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Dose–Effect Relationships in Carcinogenesis and the Matter of Threshold of Carcinogenesis

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The relationships between the degree of exposure to a carcinogen and both the risk that neoplasms will occur and the time of their appearance serve as a basis to explain the nature of carcinogenesis (*1*, *2*). There is usually a constant probability of carcinogenic effect per unit of dose—a linear dose-response relationship—but that statement must be qualified. The number of animals affected by neoplasm is proportional to $1\text{-}e^{-kD}$ (where k is risk of neoplasm per unit of dose and D is dose), and it usually requires a semilogarithmic graph to represent this "linear" relationship. The relationship implies that a sharply defined chemical reaction must have occurred in the affected cells. It affords a reasonable biological hypothesis to explain cancer induction as a process that begins with molecular transformation of cells having a potential for neoplastic transformation.

It is also observed that the time required for the detection of induced neoplasms is dose-dependent, indicating that some process other than spontaneous growth of a tumorous clone from an autonomous altered cell or cells must occur. This time-dose relationship is a common characteristic of most carcinogens ranging from cyclic hydrocarbons to radiation exposure and the relationship suggests that the stage of carcinogenesis beyond the transformation of a fraction of cells is governed by a general law relating dose and time of appearance of neoplasms. If a dose D_0 is associated with a latent period t_0 for a given species of animal and a given carcinogen under specific conditions, then the latent period t, associated with another dose D, can be expressed as:

$$t = t_0 (D_0/D)^{1/n}$$

and n usually has a value close to 3. The two mathematical relationships above describe the concentration of initially altered cells as dependent upon the dose of carcinogen, but their development into neoplasms depends on their proximity, which varies as $D^{-1/3}$. Transformation of normal cells into autonomous neoplastic tissues is, then, visualized as a process that usually involves more than one kind of transformed cell.

The model constructed from these quantitative relationships implies that neoplasms resulting from a single exposure should be closely distributed in time, producing a pulse of cases and then being essentially without effect. This contradicts a hypothesis proposed by others that radiation, even at the lowest levels, multiplies the effect of all other causes of neoplasms throughout the life span. Cancer induction does indeed occur as a wave of enhanced risk (*2*).

The stages in the development of cancer appear to be as follows: (1) changes affecting cellular functions are induced by carcinogens and are presumably alterations of DNA (perhaps RNA) transmissible to daughter cells; (2) interactions occur between clones of altered cells, and these are responsible for the relationship between dose and time of neoplasm appearance; (3) organ changes produced by these cellular alterations may reach a level at which they

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cause failure of those tissue-organizing systems which normally prevent the development of neoplasms; (4) the extension of a neoplasm to threaten the function of the body as a whole appears to depend on failure of the cancer-suppressing mechanism of the entire body (3). The final stage of development of neoplastic disease is the uncontrolled growth typical of the acute malignancies. This stage appears to relate to the failure of the cancer-suppressing mechanism which is a fixed probability throughout the duration of a neoplastic illness.

The findings regarding the $D^{-1/3}$ principle and the nonsynergistic effect of radiation on other carcinogens support the use of a "practical threshold" for low level radiation and should tend to relieve concern over the presence of low levels of radiation or of chemical carcinogens in an environment containing many of them. The consequence of theoretically calculated numbers of deaths due to those carcinogens depends on when they occur. If they occur beyond the life span, the cost is nil because a practical threshold of effect has not been exceeded.

REFERENCES

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