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MOLECULAR MECHANISMS IN RADIATION CARCINOGENESIS: INTRODUCTION*

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A practical motivation behind molecular studies of radiation carcinogenesis is the desire to develop theories that permit us to extrapolate from cellular and animal models to man. The best example of this extrapolation--but one that is still incomplete--is that of skin cancer.

There are three reasons for the emphasis on skin cancer. 1) Skin cancer is the most common of all cancers among whites[1] and there is a large amount of epidemiological data for it.[2] A better understanding of the many factors involved in its incidence could lead to improved data collection schemes. 2) There is persuasive biophysical, biochemical and genetic evidence,[2,3] some of which is discussed in this session, that a causal relation exists between sunlight-induced photochemical damage to DNA and skin cancer in man. Since we know the wavelengths of ultraviolet radiation that affect DNA,[3] we are on firm theoretical ground when we estimate the effective biological irradiances in sunlight. 3) Some chemicals that result from man's activities (such as NO_x from supersonic transports and freons from spray cans) tend to decrease the amount of ozone in the stratosphere and hence increase the biologically effective irradiance at the earth's surface.[2]

The quantitative evaluation of the increase in the incidence rate of skin cancer for a decrease of ozone is a simplified model for most environmental carcinogens. Therefore, it is important to show explicitly the limitations in making such calculations and why better models, theories and data are needed.

There are many variables involved in the induction of skin cancer in man. Some of these are enumerated in Table 1.

Table 1. Some Variables in Sunlight-Induced Skin Cancer

I:	uv irradiance averaged over the year	
T:	time of day at which exposure begins	life style
t:	time duration per exposure	life style
n:	number of exposures per year	life style
A:	age	sampling factors
G:	genetic background	sampling factors
O:	occupation	sampling factors
E:	other environmental factors (wind, visible light, temperature....)	

The probability P of developing cancer at a particular time is a function of these variables (Eq. 1):

$$P = f(I,T,t,n,A,G,O,E,\ldots) \tag{1}$$

and the quantitative evaluation of the risk to man of a decrease in ozone is represented by Eq. 2.

$$\frac{\partial P}{\partial O_3} = \frac{\partial f}{\partial I}\,\frac{\partial I}{\partial O_3}. \tag{2}$$

Since we have good estimates of the change in irradiance with the change in ozone,[2] the evaluation of the environmental hazard depends upon a determination of $\partial f/\partial I$.

Approach I

There are two simple minded approaches to the evaluation of $\partial f/\partial I$. The first is to use epidemiological data relating skin cancer to latitude (skin cancer increases with decreasing latitude). In formal terms, the change of P with latitude may depend upon many factors as shown in Eq. 3.

$$\frac{\partial P}{\partial L} = \frac{\partial f}{\partial I} \cdot \frac{\partial I}{\partial L}$$

$$+ \frac{\partial f}{\partial T}\frac{\partial T}{\partial L} + \frac{\partial f}{\partial t}\frac{\partial t}{\partial L} + \frac{\partial f}{\partial n}\frac{\partial n}{\partial L} \qquad \text{life style factors}$$

$$+ \frac{\partial f}{\partial A}\frac{\partial A}{\partial L} + \frac{\partial f}{\partial G}\frac{\partial G}{\partial L} + \frac{\partial f}{\partial O}\frac{\partial O}{\partial L} \qquad \text{sampling factors} \qquad (3)$$

$$+ \frac{\partial f}{\partial E}\frac{\partial E}{\partial L} \cdot$$

We know that in addition to I some of the factors under the headings life style factors and sampling factors are important in skin cancer and do depend upon latitude. Unfortunately, we do not know how. Therefore, we make the assumption that all these factors add up to zero and hence

$$\frac{\partial P}{\partial L} + \frac{\partial f}{\partial I} \cdot \frac{\partial I}{\partial L} \qquad \text{or} \qquad \frac{\partial f}{\partial I} = \frac{\partial P}{\partial L}/\frac{\partial I}{\partial L} \cdot \qquad (4)$$

The results of this approach are given in a recent report.[2] They indicate, for example, that a 10% reduction in ozone would result in an approximate 30% increase in skin cancer among whites.

Approach II

A completely different way of looking at the problem assumes that the important factor in skin cancer is the total dose D accumulated up to the time that skin cancer is detected.

$$D = kIA, \tag{5}$$

where k depends on life style and includes variables T, t, and n in Table 1. The potentially important role of aging, for example, as a result of decay of the immune system, is ignored and hence

$$P = f(D, G, O, E...) . \tag{6}$$

This formulation may be used at a particular latitude if one assumes that life style factors are independent of time. It is apparent from Eq. 5 that a 10% increase in ultraviolet irradiance, I, is equivalent to a 10% increase in age, A.

There is some theoretical basis for Eqs. 5 and 6. Blum[4] has shown that the induction of skin cancer in mice by repetitive exposures to uv depends upon the dose per fraction and the square of the total number of fractions delivered before the cancer is detected. At low intensities, however, the reciprocity law is not obeyed (perhaps because there is appreciable repair of damage before the carcinogenic changes become fixed in the genome), and incidence depends upon $I^2t(nA)^2$, that is, on the square of Eq. 5. The use of approach II and age specific incidence rates[1] indicates that a 10% decrease in ozone would result in roughly 100% increase in the incidence of nonmelanoma skin cancer.

Conclusion

Although the two approaches outlined above give results that differ by a factor of 3, I consider the agreement is good in view of the completely different assumptions involved and the crude averages used in data analysis. In the field of radiation carcinogenesis, we have gone much further than just the simple statement as to whether an agent is good or bad. We can make quantitative predictions. It is clear that for quantitative evaluation of hazardous environmental agents we need more than just extensive epidemiological data. We need useful cellular and animal models as well as good molecular theories.

References

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