obviously, important components of the dose-response curve may be missed if different doses are combined. In spite of these difficulties the potential for commercial use of radiation hormesis is being examined in several countries.

III. INVERTEBRATES

The results from microbes and plants are amply confirmed by data from invertebrates. Much of the work utilized the easily handled flies, moths or beetles using fecundity or lifespan as endpoints. The effect of a single dose of gamma rays upon the reproduction rate in the flour mite is illustrated in figure .5 (Melville,1959). At the end of the 6 week experiment there were 10,000 mites/gm of flour in the control colony and 16,000 in the colony which received 5.3 krad. Review of the 14 reports confirming this result (Luckey, 1980,1982) include increased number of eggs per adult per day, increased total progeny, increased total population, increased parthenogenesis, and decreased generation times. These results appear even when radiation reduced the fertility of part of the cohorts.

FIGURE .5. RADIATION HORMESIS IN MITE REPRODUCTION. Increased population in flour mite colonies was obtained following acute gamma irradiation (Melville,1959).

The same reviews list 35 reports showing increased average lifespan in invertebrates. Sometimes this is noted in one sex and not the other and sometimes it is noted in both sexes. While most find the increase in lifespan of irradiated insects is about 120% of the control values, Strehler (1959,1964) found that irradiated flies had an average lifespan twice that of controls.

The results seen in microbes, plants and invertebrates provides a unified concept about the effectiveness of radiation hormesis which may be anticipated in vertebrate data. The unity of biochemistry, physiology and nutrition throughout the

phylogenetic spectrum of life appears to be amply confirmed by the extensive data showing radiation hormesis in vertebrates, this includes epidemiology and exposure data from humans. In the same manner the data from microbes, plants and invertebrates provide both background and confirmation of the effects reported for animals, including humans.

IV. VERTEBRATES

Radiation hormesis in vertebrates was first considered seriously when Lorenz and coworkers reported increased growth rates and average lifespan in rats, mice, rabbits and Guinea pigs (Lorenz et al.1950,1954). Confirmation of this result (Fig. .6) by Morris et al. and 22 others (see Luckey,1980,1982) suggest a practical use in farm animals.

FIGURE .6 RADIATION STIMULATES MOUSE GROWTH RATE. Growth of mice as % of controls, the ordinate, is increased when exposed daily to X irradiation, the abscissa, for three weeks ($p<0.01$).

The biopositive effects of low doses of ionizing radiation upon neurologic functions (Table .1) include several examples of increased excitability of nerve tissues and acuity in hearing or sight. The studies of McDowell (1960) suggest that both learning and memory may be increased by low doses of whole body irradiation. Obviously, more systematic study is needed.

TABLE .1
RADIATION HORMESIS IN NEUROLOGIC FUNCTIONS.

Increased fecundity following light irradiation of vertebrates was found in 23 reports (Luckey,1980,82). Muramatsu et al. (1964) found the mean litter size of mice was greater ($p<0.05$) in irradiated mice than in controls (Fig. .7). The total population was greater after several generations of continuous irradiation due to decreased sterility, increased sperm viability, increased number of embryos and newborn with decreased embryo mortality (Gowan and Stadler,1962;Riordan,1964; Nishio et al.1967; French et al.1968, 1974). Kaplan (1949) reported irradiation to be helpful in the treatment ofhuman infertility. The spector of increased mutation was not evident in 82 generations of lightly irradiated mice (Spalding et al.1981) nor in the children born to exposed Japanese parents (Jablon,1983).

FIGURE .7 LITTER SIZE IS INCREASED IN IRRADIATED MICE. Chronic gamma ray irradiation increased the litter size of mice, on the ordinate, during three successive broods (Muramaysu et al.).

Immune competence appears to be one key to understanding radiation hormesis. Increased wound healing, greater radiation resistance and decreased infection and cancer morbidity provide evidence of increased immune competence as the main basis for increased average lifespan.

Wound healing was found to be accelerated over 50 years ago

using a simple,readily observed system (Schurch and Tschudic, 1929; Fukase,1930; Freund, 1931; Buntz, 1933; Lupo and Piasani, 1951). Small incisions were made in rabbit skin; then the rate of healing was observed both macroscopically and histologically in previously irradiated and control animals. Similar results were found with ulcerated epithelioma (Grigorescu,1968) and callus in bone fracture (Omarov,1973).

Radioprotection may be provided by previous exposure to ionizing irradiation. Increased resistance to lethal doses of ionizing radiation was found by several investigators, as listed in Table .2. The increased radiation required for an LD 50 was quadrupled in two papers (Maisin et al.1960; Nishio,1970). This suggests that evaluation of human responses to radiation should consider previous exposure of each individual.

TABLE .2
RADIATION EXPOSURE DECREASES MORTALITY FROM RADIATION

Increased immune competence and probably increased resistance to infection are major effects of radiation hormesis. The infection protection must be inferred because radiobiologists rarely design challenge experiments which could provide good evidence with limited numbers of animals in a short time. A delightful exception is the early controversy about the biopositive effects of ionizing radiation. It involved Prof. Wm. Schrader of the University of Missouri who provided evidence to contradict the statement by Prof. J.J.Thomson of Cambridge University that ionizing radiation was not bactericidal (Anon.1896). Schrader's in vitro studies showed these new X - rays could kill bacteria. He noted that the irradiated Guinea pig survived infection with diptheria bacilli while the control died within 24 hours with histologic evidence of diptheria. Increased resistance to diptheria toxin injection was reported by Gerhartz (1909) and Bisgard et al.(1944). Noting the resistance of invertebrates (Terzian,1953; Adler,1969) and rodents (Russ, 1909; Sacher,1956) to infection give limited direct support to this concept. The concept of radiation hormesis in infection is well supported by studies which show irradiated animals have increased serum immunoglobulins (Table .4) with some measurements of specific antibodies. Increased amounts of other immune parameters is noted on the lower part of the table. Recent findings of increased immune competence in Japanese bomb survivors when compared with controls (Bloom et al.1986) and in Chinese living with high natural radioactivity (Liu et al.1986) seem to confirm the animal reports. Immune studies with carcinogen induced cancer in mice (Hellstrom and Hellstrom,1979) support the concept of increased immune competence following low level irradiation.

TABLE .4
IMMUNE FACTORS ARE INCREASED BY LOW DOSES OF RADIATION

C. HORMESIS IN RADIATION INDUCED CANCER

Accepting its heterogeneity of types as a single entity, cancer is an obvious pathologic state which developed 3-40 years following exposure to ionizing radiation. Although most studies involved low energy transfer (LET) radiation, e.g. X- and gamma rays. the same general response pattern was found for high LET radiation, e.g. neutrons (Luckey,1984). These particulate beams, act as molecular bowling balls; they literally knock out parts of molecules, as DNA, and produce free radicals comparable with the products of low LET radiation. Excess free radicals can cause mutations which may lead to cancer. This summary of hormesis with ionizing radiation provides a concept which was ignored or considered lightly by agencies and committees which have suggested guidelines based upon the assumption that all radiation is harmful. A good example is the acceptance of the threshold model (Fig. .2) for for all physiologic functions, but not for mutation or cancer, by the Committee on the Biologic Effects of Ionizing Radiation (BEIR,1980). This BEIR III report did not accept the linear hypothesis, did not intercalate (often called extrapolate) for doses less than 10 rad, and did not speculate on the health effects of background levels of ionizing radiation. If either the hormesis or the threshold models are correct for radiation induced cancer, such guidelines may be counterproductive to public health, industry and government activities.

There are few reports of hormesis in mutation following low doses of ionizing radiation. The results of both Mulholland and Connolly (1984) and Olivieri *et al.* (1984) suggest that mutation rates are decreased in lightly irradiated cells. A practical threshold in radiation induced mutation is indicated by the lack of phenotypic changes seen in mice chronically exposed to X- and gamma rays for 82 generations (Spalding *et al.*1981), about 2000 years for humans. Although chromosomal aberrations appear, no radiation induced mutations have been found in children of the Japanese survivors of the atom bomb according to good, sensitive methods such as the electrophoretic patterns of serum proteins p (Neel *et al.*1980; Schull *et al.*1981; Jablon,1983). Thus, the most serious late effect of atomic bomb radiation appears to be limited to cancer.

FIGURE .8 SIX DOSE-RESPONSE CURVES FOR RADIATION vs CANCER.

The complete dose-response curve for the effects of ionizing radiation upon cancer induction appears to be a complex with six components (Fig. .8); the first three curves represent acute exposures and the last three are chronic exposures. There is little question about the first two. Excess ionizing radiation kills the individual before there is time to develop cancer (Fig. .8A). Smaller doses allow the subject to live long enough for cancer to develop (Fig. .8B); leukemia is the classic model for radiation induced cancer. The next four components are novel.

The V curve (Fig. .8C) was elucidated by Hellstrom and Hellstrom (1979) who suggest a mechanism involving one class of radiosensitive T suppresser cells. These thymic lymphocytes tend to suppress messages to other T cells which then can not mount an active response to foreign material. When the activity of suppresser T cells is decreased with 400 rads of whole body irradiation, other immune cells become more active to repress tumor growth. This is called the "Hellstrom effect". Sometimes total regression of tumors may be obtained. North (1982) has suggested these radiosensitive T cells may be manipulated to aid tumor therapy. This concept was reinforced by Anderson et al. (1980) who implanted tumor cells into mice following whole body irradiation. Tumor growth was slowed in mice exposed to 25 rads; repeated exposure to 25 rads was especially helpful in augmenting the host response. Although clinical application remains nebulous, these results help to explain some of the anomalies noted in humans; both the Chinese and the Japanese data indicate this response.

Hormesis in radiation induced cancer (Fig. .8D) may be a part of the Hellstrom effect with acute doses and part of the background effect for chronic doses (Fig. .8E). These may blend imperceptibly together. Curves .8D and E relate to the inverse correlation of cancer incidence and mortality with background radiation levels. No data is available to examine cancer induction in conditions of subambient levels of ionizing radiation (Fig. .8F). Information from hormesis and background levels of radiation plus microbic data suggest this curve is a reasonable, if hypothetic, possibility.

FIGURE .9 COMPLETE RADIATION vs CANCER DOSE-RESPONSE CURVE

The complete dose-response curve for radiation induced cancer (Fig. .9) is a composite of the six components (Fig.8) with the acute and chronic effects differing in the area of the Hellstrom effect. Of course, the dose for any given acute and chronic effect would be quite different. For example, 1000 rads acute radiation quickly kills most animals; however, Guinea pigs have survived 12,000 rads of chronic radiation.

Most major studies on radiation induced cancer and cancer mortality provide data which fit the concept established for many physiologic functions: high and low doses of ionizing radiation produce diametrically opposite results. Usually experiments which do not exhibit hormesis did not involve low enough doses. Animal experiments which cover a good range of doses are reviewed. The experience of humans exposed to radiation higher than background levels,1 mrad/day, and human epidemiology studies appear to involve appropriately acute doses or chronic levels of exposure. The following information supports the hypothesis that low doses and levels of radiation do not induce cancer (the threshold model) and may decrease the incidence of cancer (the hormesis model). General acceptance of either would have a dramatic effect upon our civilization.

I. ANIMAL EXPERIMENTS

Experimental evidence for the hormetic model and a threshold in radiation induced cancer in animals support the concepts obtained from human medical and accidental exposures, ecologic experiments and epidemiology. Accepting biologic variability which makes each individual different from all others, there remains a remarkable biochemical and physiologic unity in living organisms (Luckey, 1976,1977). Biochemical and physiologic responses of laboratory animals to ionizing radiation are often comparable with those in humans. Adjusted time scales are helpful for comparisons: Grahn (1970) suggested that one year for a man is equivalent to 10 days for a mouse. Since low doses of ionizing radiation often result in increased average lifespan, there is more time for cancer initiation in the older population. Thus, age specific data provide a reasonable basis for comparisons of irradiated and control cohorts.

Challenge experiments are concise and provide more information within a short time than expensive "irradiate and watch" experiments conceived by most radiobiologists. The classic experiment of Murphy and Morton (1915) gave clear results with relatively few animals (Table .4). They excised spontaneous

TABLE .4
WHOLE BODY IRRADIATION INCREASES RESISTANCE TO CANCER GROWTH

tumors from mice and regrafted them into the groins of the original host following one of three treatments: 1. a "stimulation dose" of X-rays to the mouse only; 2. no irradiation to either mouse or tumor; and 3. a "stimulation dose" of X-rays to the tumor before replacing it into the host. They found whole body irradiation induced host resistance to both the original tumor and to the subsequent appearance of new tumors. They presumed the cause involved the increased lymphoid tissue which they noted following the whole body irradiation, a conclusion remarkably close to present evaluations.

FIGURE .10 REDUCED TUMOR INCIDENCE IN IRRADIATED MICE.

This concept was extended by Lisco et al.(1958) with carcinogen induced tumors (Fig. .10). Young mice were given two large doses of X-rays with a few weeks rest after each. Then control and irradiated mice were injected with a carcinogen, methylcholanthrene. After 69 days five tumors were palpable in the control mice and none in the irradiated mice. The decreased susceptibility of irradiated mice to chemically induced tumors was significant ($p<0.01$) from day 96 through 129 following the injection; during this time about twice as many chemically induced tumors were found in control as in the irradiated cohort. The numbers of non-induced tumors,i.e. tumors remote from the injection site, were comparable in the two cohorts.

The above result was confirmed in mice given drinking water with 0.1 uCi 137Cs and 0.4 uCi 90Sr per ml through several

generations. The irradiated mice were found to be more resistant than unirradiated controls to implantations of Erlich acites tumor (Nishio et al. 1967). However, cancer induction was enhanced when methylcholanthrene was administered immediately following or concomitant with irradiation (Furth and Boon,1943; Figg,1947; Ong,1963). These decisive results make it difficult to understand why challenge experiments are generally ignored by radiobiologists.

Oak Ridge National Laboratory has contributed two decades of research to the study of the incidence of cancer in irradiated mice. Dose-response curves presented by Upton et al.(1970) relate cancer incidence in mice to single and daily exposures of either gamma rays or fast neutrons. The high incidence of neoplasms in control mice should provide a good test of hormesis; however, the low numbers allowed variation to preclude serious conclusions. Excepting a small initial increase with the lowest doses, no consistent pattern was established for either males or females. This may be due to the smallest dose being 25 rads.

An extensive study involving 30,000 mice provided more definitive results from this laboratory (Ullrich et al.1976,1977, 1979; Storer,1979). When 10 rads of gamma radiation were administered at 45 rad per minute, both sexes exhibited hormesis for all cancers studied with the exception of cancer of the Harderian gland, the third eyelid. When 50 rads was the minimum dose, chronically irradiated mice showed hormesis in radiation induced cancer. However, an acute does of 50 rads appeared to exceed the threshold for several types of cancer. Neutrons at 25 rads gave a threshold for leukemia incidence and appeared to exceed the threshold dose for solid tumors. Since the relative biologic effectiveness (RBE) for neutrons is usually estimated to be 4-20 times that of gamma and X-rays, it is unfortunate that lower doses were not utilized. Less extensive work with a different strain of mice was reported; the lowest dose of 50 rads of high LET radiation exceeded the threshold for most tumors.

Other less extensive studies have found hormesis or threshold responses to low doses of ionizing radiation. "There is also evidence for threshold dose or dose rates below which early tumors are not induced."(Brues et al.1949). Low doses of ionizing radiation resulted in a five fold reduction in mouse leukemia (Grahn et al.1972). This group also reported (Grahn et al.1968) that low doses of ionizing radiation increased leukemia and lung cancer while all other cancer types were decreased (Fig. .11). Fewer reticulo-endothelial cancers were found in mice exposed to fast neutrons than on controls (Mewissen and Rust,1976). The incidence of non-lung cancer in mice following plutonium oxide inhalation was only 25-30% as great as that of untreated controls (Nolibe et al.1983).

FIGURE .11 MOUSE CANCER INCIDENCE WITH CHRONIC IRRADIATION. Cancer incidence of lung and leukemia were increased while "all other cancers" showed decreased incidence (Grahn et al.1968).

The increased danger of low doses of ionizing radiation to embryos is not evident in the following studies. When male mice were exposed to 6.6 rads from deuterium water in utero for 22 days, they subsequently developed only 56% as many tumors as the unexposed controls; the females showed a threshold,103% of controls (Cahill et al.1975. This study confirmed previous results showing a lower incidence of tumors found in mice and rats which had been irradiated with X rays in utero (Upton et al.1960; Rencke et al.1964: Friedberg et al.1975). These results appear to substantiate the conclusion of Webster (1981) that there is no established risk of childhood cancer following in utero low dose irradiation.

II. HUMAN EXPOSURES

Although the use of ionizing radiation in medicine will not be reviewed generally, clinical data suggest the existence of hormesis or a threshold. Webster (1981) and Boice and Land (1982) provide general reviews of the medical aspects of ionizing radiation in cancer induction. "New radiation-associated tumors have been predicted for 1 in 100 children receiving 1000 rads or more" (Sutow et al.1984). This is a surprisingly low incidence for such a high dose. Webster (1981) could find no adequate explanation for the failure to demonstrate excess leukemia in women treated for cancer of the cervix. The narrow beam doses were 500-1000 rads with a major portion of the bone marrow exposed to 100+ rads. Only 9 leukemia cases were observed while the BEIR III (1980) prediction was 42-85 cases for this group.

Leukemia, especially acute lymphacytic leukemia, is readily induced by high doses of ionizing radiation; low doses do not evoke the same reaction according to Gunz and Atkinson(1964) and Linos et al.(1980). The latter group questioned the interpretation of several reports involving clinical studies which suggested a positive association between low doses of ionizing radiation and leukemia. When diagnostic exposures were correlated with two carefully selected controls for each of 138 leukemia cases found in one county over a period of 20 years,Linos et al. state: "No statistically significant increase was found in the risk of developing leukemia after radiation doses of 0 to 300 rads (3Gy) to the bone marrow when these amounts were administered in small doses over long periods of time,as in routine medical care." In fact, their extensive and thorough examination for doses of 1-50 rads suggest that the risk of either acute or chronic lymphacytic or myelocytic leukemia is lessened by low doses of ionizing radiation. This fits the hormesis model.

1. ATOMIC BOMB SURVIVORS

High doses of ionizing radiation result in the production of cancers comparable with those induced by other carcinogens or those which occur spontaneously (Beebe,1978; Sanders and Kathren, 1983). The 83,000 survivors from Hiroshima and Nagasaki had an average whole body dose (Kerma) of 27.2 rads, revised dose, and provided a cohort of 527 million person-year-rads (Kato and

Schull,1982; Wakabayashi et al.1983).

Recent revision has lowered dose estimates for both neutron quantity and energy in Hiroshima, with a concomitant increase in the gamma ray/neutron ratio, while leaving the radiation estimates for Nagasaki at about 98% gamma rays. Kerma adjustments from these changes have little effect upon the general shape of the dose-response curves (Fujita et al.1983). Refinements in this data base should include identification of prior radiation experience for each subject (Luckey,1980) and better estimates of radiation from fallout (Schmitz-Feuerhake and Carbonell,1983). Close routine inspection of all households plus determination of the cause of all deaths provide unusually good data for comparing exposed with control populations. Over 70% of all cancers were confirmed by autopsy. About 99% of any excess cancer mortality is expected to end at finite times following acute whole body radiation: 27 years for leukemia and 45 years for other cancers (Sander sand Kathren,1978).

The observed mortality data from individual types of cancer at Hiroshima-Nagasaki (Kato and Schull,1982) were used to calculate mortality per 10,000 persons and expressed as % of control. The dose response curves for leukemia and "all other cancers" (Fig._.12) suggest hormesis and a threshold for cancer induction at about 8 rads; doses less than 8 rads gave no increased leukemia or "all other cancers". There was decreased incidence for most of the 13 specific cancer categories (Table compared with that at 224 rads, no mortality was found in four categories. Confirmation of this effect in animal experiments suggest that radiosensitive suppresser T cells may be involved (Hellstrom and Hellstrom,1979). Recent study of survivors indicate they retain increased cellular immunity when compared with controls (Bloom et al.1983, 1985).

a. Leukemia

Special attention has focused upon leukemia as the most prominent radiation induced cancer in atomic bomb survivors. High doses induce leukemia with 100% mortality within 30 years following exposure. However, the low dose cohort had only 71% of control leukemia mortality (Table .5). Detailed examination of the low dose data makes it clear that the data do not fit any version of the non-threshold models as well as they do the hormesis model (Fig. .13).

TABLE .5

FIGURE .13 RADIATION INDUCED LEUKEMIA MORTALITY IN NAGASAKI.

.13A Comparison of low dose irradiation induced leukemia in Nagasaki according to Land (1980) and Pagnementa (1983) with the 50% confidence limits displayed, including the point at 20 rads.

.13B Dose-response curve of radiation induced leukemia mortality showing the radiation on a logarithmic basis (Pagnementa, 1983).

b. Esophagus

When compared with controls, esophageal cancer mortality exhibited a decreased incidence in the lowest dose cohort, a threshold at approximately 15 rads, and unusually low incidence at 345 rads (Table .5). No increment in the incidence of esophageal cancer was noted in the Nagasaki data (Wakabayashi et al.1983); however the total numbers involved is small.

c. Stomach

The high incidence of stomach cancer in the control population was not increased by low dose irradiation (Table factor" of Japan and radiation are synergistic.

d. Colon,Rectum and Pancreas

Radiation induced colon cancer mortality data revealed hormesis with a threshold dose at about 100 rads (Table .5). The data for rectum and pancreatic cancer show no correlation with radiation dose.

e. Other Digestive Organs

The dose-response curve for cancer mortality from other digestive organs show a gradual increased incidence correlated with dose (Table . 5). However, details from only the Nagasaki cohort indicated no increase with dose for gall bladder or salivary gland cancers (Wakabayashi et al.1983). The dose-response data from liver cancer mortality showed a threshold at about 200 rads.

f. Lung

The Nagasaki data suggested that radiation hormesis may be exhibited in lung cancer (Wakabayashi et al.1983). While no threshold was exhibited in data from the combined cities (Table 5), hormesis was exhibited in non-smokers (Kato and Schull,1982). The incidence of lung cancer per 1000 persons was 16.6 in persons exposed to 0-9 rads (a category unfortunately substituted for 0 rads) and only 7.5 in those exposed to less than 100 rads.

g. Breast

Although radiation induced breast cancer mortality is generally accepted for humans, both hormesis and the Hellstrom effect were found in the data from the combined Japanese cities (Table . 5). When the 0 and the 1-9 rads were combined (Kato and Schull,1982), the combined results decreased the possibility of observing hormesis.

h. Uterus and Prostate

Low doses of ionizing radiation may increase uterine cancer mortality; however, most higher doses do not appear to increase cancer mortality (Table .5). The Nagasaki data for prostate cancer mortality (Wakabayashi et al.1982) indicated hormesis at the lowest doses with no increased incidence with increased radiation.

i. Urinary Tract

Radiation induced urinary tract cancer mortality may show hormesis at the lowest dose with a threshold above 22 rads and increased incidence at high doses (Table .5). The high doses at Nagasaki (primarily gamma radiation) gave no increased incidence while those at Hiroshima resulted in increased cancer mortality.

j. Thyroid

The incidence of radiation induced thyroid cancer mortality in the Nagasaki study showed an increase with low doses and no correlation with higher doses ((Wakabayashi et al.1982).

k. Summary of Japan Data

The data from Hiroshima and Nagasaki provide the best information regarding a dose-response relationship for radiation induced cancer mortality. Probably little new information will accrue after 40 years. Several trends are evident. The hormesis model fits most cancer categories. The non-threshold model fits only the smoker lung cancer and "other digestive organs"; it is certainly a poor model for most of the data. The frequently noted decreased cancer mortality at 345 rads suggests the power of decreasing the activity of suppresser T cells, the Hellstrom effect. This could account for the low incidences found for esophagus, colon, rectum, breast, uterus, pancreas, and multiple myeloma.

2. THE CHINA STUDY

During the past decade the High Background Radiation Research Group (HBRRG, 1981,1985) began an excellent "controlled ecology" study of two areas in China in order to determine whether there is a threshold for ionizing radiation for a variety of parameters. Both areas are at the same altitude, average about 32 m, with homogeneous radiation fields. The 73,000 inhabitants of the areas with monazite in the soil receive 330 mrem/year, this is the high radiation cohort. The low radiation cohort comprises 77,000 inhabitants in carefully chosen, very similar control villages and receives an average of 104 mrem/year. The difference in radiation levels appears to be attributable to radionuclides in the soil, which is reflected in food, water,air and body tissues. No differences were found in 13 trace elements of the soil, e.g. zinc, copper, cobalt, manganese and arsenic.

Both areas have stable, high density populations of peasants of the Han race with little exposure to industrial carcinogens. Pesticides used were 125 g/mo and 84 g/mo for the control and high radiation groups, respectively. About 2 g/y per person of antibiotics and negligible amounts of other medicants were used in each group. Medical exposures were 5.1 and 6.5 exposures per person per year in the control and high radiation groups, respectively. Families living along the borders of the two areas are excluded from the study. There are relatively few visitors and the peasants travel very little, particularly the high radiation cohort. Food, clothing and housing are largely

from local sources. Families have lived here for 2-15 generations; 6 or more for 67% of the control cohort and 91% of the high radiation cohort.

A medical survey indicated that the total chromosomal breakage and incidence of Downs syndrome may be higher ($p>0.05$) and there is a statistically valid increase ($p<0.05$) in the two hit chromosomal breaks in the high radiation group. However, "Chromosomal damage in an individual exposed to radiation has not been associated with subsequent illness" (Webster, 1981).

A comparison of total cancer mortality, lung cancer mortality and liver cancer showed the control cohort to have higher rates ($p<0.05$) than the high radiation cohort. Leukemia mortality rate in the high radiation cohort was only half that of the control cohort.

3. Radionuclide Exposure

a. Radium

Radium is a bone seeking radionuclide which deposits in regions of new bone growth and later redistributes during the dynamic bone remodeling processes. Cells adjacent to such bone tissue receive the greatest doses of high LET radiation; these provoke primarily osteosarcomas with some fibrosarcomas and a mix of other sarcomas (the double names indicate that the tumor is malignant, i.e. a cancer). Rowland et al. (1983) reviewed the dose-response relationships for radium induced bone cancers. Only one bone sarcoma was found in 413 known cases of non-medical intake of radium other than the radium dial painters. None of the 273 male dial painters developed bone cancer; perhaps males are more resistant than females. Of the 3055 female dial painters who started before 1950, 63 developed bone cancer. The dose-response curve (Fig. .14A) indicates a threshold at about 100 uCi radium. This cohort would be prime material for a hormetic study of the incidence of other tumors, infections, fecundity and lifespan.

FIGURE .14 BONE CANCER IN RADIUM DIAL PAINTERS.

.14A Radiation induced bone cancers in the radium dial painters after 33 to 45 years according to the amount of radium intake (Rowland et al. 1983).

.14B Bone and head cancer in radium dial painters relative to the total radiation (rads) over 50 years (Evans, 1981).

When the incidence of bone sarcomas plus head carcinomas were plotted against the log of the dose (Fig.14b), the results clearly indicated a threshold at about 1000 rads over a period of 50 years. Evans (1981) commented: "A linear nonthreshold model would have predicted in this group some 15 radiogenic tumors between 0 and 100 rad. The probability of observing none, if a linear nonthreshold model were correct, is 1 in 5 million. Clearly any nonthreshold model used in much 'prudent' radiation protection work is strongly rejected by good data in the case of 226Ra and 228Ra in man."

b. Iodine

Quimby and Werner (1949) investigated the possibility that 131I used in treating hyperthyroidism might be carcinogenic and concluded that it was not. While this opened the issue, it did not settle it. Boise and Land (1982) reviewed the evidence that thyroid nodules and cancers develop after excess radiation. The 1378 children of Utah who ingested 131I in milk following the fallout from atomic bomb tests in the early 1950s showed no thyroid cancers and 18 nodules (1.3%) while a cohort of 1313 unexposed children who moved into the area after the fallout showed 2 thyroid cancers and 19 nodules (1.4%) (Rallison et al.1974; Webster,1981).

Saenger (1968) reported that 22,000 hyperthyroid patients treated with 131I showed a decreased leukemia rate (0.09%) when compared with 14,000 treated with surgery (0.15%). The same group (Dobyns et al.1974) reported that 131I treatment induced no excess cancers; the number of cancers which develop during the 20 years after treatment, involving about 600,000 person-years, was fewer when 131I was used than when thyroidectomy or antithyroid drugs were used (Fig .15). No new thyroid cancers developed in the 131I treated patients while new cancers were found in the thyroidectomized patients after a 10 year period. Chapman (1983) summarized the viewpoint of this group: radioiodine is the preferred treatment and it costs less.

FIGURE .15 Comparison of cancers found after the use of surgery, 131I or drug therapy for hyperthyroidism in humans.

The data from the United States are supported by results from Sweden. Holm (1980) and Holm et al. (1980) found that the diagnostic and therapeutic administration of 131I to 10,133 patients did not induce thyroid cancers in excess of those found in carefully matched patients from the same hospitals. The administration of an average of 60 uCi dose of 131I resulted in about 1/10th the number of cancers estimated by the linear model during the follow-up period of 18 years. Holm suggested the possibility that radioiodine therapy may reduce the probability of developing thyroid cancers in adults.

Sanders and Katren (1983) note that only one bone sarcoma originated at skeletal doses of less than 1000 rads in the 2000 German patients who were injected with 224Ra for tuberculosis or ankylosing spondylitis between 1944 and 1951. They note that radiotherapy with greater than 1000 rads occasionally are correlated with increased bone tumors in adults.

c. Plutonium

Voeltz et al.(1983) studied 224 white males who had internal depositions of 10 nCi or more of 239Pu, including 238Pu, for an average of 26 years, beginning in 1955+8 years. They report 100% follow up involving 6000 person-years with an average exposure of 19 nCi (<1 to 180 rem). Most exposures were by inhalation; the lungs then retain half of the body content for 30 years. For the

181 men still living, the calculated cumulative tissue dose and individual dose rates (rads/rads per year) are: lung, 43738/1.01; bone surface, 7897/1.69; and liver,527/0.112. The average subjects age was 64 in 1980 when the study was updated; at that time only 43 had died from all causes , a low rate attributable to worker selection and the "healthy worker effect". Mortality from cancer of the digestive tract and lymphoid tissues were close to the national averages (Table 6). No bone or liver cancers occurred. Mortality from lung cancer was definitely less than that expected; less conservative models predicted 65 to 192 lung cancers for the exposures noted, conservative models would predict more.

TABLE 6
CANCER IN PLUTONIUM WORKERS

Excluded from the above discussion were 17 female workers who had an average of 9 nCi Pu deposition and no cancer mortality.

d. Uranium and Transuranic Elements

The main long-lived radionuclides to which nuclear workers are exposed are uranium, plutonium and other transuranic elements. Webster (1981) and Boice and Land (1982) critically reviewed the controversial literature in this area. When age adjusted data was evaluated, the previously reported excess lung cancer mortality disappeared. They both concluded that it is highly questionable whether the radiation exposure of nuclear workers results in any substantial increased risk for cancer. Gilbert and Marks (1979) reported that leukemia mortality in nuclear workers is only about half that expected nationally. No increased mortality was found in Hanford workers for leukemia, lymphoma, or other solid tumors other than the pancreas (Hutchinson et al.1979). The last may be a "small sample artifact"(Webster,1981). Darby and Reissland (1981) confirmed the negative associations between radiation levels and cancer induction in the Hanford workers. They seriously criticized some of the previous studies which had indicated an excess cancer risk for this cohort.

The Canadian study eliminates the "healthy worker effect" by using different groups of workers which had the same preliminary examinations and health facilities. Preliminary results indicated that 18,500 past and present employees of Atomic Energy Of Canada,Ltd. have less cancer mortality than the general population of Canada (Abbat et al.1983). The possibility for the healthy worker effect was also negated when nuclear workers were compared with other workers in the same organization and with the same medical care. A study of 25,000 persons in three cohorts from Ontario Hydro indicated that total deaths and cancer mortality were lower in the nuclear workers than in the other two groups, thermal energy workers and other workers in the company. The nuclear workers also had less cancer mortality than was found in carefully matched controls in Ontario.

No excess cancer was found in 25,000 workers at the Portsmouth naval shipyard for nuclear powered vessels at Kittery, Maine (NIOSH,1980; Webster,1981). The average lifetime occupational radiation dose for 7615 of these workers was 2.8 rem (the range was 0.1 to 91 rem).

4. Epidemiology in the United States

Frigerio et al.(1973,1976) began a study of human cancer mortality with the presumption that background cancer must be carcinogenic. They were forced to conclude, as did Oakley (1972) that it was not. The risk of cancer is inversely correlated with background radiation. When age specific deaths were considered, the pattern of response was the same. This study has been repeated with regions, states and counties: the results are similar in all studies (Eckhoff et al.1974; Mason and Miller, 1974; Jacobson et al.1976; Sanders,1978;Cohen,1980; Hickey et al.1981a,b,; Yallow,1981; Sauer et al.1982) for 56 types of cancer mortality, including the classic example of radiation induced cancer, leukemia (Fig. .16). None of the other correlations tested were as high as that of radiation and cancer.

FIGURE .16 Negative correlation of terrestrial radiation and leukemia mortality in the contiguous 48 United States.

Other diseases and lifespan showed the same negative correlation with background radiation. Sauer et al.(1982) suggested that background radiation levels provide ample explanation for the "enigma of the Southeast"; nothing previously examined had given any correlation to explain the high death rates in that region (Sauer,1980). Cohen (1980) found the negative correlation between age adjusted cancer mortality rates and background radiation levels in the 48 contiguous states to be highly significant ($p<0.001$). Hickey et al.(1981b) reported:"Bivariate correlation coefficients between radiation and mortality rates were significant for cancer of the lung and respiratory organs, cancer of the buccal cavity and pharynx, cancer of the digestive organs and peritoneum, total cancer and diseases of the heart".

Eckhoff et al.(1974) stated "--the leukemia mortality rate actually appears to decrease with increasing altitude" for more than 5000 geographic areas of the United States. Yalow (1981) noted that Colorado residents show one of the lowest cancer death rates while receiving more radiation from cosmic rays, rocks and mine tailings than is received by the Hanford workers. Utah had the lowest mortality rate in spite of the fallout deposited from the Nevada atomic blasts in the 1950s. Yalow further suggests that up to 15 rem radiation may be protective against malignancies, based upon the finding of only 14 cancers in the Utah cohort where 24 were expected.

Frigerio et al.(1973) suggested that knowledge of the decreased cancer rate with increased background radiation levels

is more pertinent to the life of everyday people than information about radiation exposures of victims of the atom bomb, uranium miners or spondylitic patients. Differences in background radiation would be found to be greater if consideration had been given to the type of housing and the concentrations of radon which is generally elevated in homes with increased energy efficiency (Steinhausler et al.1983).

Epidemiologic evidence clearly shows that low level ionizing radiation is not associated with increased risk of cancer mortality. Low levels of ionizing radiation are clearly correlated with decreased cancer mortality risk. This agrees with information from accidental association with low doses of radiation in workers, medical patients and atom bomb victims. The human data and the animal experiments give similar information. The knowledge clearly fits the model of hormesis for radiation induced cancer.

5. Chernobyl

The Chernobyl nuclear power plant accident was a unique disaster in mankind's peaceful uses of atomic power. If the intensity of study follows that of other exposed populations, these unfortunate individuals will contribute much information about the dose-response effects of different levels of ionizing radiation upon cancer. Hopefully two deficiencies of the Japanese bomb study will be remedied. 1) Careful monitoring of fallout for individuals and different cohorts. 2) Obtain previous irradiation data for each individual. The latter appears to be an important factor in reducing radiation sickness and mortality.

Three decades from now 95% of cancer induction and mortality of Chernobyl will be known. Can the results be predicted with any degree of accuracy? They should be if the information gleaned from the past could be utilized. The population affected is about the same size as that of the Japanese bomb victims. The character of the radiation and the effects of fallout also are not too different. What is needed is a "Rosetta Stone" for radiation induced cancer. It can be produced by compiling all the above information into one chart, deducing the frequency of each type of cancer for different doses and weighting the human values where information is adequate. The general information obtained can be used to deduct the patterns of cancer induction and mortality in any population, as Chernobyl.

The Rosette Stone for radiation induced cancer involves a characterization of the dose-response curve for each type of cancer mortality for the Japanese bomb victims. The data for leukemia and the average from 23 other cancer types and organs is presented (Fig. .17). The remarkable similarity of this curve to that from the animal data (Fig.9) gives credence to the different parts of each curve. This provides a guide for anticipated cancer mortality for Chernobyl, or any other comparable unfortunate population. The only exceptions to the patterns displayed were uterus and smokers lung cancers which showed

increased incidence with low doses. The pattern of coincidence will be clear by the turn of the century and the picture will be clear by 2020.

FIGURE .17. Predicted Chernobyl Cancer Mortality.

D. HORMESIS IN LONGEVITY

Since low levels of ionizing radiation appear to increase immune competence and reduce susceptibility to infection and cancer, the average lifespan should be increased. This is indeed the case for many invertebrate and vertebrate experiments where good objective data can be obtained and confirmed. Luckey (1980, 1982,1983) cites 62 reports with invertebrates and 92 with vertebrates in which hormesis was noted for the average lifespan of lightly irradiated animals when compared with controls. In some experiments (Lorenz et al.1954; Grahn et al.1972) the mortality of the control animals was so bad that they were not used in evaluation of the results. Two examples where all the data is available are presented.

I. ANIMALS

While radiobiologists discuss possibilities to perform a "megamouse" experiment to differentiate between threshold and nonthreshold models, they have ignored the "megafish" experiment reported in the last decade (Bonham and Donaldson,1966; Donaldson and Bonham,1970; Hershberger et al.1978). Not counting years of preliminary experiments to establish reliable methodology, this group marked and released over a million salmon into streams for their ocean sojourns of 1-5 years before returning to spawn after all the vigors of natural life. One study of whole body chronic 60Co irradiation during egg incubation and salmonid development involved 315,000 controls and 314,000 irradiated fish or their siblings. About 35 rads of gamma radiation were administered to each at a rate of 0.5 rad/day. Of the identified fish that returned to spawn, 2876 (0.913%) were controls and 3562 (1.13%) were irradiated stock, 24% more than the controls. The natural environment allowed in this experiment distinguishes it from the usual laboratory experiments.

Spalding et al.(1982) recently completed a study of lifespan in about 4000 male mice exposed to daily 60Co irradiation until the desired dose was attained. The consistency of results is highlighted with mice started at two months of age (Fig .18). Irrespective of dose rate, each set showed better survival than controls ($p<0.05$) when 50% of the controls had died. This confirms other results which showed that low doses of radiation increased average lifespan. Individual animals do not survive to an unusual age; midlife morbidity and mortality is lessened in the irradiated animals which gives a longer average lifespan for the group.

FIGURE .18. RADIATION HORMESIS IN MOUSE LIFESPAN. Comparison of survival of mice chronically exposed to 0.7 to 3600 rads/day with that of control mice when one half of the control mice had died.

II. HUMANS

Although the risk of excess radiation to early radiologists was great (Brown,1936), in 1938 G.Pfahler (Hildreth,1981) noted that the response depended upon dosage and suggested that small doses of radiation might be beneficial:"-- if you wish to live a long life, see to it that you spend part of it in an X-ray department." Hildreth (1981) noted that while the 204 radiologists born between 1860 and 1900 had a life expectancy of 43 years, 88 had lived past their 78th birthday. Smith and Doll (1981) found that radiologists who began practice after 1920 had cancer mortality only 88% of that of other British physicians; radiologists who began after 1935 had only 80% that of the cancer mortality of other British physicians.

Mortality in the United States from chronic diseases correlates indirectly with background ionizing radiation according to many investigators who could not find valid correlations to other environmental,ethnic, social,or economic factors (Frigerio and Stowe,1976; Eckhoff et al.1974; Sanders, 1978; Cohen,1980; Hickey,1981; HBRRG,1981; Sauer,1980;Sauer et al.1982). One possible explanation is that high background levels of ionizing radiation increase health and longevity. When compared with the average, the high death rates in the Southeast coast of the United States was an anomaly in human population studies. Mortality rates correlated well with chronic diseases, but no factors could be identified to explain "the enigma of the Southeast" (Sauer,1980). Cosmic radiation is lower in coastal areas than in mid continent and the terrestrial ionizing radiation of the Southeast coastal area averages 23 mrem/year (BEIR,1980). This is about 1/2 that for the average United States and 1/4 that of the Colorado plateau where mortality from cancer and chronic diseases are lower than the average for the country (Sauer,1980). This enigma appears to be explained by the epidemiologic correlation of low background ionizing radiation levels with death rates (Fig. .19). The correlation is good (Sauer et al.1982).

FIGURE .19 CORRELATION OF RADIATION WITH CHRONIC DISEASES. The inverse correlation of mortality from chronic diseases was high ($p<0001$) according to Sauer et al.(1983).

While spontaneous abortions and neonatal mortality appeared to be less in the high radiation group than in the control group in the China study (HBRRG,1981), these differences have not yet reached statistical significance. Infertility was significantly less ($p<<0.05$) in the high radiation group than in the controls. The later study indicated the high radiation cohort had more active immune function than the control cohort. Most comparisons

of lifespan showed no differences; however, the lifespan of males over 40 years old in the high radiation was increased ($p<0.05$) over that of controls.

Information from Kerala, the most densely populated state of India, supplements the data from China and allows interpretation of the "paradox of Kerala" (Kemala,1981). The people of Kerala have the highest literacy rate and the best health status in India; yet their expenditure for health care was not appreciably above average. They have the lowest food intake and the least adequate diets; three fourths of the families are deficient in calories and one half are deficient in protein (Paniker,1979). Yet, Kerala has fewer frank deficiencies in young children and lower gross mortality than any other state in India. This unusual health status is exemplified by the exceptional agile and exhaustive dancing in the ancient, ritualistic theater movements derived from kalarippayat, a possible precursor of kung-fu and karate (Mazo and Mehta,1981).

A possible explanation of this paradox is the unusually high background radiation derived from the high radium and thorium content of some of their soil, water and food. The average terrestrial radiation for the United States is 43 mrad/year; some of the Kerala population receives 1000 to 3000 mrad/year, a level comparable to the optimum in some of the animal experiments reported above.

This brief summary showing increased average lifespan in animals,including humans is well supported by the evidence of increased immune competence following low level irradiation. The decreased midlife morbidity and mortality of irradiated cohorts compared with unirradiated controls results from faster wound healing and increased resistance to high doses of ionizing radiation, to infection and to cancer induction. The beneficial effects of ionizing radiation appear to include less infertility, less neonatal deaths, faster growth rates, greater visual, hearing and mental acuity, and improved general health during life. The average age of a given population is increased without individuals living to unusual ages. The mechanism of this apparent higher plateau of health must be important.

E. HORMESIS VERSUS NURTURE BY ESSENTIAL AGENTS

Nurture is the action of the environment upon an organism. The literature suggests that low doses of ionizing radiation evoke reactions which appear to be beneficial to most organisms. This raises a tremendously important question. Is ionizing radiation stimulatory as any toxic material might be, or is it an agent which is essential for vital physiologic functions. There are remarkably few well defined lines between agents which are essential, stimulatory, or toxic (Luckey,1976a,b). The continuum of nurture, hormology and toxicology is well illustrated by those metals which were first considered to be toxicants, then were recognized stimulants, and now are being examined as possible essential nutrients: selenium, tin, arsenic, silicon, strontium, and even lead (Luckey,1975,1977b). The cumulative evidence for hormesis with ionizing radiation has focused a vital question. Is ionizing radiation essential for life?

FIGURE .20. MODELS FOR COMPLETE DOSE-RESPONSE CURVES

One experimental approach to this question is to determine the effects of subambient levels of ionizing radiation, as illustrated left of the ordinant in figure .20. If all quantities of the agent, ionizing radiation, were harmful, the data should approximate the straight line-S curve. Decreasing the amount of an agent showing a threshold should have no effect; this is the threshold-T curve. Stimulatory agents would show the hormesis peak and then form the horizontal curve as background amounts were removed, the hormesis-T curve. Mercury or antibiotics would fit such a curve (Luckey,1959). Only an essential agent, as a vitamin or oxygen, would approximate the hormesis-H curve. Removal of an essential agent should disturb vital physiologic functions with development of a deficiency syndrome. This has been done for ionizing radiation in protozoa (Luckey,1986).

The laboratory was in an underground vault, to reduce cosmic radiation, inside a room with thick steel and lead walls, to reduce earth radiation, and had carbon filters to reduce radon and other airborn radionuclides. The protozoa were grown in a special copper-cadmium clad lead box inside an air incubator. The culture medium was composed of reagent grade chemicals with natural potassium, which is radioactive, being replaced with the nonradioactive isotope,39KCl. Increased levels of ionizing radiation were obtained with the addition of 40KCl for endogenous irradiation or with an external radiation source of $^{137}CsNO_3$.

The reproduction rate of the protozoan, T.pyriformis, in subambient radiation levels was statistically lower ($p<0.01$) than that of the control near ambient radiation levels, about 0.5mR/d (Fig .21). All cultures irradiated at levels greater than ambient replicated faster than the control culture. These results confirm those of Planel and coworkers (Planel et al. 1981 and Conter et al.1984) with impure cultures of protozoa and an alga.

FIGURE .21. EFFECT OF RADIATION ON PROTOZOAN GROWTH RATE . The growth (replication) rate of pure cultures of T.pyriformis in a chemically defined medium was directly determined by the amount of ionizing radiation.

The question of stimulant or essential agent is partially answered. The microbic data clearly indicate that ionizing radiation is essential for fast growth rates, a most essential physiologic function in natural habitats where the battle for food supplies is won by those microbes which can outgrow their competitors. The tentative conclusions are astounding. Ionizing radiation is essential for life and the amount provided by usual background levels is less than optimum.

F. DISCUSSION AND CONCLUSION

Consistent and extensive literature of the past 90 years show that microbes, plants and animals are stimulated by low levels of ionizing radiation. This includes very important physiologic parameters such as growth, maturation, reproduction, mental acuity, immune competence and reactions to stress. The resulting benefits include decreased infertility, improved resistance to infection, cancer and radiation sickness, less midlife mortality and, consequently, longer average lifespan. The new evidence is that plant and animal microbes perform suboptimally when the radiation flux is lowered below ambient levels. A parabola (Fig. .22) is the model which incorporates the harmful effects of excess ionizing radiation, stimulation by low doses of the same agent, and evidence of a deficiency when the quantity of that agent is reduced below ambient levels.

FIGURE .22. A COMPLETE DOSE-RESPONSE CURVE FOR THE EFFECTS OF IONIZING RADIATION UPON ORGANISMS.

A distinctive feature of this curve is its placement on the abscissa. This curve could represent vitamin A, vitamin C, iron, selenium, calcium, or any other essential agent where a given population received an inadequate supply of that agent. For such an agent considerations are made to supplement the deficient individuals. The usual scientific interpretation of the above information would conclude that ionizing radiation is an essential agent which is present in suboptimal quantities for most populations. This revolutionary concept is a reasonable interpretation of information from protozoa, invertebrates, and vertebrates, including humans. The increased physiologic function found with ionizing radiation is not due to low doses of a toxicant, as mercury or antibiotic; rather it is due to insufficient amounts of an essential agent. The data suggest that in many populations more ionizing radiation is needed for optimum health.

One advantage of the model is the presence of a definitive zero equivalent point (ZEP). For any given parameter being studied, a few points above and below ZEP can establish an

acceptable definition for a harmful dose, i.e. any dose greater than ZEP. However, things get more complex when it is realized that there are many parameters, many different populations and many conditions which would give different ZEP values as well as the more important concept of different optimum levels for ionizing radiation. Pragmatic solution to the quagmire of recommended allowances for optimum levels of ionizing radiation for farm animals and humans may follow the pattern set for other essential agents, committee evaluations and consensus.

Extensive data from microbes, plants, invertebrates and laboratory mammals give confirmation to the evidence from Japanese bomb survivors, accidentally exposed humans. the China study and epidemiologic data from the United States. The consistency of the results with low levels of ionizing radiation provide convincing evidence that reasonably increased background levels of ionizing radiation are not harmful. Indeed, the information presented suggest that somewhat increased levels of ionizing radiation may provide a new plateau of health.

Acceptance of ionizing radiation as an essential agent which is usually present in suboptimal amounts is vital for future allocation of research funds, experimental design, government standards and regulations, and changed societal perception. This new concept encourages enlightened discussion of protection versus utilization of ionizing radiation as a natural resource.

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TABLE .1

RADIATION HORMESIS OF NEUROLOGIC FUNCTION *

DATE	AUTHORS	OBSERVATIONS
1903	Zhukovskii	Dog Cortex Excitability
1933	Girden & 1935	Auditory Acuity of Dogs
1937	Brogden et al.	Dog Acoustic Acuity
1952	Galkovskaya	Nerve Regeneration
1956	Lomonos	CNS Excitability
	Rugh	Neonatal Mice
1958	McDowell & 1960	Monkey Learning
1960	Lott	Rat Nerve Excitability
	Livanov et al.	Rat Brain Excitability
1962	Dawson et al.	Frog Nerve-Muscle Prep
	Hunt et al.	Rat Arousal
1963	Garcia et al.	Sensitivity of Brain Receptors
	Smith et al.	Moth Flight Induced
1965	Kimaldorf	Shrimp eye Reaction
1968	Pora	Rat Brain Activity
1969	Grigeryev	Rabbit Vestibular Excitability
1975	Semaginin	Cerebral Cortex Development
1978	Carpenter et al.	Pacemaker Neuron Stimulated

* Taken from Tables 4 5 and 7 of Luckey (1980).

TABLE 2

RADIATION HORMESIS IN RADIORESISTANCE*

DATE	AUTHORS	OBSERVATIONS
1950	Cronkite et al	Three weekly exposures of 144 rads with 1 mo. rest.
	Betz	Similar Data
1954	Lorenz et al.	Used continuous low level (1.1 rad/d) pretreatment
1960	Maisin et al.	Acute (20 day) or chronic irradiation of fetal mice quadrupled radioresistance.
		Young mice given 5 rads showed double radioresistance over controls.
1963	Mezentsev and Gubin	Pretreatment with 43 rads increased radioresistance
1964	Vlasenko and Shakhnazaryan	Pretreatment prolonged life.
1970	Nishio	Drinking 0.1 μCi ^{90}Sr and 0.4 μCi ^{137}Cs/ml quadrupled
1978	Stienon-Smoes et al.	Preexposure of mice increased LD_{50} about 50%
1979	Spalding and Holland	Early irradiation gave dogs increased survival times

* Taken from Tables 4 5 and 7 of Luckey (1980).

TABLE 3

RADIATION HORMESIS OF IMMUNOGLOBULINS*

*Taken from Tables 4,5 and 7 from Luckey (1980).

ANTIBODY
- 1913, Manoukhine
- 1920, Hektoen
- 1921, Kaznelson and Lorant, - Typhoid Toxin
- 1937, Thompson et al.
- 1950, Burrows et al. - Cholera toxin - transient
- 1963, USAEC
- 1964, Taliaferro and Taliaferro
- 1975, Gras et al.
- 1976, Servant et al.
- 1977, Macedo; Gorini et al. - Antibody affinity
- 1978, Onletz; Shubin

HEMOLYSINS AND BACTERIOLYSINS
- 1913, Manoukhine

TOTAL AMOUNT OF LYMPHOID ELEMENTS
- Murphy and Morton, 1915
- Tanaka and Sakai, 1979

LYMPHOCYTOSIS - Medium doses gave no effect
- Thomas et al., 1919; Murphy, 1926
- Pape, 1951; Lorenz et al, 1954

GRANULOCYTOSIS - Transient
- Sacchetti et al., 1960

LYMPHOCYTE STIMULATING FACTOR
- Metcalf, 1959

PHAGOCYTOSIS
- Buzine, 1962; Vorbrodt, 1975

SPLEEN LYMPHOCYTE ENZYMES AND BACTERICIDAL ACTIVITY
- Paul et al., 1976

SPLEEN FOLLICLE DEVELOPMENT
- Pape, 1951

SPLEEN PLAQUE FORMING CELLS
- --Prior to antigen administration
  - Zaalberg et al., 1973

TABLE .4

X-Rays Stimulate Resistance to Cancer

Group	No.	Irradiation		% With Tumor Resorption	% With New Tumors
		Mouse	Tumor		
1	52	+	-	50	21
2	29	-	-	3	48
3	10	-	+	0	40

(a) A palpable spontaneous tumor was extirpated from each mouse and held a given time before being regrafted into the groin of the same mouse following the treatment indicated. Murphy and Morton (Mu15).

TABLE . 5

1950-78 Cancer Mortality in Atomic Bomb Subjects
(Kato and Schull, 1982)

Rads	0	1-9	10-49	50-99	100-199	200-299	300-399	400+
Ave Rads	0	3.4	22	71	142	244	345	526
Persons	31,581	23,073	14,942	4,225	3,128	1,381	639	887
	controls per 10,000	% of control						
All Cancer	575	94	107	111	123	156	182	190
All NonLeukemia	560	95	106	109	117	140	120	153
Leukemia	15	71	151	178	371	794	1,287	1,616
Multiple Myeloma	2	100	65	235	-0-	700	-0-	1,100
Malignant Lymphoma	12	58	92	98	33	233	133	92
Esophagus	22	50	109	107	73	264	-0-	155
Stomach	224	92	102	96	92	104	119	146
Colon	20	85	90	95	110	180	80	340
Rectum	20	95	110	119	80	110	-0-	-0-
Pancreas	19	111	89	50	100	115	87	58
Other Digestive organs	69	103	107	174	120	178	181	146
Lung	49	110	120	129	229	178	255	184
Breast	14	90	121	136	321	100	-0-	400
Uterus	36	131	139	86	125	122	92	156
Urinary Tract	12	92	100	138	183	233	258	92

TABLE .6

THIRTY THREE YEAR MORTALITY IN PLUTONIUM SUBJECTS

Data from Voeltz et al. (Vo83 a,b)

Cause of Death	Number	
	Observed	Expected[a]
All	44	77.1
External	8	7.6
Respiratory	2	4.4
Circulatory	18	40.0
Cancer Total	8	14.9
Digestive	5	4.67
Respiratory	1	5.04
Bladder	1	0.43
Lymphopoietic	1	1.5

(a) US Population rates (Voelz et al., 1983)

F I G U R E L E G E N D S

Figure .1. NATURE AND NURTURE. Each individual is a composite of his nature, his genetic potential which directs his ontogenetic development according to his nurture, the impact of his total environment, from conception to death.

Figure .2. DOSE-RESPONSE MODELS FOR IONIZING RADIATION. The three major dose-response models for the effects of ionizing radiation are the linear model, the lower curve which has several variations, the threshold model, and the hormesis model in which the curve crosses the threshold, the zero equivalent point (ZEP).

Figure .3. EFFECT OF A SINGLE DOSE OF X-RAY UPON EUGLENA GROWTH. The rate of growth, as measured by cell division, of Euglena gracilia is given on the ordinate as % of control growth. The abscissa indicates the doses at 3.5 krad/min (Seuberling, 1970).

Figure .4. RADIATION HORMESIS IN PLANTS.

.4A. X-RAY EXPOSURE OF STRAWBERRY CLONES. Exposure of young strawberry plants, Senga precosa, increased early and total yield (Fendrick and Glubrecht, 1972).

.4B. X-RAYS STIMULATE GROWTH OF Lemna minor. The irradiated plants weighed more than control with 6 hours of light at 26oC. The ordinate is & of control and the abscissa indicates the acute doses administered at the start of the experiment (Feldman,1971).

Figure .5. RADIATION HORMESIS IN INSECT REPRODUCTION. Increased population in flour mite colonies was obtained following acute gamma irradiation (Melville, 1959).

Figure .6. RADIATION STIMULATES MOUSE GROWTH RATE. Growth of mice was significantly increased ($p<0.01$) by daily exposure to X-rays from 30 to 60 days of age (Luckey,1980).

Figure .7. LITTER SIZE IS INCREASED IN IRRADIATED MICE. Chronic gamma ray exposure increased the litter size of mice for three successive broods (Muramaysu et al. 1964).

Figure .8. SIX DOSE-RESPONSE CURVES FOR RADIATION INDUCED CANCER.

Figure .9. COMPLETE DOSE-RESPONSE CURVE FOR RADIATION INDUCED CANCER.

Figure .10. REDUCED TUMOR INCIDENCE IN IRRADIATED MICE. The mice were exposed to two large doses of X-rays (450 rads) prior to the administration of methylcholanthrene (Lisco, 1958).

Figure .11. CANCER INCIDENCE IN CHRONICALLY IRRADIATED MICE. The incidence of lung cancer and leukemia were increased while "all other cancers" decreased (Grahn et al. 1968).

Figure .12. CANCER MORTALITY IN JAPANESE BOMB VICTIMS. Hormesis is noted in the dose-response curves for both leukemia and "all other cancers" in both cities (Kato and Schull, 1982).

Figure .13. DETAIL OF RADIATION INDUCED LEUKEMIA.
.13A. Comparison of low dose irradiation induced leukemia in Nagasaki according to Land (1980) and Pagnementa (1983) with 50% confidence limits displayed. Note that the point at 38 rads is ignored in all but the hormesis curve.
.13B. Computer model of the dose-response curve for radiation induced leukemia at Nagasaki (Pagnementa, 1983).

Figure .14. BONE CANCER IN RADIUM DIAL PAINTERS.
.14A. Radiation induced bone cancers in the radium dial painters after 33-45 years, ordinate, plotted against the radium intake (Rowland et al. 1983).
.14B. Bone and head cancer incidence of radium dial painters compared with the amount of total radiation over a period of 50 years (Evans, 1981).

Figure .15. THYROID CANCER IN TREATED HYPERTHYROID PATIENTS. Comparison of cancers found in hyperthyroid patients following the use of surgery, radioactive iodine, or drug therapy in humans (Dobyns et al. 1974.

Figure .16. CANCER EPIDEMIOLOGY IN THE UNITED STATES. There is a significant negative correlation ($p<0.03$) between terrestrial radiation and leukemia mortality for the contiguous 48 United States (Cohen, 1981).

Figure .17. PREDICTED CHERNOBYL CANCER MORTALITY. The cancer mortality at Chernobyl should follow the hormesis model for both leukemia and "all other cancers".

Figure .18. RADIATION HORMESIS IN MOUSE LONGEVITY. Comparison of the survival of non-irradiated control and chronically exposed mice (0.7 to 3600 rads/day of gamma rays) at the time when one half of the controls had died Spalding et al., 1982).

Figure .19. CORRELATION OF BACKGROUND RADIATION WITH CHRONIC DISEASE. The inverse correlation of mortality from chronic disease with background radiation was high ($p<0.001$) (Sauer et al. 1982).

Figure .20. MODELS OF COMPLETE DOSE-RESPONSE CURVES. Note that extension of each curve into subambient levels of ionizing radiation is a theoretic postulation.

Figure .21. EFFECT OF RADIATION UPON PROTOZOAN GROWTH RATES. The growth (replication) rates of pure cultures of T. pyriformis in a chemically defined medium was directly proportional to the amount of ionizing radiation.

Figure .22. GENERALIZED COMPLETE DOSE-RESPONSE CURVE FOR THE EFFECT OF IONIZING RADIATION UPON ORGANISMS.

Fig. 1

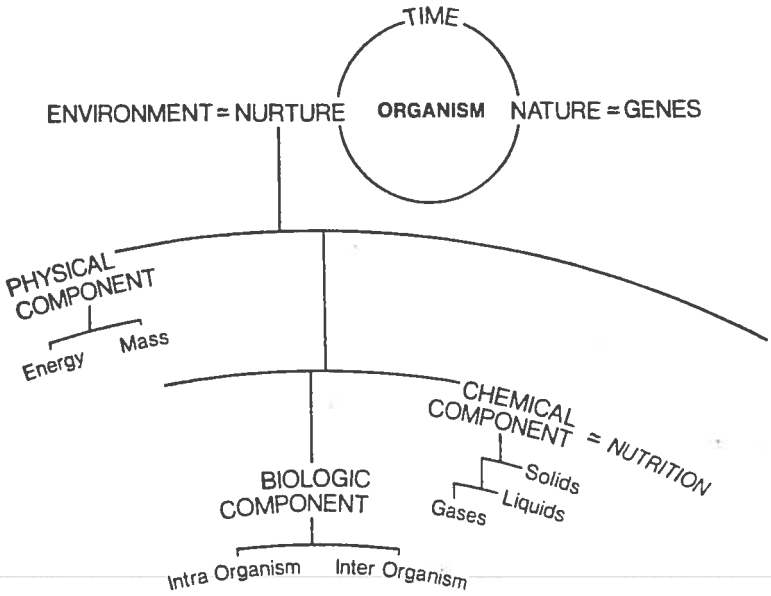


Fig. 2

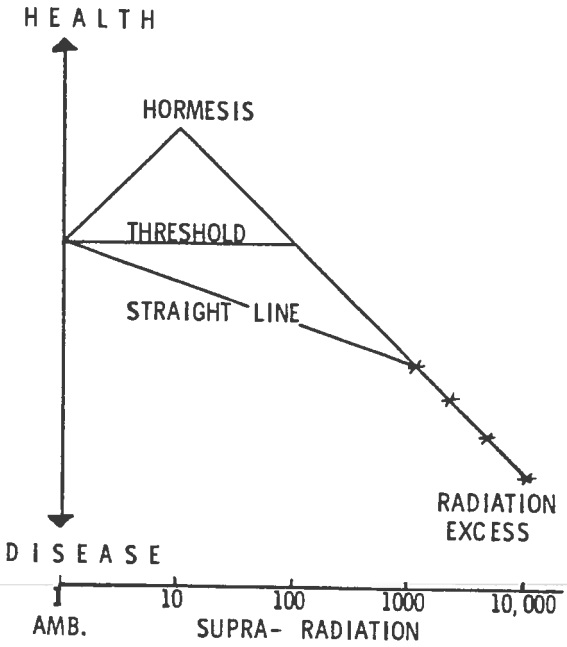
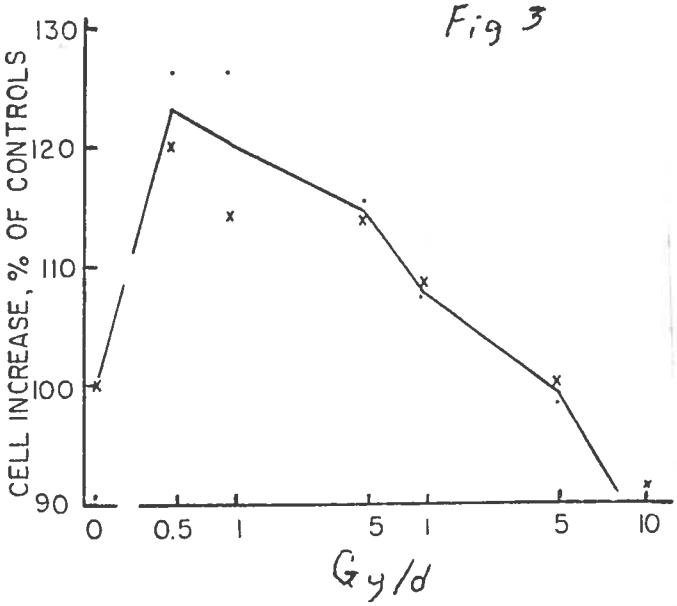


Fig 3



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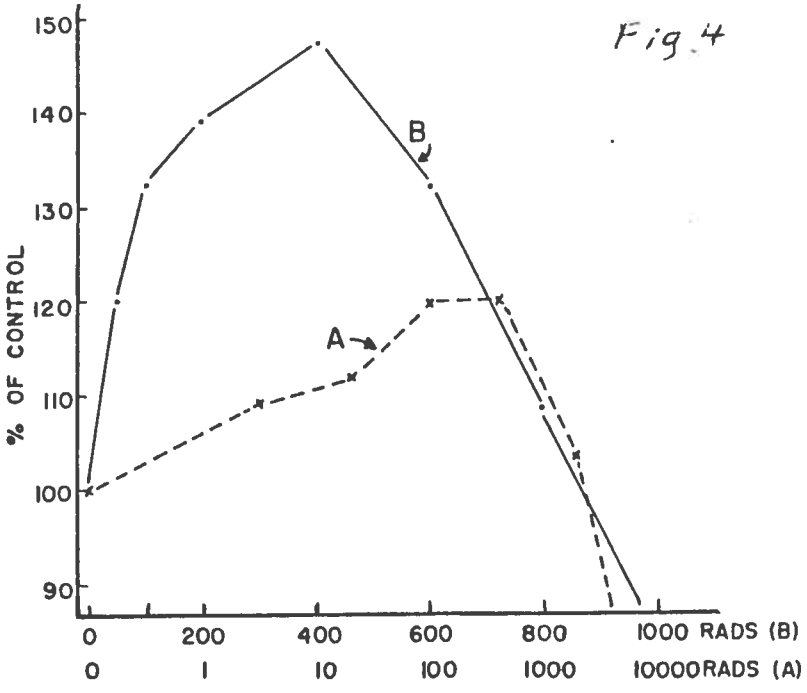

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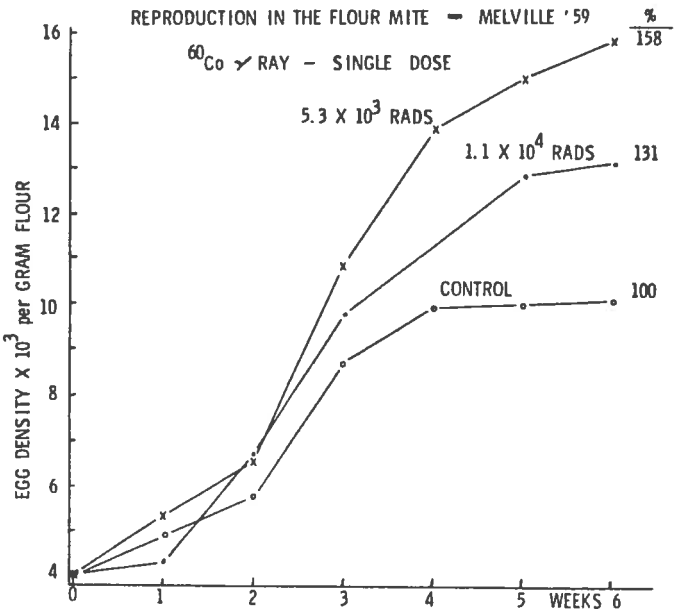

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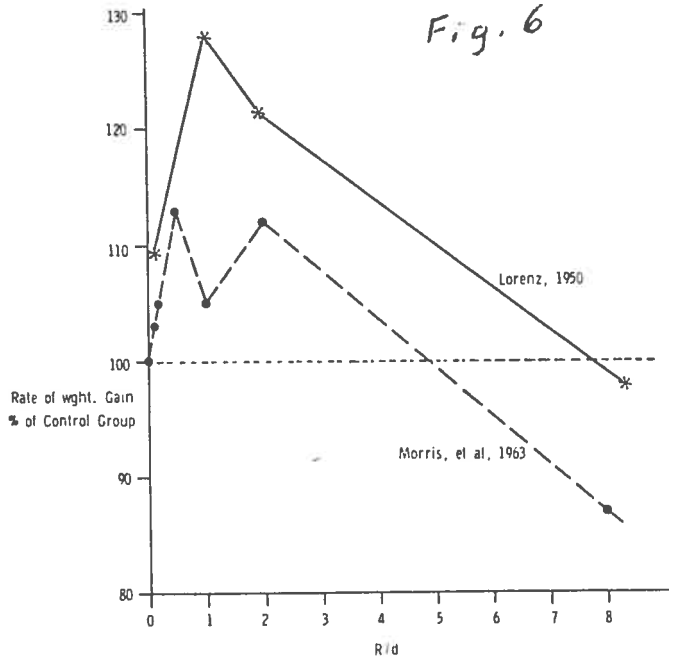

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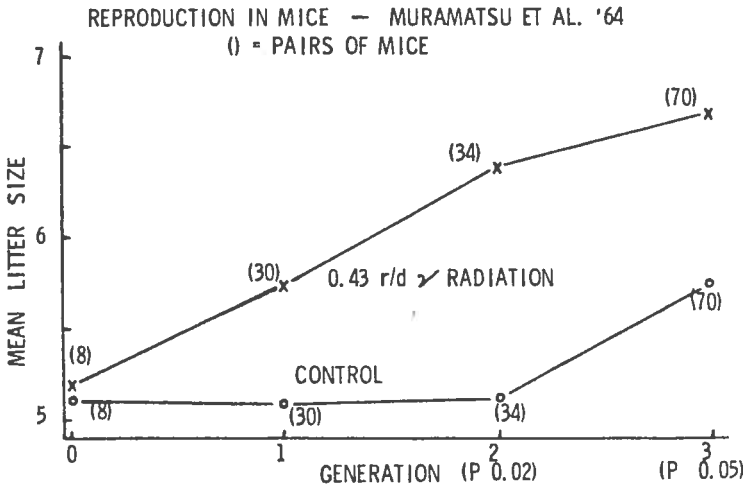

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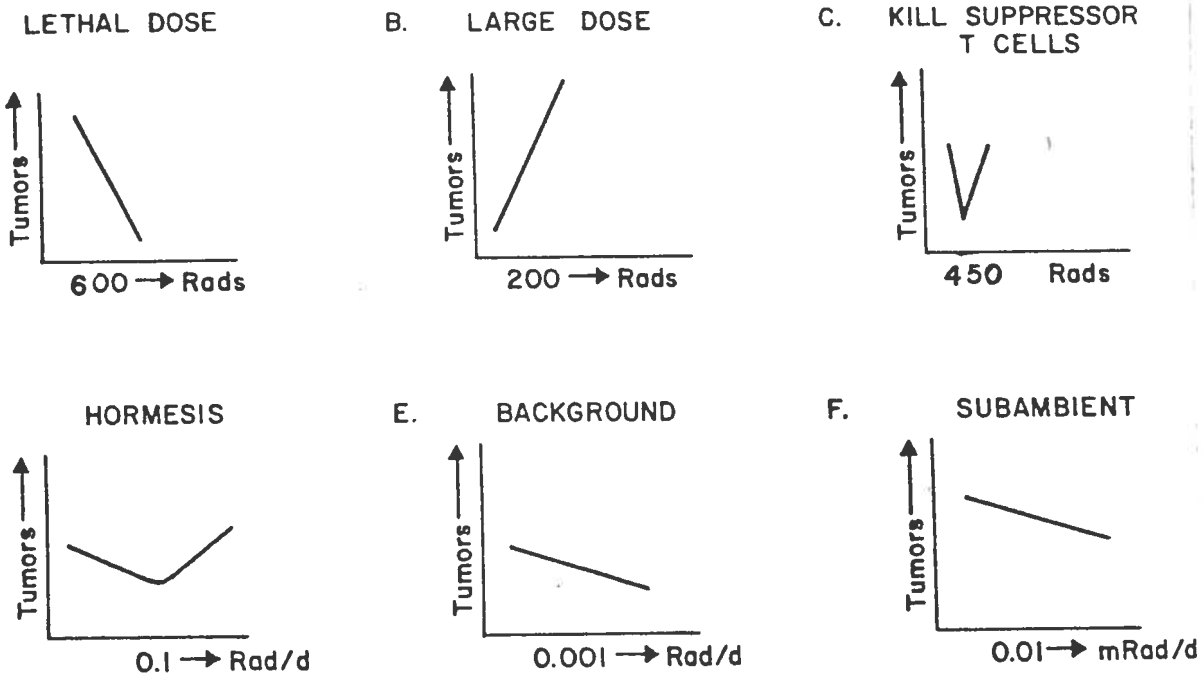

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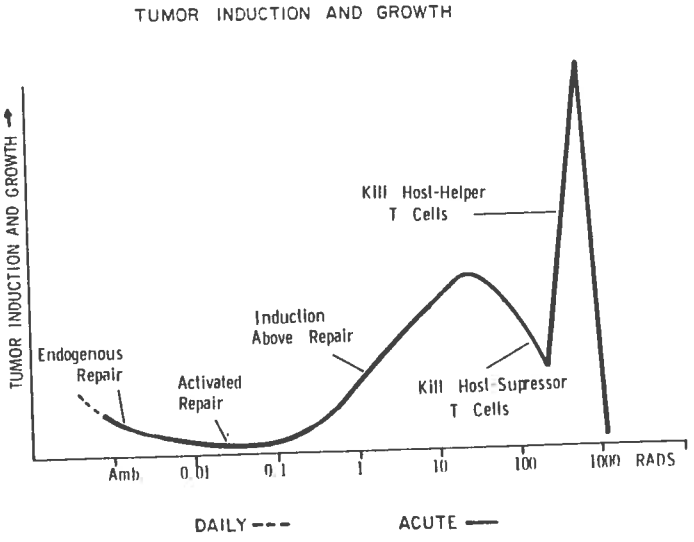

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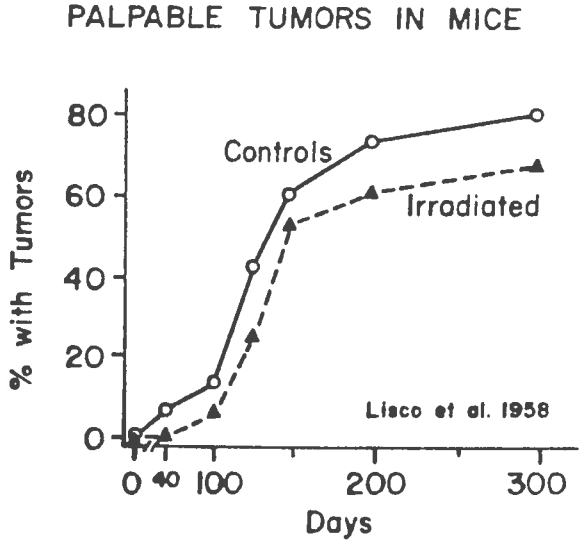


Fig. 11

OVARIAN, PULMONARY AND HEPATIC TUMORS (4000 MICE)
Grahn et al. 1968

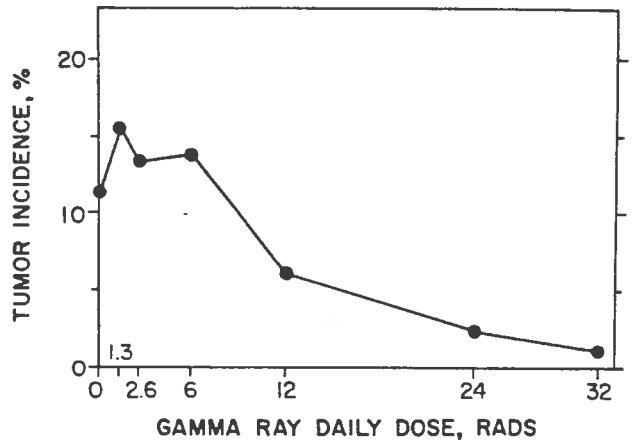


Fig. 12

1950-78 CANCER MORTALITY IN HIROSHIMA-NAGASAKI
Kato + Schull, 1982

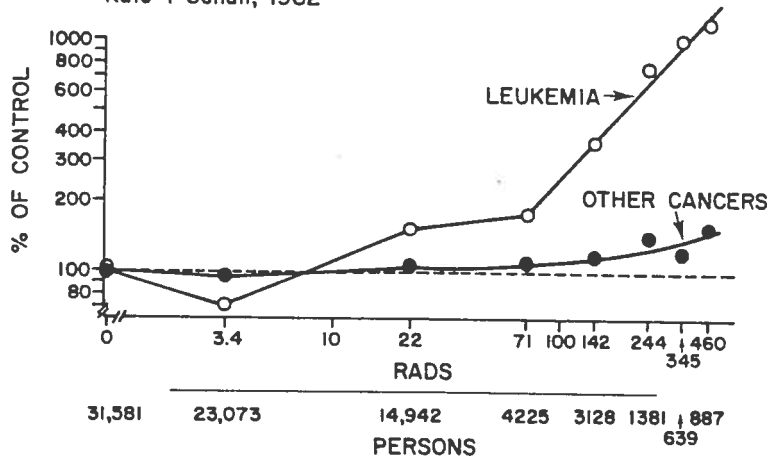
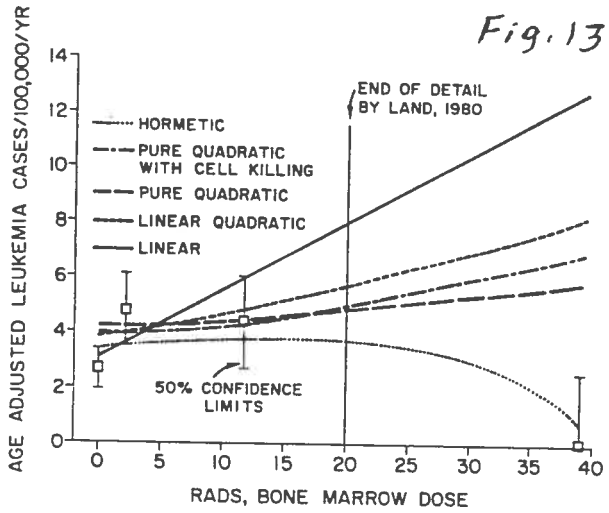


Fig. 13 A



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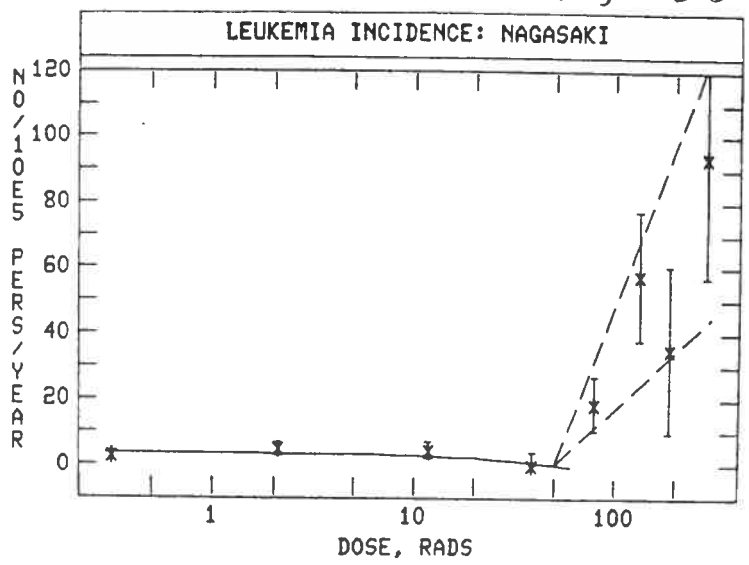

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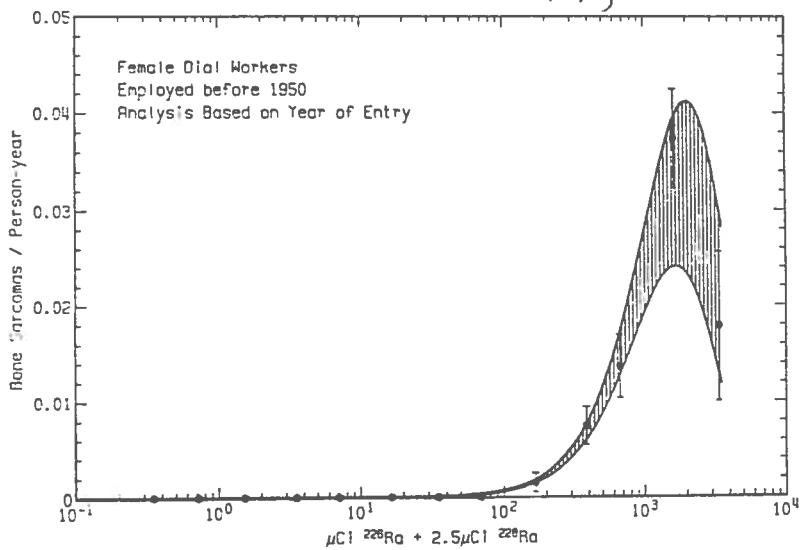

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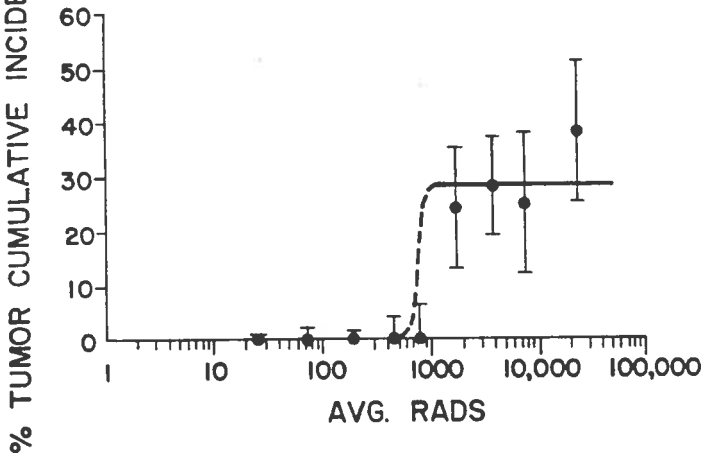

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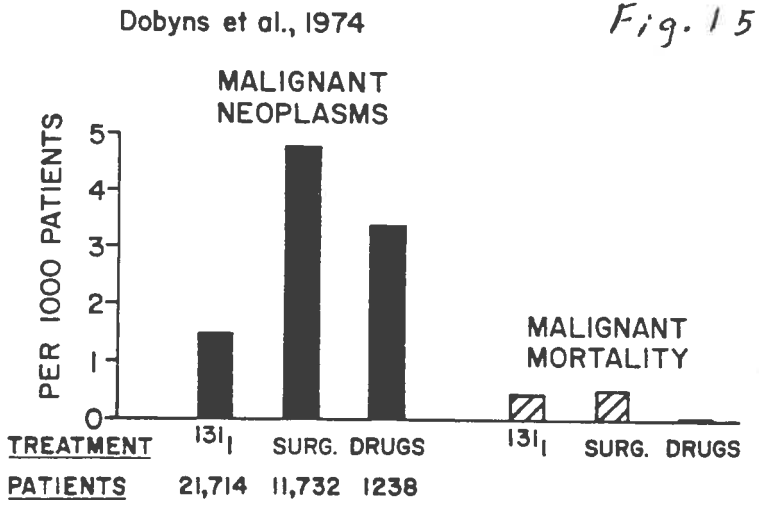

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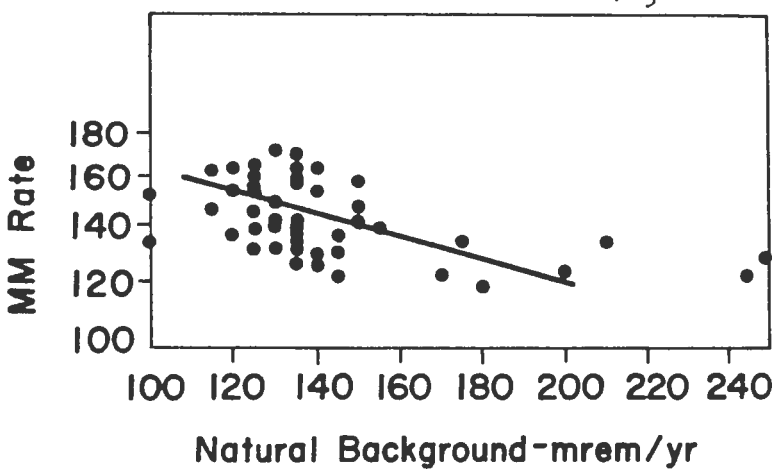

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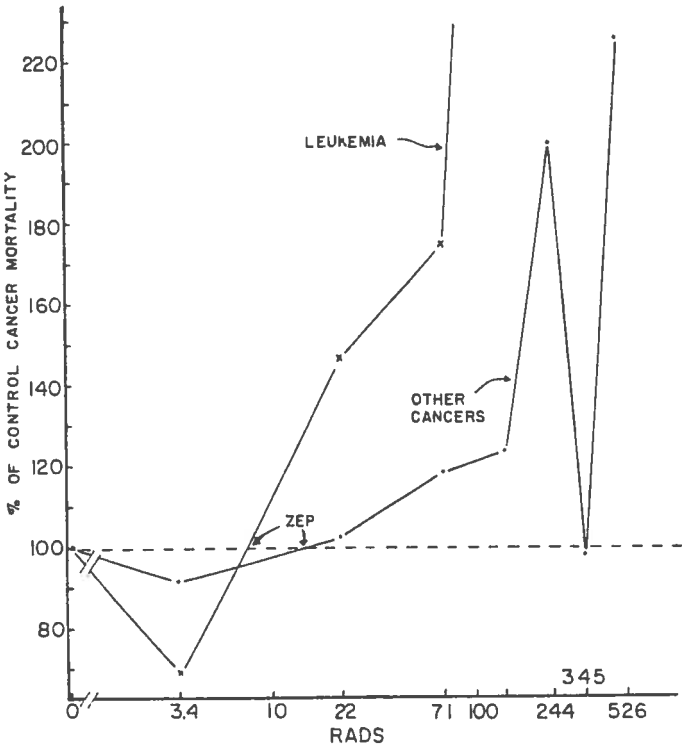

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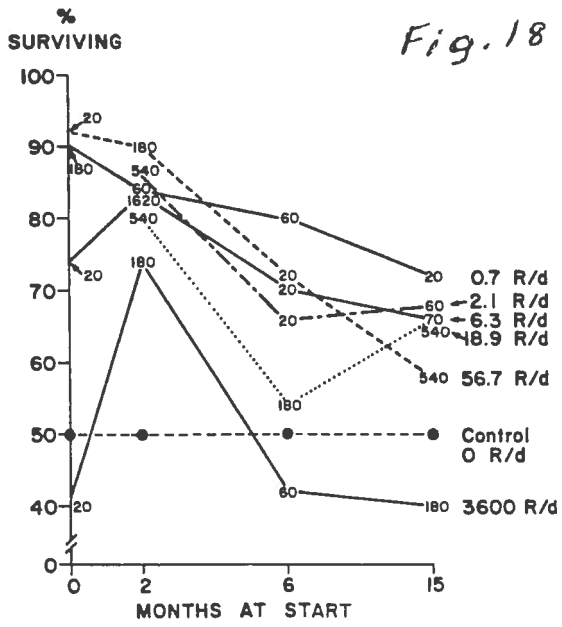

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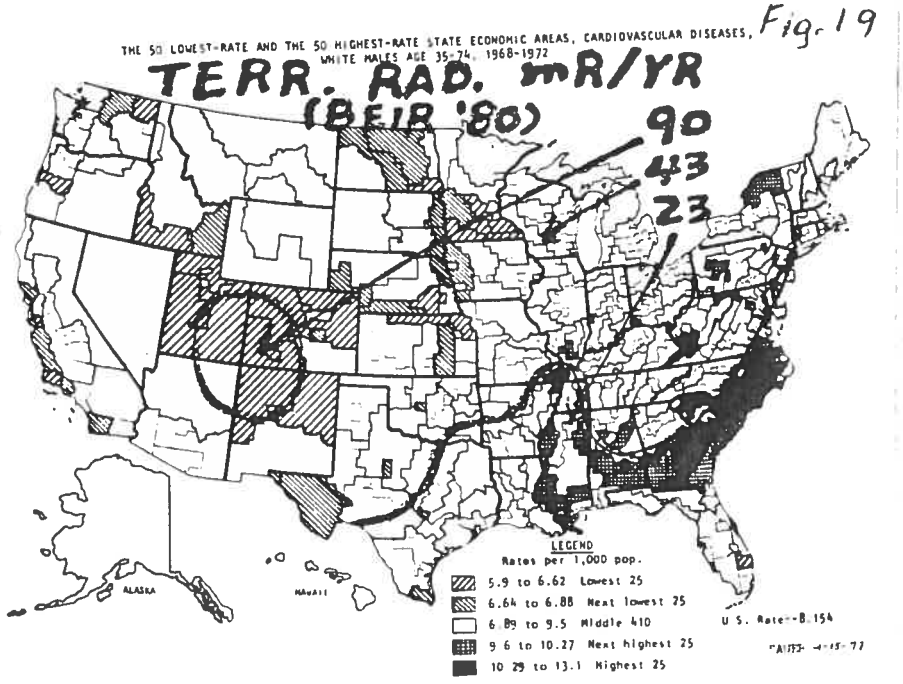

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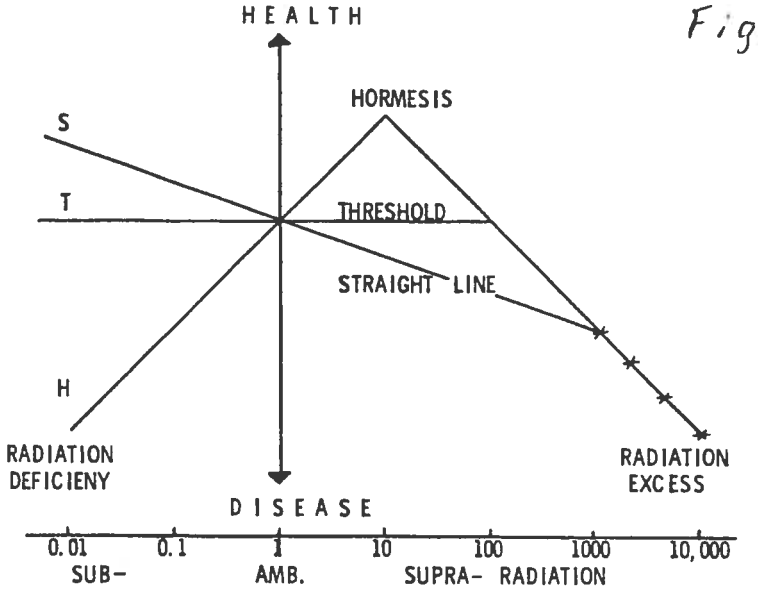

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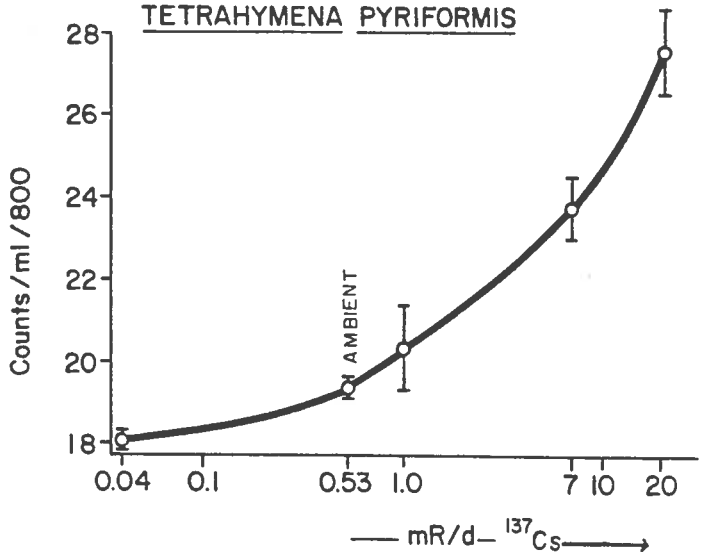

Fig. 22