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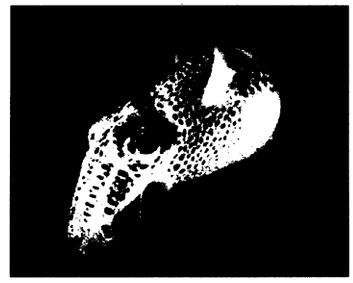
LETTERS

Glowing reviews



RUBY/MCFALL/NGAU/ORMEROD

Applause is given to scientists who have helped unlock the secrets of cultivating a new research "model" of animal-microbe symbiosis: a Hawaiian squid that harbors glow-in-the-dark bacteria (right). Questions about radiation and cancer dose-risk theories are raised: Is there a threshold below which exposure to radiation can be deemed safe? Is acute or continual exposure more dangerous? According to public health specialists, many lives could be saved by acknowledging the safety of plasma-derived hepatitis B vaccine in developing countries. And theories of immune system functioning and evolution are discussed.

Squid Pro Quo?

I was pleased to see the coverage in Random Samples (5 Apr., p. 37) of the new little squirt (*Euprymna scolopes*) now under culture at the Marine Biological Laboratory (MBL). It is exciting to have a new squid in the village and to look forward to the future research use of the organism.

It seems appropriate, however, to also credit the work of the scientists who are making this development possible. Roger Hanlon, the MBL's Director of Marine Resources, working with Paul Dunlap, Susan Ashcraft, Michael Claes, and others, have conducted the first significant egg-to-egg cultivation of *Euprymna* since they were raised by John Arnold in Hawaii (the squid's home waters) in the 1970s (*1*). Without the provision of a stable source of these fascinating cephalopods, *Euprymna*-based research could not progress to its next stage.

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1. J. Arnold, C. Singley, L. William-Arnold, *Veliger* **14**, 361 (1972).

■

Risks from Low Doses of Radiation

We disagree with some of the statements in Marvin Goldman's Perspective (29 Mar., p. 1821) challenging the traditional linear-nonthreshold paradigm for estimating cancer risks at low doses of ionizing radiation. It contains, in our opinion, a number of misleading interpretations of scientific data and ignores the considerable weight of evidence in support of linearity.

It is widely accepted that carcinogenesis is a multistage process in which a single cell gives rise to a tumor, with mutation of cellular DNA required in one or more of the steps leading to malignancy. Since cancer is a common disease, obviously the background rate for each of these steps is not zero, and any filtration mechanism for removing precancerous cells is imperfect. Therefore, any exposure that increases the rate of somatic mutations would be expected to increase the risk of cancer. Radiation is believed to be mutagenic down to the lowest doses, as ionization clusters generated by a single track can produce DNA damage that is not always faithfully repaired. Consequently, a threshold for radiation carcinogenesis seems unlikely.

Goldman states, "We now know that continual radiation exposure is less carcinogenic than acute exposure, all else being equal." Although this has been demonstrated in laboratory experiments, the limited evidence in humans suggests that the reduction risk is generally very modest (about a factor of 2 or less) (*1*, *2*). Goldman writes that comparative studies of cancer rates in areas of differing background levels are suggestive of a beneficial effect of radiation but does not point out that most epidemiologists consider such "ecologic" studies to be noninformative because of statistical limitations and potential confounding. He cites data on bone cancer induction by ingested radium as evidence that the latent period between irradiation and cancer expression increases with decreasing dose rate to suggest that there may be a "practical threshold" at low dose rates, below which the latency would exceed the lifespan. A refutation of this interpretation of the bone cancer data has been published by Mays (*3*), and there is no suggestion at all of a varia-

tion in latency with dose or dose rate for induction of other types of cancers.

Finally, Goldman's projection of 1500 fatal cancers from a 1-inch increment in altitude for the world's population is high by three orders of magnitude. The annual dose increases by about 50 micro Selvins for each 1000-foot increase in altitude; thus, an added inch would result in about a 4×10^{-9}–Selvin-per-year dose increase. Multiplying by the standard generation population lifetime risk coefficient of 5×10^{-2} fatal cancers per Selvin (*4*) and a global population of 5.8 billion, one projects only about 1.2 fatal cancers.

It is our view that the linear nonthreshold assumption remains a sound basis for radiation protection policy. Measures for further reducing very low doses of radiation must nevertheless be considered in light of their costs.

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1. *Sources and Effects of Ionizing Radiation* (U. N. Scientific Committee on Effects of Atomic Radiation, United Nations, New York, 1993).
2. *Risk of Radiation-Induced Cancer at Low Doses and Low Dose Rates for Radiation Protection Purposes* (National Radiological Protection Board, Didcot, Oxon, UK, 1995).
3. C. W. Mays, *Health Phys.* **55**, 637 (1988).
4. *1990 Recommendations of the International Commission on Radiological Protection: ICRP Publication 60* (Pergamon, Oxford, UK, 1991).

Goldman laudably pleads for risk assessment to be based on "sound and solid science." However, he does not discuss a large body of scientific evidence, including relevant discussions in his first reference, the BEIR V report by a select committee of the U.S. National Academy of Sciences (*1*), and more recent refereed surveys of the many inconsistencies and open questions in this highly politicized and controversial field of health science (*2*, *3*). He states that "we now know that continual radiation exposure is less carcinogenic than acute exposure, all else being equal," and references BEIR V (*1*), but does not cite other points of view on this subject (*2*). In support of his contention of reduced cancer risks at protracted exposures, Goldman cites two 25-year-old animal studies with questionable relevance to human cancer induction. He does not note, however, that the opposite conclusion was recently drawn by the U.S. Department of Energy (DOE), the funding agency for practically all radiation health studies, including those Goldman cites. The DOE states (*4*)

In general, the risks of adverse health effects are higher when exposure is spread over a long period than when the same dose is received at one time.

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1. National Research Council, *Health Effects of Exposure to Low Levels of Ionizing Radiation, BEIR V* (National Academy Press, Washington, DC, 1990).
2. R. H. Nussbaum and W. Köhnlein, *Environ. Health Perspect.* **102**, 656 (1994).
3. ———, *Med. Glob. Surviv.* **2**, 198 (1995).
4. *Closing the Circle on the Splitting of the Atom* (Office of Environmental Management, U.S. Department of Energy, 1995), p. 39.

Goldman states that the Radiation Effects Research Foundation (RERF) follow-up is a "high-dose study" and that most of the excess cancer deaths (hence most of the information in the study) pertain to survivors with very high doses, that is, doses greater than 1 Selvin (Sv). Goldman also states that RERF analyses consist of comparisons of survivors in dose categories of less than 0.1, 0.1 to 0.2, and more than 0.2

Sv, with the implication that this may obscure evidence for a threshold dose below which there is no excess cancer risk. These allegations are not correct.

Of the 86,572 subjects with individual dose estimates, 38,316 received doses in the range from 0.005 to 0.20 Sv, and a comparable sample of 36,549 received essentially zero doses of less than 0.005 Sv. Thus, about 85% of the cohort received doses in the range of direct interest for radiation protection, whereas only 2.6% of the cohort received doses of more than 1 Sv.

We stress that the RERF study is not just a high-dose study. There is a lack of focus on low-dose risks for solid cancers because the dose response is very linear, and important issues involving age at exposure and time since exposure should be addressed using all the data.

Modern analyses of these data, including those carried out by committees of the United Nations (*1*) and of the National Research Council (*2*), are not based on comparisons of broad dose categories.

The data for solid cancers, including tumor registry incidence data as well as cancer mortality data, are inconsistent with the notion of a threshold for radiation effects. However, epidemiological studies have inherent limitations in assessing such issues, and it is important to also consider basic radiobiology results.

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Safety of Hepatitis B Vaccine

The editorial by Gerald R. Fink describing the development of yeast recombinant technology at the National Science Foundation (1 Mar., p. 1213) was enlightening. However, readers may be left with the misconception that persons who receive plasma-derived hepatitis B vaccines risk "infection with other blood-borne viruses carried by the vaccine." There is no evidence that plasma-derived hepatitis B vaccines have ever posed an increased risk of infection with blood-borne pathogens. The decision to use any vaccine should be based on three criteria: safety, efficacy, and cost. All available data indicate that plasma-derived hepatitis B vaccine is as safe and efficacious as recombinant vaccines, while costing considerably less.

Currently, all plasma-derived hepatitis B vaccines undergo inactivation procedures (formalin treatment alone or in combination with heat treatment) that eliminate the risk of infection with blood-borne pathogens (*1*). Furthermore, epidemiologic studies and national surveillance of vaccine-related adverse events in the United States and other countries have demonstrated no association with infections transmitted by blood in children and adults who received plasma-derived hepatitis B vaccine (*2–4*). Studies of hepatitis B vaccine have shown that the antibodies produced after administration of plasma-derived vaccine or recombinant vaccine are alike in terms of their ability to elicit protective determinants and that the efficacies of plasma-derived and recombinant vaccines are comparable (*2*, *5*, *6*). Although the cost of recombinant vaccine continues to decline, it still is more expensive than plasma-derived vaccine. Factors that contribute to the higher cost include start-up expenses associated with recombinant technology and patents that protect the products.

Primary hepatocellular carcinoma and