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in the absence of significant greenhouse warming, a major challenge will be to anticipate future climate surprises of the type recorded in the paleoclimatic record of the last 10,000 years. This period included significant shifts in climate forcing, warmer Northern Hemisphere summer temperatures, and perhaps our best observational record of significant climatic change (*17*). If the climate system turns out to be highly sensitive to elevated atmospheric trace gas concentrations, then we may be confronted with modes of climate variability without precedent. This possibility further highlights the need to expand our testing of predictive models against the varied patterns of significant paleoenvironmental change, just as we now exercise our modeling ability against the relatively small variability of the 20th century. Major warm climate surprises of the type apparent in the Holocene interglacial paleoclimatic record may be our biggest worry in the years to come.

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Cancer Risk of Low-Level Exposure

Marvin Goldman

It is time to scientifically challenge the old tenet stating that cancer risk is always proportional to dose, no matter how small. This seemingly blasphemous statement is based on new approaches that allow testing of the hypothesis that cancer risk is linearly proportional to dose with no threshold, the basis of much regulatory and assessment documentation. We hear much these days about the need for all assessments and regulations for risk to be based on sound and solid science. This has not been the case for physical and chemical cancer risks to humans.

For both physical and chemical exposure to agents that are thought to increase cancer risk, it has been traditional to state that responsible evaluations and recommendations should assume that all exposures, no matter what the amount, carry an associated cancer risk. This assumption allows estimation, for example, of the lifetime cancer risk of a single ionization or the risk from intake of a single molecule of a putative carcinogen. It further leads to the concept of a collective dose, where all the ionizations are added up in all the people, and the product [for example, person–roentgen equivalent man (rem) or person-sievert (Sv)] is related to (multiplied by) a cancer risk factor to give a potential population body count (*1*). Such a calculation is the origin of predictions, for example, that so many persons will die from radon exposure, or so many cancers will result from treating apples with a chemical.

As an extreme extrapolation, consider that everyone on Earth adds a 1-inch lift to their shoes for just 1 year. The resultant very small increase in cosmic ray dose (it doubles for every 2000 m in altitude), multiplied by the very large population of the Earth, would yield a collective dose large enough to kill about 1500 people with cancer over the next 50 years. Of course no epidemiological confirmation of this increment could ever be made, and although the math is approximately correct, the underlying assumptions should be questioned. Most of the environmental risks we now face from present or proposed activities probably are of this magnitude, and many of our policies say that prudence requires us to reduce these small values even further. We do not seem to have a realistic process whereby we can uniformly both protect the public health and avoid seemingly frivolous prevention schemes.

A large part of the problem is that all cancer risk assessments are derived from studies of cohorts exposed to very high levels of insult (*1*, *2*). The conservative assumption is to connect the high-level risk values to the zero intercept and describe the slope of the resulting line as a "risk coefficient," fatal cancers per unit of dose. The radiation risk issue is the most thoroughly studied, but a similar situation also exists for the case of chemical exposures (*3*). However, it is now possible to evaluate the results of low levels of exposure and to apply newly developed analytical and biological tools and thereby test whether this type of extrapolation is warranted.

Historically, the stochastic or probabilistic radiation linearity issue began some seven decades ago when Nobel laureate H. J. Müller demonstrated that mutations in fruit flies increased linearly with exposure dose (*4*). (It was not actually linear; he said that "...the number of recessive lethals does not vary directly with x-ray energy absorbed, but more nearly with the square root of the latter...we should have to conclude that these mutations are not caused directly by a single quanta of x-ray energy absorbed at some critical spot.") The smallest doses, about 0.25 gray (1 gray = 100 rad), were quite high by today's standards. Linearity was later related to radiation cancer risk during the era of atmospheric weapons testing (*5*). This concept was expanded to apply to chemicals in the Delany Amendment of 1958, where any compound found carcinogenic in any test system at any level of exposure could not be added to foods sold to the public. We have since learned that some natural products and many normal foods (nitrosoamines and smoked or charred meat, peanut butter, and aflatoxin) contain compounds that are carcinogenic at high concentrations.

Radiation exposure is ubiquitous throughout the planet and is higher in some areas than in others (*1*). Interestingly, when cancer mortality in populations in higher natural background regions is compared with that of comparable populations living in low-background regions, there is no cancer incidence increase in the higher background areas (*6*). In fact, most of the studies show the opposite, giving support to a concept of hormesis, a beneficial effect of a

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low-level exposure to an agent that is harmful at high levels (*7*, *8*).

For radiation risks, the keystone data are derived from the elegant and careful study of the survivors of the atomic bombings of Hiroshima and Nagasaki 50 years ago (*1*–*6*). In addition, cohorts of medically or occupationally exposed persons and some accidental exposures add to the database (*1*–*6*). Some 500 cancer fatalities more than would normally be expected have now been reported in the Japanese A-bomb–exposed populations (*1*). Most of these were in persons who received an acute radiation dose of more than 1 Sv (100 rem); the lowest exposed dose cohort is set at 0.2 Sv (20 rem) (*1*). Much attention has been paid to determining the lowest level for study. The comparison control group consists of all those with zero to 0.1 Sv of exposure; thus, not all received "no dose." There is another "not in city" group that also served as a parallel control population; the two control groups seem identical. The 0.2-Sv group is actually a cohort from 0.2 to 0.49 Sv, with a median of about 0.3 Sv. A discussion of whether this might be considered a threshold for effects is beyond the purpose of this discussion, especially because the uncertainties about individual radiation sensitivity, of dose, and of the possible effect of neutrons have not yet been resolved. Although a fetus is much more sensitive to radiation than an adult, the exact nature of age dependency for radiation risks is not clear, nor whether dose-rate amelioration factors are age independent.

In contrast, most people receive a normal, natural lifetime dose of background radiation of about 0.2 Sv from cosmic rays, from the radiation naturally in the Earth (including natural radon), and from the small amount of radioactivity in all tissues (*1*–*6*). We now know that continual radiation exposure is less carcinogenic than acute exposure, all else being equal (*1*). Animal studies further show that as the dose rate is decreased, the risk per unit dose not only decreases, but the latent period becomes longer (*9*, *10*). If the latent period exceeds the life expectancy, we see in the intersect the equivalent of an effective threshold (*11*). It also appears that combined exposures to both radiation and chemicals at "low" levels exert an additive and not a multiplicative effect (*6*).

It is true that fetuses and children are about twice as radiosensitive as adults, but not much more than that (*1*). It is also true that a minute fraction of the population may carry a genetic defect that renders them more radiosensitive than the norm; for example, they may lack certain genes or cellular repair tools (*6*). But even this sensitivity is less than 10 times the norm.

The evidence now available suggests that cancer induction follows more than one step (that is, it does not follow first-order kinetics), and thus a single ionization and the resultant submolecular lesion is not the whole story of carcinogenesis (*12*). The intracellular repair mechanisms of mammalian cells—the intrinsic quality-assurance systems—are designed to execute amazingly sophisticated repair and removal of such lesions (*8*). The few defects that remain may constitute the first step in the carcinogenesis process (*12*). Each subsequent step, such as altered cell division rates and supressor gene efficiency (and we do not yet know them all), has its own influence and probability of success. Risk may be the integrated sum of the failure probabilities of all the steps. Thus, the universal cancer risk curve may later prove to be more of an S or sigmoid curve. Our limited data, shortsightedly, only one order of magnitude wide, are seemingly straight-line segments of that curve.

It is time to update our thinking and policies so that a clear distinction is made between what the science says and what the policy means. The difference between the exposure levels, where almost all the data about effects lie, and the levels to which most people might conceivably be exposed is so great that it is time to seriously consider the utility of implementing a concept of an effective or practical threshold for risk, that is, negligible risk. This would be a value below that demonstrated to show harm, but not zero. It is time for us to step back and take a careful view of the way we use science to estimate possible risks from low-level exposures, especially delivered at very low dose rates. We should review the molecular biology, the newer models, the available human data, and other pertinent scientific information and decide whether to develop new paradigms for risk that better relate low levels of exposures to scientifically based determinations of potential harm.

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Notch and Wingless Signals Collide

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During development, the identities of many cells are determined by signals produced by adjacent or distant tissues. Cells often receive several signals simultaneously and must integrate them in order to take on the correct fate. Although genetic experiments can provide strong evidence for interactions among signaling pathways, whether such interactions are direct or indirect can be difficult to determine by genetics alone. In this issue, Axelrod and coworkers use both genetic and molecular techniques used to examine the interaction between the Notch (N) and wingless (Wg) signaling pathways in *Drosophila* (*1*). They show genetically that the two pathways can be mutually inhibitory and suggest that at least some of this inhibition is due to a direct physical interaction between Dishevelled (Dsh), a cytoplasmic protein required for reception of the Wg signal, and the intracellular COOH-terminus of the N protein.

Both N- and Wg-like signaling provide critical patterning information in a variety of developmental contexts and in a number of species. Our understanding of the intracellular mechanisms responsible for transducing these signals is still incomplete. N (like Glp-1, Lin-12, Xotch, and other members of the N family) is a transmembrane protein bearing extracellular epidermal growth factor–like repeats and characteristic intracellular domains (*2*). Although N can function as a receptor (*3*), it contains no previously characterized signal-transduction motifs. Rather, when bound by its ligands Delta or Serrate, N likely activates the Suppressor of Hairless [Su(H)] protein, which then moves to the nucleus and acts as a transcription factor (*4*). A recent study of mammalian homologs of N and Su(H) (mNotch and RBP-J_κ) suggests that this activation occurs by truncation of the intracellular portion of N and its

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