Pollution from Reactors

Those who wonder why our energy worries have come upon us so suddenly will have considerable interest in this chapter on low-intensity radiation. The difficulty of developing safe nuclear energy sources, according to the account given by Professor Sternglass, involves not only the difficulty of disposing of radioactive waste products, but also the untoward effects arising from changes in the background radiation. This is a new concept, born about 1972, which may have a significant effect on the future planning of our energy sources.

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Radioactivity

E. J. Sternglass

1. Introduction

Man's awareness of the existence of natural radioactivity in the environment dates back more than three-quarters of a century to Becquerel's discovery that radiation is continuously released from uranium-containing minerals, just a few months after Roentgen's discovery of X rays in November, 1895. But only within the last 30 years has concern over man-made radioactivity arisen, as a result of the discovery of fission and its use in weapons that release large amounts of radioactive chemicals into the atmosphere.

Although the existence of serious health effects due to high levels of radiation was recognized within the first few years of its discovery, until very recently it was widely believed that there exists a safe level below which there are no detectable effects on human health. Thus it seemed that the very small doses from natural radiation sources and the still smaller man-made contributions to the background levels would have no significant effects on man or other living systems.

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From
Environmental Chemistry
Plenum Press, London, 1977
Ed. by J. O'M. Bockris

The strongest argument was that life apparently evolved successfully in the face of a continuous exposure to low levels of environmental radiation. And this argument seemed to be supported by the long experience with comparable levels of diagnostic X rays, for which there appeared to be very little risk of any detectable health effects.

It is the purpose of the present article to summarize the recently discovered evidence that we were misled by the relatively benign nature of medical X rays, and by the difficulty of detecting the subtle effects of environmental radiation, into regarding small continuous doses from background sources as relatively harmless.

As will be shown, the evidence gathered by a number of different investigators within the last few years now suggests that we may have underestimated the health risk of small trace quantities of radioactive chemicals in our air and water by 100–1000 times. And this has happened at the very moment when mankind has counted on being able to meet its enormous needs for energy by using uranium fission to replace the rapidly dwindling sources of fossil fuel.

2. *The Nature of Radiation and Its Biological Action*

In order to be able to understand how the magnitude of the biological effect of environmental radiation could have escaped detection in the face of a vast body of experience with medical radiation and many decades of laboratory and animal research, it is necessary to understand the nature of the various forms of radiation and their different modes of action on biological systems.[1–3]

2.1. *Forms of Nuclear Radiation*

As already recognized by the early pioneers at the beginning of the century, atomic radiation occurs in two basic forms; waves and particles. The wave type is essentially like ordinary light, but of a much shorter wavelength and therefore of greater energy per photon, or "bundle," of energy. This is the type of radiation discovered by Roentgen, and since then produced in X ray tubes for medical purposes. It is also the form of the very penetrating high-energy component of the radiation, emitted from radioactive chemicals such as radium, called gamma rays, where each photon or "quantum" carries typically the equivalent of 1-million-volt X ray photons.

The other form of energy emitted by radioactive nuclei consists of very rapidly moving particles of matter, such as the so-called beta rays, which are simply electrons, and alpha rays, which are helium nuclei. Since the discovery of these particles at the turn of the century, many other nuclear particles have been found to exist, such as the proton and a whole family of very short-lived mesons; only the neutron is of importance in the radiation effects of naturally occurring chemicals, being spontaneously emitted by some of the heavier elements, such as uranium.

One other form of corpuscular radiation is of great biological importance, and these are the so-called fission fragments, or the pieces of fast-moving nuclei created when uranium or plutonium nuclei break apart after having absorbed a neutron. These fission products are in fact isotopes of normal chemical elements such as barium, strontium, and iodine, differing only in mass from the stable chemical forms, or trace elements, in the environment. Because they are generally unstable, they in turn emit radiations in the form of gamma rays, beta rays, and X rays, often transforming themselves into other chemical elements and giving rise to a whole series of so-called "daughter products" that are taken up by biological systems along with the stable chemical trace elements in the environment.

Both wave and corpuscular forms of radiation are ultimately absorbed in matter through collisions with the atomic electrons, leading to fast-moving electrons that in turn are slowed down in a series of *ionization* and *excitation* processes. The biological damage in living cells is therefore ultimately due to the action of rapidly moving electrons, regardless of whether the original radiation was of the wave or corpuscular type, but the *spatial distribution*, or *density of energy deposition per unit distance*, will be very different on a microscopic scale.

Thus, heavy particles, such as alpha particles, produce a zone of extremely high ionization, or excitation density, in their wake. On the other hand, low-mass beta particles or atomic electrons ejected by X rays and gamma rays produce a very low density of ionizations and excitations on a microscopic scale, with very different biological effects, as will now be discussed.

2.2. *Modes of Biological Action*

There are basically two different ways in which the ionization and excitation of molecules in a biological system consisting of individual cells results in functional damage, and the two basic forms of radiation discussed above have very different efficiencies in producing this damage.

The first and most widely studied type of damage is of a physical, or "bullet-like" type, in which molecular bonds are broken directly in the target structure by the ejected electrons, producing ionizations or excitations. This is the type of fast, direct action that has been observed to be the principal cause of DNA damage in the nuclei of cells, leading to what is generally referred to as genetic damage, which is transmitted to future generations of cells if it is not lethal or if it is not repaired before the cell reproduces itself.

The second type of damage is of an indirect type, in which the ultimate harm to the critical target is initiated by the production of *highly reactive chemical species* which must diffuse some distance from their point of production to the critical target site. This type of *indirect, or chemical, action* is, for instance, involved when dissolved oxygen in the cell fluid captures a free electron to become the highly toxic O_2^-, or superoxide radical. This active form of oxygen is in turn able to initiate various chemical reactions that can lead to

the membrane surface, due to the fact that positively charged molecules generally project outward to a greater distance than negatively charged ones.

As a result, it has been found that cell membranes produce an electric field in the cell fluid that tends to attract negatively charged molecules, such as the highly toxic O_2^-. Furthermore, it was found by detailed computer calculations that the greater the concentration of free ions, the weaker the electric field becomes that attracts the O_2^-.[6] Thus, when ion concentrations are high, as from the passage of an alpha particle or a very high dose rate produced by an intense X ray beam, O_2^- molecules are not able to reach the sensitive cell structures as efficiently as when the instantaneous ion concentration is very low.

One therefore obtains the paradoxical result that for a given total dose, densely ionizing radiation—either from an alpha particle or from a short burst of X rays, as produced by medical diagnostic equipment—*can be biologically less damaging to cell membranes* than the protracted, low-level background radiation produced by an occasional fast cosmic ray particle or electron ejected by gamma rays from radioactive elements in the air, on the ground, or in the body.

The basic theory of recombination has been known for decades.[1] But the fact that it actually takes a much smaller absorbed dose to rupture phospholipid membranes of the type occurring in living cells when the radiation is protracted over long periods of time than when it it is given in a brief burst was only discovered within the last few years; as so often in the history of science, it happened quite accidentally, in the course of radiochemical studies of the action of radiation on synthetic phospholipid membranes immersed in water that were being carried out by Petkau, a Canadian biophysicist working in a laboratory of the Canadian Atomic Energy Establishment, in Manitoba.[7]

While carrying out measurements of the pH of an aqueous solution surrounding a small phospholipid membrane in the presence of radiation, Petkau observed that the membranes would rupture more quickly than when the X rays were turned off. He therefore decided to investigate this phenomenon further, and carried out a series of experiments to determine just how much of a dose was required to break the membranes at different radiation intensities.

Using radiation from a diagnostic X ray machine operating at 26 rads/min, he found that it took the enormous dose of 3500 rads to break the membrane, or some 35,000 times the annual dose from normal background radiation, which is close to 0.1 rad, or 100 mrads in most areas of the world. This was certainly reassuring, indicating that the membranes of living cells are not likely to be damaged by typical diagnostic X ray exposures, whose doses to the skin are generally in the range of 0.1–1.0 rad.[8]

But when he substituted a very small amount of radioactive sodium salt ($Na^{22}Cl$) in the water for the external X ray beam, such that the dose rate was reduced to only 1 mrad/min, he found that it took only about 0.7 rad to rupture the membrane, or some 5000 times less than with the high-intensity beam of medical X rays.

Subsequent studies showed that only a factor of 10–20 could be attributed to the difference between the types of radiation produced by the two different radiation sources. The remainder was found to be due to the difference in the rate at which the radiation was emitted, the dose required to rupture the membrane declining slowly as the dose rate was lowered, as shown in the plot of Fig. 2, taken from Petkau's original paper.[7]

Detailed measurements of pH in the presence and absence of the membrane confirmed that it was indeed the production of the O_2^- radical which was involved.[9] Subsequent studies on the membranes of living microorganisms in the presence of chemicals known to capture O_2^- decreased the sensitivity to damage, exactly as required by an indirect chemical action of radiation in which the free radicals reaching the membrane initiate an oxidative chain reaction that eventually destroys the membranes.[10,11] Since then, experimental studies on mice exposed to various levels of radiation have shown that enzymes known to deactivate excited forms of oxygen molecules provide a significant degree of protection to the white blood cells, which form an essential part of the defense against infectious diseases.[12]

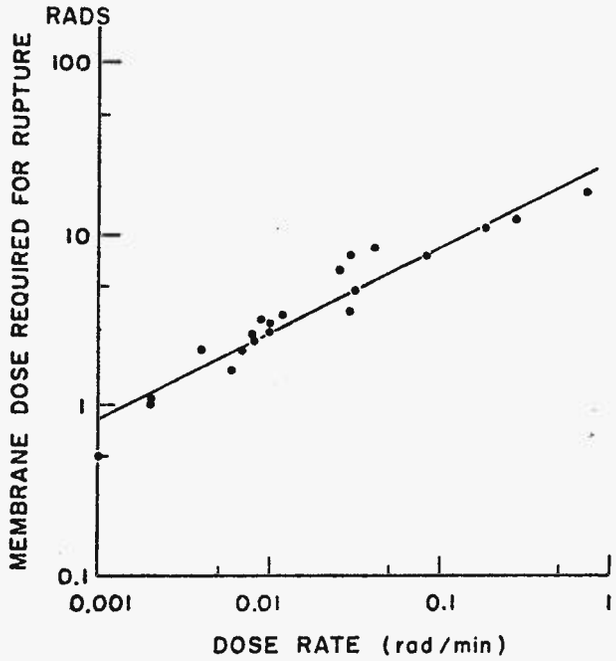

Figure 2. Effect of dose rate on the total dose required to rupture a cell membrane. Note the strong decrease in the absorbed dose measured in rads as the dose rate is reduced. (Data from Petkau.[7])

2.3. *Implications for the Risk of Environmental Radiation*

It is clear that the discovery that cell membranes require a smaller total dose for rupture as the dose rate is reduced has very serious potential implications for the likely effects of protracted background radiation, as compared with the known effects of high-dose-rate radiation. For this reason, it is essential to investigate whether this decrease in the dose needed to produce biological damage holds all the way down to the small dose rates of 10–100 mrads/year produced by global fallout,[3,11] and the normal releases from nuclear facilities.[12,13] Furthermore, it must be established whether this holds not only for isolated membranes in a test tube, but also for membranes in complex living systems where natural protective mechanisms can operate, not only in lower animals, but also in the case of man.

That this appears to be the case has recently been shown[14] by an analysis of two separate studies using very low total doses and dose rates. The first involved the precursors of blood cells formed in the bone marrow of rats,[15] and the other dealt with a study of the permeability of human red cells (erythrocytes) for individuals occupationally exposed to X rays at only a few times the normal background levels.[16]

The animal study was carried out by a group of investigators at the Oslo Cancer Hospital,[15] using very small trace quantities of strontium-90, of the order of picocuries* per gram of body weight, comparable to the concentrations observed in the bodies of newborn children during the peak of nuclear weapons testing.[17]

Using a series of matched pairs of animals given different amounts of strontium-90, these investigators found that the number of bone marrow cells was more strongly depressed for a given concentration of strontium-90, and therefore for each unit of radiation dose, the lower the concentration. Typically, the percentage decrease in the number of bone marrow cells ranged from 3.1%/mrad at an average body concentration of 1.2 pCi/g to 0.01%/mrad at a concentration of 2700 pCi/g. But this was exactly the type of behavior noted by Petkau for the case of cell membrane rupture, the sensitivity to damage becoming greater the lower the concentration of radioisotope in the liquid surrounding the cell membrane.[7]

Since the study of bone marrow cells by Stokke and his co-workers in Oslo was done before Petkau discovered the membrane rupture phenomenon, no ready explanation of the results was available at the time they were published, in 1968. But in the light of Petkau's subsequent findings, confirmed more recently by the observation of white cell depression in mice that could be protected against by an enzyme specific for the excited states of oxygen,[12] it is now clear why the lower concentrations of Sr^{90} showed a greater efficiency in depressing bone marrow cellularity than the higher concentrations.

* A picocurie (pCi) is 10^{-12} curies, the curie (Ci) being a unit of radioactivity corresponding to the number of disintegrations per second of 1 gram of radium, or 3.7×10^{10} disintegrations per second.

It appears that the smaller the number of radioactive atoms per unit volume, the more efficiently are the activated oxygen molecules produced able to reach the critical sites in the developing cells. Since a single molecule is able to initiate a self-propagating oxidative chain reaction over a period of hours or days, increasing the concentration has only little further effect.

In fact, one has a situation quite analogous to the case of pesticide molecules acting on critical membranes of glands controlling the thickness of eggshells in birds.[18] There, too, the effect per unit dose is greatest at the lowest concentrations, a single molecule of DDE apparently being able to affect a critical membrane site.

Thus, one is led to a dose–response function which rises very rapidly at low concentrations and then saturates rapidly for higher doses, exactly in the manner of a logarithmic type of response familiar in many sensory responses in complex living systems, such as the sense of smell (see Fig. 3[19]).

The question remains whether a similarly increased efficiency of small amounts of radiation can be demonstrated in human cell membranes. Such evidence was in fact supplied by a recent study of erythrocyte permeability carried out by Scott and his associates at San Francisco Hospital.[16]

Using groups of individuals exposed to low levels of radiation in the course of their normal work, such as radiologists and X ray technicians whose

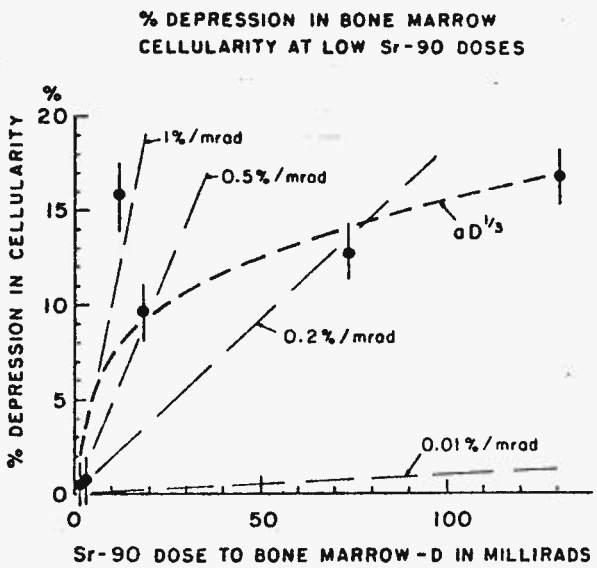

Figure 3. Form of dose-response relationship for the action of very small dose of radiation on bone marrow cells. (Data from Stokke *et al.*[15]) Note the large rise at very low doses, followed by a much more gradual rise in the effect for larger doses. Also shown is a curve of the form $aD^{1/3}$, expected on the basis of an indirect chemical action as observed by Petkau.[7]

exposure was known from their personal dosimeter readings, samples of their blood were analyzed for the permeability of the erythrocyte membranes to the passage of monovalent cations using a tracer technique that employed Rb.[86] The permeability of the erythrocyte membranes of the occupationally exposed group was compared with that of other individuals in the hospital with no X ray exposure, and a significant excess permeability was detected for the exposed individuals.

Furthermore, a plot of the percentage increase in permeability showed the same rapid rise for the lowest exposure and a leveling for the higher exposures, also observed in the animal studies of Stokke,[15] and consistent with the logarithmic, or fractional power, type of response measured by Petkau for cell membranes.[7]

Even with regard to the absolute magnitude of the effect per millirad, the result of Scott for human red-cell membranes agrees closely with the result of Stokke for the depression of the precursor cells in the bone marrow of animals given tracer doses of Sr.[90] Thus, Scott found a permeability change of some 20% for a monthly dose of about 8 mrads, which, for a typical lifespan of red cells of 3 months, works out to 0.8%/mrad. This may be compared with an effect of 0.6%/mrad at a comparable dose rate of 6 mrad/month, observed by Stokke.[15]

Clearly, all this evidence suggests that at very low dose rates, where the repair of direct damage to the DNA is apparently very effective, it is the indirect, chemically mediated damage to cell structures, such as the phospholipid membranes that dominates, owing to the lower total dose needed to produce functional damage when the ion concentrations are very low.

That the nature of this difference is dependent on the ion density, or dose rate, can be seen from an examination of Fig. 4, taken from Sternglass.[14] In this plot, the total dose D_o needed to produce a given effect, such as membrane rupture, or doubling of the normal rate of genetic defects, has been plotted against the dose rate in rads per minute.

It is seen in the figure that the data points involving some form of membrane damage fall along a broad band that declines as the dose rate is lowered from very high rates to those encountered in the natural environment. In particular, the data on isolated membranes obtained by Petkau are seen to fall along a line roughly parallel to that found by Stokke for bone marrow cellularity, but with a lower absolute value corresponding to the absence of natural protective chemicals in the *in vitro* laboratory study.

By contrast, the data observed for genetic mutations in mice[20] and for cancer risk in both animals[21] and man[22] show the opposite tendency at high dose rates, the amount of dose needed for permanent genetic damage of increased cancer risk declining slowly as the intensity of the radiation is increased. This fits the hypothesis that genetic damage is primarily due to a direct-hit type of process, where the likelihood of damage to both strands of the DNA before repair can take place increases directly as the instantaneous density of ionization is increased.

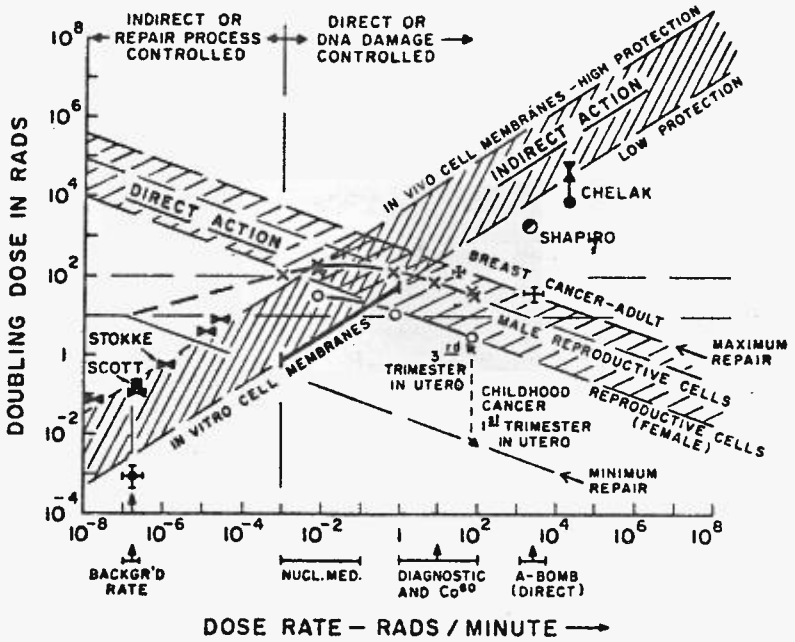

Figure 4. The effect of dose rate on the total dose needed to produce a given amount of biological damage for both the direct and indirect mechanisms.[14] Note that the indirect action causes the critical dose D_0 required to decrease as the dose rate declines toward those of background radiation, opposite to the trend for the direct action, where D_0 tends to increase as the rate of radiation absorbed decreases, leading to very large differences between expected and observed effects when the direct action on the genes is assumed to be the dominant mechanism at low dose rates.

In terms of a complex organism consisting of many cells, it is clear that whichever mechanism requires the lowest dose will dominate at a given dose rate. At high doses and dose rates, it will be the DNA damage, leading to cancer through the triggering of uncontrolled growth, for which the "doubling dose" is of the order of 10–100 rads according to a series of recent reviews of the subject.[21,22,23] On the other hand, below a dose rate of about 10^{-3} rad/min, which is 10,000 times the natural background dose rate of 10^{-7} rad/min, the indirect, chemically mediated damage has the lower doubling dose. This leads to such functional effects as a depletion of white blood cells involved in the immune process, thereby decreasing the resistance to infectious diseases,[24] a phenomenon previously associated only with very high doses given at high dose rates, such as those that result from the flash of a nuclear bomb.[25]

Other conditions associated with cell membrane damage dominating at background rates would be expected to occur in large populations exposed to very low radiation levels. These would involve developmental defects produced by failures of proper cell division or cell differentiation during embryonic

development, leading to increased rates of birth defects, spontaneous abortions, and deaths in early infancy as a result of immaturity, hormonal deficiencies, and accompanying defects in the immune system.

The same damage to the immune system would also be expected to lead to a decreased ability to detect and destroy cancer cells,[26] thus leading to a rise in cancer mortality associated with a decreased resistance to the spread and growth of tumor cells.

In fact, all the diseases normally associated with aging, such as those of the lung, the heart, and the circulatory system, would be expected to increase as the production of free radicals leads to an increased efficiency of free radical damage to cell membranes. Such generalized aging effects of radiation have long been observed for animals exposed to radiation at the high dose rates used in all early laboratory studies,[27] but because of the large dose required for membrane or DNA damage at high dose rates, the small dose from background radiation had been discounted as a significant factor in the normal aging process.

However, it is now apparent that the new evidence of Stokke, Scott, and Petkau on the indirect chemical effect of radiation completely alters this expectation. Since the dose required to double the normal changes of membrane-type damage appears to be of the order of 100–200 mrads at background rates, as compared with 100–200 rads at the dose rates of the medical X rays on which both our human data and animal studies were largely based, it now seems that the role of background radiation on human health, as distinct from its genetic effect, was underestimated by some 100–1000 times.

The new findings of strong dose-rate effects indicate that the assumption of a constant risk per rad independent of dose rate—and underlying all existing estimates of the likely health effects of small radiation exposures arrived at by the various national and international bodies who had set the existing permissible doses prior to the discoveries of Petkau, Scott, and Stokke—can no longer be regarded as valid. The assumption of strict linearity for the relation between dose and risk used in these estimates to extrapolate from high doses to low doses, accepted as the more conservative hypothesis when compared with the threshold hypothesis, now turns out not to have been conservative enough. The studies of Petkau, Stokke, and Scott, carried out at low dose rates for which no previous experimental information had been available, show that the dose response obeys a logarithmic or fractional power law that is much steeper at low doses than at high doses, as illustrated in Fig. 5 taken from a paper by Baum.[28]

Since the slope of the dose response curve is proportional to $(1/D_o)$, it means that the slope at very low doses, found by drawing a straight line from the high-dose data obtained at high dose rates, is some 100–1000 times smaller than the actual slope for small increments of radiation above background.[14] Instead of the hoped-for "safe threshold" or even the "conservative" linear relation between dose and response, the new data show that the biological effects on cell membranes are "superlinear" near the origin, rising very rapidly

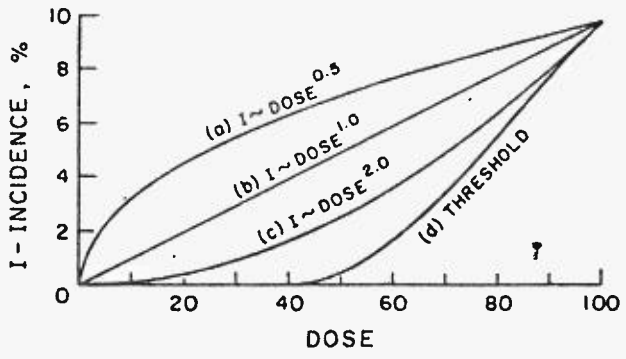

Figure 5. Various theoretically possible forms of the dose-response relationship for the effect of radiation on living organisms. (a) is the type of fractional exponent low predicted by an indirect chemical mechanism of the type found to hold for phospholipid cell membranes by Petkau.[7] (b) is the direct or linear dose response observed whenever the dose rate is constant and the range of total doses is not too large, previously believed to represent the most "conservative" possible assumption. (c) represents a quadratic type of law found to hold for cancer incidence at high total absorbed doses. (d) represents the "threshold" type of response observed for some effects such as immediate death at high whole-body doses. Note the large differences in risk predicted for low doses using the various assumptions.

at low levels, and then saturating for higher doses absorbed in a given period of time.

It remains to be seen whether the effects on cell membranes observed in the laboratory have resulted in detectable increases in the effects on human health.

3. *Low-Level Radiation and Human Health*

The discovery that protracted radiation is more damaging to cell membranes than to the genes of living cells completely changes our expectations as to the type and magnitude of health effects that we would expect to find for large human populations exposed to small amounts of radiation over long periods of time.

The dominance of somatic damage to cell membranes by free radicals over genetic damage to the reproductive cells by direct action means that birth defects among the newborn would be developmental rather than genetic in origin. Similarly, any increases in cancer would reflect damage to the body's defenses against the proliferation of cancer cells, rather than the triggering effects of damage to the genes. But most important would be the fact that conditions never previously associated with small radiation doses should be

detectable, namely, infectious diseases such as influenza and pneumonia, as well as chronic diseases associated with aging such as emphysema, heart disease, diabetes, kidney disease, and stroke.

As to the magnitude of the effects to be expected, instead of the changes of the order of a few percent per rad expected on the basis of all earlier genetic and high dose rate somatic effect studies,[22] the results of Petkau, Stokke, and Scott would lead one to expect effects of the order of 0.1–1.0%/mrad, or about 100–1000 times greater.

Added doses up to a few times the normal background of 50–120 mrads/year are known to have been experienced by many population groups. These fall into the following major categories:

1. Those exposed to abnormally high concentrations of naturally occurring radioisotopes
2. Those exposed to low levels of diagnostic X rays and radioisotopes
3. Those exposed to fallout from distant weapons tests
4. Those exposed to the releases from nuclear reactors and associated chemical fuel reprocessing facilities.

3.1. *Exposures to High Levels of Natural Radiation*

3.1.1. *Uranium Miners*

The earliest health effects of naturally occurring isotopes were observed among the men who worked in the European uranium mines of Joachimsthal and Schneeberg.[8,29] The miners were known to suffer from a mysterious lung disease that was eventually identified as lung cancer. The agents responsible were found to be the radioactivity decay products of radon, a chemically inert but radioactive gas which was itself a daughter product of uranium. Subsequent detailed studies of American miners showed that the doses received varied from as little as 0.5 rads/year for well-ventilated mines, to 100 rads/year in those with no ventilation. The presence of dust and the effects of smoking were found to increase the biological risk by 5–10 times, a finding subsequently confirmed in animal studies.[30]

Since the dominant type of radiation producing the exposure of the lung membranes are alpha particles,[29] one would expect an effect nearly independent of dose rate.

This is indeed found to be the case, the risk increasing directly with the calculated exposure up to rather large accumulated doses of 2000 rads and an estimated doubling dose D_0 of the order of 50–100 rads.

However, it was found that the risk per rad tends to be somewhat higher for individuals in the low exposure groups.[29] This observation is consistent with the fact that a portion of the exposure derives from the formation of free radicals, especially by the beta rays and gamma rays emitted by some of the radon daughter products whose role becomes relatively more important as the dose, and thus the dose rate, approaches normal background values.

3.1.2. *Radium Dial Painters*

Another group of individuals exposed to high doses of naturally occurring radioisotopes were the radium dial painters.[8] Here the exposure resulted primarily from radium ingested accidentally when the workers licked the brushes used to paint the luminous dials. Since the primary type of radiation exposure was again due to alpha particles, this time to the bone, where radium concentrates because of its chemical similarity to calcium, one would expect a relatively high D_0. This is in fact found to be the case, typical doubling dose estimates being on the order of 140 rads, characteristic of all such measurements involving high instantaneous ion densities in the more radiation-resistant organs.

Unfortunately, the relatively high dose required for the densely ionizing alpha particles emitted by radium to produce bone cancer misled the early investigators, who were attempting to set permissible levels of bone-seeking radioisotopes. As compared with the much lower doubling doses for the beta rays from Sr^{90} producing bone-marrow cell damage and discovered by Stokke many years later, the relatively low biological effect of radium in bone caused the permissible limit for beta ray emitting isotopes—arrived at during the time of the Manhattan Project, in 1941[8]—to be set at too high a value.

3.1.3. *Developmental Defects in Newborn Children*

A third population group exposed to abnormally high background radiation are children born in areas with high uranium and thorium content in the local rocks or soil. In this case, it is primarily the externally produced gamma rays that are the source of the exposure, rather than the very short range alpha particles that dissipate their energy typically in distances of less than 0.1 mm in solids, or in a few inches of air.

A study of the number of children born with some form of visible birth defect, in areas of New York State that differed widely in their concentrations of naturally radioactive isotopes in the local rock, did in fact show a significantly higher incidence in areas of high granitic rock and shale concentrations than in basaltic sandstone and limestone areas, corresponding generally to their uranium and thorium content.[31] The observed rates of congenital defect mortality in areas of rock possessing high activity were typically some 20–40% greater than in areas of rock with lowest activity. Although no detailed population–dose measurements were carried out in this study, subsequent surveys of variations in terrestrial gamma activity indicated that the ground gamma doses per year after shielding corrections vary typically between 30 mrads and 60 mrads in the northeastern United States.[32]

These variations must be compared with the total dose from all natural sources, including cosmic rays, which add about 50–60 mrads/year in this area, and another 18 mrads from internal emitters, mainly K^{40}. When shielding by building materials as well as by the body itself is taken into account, Oakley[32]

arrives at total bone marrow doses of about 87 mrads/year for the average United States population.

Thus, the percentage increase of the effect per millirad of about 30% for 30 mrads, or close to 1% per mrad, is of the same order as observed many years later by Stokke in studies of reduction in the number of bone marrow cells in animals.[15] Likewise, it fits the permeability changes in the red cells of occupationally exposed individuals observed by Scott.[16] However, because the effects of background were so much larger than expected, on the basis of genetic studies carried out with X rays and gamma rays at high dose rates as well as with individuals who accidentally ingested radium, these and similar findings by Wesley[33] were unfortunately discounted and regarded as spurious.[34]

In particular, the very strong correlation of the mortality rate due to congenital malformations with cosmic ray intensity all over the world—from about 1.8 per 1000 births near the equator to more than 5 beyond 50°N, as demonstrated by Wesley[32]—could not be reconciled with the known low sensitivity of the genes. But it clearly fits the sensitivity for indirect chemical action on the cells of the developing embryo, according to which almost the entire variation in the rate of malformation can be explained by the background levels, as concluded by Wesley.[32]

3.1.4. *Chromosome Abnormalities*

More recently, studies have been reported of the incidence of chromosome abnormalities in individuals who live in areas of high background radiation from thorium-bearing sands (e.g., monazite sands in Brazil),[35] and in individuals who work in factories where monazite sand is processed commercially.[36]

In this case, the exposure is due primarily to the airborne activity of Pb^{212} and the external gamma radiation from the ground, both of which give rise to relatively low ionization densities since the Pb^{212} emits beta but no alpha particles.[36]

Both the population living in the high monazite areas and the workers in the monazite plant had a higher incidence of chromosome abnormalities, as compared with control groups of the same population. However, the most significant finding was that the dose response for workers known to be exposed to different levels of radiation showed the same logarithmic type of response that was observed by Scott[16] and by Stokke[15] (Fig. 3), rising very rapidly at low exposures and leveling off for the more heavily exposed individuals.

Thus, in the case of defects involving deletions, the frequency increased from 0.90% to 2.00% as the average air concentration of Pb^{212} increased nearly tenfold, from 0.007 to 0.09 pCi/liter. But a further tenfold increase to 0.90 pCi/liter for the most heavily exposed group only increased the frequency of deletions to 2.57%, consistent with the logarithmic type of response observed by Petkau and Scott for indirect, chemically mediated effects on critical cell membranes.

In summary, both the dose-rate independent sensitivity to the densely ionizing radiation produced by alpha particles and the rapidly changing sensitivity per millirad at very low doses of beta and gamma rays are now seen to be consistent with the most carefully studied effects of natural sources of background radiation on man available at the present time.

3.2. *Low-Dose Medical Exposures*

Although most diagnostic X ray exposures, involving typical total doses of 10–1000 mrads take place in very brief periods, or at dose rates of 1–100 rads/min, which are millions of times greater than the exposure rates for environmental sources (Fig. 4), it is nevertheless of interest to briefly summarize our experience with health effects for this type of source, especially for those cases where the total doses accumulated in a few hours or days are very low.

3.2.1. *X Ray Exposure of Radiologists*

Perhaps of greatest relevance are the extensive epidemiological studies comparing radiologists with physicians in other specialities, carried out most recently by Seltser and Sartwell.[36] Because the precise doses and dose rates were not available, these investigators compared the leukemia rate, heart disease mortality, and life expectancy of radiologists with the rates for groups of specialists in orthopedic surgery, internal medicine, ophthalmology, and pathology, known to use X rays in decreasing order.

Furthermore, they were able to compare the incidence of mortality rate for those radiologists who were more heavily exposed in the period before 1945, when awareness of the hazard was less, with the rates for those who began their practice in later years.

The results indicated that the mortality rates were indeed ordered in the expected manner, with radiologists showing the highest rates in the early years prior to about 1950, when the excess mortality ranged from about 60% for heart disease to 600% for leukemia. Furthermore, again as expected, in the most recent period the excess risk for radiologists disappeared as both awareness of the risk and the use of dose-reducing advanced technology increased.

Rough estimates of the accumulated yearly doses and the rate at which the dose was received may be obtained as follows. The present maximum permissible dose for occupationally exposed individuals is 5 rads/year. The majority of radiologists today receive no more than one-fifth to one-tenth this dose, mainly in the course of fluoroscopic examinations, or some 5–10 times the normal background dose of 0.1 rad in any given year.

For this total dose, the instantaneous dose rate is roughly 10–100 times 0.5–1.0 rad/yr, or at a rate 50–1000 times the background rate of 2×10^{-7} rad/min, since fluoroscopic procedures typically occupy less than 20 hr/week and the X ray beam is turned on only about 10% of the total time needed for the entire procedure.

Examination of Fig. 4 indicates that for dose rates of 10^{-5}–10^{-4} rad/min the doubling dose D_o for membrane-type effects on bone marrow cells, as measured by Stokke,[15] is 3–10 rads. Thus, at the present total yearly doses of 0.5–1 rad, one would not expect to find more than a 5–10% increase in mortality rates, below the sensitivity of the epidemiological technique employed.

However, prior to the 1950s, when annual exposures were 10–100 times larger, or 5–100 rads, the situation was different. For these annual doses, the dose rate was also 10–100 times greater, increasing the doubling dose to 10–30 rads according to Fig. 4. Thus, doses of 5–100 rads accumulated per year would be expected to have resulted in mortality rate increases of the order of 50–500%, and this was in fact the range of health effects observed for the early radiologists.

Therefore, the most detailed study of a large population group exposed to X rays at dose rates below 10^{-3} rad/min appears to be consistent with the type of dependence on dose rate discovered since then for cell membrane damage by Petkau,[7] observed for bone marrow cells in animals by Stokke,[15] and reported for red cells in occupationally exposed individuals by Scott.[16]

The reason that these studies aroused no particular concern at the time they were published is also clear in retrospect. Since the doubling doses deduced for the more heavily exposed early radiologists were in the range of 10–30 rads (or higher, depending on the years of dose and assumed accumulation) they were not very different than what was measured in animal studies, or for the survivors of Hiroshima and Nagasaki at much higher doses. In fact, they reinforced the belief that the existing animal and human data were indeed an adequate basis for predicting the effects of small doses from environmental radiation, in the absence of the recognition that the 1000-fold higher dose rate of the X ray exposures was a crucial factor.

3.2.2. *Intrauterine Exposure of the Developing Infant*

The other large human population group for which the health effects of very low total doses have been studied extensively are children who were exposed during their early development in the course of abdominal X rays taken of their mothers during pregnancy.

The first of these studies was carried out by Dr. Alice Stewart of Oxford University in 1958.[38] This pioneering study represents the first quantitative evidence that total doses comparable to those received from background radiation in one year can produce serious health effects in man. Stewart discovered, in the course of interviews with mothers whose children had died of leukemia, that those mothers who had been exposed to a typical series of about three X ray films had nearly twice the likelihood that their children would develop leukemia before age ten than those who had reported no X rays during pregnancy.

These initial findings were seriously questioned because the typical dose per film to the infant was only about 0.3–0.5 rad, giving an average doubling

dose of only 1–2 rads, much lower than had ever been observed in animal studies, and far below what was then widely believed to be a safe threshold dose. However, these results have since been fully confirmed by the comprehensive studies of MacMahon,[39] who used the hospital records of some 800,000 children born in New York and New England, and by a still larger study by Stewart involving a follow-up of more than 10 million children born in England and Wales between 1943 and 1965, published in 1970.[40]

Not only did the latter studies confirm an average increase in risk of childhood cancer and leukemia of about 572 extra cases for a population of 1 million children exposed to 1 rad, corresponding to a dose of only 1.2 rads needed to double the spontaneous rate of about 700 cases per million children born, but it also disclosed a direct, linear relation between the risk and the number of films taken during the examination (see Fig. 6).

Such a linear dose–response curve is, of course, a very strong argument for a cause-and-effect relationship since there is no connection between the number of films taken and any possible prior condition of the mother that might influence the risk of the child developing some form of cancer. It is also an extremely strong piece of evidence that there is no safe threshold for cancer in man, at least down to total doses of a few hundred millirads, below the presently permissible population dose of 500 mrads in any given year.

However, the evidence for a linear dose response was misleading as far as the true hazard of environmental radiation is concerned. It did not give any indication of the fact that when indirect, membrane-type damage is involved, for which dose rate becomes a crucial factor, one gets a "superlinear" curve where different doses are administered over the same period of time, that is, at different instantaneous dose rates.[14]

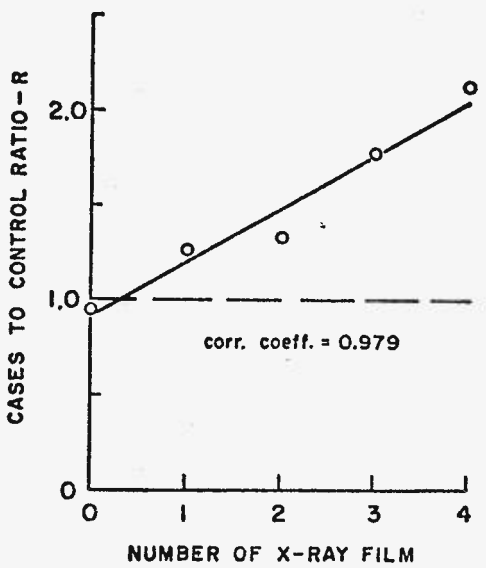

Figure 6. The relative risk of childhood cancer as a function of the number of X-ray films during pregnancy (after Stewart and Kneale[4]). These data are obtained at a constant dose rate, and show no evidence for a safe threshold.

Unlike environmental exposures, in the case of exposures from a series of X ray films each exposure is essentially of the same length, and the dose per exposure is very nearly constant. As a result, no matter how large the total number of films or the total dose received, each point on the curve of Fig. 6 is taken at the same instantaneous dose rate. Typically, the rates are 1–5 rads/sec, or 60–300 rads/min in an exposure lasting only $\frac{1}{10}$–$\frac{1}{5}$ sec, for which the total dose is typically 100–500 mrads per film.

This is very different than the situation in an environmental exposure, where, for instance, a given population group receives 100 mrads in one year and 200 mrads in another year, as a result, for example, of localized fallout. In this case, the lower dose is given at half the dose *rate* of the higher exposure, for which the studies of Petkau revealed a 40% greater sensitivity per millirad absorbed, thus leading to a steeper than linear dose response as the dose declines.

But there is still another reason why the plot of Fig. 6 seriously underestimates the true magnitude of the hazard of small environmental radiation doses as compared with the same dose from medical X rays. It turns out that the overwhelming majority of pelvic X ray exposures take place in the last 3 months of pregnancy, when the infant is far advanced in its development, including its ability to repair DNA damage and to recognize bacteria, viruses, and cancer cells. Thus, for the full-term infant at the time of birth, the risk of cancer is already quite low, within a factor of 10–20 of that for an adolescent or young adult.

However, for the case of radiation received from environmental sources, the dose is given throughout the period of development. This includes the time of greatest sensitivity in the first 3 months, when cells are dividing most rapidly, cell differentiation is proceeding, and organs are still being formed. During this period, the enzymes involved in DNA repair are still incompletely produced, and the ability to recognize and destroy cancer cells, viruses, and bacteria is still in its early stages. Thus one would expect to find a greatly increased sensitivity to any environmental agent at this time, and this has, of course, been most tragically demonstrated in the case of thalidomide.[41,42]

Such an enhanced sensitivity is exactly what Dr. Stewart found when she examined separately the small fraction of all cases where the mother was accidentally exposed to X rays in the first 3 months of pregnancy.[39,40] For these cases, the risk of subsequent development of cancer was 15 times greater, corresponding to a doubling dose of a mere 80 mrads, an amount of absorbed radiation equal to less than one-sixth of the presently allowed maximum permissible level for the general population by the Federal Radiation Council, and one-sixtieth of the annual dose presently permitted for those occupationally exposed.

In still another respect, the data on childhood leukemia and other cancers obtained by Stewart and MacMahon fail to reveal the full nature of the hazard of small amounts of protracted radiation. Childhood cancers are relatively rare, occurring only in about 1–2 children out of every 1000. Other causes of death

in childhood are some 10–20 times more frequent, and it was only in the last few years that a study was published showing that not only the risk of cancer, but also the risk of mortality from other diseases, such as infectious diseases associated with damage to the immune system, is increased by a comparable amount.

This detailed study, involving a carefully planned follow-up of thousands of children whose mothers were exposed to X rays during pregnancy for various medical reasons, was carried out by a group of physicians and statisticians at Johns Hopkins University over a period of 10 years.[43] As reported by Dr. Lilienfeld and his co-workers, the most clear-cut evidence was found in the white population group, although increased risk of death from infectious diseases was observed for both white and nonwhite children.

Thus, among the 5264 white children who had received intrauterine X ray exposures consisting typically of 3–5 films, the leukemia rate was 18.2 per 100,000, compared with a rate of 6.1 for the control group, or a 200% increase in risk. For infectious diseases, the rates were 14.2, versus 7.2 for the exposed and control groups, and for diseases of the respiratory system, 50.7 versus 16.4. For the typical dose of 1000–2000 mrads, these results represent a sensitivity of the order of 0.1%/mrad, or about 10 times less than for infants irradiated in the first trimester, as found by Stewart.

There was almost no increase in the rate of congenital anomalies (24.3, versus 21.5 expected), in accordance with the fact that most of the X rays were given late in the course of pregnancy, just before birth, when organ development had already been completed.

Once again, these results illustrate the point that data obtained in studies of effects due to medical X rays tend to underestimate the seriousness of the problem of environmental exposures, when radiation is delivered not only at a much lower rate but also continuously throughout the developmental process. One should therefore not be surprised that radiation doses received from radioactive chemicals in the environment will be more serious in their biological effects on the developing young infant than one would be led to believe either from data observed for brief, high-dose-rate exposures of human and animal populations, even when such factors as biological concentrations in the food chain and various organs have been taken into account.

3.3. *Health Effects of Low-Level Fallout*

Concern about the possible health effects of fallout from nuclear weapons was initially confined to the rather heavy local fallout of fission products and radioisotopes produced by the absorption of neutrons in the air, the soil, and the bomb casing which reaches the ground in a matter of only minutes to hours, particularly for weapons detonated near the ground.[12,44] For this situation, radiation doses can be many tens to thousands of rads, and therefore there was never any doubt as to the great biological hazard of massive nuclear fallout.

However, the situation was very different for the so-called "distant" or "global" fallout, produced by the gradual descent of small fallout particles that were carried to very high altitudes above 30,000–40,000 ft, where the radioactive dust would be carried around the globe in a matter of 10–14 days by the circulating jet stream. It was expected that the particles would spend many months or even years in decaying before they reached the ground, so that the radiation doses would be small compared with the natural background levels of some 80–100 mrads/year.

Since about 90% of the high-altitude fallout is brought down by rain or snow,[45] it was found that the ground deposition, and thus the amount of radioactivity in water, milk, and general diet, was closely proportional to the annual rainfall in areas of the same latitude (see Fig. 7).

As a result, the primary concern centered mainly around the contamination of milk by isotopes that were known to be taken up by cows and secreted with the milk, particularly the elements iodine, cesium, strontium, and barium, whose radioactive isotopes were particularly strongly represented among the fission fragments of uranium and plutonium nuclei.[12,45]

Iodine was early recognized to present a special hazard because it concentrates chemically in the thyroid gland and produces energetic beta rays, therefore resulting in a very high dose to this critical organ, typically some 100 times greater than the gamma-ray dose due to the iodine in the body or on the ground.

The isotope I^{131}, with a half-life of 8 days, is of particular concern, since a short half-life means that a given number of atoms produce many disintegra-

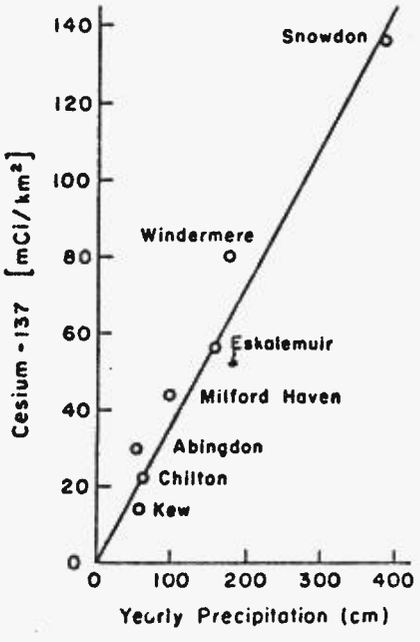

Figure 7. Typical relation between fallout deposition and yearly precipitation. (From P. Weish and E. Gruber, *Radioactivity and Environment*, Fischer, Stuttgart, 1975.)

tions per unit time, making it a much more intense source than other isotopes of longer half-life, such as I^{129}. Furthermore, the time during which one-half of the radioactive atoms created decay is long enough to allow passage of I^{131} through the milk pathway, from the production of the isotope to its deposition on the grass and its consumption in the milk, all taking place within a matter of 1–2 weeks.[12]

The isotopes of cesium are also of great biological concern since they are readily taken up by all animals, having the same chemistry as the essential trace elements Na and K. Because Cs^{137} has a very long physical half-life (30 years), it tends to accumulate in the environment, even though the typical time it spends in the human body, or the "biological half-life," is only about 100 days. Since it resembles Na and K, it goes to all cells of the body and gives a fairly uniform whole-body dose of about 1 mrad/year for every 100 pCi per kilogram of body weight.[46]

It has been found that if milk containing 3600 pCi/liter and weighing about 1 kg is consumed continuously, the internal concentration of Cs^{137} due to the milk alone leads to a maximum whole-body dose of about 500 mrads, or to an average dose of about 170 mrads in a large population, presently regarded as the maximum permissible dose for the general population in the United States. Since the external dose from cesium on the ground is about twice the internal dose, and since other, shorter-lived fission products give an external dose roughly comparable to the Cs^{137} alone, it turns out that, to a very rough approximation, the yearly dose to the whole body from all sources is about 0.2–0.3 mrad whenever the milk contains 1 pCi/liter of Cs^{137}.

Thus, since the levels of Cs^{137} in milk were in the range 10–150 pCi/liter during the height of nuclear testing in the Northern Hemisphere,[47] whole-body doses ranged up to 45 mrads/year in the early 1960s, comparable to the magnitude of the typical annual doses in the United States from cosmic rays (40–50 mrads/year) and natural radioactivity in the ground (35–45 mrads/year), as recently summarized by Oakley.[48]

Comparable doses are received by the bone marrow as a result of Sr^{90}, a daily consumption of 200 pCi/liter of milk leading to an average of about 170 mrads/year.[49] This works out to about 1 mrad/year when the milk concentration is 1 pCi/liter, leading to the rule of thumb that for almost any of the most important isotopes, 1 pCi/liter consumed during a whole year adds about 1–2 mrads to the natural radiation dose for organs that selectively concentrate certain isotopes such as Sr^{90} and I^{131}.

However, because Sr^{90} accumulates in bone and is only slowly released with time, with a typical biological half-life of 3–5 years depending upon age,[50] it builds up in the human body and thus represents a greater long-term hazard than Cs^{137} with regard to leukemia and cancers of those organs where Sr^{90} and its radioactive daughter Y^{90} concentrate.

These considerations make it clear that if the levels of natural radioactivity are indeed able to produce detectable differences in disease at the sensitivity of 0.1–1.0% per mrad typical of membrane damage at low dose rates, then one

would expect to find comparable effects of fallout from distant nuclear detonations. These would be most easily detected not for direct effects on the genes, but for somatic damage on cell membranes and therefore for such conditions as developmental disturbances in the early embryo leading to birth defects.

3.3.1. *Fallout and Congenital Anomalies*

The first evidence suggesting the possibility that relatively low levels of fallout from distant nuclear tests were capable of increasing the incidence of developmental defects in man was discovered by Dr. L. J. leVann, in the course of a survey requested by the Canadian Minister of Health for the Province of Alberta, in March, 1960.

As described by Dr. leVann,[51] the initial survey, for children born in Alberta in 1959, showed a relatively low rate of anatomically recognizable birth defects of only 7.76 children per 1000 births, corresponding to 257 children out of 37,996 born, 89% of which could be traced.

However, a second survey, carried out in 1962 for children born the previous year, and undertaken because of the rising concern over malformations attributable to certain drugs such as thalidomide that had just been introduced in Canada, showed a very much greater incidence. In this survey, out of 38,762 births recorded, 99% of which could be traced, there were 528 children with 631 separately identified birth defects. This was a rate of 13.8 per 1000 children born, representing an increase of 271 cases, or close to a 78% rise in only 2 years.

There were a number of reasons why it did not seem possible to attribute this sudden and statistically highly significant increase to the introduction of new drugs such as thalidomide. Out of the 528 children born with birth defects, only two were found to have been born with the characteristic limb deformities to mothers who had taken this drug. In fact, it is known that thalidomide acts primarily during organ development in the first 2 months of pregnancy, and since the drug was not introduced into Canada before 1961, only children born in the last 4 months of 1961 could have been affected.[40]

The second reason that led Dr. leVann to conclude that drugs were not likely to account for the sharp rise was the fact that the greatest increase took place in the most northerly part of the province closest to the Arctic Circle, where the precipitation was greater than in the southern part of Alberta during 1960–1961. Thus the long-lived, high-altitude fallout from the large series of 22 nuclear tests carried out by Russia at Novaya Semlya, north of the Arctic Circle, in 1958, would affect children born in northern Alberta much more than it would those in southern Alberta, some 850 miles to the south. In fact, the ratio of the rates for the northern and southern regions was 18.6 to 14.0, or 1.32, similar to the ratio of the rainfall, namely, 17.62 to 12.33 inches, or 1.42.

Furthermore, if there was any variation in the use of drugs between the southern, more densely populated urbanized area and the sparsely populated,

rural northern area, one would clearly expect the greater use of newly introduced drugs to be in the south and not in the north.

Nevertheless, because of the absence of any figures as to what fraction of the mothers in the different regions had taken some drug during pregnancy, it was possible to raise doubts as to the conclusiveness of the evidence that linked the rise in congenital defects to fallout rather than to drugs. Furthermore, the lack of any direct measurements of fallout levels for the different areas in Alberta represented a serious drawback.

These problems can be overcome, however, in the light of our more recent knowledge, on the basis of which it is now possible to arrive at the necessary information on the percentage of children exposed to drugs, as well as the approximate levels of radiation involved.

With regard to the fraction of the mothers who used drugs in each region, this can be obtained from an analysis of the detailed figures given by leVann for the number of congenital malformations in each region among children whose mothers had taken drugs and for those whose mothers had not, as summarized in Table 1.

The analysis is based on the assumption that for small increases in radiation levels close to background, the effect is very nearly linearly dependent on dose when the dose rate is nearly the same. Furthermore, it is now known, from numerous studies carried out since 1963, that the effect of a small increment of radiation on different segments of a population with different "spontaneous" rates is to increase each by very nearly the same factor.[21] Thus, a dose that increases the incidence of cancer in one segment of a population with a spontaneous rate of 100 per 100,000 by 50%, to a rate of 150 per 100,000, will in general produce the same 50% increase in another group that has a spontaneous incidence rate of 200 per 100,000, causing it to increase to 300 per 100,000.

As applied to the data gathered by leVann, this means that the children, both those exposed to drugs and those not exposed, can be assumed to have had their risk of developing a congenital malformation increased by essentially the same factor for a given fallout dose. Using the data on the number of malformations supplied by leVann for the two regions with the greatest difference in rainfall, namely, the southern and northern areas, as summarized

Table 1. Number of Congenital Malformations in Alberta for 1961 With and Without Drugs Taken by Mother During Pregnancy

	Northern area (18,072 births)	Southern area (14,240 births)
No drugs	192	78
With drugs	145	122
Total malformations	337	200

in Table 1, one can write the following two pairs of equations for the number of malformations for the drug-exposed children and those not exposed to drugs for each of the two different regions:

$$N_{ds} = [c \times n_s \times f_{ds}][a_d \times D_{rs}] \quad (1)$$

$$N_{os} = [c \times n_s \times (1 - f_{ds})][a_0 \times D_{rs}] \quad (2)$$

In these equations, N_{ds} is the number of malformations among children exposed to drugs in the southern area, and N_{os} is the corresponding number for those not exposed to drugs, n_s is the total number of children born in that region, c is the average number of different malformations per child (equal to 1.19 from le Vann's data), f_{ds} is the fraction of all children exposed to drugs during their development, a_d is the risk per unit of radiation for children also exposed to drugs, a_0 is the risk per unit radiation for those who were not exposed to drugs, and D_{rs} is the radiation dose in the southern region.

The second set of equations contains the same quantities for the northern region:

$$N_{dn} = [c \times n_n \times f_{dn}][a_d \times D_{rn}] \quad (3)$$

$$N_{on} = [c \times n_n \times (1 - f_{dn})][a_0 \times D_{rn}] \quad (4)$$

By taking the ratios of the equations (1) to (3) and (2) to (4), the actual values of the doses drop out, and it is possible to solve for those values of f_{ds} and f_{dn} which give the same ratio of (a_d/a_0) for both north and south.

The result is $f_{ds} = 0.42$ and $f_{dn} = 0.26$ for a common value of $(a_d/a_0) = 2.15$. This means that 42% of the mothers in the more urban southern area probably took drugs during their pregnancy, as compared with only 26% of the mothers in the more rural and remote northern region, a result that agrees with what one would expect from the difference in the availability of drugs in the two areas, as well as what has been reported for various populations in different western countries, including nearby Manitoba.[52]

Most interesting is the fact that the ratio of the risk per unit of environmental radiation for children of mothers who took drugs, a_d, to that for those who did not, a_0, is very nearly 2 to 1. This clearly indicates that the risk of malformation in the presence of either normal background radiation or fallout is essentially twice as large when drugs are taken during pregnancy as it is normally, thus fully justifying the present medical practice of avoiding all types of medication as much as possible, especially during the first 3 months of pregnancy.

The absolute values of a_d and a_0 can be obtained from knowledge of the normal background radiation levels in southern Alberta, D_{rs}, which is very close to the United States, for which detailed studies were carried out by Oakley.[31] According to Oakley, the cosmic ray levels for the high plateau just east of the Rocky Mountains are 50–60 mrads/year. For the radiation from terrestrial sources for this type of area, Oakley gives a best estimate of 45.6 mrads/year, so that the total external dose for southern Alberta may be estimated at 95–105 mrads/year to within ±15%.

Using $D_n = 100$ mrads/year so as to include a small contribution of 5–10 mrads due to fallout, equations (1) and (2) give $a_0 = 0.79\%$/mrad and $a_d = 1.70\%$/mrad. These values can now be checked for the northern region, making use of the fact that the ratio in rainfall as given by leVann for the two regions is 1.42. The dose from the combined effect of fallout and background radiation in northern Alberta for 1960–1961 may thus be estimated as close to 142 ± 20 mrads/year.

This estimate, based on natural background and rainfall, is further substantiated by direct measurements of Cs^{137} in milk for Canada and other areas of the northern hemisphere for 1960, given in the United Nations Reports on the Effects of Radiation,[53] and more detailed measurements of radioactivity in whole milk for northern and southern Alberta reported by the Canadian Ministry of Health and published by the U.S. Department of Health, Education and Welfare.[54]

For 1960, the year that most of the children studied in 1961 were conceived, the average concentration of Cs^{137} in the Canadian milk was 55 pCi/liter.[53] This corresponds to an average whole-body dose of about 10–20 mrads/year from all fallout sources consistent with a range of 5–40 mrads/year in going from the southern to the northern part of Alberta. This pattern is consistent with the lower average of 32 pCi/liter for the United States to the south and the sharply higher value of 150 pCi/liter for Norway, whose latitude is just north of that of Alberta.[53]

The existence of an increase in fallout levels with distance toward the Arctic Circle following large-scale tests at Novaya Semlya is further confirmed by the direct measurements of the activity in milk for the northern part of Alberta that includes Edmonton, and for the southern part that includes Calgary.[54] Thus, following the last atmospheric tests in the arctic, the milk analyzed by the Canadian Ministry of Health in the spring of 1963 for the months of May and June showed 117 and 211 pCi/liter of Cs^{137} for the northern zone, while for the southern zone the values were 92 and 199 pCi/liter, again confirming the fact that northern Alberta received more fallout following large atmospheric tests in the arctic than the southern part, a pattern continued southward into the United States.

With the dose estimate of 142 mrads/year, equations (3) and (4) lead to $a_0 = 0.85\%$/mrad, and $a_d = 1.82\%$/mrad, in good agreement with the values obtained for the southern region. Thus, the sensitivity of the fetus to environmental radiation is essentially the same as that of cell membranes as found by Stokke[15] and Scott,[16] corresponding to an increase in risk of about 1% for each mrad.

The data are summarized in the plot of Fig. 8. They indicate that for the population of the southern region not exposed to drugs, the number of congenital malformations was only about 8 per 1000 births, not very different than the rate of 9.2 separate malformations per 1000 births for the total population of Alberta in 1959, when the accumulated Sr^{90} and Cs^{137} was much lower and thalidomide had not yet been introduced. Those exposed to the

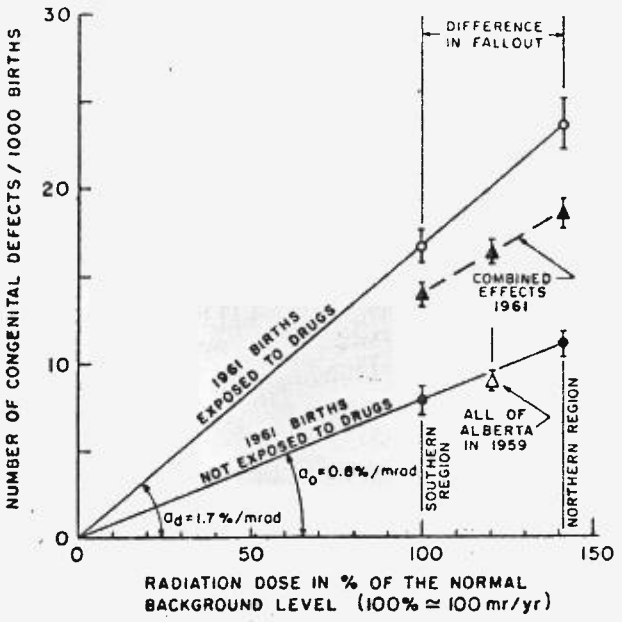

Figure 8. The effect of radiation and drug exposure during pregnancy on the incidence of congenital malformations for infants born in Alberta, Canada, in 1959 and 1961. The lower curve represents those not exposed to drugs, the upper curve represents those exposed to drugs in addition to fallout for children born in 1961. The dotted curve represents the data when those who were exposed to drugs were counted together with those not so exposed. In all cases, those who received the heavier fallout radiation in the northern region are seen to show a greater incidence of birth defects. Also, for all of Alberta, the total incidence rose between 1959 (△) and 1961 (▲).

heavier fallout in the northern part in 1960–1961, but not exposed to drugs, had their risk increased to 11.4 per 1000 births.

Contrary to the misleading impression gained by leVann that drug use had little influence based on a comparable frequency of reported drug use by mothers of normal and congenitally defective children, the plot clearly shows the now well-established effect of drugs during pregnancy.[41,42] For the 42% exposed to drugs in the southern region that had low fallout, the rate of malformations doubled from 8 to 17 per 1000 births. For the 26% of all infants in the north who had received exposures to both drugs and heavy fallout, the data indicate that the rate of malformations actually tripled, from 8 to 24 per 1000 infants born. Thus it was the mistaken implicit assumption that about half the mothers everywhere in Alberta had taken drugs which led leVann to interpret the data as showing no significant effect of medication during pregnancy. However, the detailed analysis indicates that only about one-third of all mothers appear to have taken some form of medication during the critical

period of early pregnancy, so that if drugs were not a factor, only one-third of those born malformed in all of Alberta should have been found to have been born to mothers who took some form of medication.

These findings indicate that Wesley was probably correct in his conclusion that the broad pattern of the geographic distribution of congenital defects with latitude, other than those due to local differences in drugs, diet, or fallout, is connected with the increasing natural background radiation levels toward the poles. However, radiation from such other natural sources as uranium and thorium daughter products released from rock or in the fly ash of coal would also be a factor in the heavily industrialized northern countries.

3.3.2. *The Relative Toxicity of Drugs and Environmental Radiation*

The conclusion that drugs typically involving doses of 1–100 mg/day can produce detectable effects seems easier to accept than the idea that very much smaller amounts of radioactive chemicals in the diet should be able to produce comparable biological damage. However, the reason for the much larger toxicity of radioactive elements can be understood in terms of the indirect chemical action of the radiation emitted by these substances, whose total energy per decay process is millions of times greater than the energy needed to produce an excited molecule.

In the case of Cs^{137}, each gram has an activity of about 90 Ci, or a rate of disintegration equal to that of 90 g of radium. Thus, the typical daily intake of about 100 pCi, or 100×10^{-12} Ci, for individuals in northern Alberta in 1960 from all dietary sources represents only 1.1×10^{-12} g. This is a mere one-millionth of one microgram, a billion times less than even a small 1 mg daily dose of a drug.

Due to the finite biological half-life of 100 days for Cs^{137}, however, there is a build-up in the body that accounts for a factor of about 100 in relative toxicity, leaving a factor of 10^7 to be explained. Now each disintegration of a typical fission product such as Cs^{137}, Sr^{90}, or Y^{90} leads to the release of one or more beta rays whose energies are generally between 0.2 and 2 MeV. This may be compared with the typical energy needed to excite a molecule, which is of the order of 0.1–1.0 eV.

It follows that a single radioactive atom can give rise to as many as 10 million excited molecules, spread throughout a volume dictated by the range of the ejected electron of many millimeters, typically some 10,000–100,000 cells, each 10^{-4}–10^{-3} cm in diameter. Thus, whereas a single nonradioactive atom or molecule might lead to the excitation of a single critical molecule in a single cell, a radioactive atom emits enough energy to lead to as many as 10 million excitation processes spread over some 100,000 neighboring cells. And when the instantaneous density of excitations is small, the chance that some of the activated molecules created will diffuse to a vital part of the cell structure before being deexcited is much greater than when the density is high. This accounts for the very great toxicity of trace quantities of radioactive chemicals in our environment, especially for rapidly dividing and differentiating cells.

That the effect of low-dose-rate background radiation leads primarily to somatic rather than to genetic damage is perhaps most clearly evident from an examination of the effect of fallout on the mortality rate due to infectious diseases. Such increases in mortality rates result from a lowered ability to recognize and destroy viruses and bacteria, an effect known to follow radiation damage to the bone marrow cells involved in the production of white cells, as studied by Stokke[15] for low doses of Sr^{90} in laboratory animals.

Figure 9 shows a plot of the mortality rate of newborn infants in the United States in the first year of life due to influenza and pneumonia, as given in the U.S. Vital Statistics[35] for the period 1938–1974. It is seen that there was a very rapid decline in the mortality until shortly after the end of World War II, the rate dropping from about 8 to only 3.4 between 1938 and 1946, presumably due to the improvement in medical care and the introduction of sulfa drugs and antibiotics.

However, beginning in about 1951, at the same time as the beginning of the first atmospheric tests of nuclear weapons in the continental United States which caused Sr^{90} levels to rise sharply, there was a complete and sudden halt in this downward trend. In fact, the trend began to compietely reverse itself in coincidence with the largest nuclear test series in Nevada, which took place in

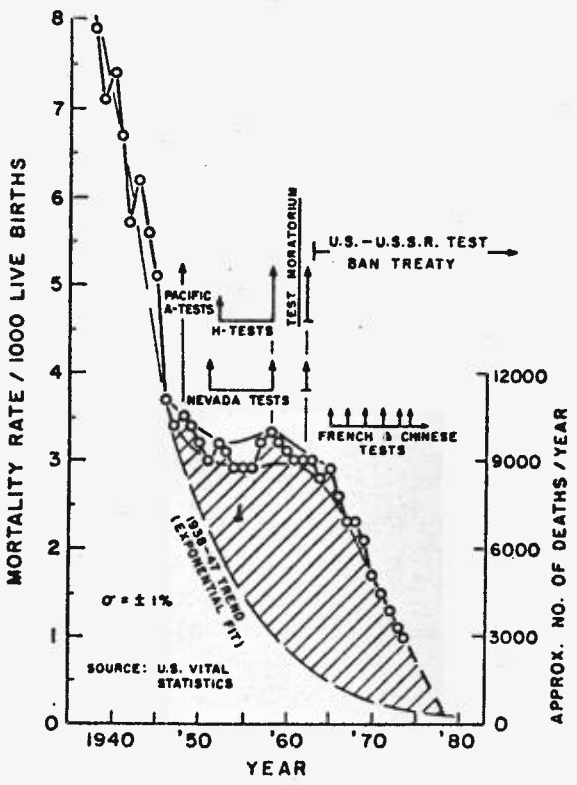

Figure 9. Effect of low levels of fallout radiation on the resistance to infectious diseases among the newborn. The data plotted is that for influenza and pneumonia mortality rates in the United States for infants 0–1 year old before, during, and after the period of heaviest nuclear weapons testing in the atmosphere (1951–63).

1957,[44] beginning a renewed decline during the period of the test moratorium which ended again with the resumption of testing by the U.S.S.R in 1961.

Only after the large amount of Sr^{90} in milk from the renewed tests had begun to decline, following the signing of the test ban treaty in 1963, did a renewed drop in mortality rate take place. The rate of decline was not as rapid as prior to the onset of nuclear weapon detonations, in accordance with the fact that some atmospheric tests by France and China continued to add Sr^{90} and other radioactive isotopes to the world's air and water even after 1963.

Nevertheless, the sudden renewal of a decline in mortality rates, in coincidence with the measured decline of fallout in milk,[56] means that the effect could not have been of a genetic type, affecting the reproductive cells of the parents rather than the cell membranes of the developing infant. The sharp decline from 3 deaths per 1000 births in 1965 to only about 1 per 1000 in early 1974 thus confirms the importance of the indirect, somatic action of radiation, with a risk increase per millirad consistent both with the results for bone marrow cells damaged by Sr^{90} as measured by Stokke,[15] and with the effect of fallout on developmental defects as observed by leVann.[51]

The data on influenza and pneumonia mortality rates for the newborn also point out that it is not only the obvious anatomical defects that one must be concerned about, but the more subtle, and often more numerous biochemical disturbances that lead to mental retardation and a host of metabolic diseases that are only discovered later in life. It is apparently these chemical effects on cell membranes and other vital cell structures that contribute to the lowering of the immune system's ability to detect and destroy viruses and bacteria, a subtle form of damage that may also be an important factor in the body's ability to control the proliferation of cancer cells.[57,58]

The possibility that the dose-rate-dependent indirect form of radiation damage may be the dominant factor in the body's ability to prevent the proliferation of cancer cells at the low doses encountered for environmental radiation is strongly supported by a number of recently published investigations.

Thus, the first study of cancer induction in animals by the protracted action of inhaled plutonium at total doses well below 50 rads, reported by Sanders and his co-workers in 1973,[59] indicated a form of dose–response relationship that rises much more rapidly at small than at large doses (Fig. 10). This is exactly the type of dose–response relation observed by Stokke[15] for small doses of Sr^{90} affecting the number of cells in the bone marrow involved in the immune process, where again the effect per rad increased as the dose was reduced (see Fig. 3).

Using a logarithmic plot (Fig. 11), it is seen that the cancer incidence of 4.3% for the control group that received only background radiation fits on a straight line with the data points at 9, 32, and 375 rads.

This result is consistent with the hypothesis that a significant fraction of the so-called spontaneous cancers are in fact induced by the normal background radiation during the 2-year life-span of these animals. Figure 11 shows that a

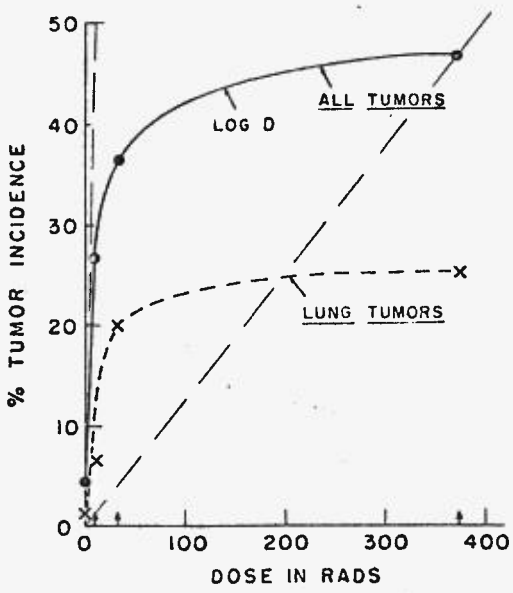

Figure 10. Form of the dose-response relation for cancer induction by small doses of inhaled plutonium-238 in rats (after Sanders[59]). Solid curve shows the trend of incidence for tumors of all organs other than the mammary gland; the dotted curve shows the data for lung cancer alone. Note the sharp rise at very low doses, similar to that expected for an indirect chemical mechanism, giving an incidence much above that expected by a linear extrapolation from high doses (dashed line).

dose of only about 180 mrads is needed at background levels to double the spontaneous incidence rate of cancer. This value is some 200 times smaller than the 34 rads which would have been obtained on the basis of an assumed "conservative" linear dose–response relationship from the point at 375 rads, typical of the values of 10–100 rads that have until now been widely accepted as the doubling dose for estimating the risk of cancer from environmental sources.

The results of Sanders and his co-workers have since been confirmed by an independent study in other animals by Little *et al.* at the Harvard School of Public Health using very small amounts of polonium instilled into the lungs.[60] Furthermore, the more rapid rise in the incidence of lung cancer for the smallest doses occurred both when the polonium was given attached to small insoluble particles such as are found in cigarette smoke and air-pollution, and without such particles. But the rate of lung cancer was greater when insoluble dust particles acted as carriers, in agreement with observations for uranium miners.[29]

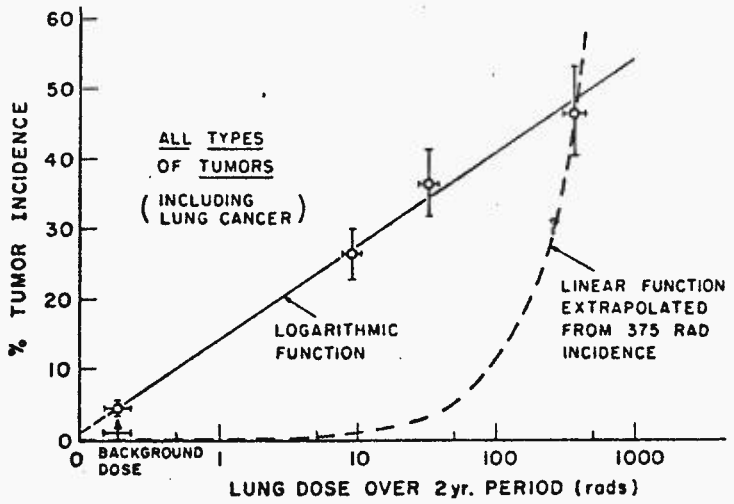

Figure 11. Data of Fig. 10 for tumors in the rat following low doses of plutonium-238 inhalation replotted on a semilogarithmic scale. Note fit to a straight line on this plot, passing through the point for the controls exposed only to background radiation. The dashed line represents the prediction of the linear relation of Fig. 10. From this plot, it is possible to determine that the dose required to double the incidence from its normal value of 4.3% is only 180 mrads when given over a 2-year period.

These results, together with the discovery that radioactive isotopes such as naturally occurring Pb^{210} and Po^{210} are trapped by the fine hairs of tobacco leaves[61] has now led to the suggestion that the very small amounts of radioactivity in cigarette smoke may be the single most important factor in the large increase in lung cancer throughout the world.[62]

Thus, environmental radioactivity, acting synergistically with dust and chemical air pollutants, may play a far greater role in all types of cancers and other diseases than has been realized in the past. It is consistent with the otherwise unexplained sudden rises in certain types of cancers a few years after nuclear weapons fallout began to appear in the atmosphere, as illustrated for the cases of pancreatic and lung cancers in Japan by Figs. 12 and 13.[63]

4. *Summary and Conclusion*

The discovery that the indirect chemical effect of radiation on cell membranes dominates over the direct physical action on the genes at very low dose rates has many far-reaching implications.

First of all, it explains the totally unexpected large effect of very small doses of natural and man-made background radiation as compared with

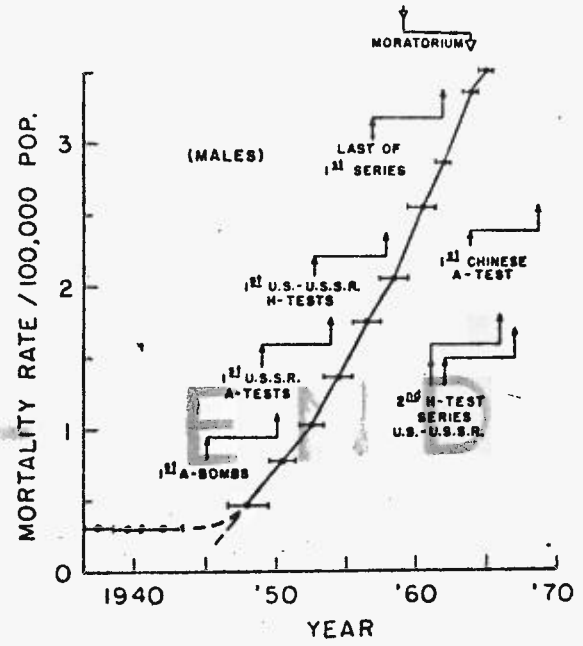

Figure 12. Mortality rate for pancreatic cancer in Japan before and after the onset of nuclear fallout. Note the sharp rise of 1200% in 20 years for male Japanese beginning in 1948, preceded by an essentially level trend during the preceding 10 years.

similarly small doses from medical X-ray sources in terms of the great difference in the instantaneous ion concentrations on the scale of single cells.

Thus, the discoveries of Petkau, Stokke, Scott, Sanders, and Little, provide an explanation for the origin of the radiation controversy,[64] brought about by the fact that the actual number of infant and fetal leukemia deaths as correlated with the levels of radioisotopes in milk during the period of nuclear testing was some 100–1000 times larger than expected, on the basis of the known genetic damage or the carcinogenic effect of high-dose rate medical and direct bomb radiation.

Only through the dose-rate dependence of the efficiency with which free radicals such as O_2^- can initiate oxidative chain reactions in phospholipid membranes can the unexpectedly high degree of toxicity of background radiation be explained. As the data of leVann[51] show, it now appears that for the most sensitive stages in the development of multicellular organisms such as man, each radioactive atom is some 10–100 million times more toxic than a molecule of the most potent teratogenic substances such as thalidomide.

The physical reason lies in the large number of excited molecular states of oxygen that can be created by a single disintegration process, turning a molecule essential for life and found in large concentrations in the cell fluid of all aerobic cells into a highly toxic substance, such that a single excited oxygen molecule can initiate the destruction of an entire cell. Thus, oxygen, on which all higher forms of life depend, turns out also to be the source of greatest vulnerability when combined with low densities of ionizing radiation compara-

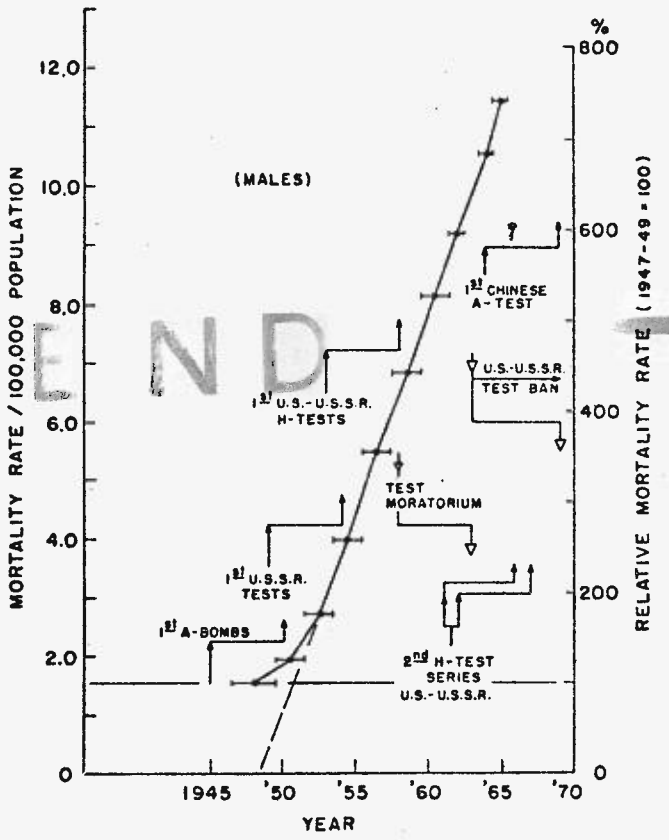

Figure 13. The mortality rate for lung cancer in Japan following the onset of nuclear weapons fallout. Note the sudden acceleration of the mortality rate some 5–10 years after the first nuclear detonations in 1945, the same delay observed for the uranium miners after they began to work in the mines.

ble to those of the natural background levels now existing in the earth's environment.

Thus, the extreme efficiency of the oxidative processes initiated by low levels of radiation not only explains the statistical findings of fetal deaths,[65] infant mortality,[65] prematurity,[65] leukemia,[63,65] and other cancers associated with low levels of fallout,[65] and releases from nuclear facilities that have typically been no greater than 10–100 mrads, well below the present permissible level of 500 mrads for the general population.[67,68] They also explain why total mortality rates from all causes for adults as well as the newborn[66] can be affected so much more strongly when the radiation is spread out over days or weeks than when it is received in short bursts, as in the case of diagnostic X rays.

From the point of view of evolution, the primary emphasis had to be given to the protection of the genes through the development of extremely efficient

chemical repair mechanisms. Only this way could the gene pool be protected against the effect of the ever-present natural radiation background, and the relatively high stability of species over periods of millions of years be ensured.

But the same consideration does not hold either for the individual cell of a multicellular organism, or for the member of a large species. Both the individual cell and the individual member of a whole species are not vital; in fact, their continual death and replacement through reproduction is an essential feature of the whole evolutionary process. Once the individual cell or member of a species has performed its evolutionary function of reproduction, it is no longer needed, so that extension of its life span beyond the age of reproduction is not necessary.

Thus, premature aging, which can be produced by the action of free radicals,[69] is not a serious threat to the survival of a species, even though it is a major problem for human society, where each individual hopes for a long and healthy life far beyond the age when the individual has performed his evolutionary task of reproduction.

The implications are therefore clear: if man wants to enjoy a long and healthful life, as free as possible from the debilitating effects of birth defects, cancer, heart disease, and other chronic conditions normally associated with aging, he cannot afford to increase to any significant degree the levels of unavoidable background radiation already existing in his environment, anymore than he can afford to add carcinogenic or teratogenic chemicals to his air, water, or diet.

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