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Resistance to Carcinogens at Early Developmental Stages and the Latent Period of Induced Neoplasms

Carcinogenesis is extremely complex. Therefore, it is paradoxical but nonetheless important in cancer research if, in an animal whose parental strains are normally sensitive to cancer induction, we could find mutant strains which are resistant to various carcinogens as a result of mutations in one or two genes. No such mutants have been reported so far as I am aware but we do know that at early stages in their development, fish, mice, and humans are highly resistant to cancer induction by chemicals and radiation. I will give a brief overview of the stage-dependent resistance of fish, mice and humans to cancer induction and discuss the stem-cell mutation theory to explain the cancer-resistant stages. Finally, the latent period of induced neoplasms will be discussed in relation to the stem-cell mutation theory.

1) Persistence of caffeine-sensitivity of 4NQO-treated cancer-susceptible cells in adult mice: In adult mice, 4NQO(4-nitroquinoline 1-oxide) initiated tumor induction in the lung can be greatly suppressed by caffeine injected as 20 days or more after treatment with 4NQO whereas in fetuses, 4NQO tumorigenesis is fixed within only 2 days(Nomura 1980).

2) Resistance to cancer induction of immature cells: Mice irradiated with X rays *in utero* are very resistant to the induction of myeloid leukemia(Upton et al 1960). Similarly, men *in utero* seem also to be resistant to leukemia induction by ionizing radiation(Kato 1978). Mouse fetuses before completion of lung organogenesis, i.e., Day 7 to 11, are resistant to tumor induction by urethan in the lung but they become sensitive to urethan tumorigensis around Day 13 and thereafter(Nomura 1974).

3) The working hypothesis—mutation of stem cells initiates carcinogenesis: Nomura's findings (1974, 1980) suggest that an organ under test becomes sensitive to cancer induction only after its organogenesis is completed. This and other lines of evidence support the idea that cancer-prone cells are stem cells existing in various types of cancer-prone organs. Thus, I assume the hypothesis previously proposed by Cairns(1975) to be true, namely, that mutation in stem cells initiates carcinogenesis. Some of the unusual characteristics of stem cells will be discussed.

4) Ionizing radiation does not shorten the latent period of solid tumors: Kato and Schull (1979) have reported that the latent period of lung cancers and some other solid tumors is not shortened by radiation since these tumors have appeared only at older ages with a similar age-dependent increment between irradiated and control groups. This important finding indicates that whether the precancerous mutations induced by ionizing radiation in the stem cells of solid-tumor-prone organs develop to neoplasms is controlled by complex systemic factors probably common to some of the aging factors. Man may be more resistant to cancer than mice simply because man lives more than 30 times longer on the average. If so, any factors accelerating aging could be hazardous carcinogens. In fact, solar UV accelerates skin aging and the latent period of skin cancer is shortened by an increase in solar UV intensity. The stem-cell-mutation theory can explain most of these diverse phenomena.