CARCINOGENIC EFFECTS OF RADIATION-INTRODUCTION

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The world has always been full of hostile physical and chemical agents. Living creatures have evolved and adopted life styles that permit them to survive this environment. However, as a result of man's activity the hostility is increasing rapidly—probably too rapidly for life to adapt to them. Some of the present hazards are shown in Fig. 1. It is important to evaluate quantitatively these potential dangers to life, so as to make reasonable regulatory decisions concerning them. The evaluation for man is a difficult one. One cannot legitimately do experiments on people and moreover people are not good experimental material. The solution to this difficulty is to have basic insight into the modes of action of physical and chemical agents on cells and organisms and to use our basic biological theories to extrapolate to man.

The recent results of photobiological research have altered our ways of looking at such extrapolation procedures and, for a number of reasons, light-induced skin cancer is the best example of

Figure 1. A schematic diagram illustrating some of the environmental hazards to which man is exposed.

how to approach the general problem of environmental carcinogenesis. The reasons are simple to enumerate.

1. The dosimetry of light radiation for both cells and for populations of people is far superior to that for chemicals. The superiority is illustrated schematically in Fig. 2. The average number of photons incident and absorbed by cells is relatively easy to measure. However, the concentrations of active carcinogens in the region of target organs are very difficult to ascertain because many carcinogens are not reactive by themselves but must be activated by cellular enzyme systems to the ultimate carcinogenic form. The tricks used for chemical dosimetry--the number of products in DNA and the stability of these products--are derived from those of photobiology.

2. The quantitative photochemistry of DNA is well worked out and one of the photoproducts--cyclobutane pyrimidine dimers--is associated with many of the lethal and mutagenic effects of UV radiation (1). Such photoproducts are subject to a number of repair systems whose pathways in microorganisms are partially known at the molecular level and which have their analogs in mammalian cells (2). An important repair pathway is enzymic photoreactivation because this pathway does only one thing to UV photoproducts. It monomerizes pyrimidine dimers. Hence, if there is a biological property that is affected by UV radiation and if the effect is reversed by subsequent exposure to visible light, one concludes safely that the initial change made by UV was the production of pyrimidine dimers in DNA. Photoreactivation is a trick if you like, for assessing the biological importance of one of a large number of photoproducts. Such a simple trick is not available for chemical damage.

3. The fish, Poecilia formosa, may be grown as clones. Cells from one animal may be treated in vitro and injected into isogenic recipients. If UV irradiated cells are injected, they

Figure 2. UV radiation and a chemical carcinogen (o) incident on cells. The chemical carcinogen goes through a series of changes to give the ultimate carcinogen (Δ).

give rise to thyroid carcinomas. However, no tumors appear if the irradiated cells are exposed to photoreactivating illumination before injection (3). These data are clear evidence that UV irradiation gives rise to transformed cells as the result of the production of pyrimidine dimers in DNA. The importance of such a finding is that many chemicals mimic the action of UV radiation insofar as the type of dark repair system that operates on them is similar to that that operates on dimers and the fact that cells defective in the excision repair of UV damage are also defective in repair of a large class of chemical damages (4,5).

4. Individuals with the genetic disease xeroderma pigmentosum (XP) have a very high risk of getting skin cancer--both nonmelanoma and melanoma (Table 1). Such individuals are defective in one or more pathways involved in the repair of pyrimidine dimers in their DNA. The defects in repair are discussed in this and in other symposia (Papers by Bootsma, Lehmann,

Table 1. Some characteristics of xeroderma pigmentosum (from data on thirteen light exposed individuals described in ref. 6).

% with skin tumors	100
average age of first tumor	10 ± 5 years
tumors per individual	40 ± 30
% with malignant melanoma	54

and Sutherland). The existence of such individuals is the best direct experimental evidence for the close association of DNA damage with carcinogenesis.

5. In bacteria UV radiation stimulates an error-prone repair pathway (7). The pathway--associated with post replication repair (8)-- involves replication of DNA containing lesions. A simple view is that the chance of an error (an initiating carcinogenic event) during replication is the product of the probability of a replication fork passing a lesion and the probability of making a mistake if it passes one. Cells from most XP individuals do not excise dimers from their DNA. In a simple model the dimers remain for appreciable periods of time and increase the probability of an error during subsequent replication. In XP variant individuals excision is normal but post-replication repair is slow (9). It is an inference that in such cells the probability of a carcinogenic event is high not because many dimers remain but because replication past a dimer is more error prone than in normal cells. In normal human cells there are no defects in excision or postreplication repair and the probability of a carcinogenic event taking place as a result of an initial pyrimidine dimer is very small but not zero.

In cells from XP variants one can also observe a stimulation of postreplication repair as a result of small doses of UV radiation (10). It is tempting to suppose that this stimulated pathway is an error-prone one.

The weight of experimental evidence reviewed above indicates that UV damage to DNA--probably pyrimidine dimers--is the best molecular candidate for the initiating damage that leads to skin cancer. As a result, we can take a superior guess that the carcinogenic action spectrum should be similar to the DNA action spectrum filtered through the upper layer of skin (11). The use of such an action spectrum (Fig. 3, next page) is necessary to evaluate the effects of the change in UV striking the earth as a result of changes in stratospheric ozone--a subject considered in much more detail in Symposium XIII.

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Figure 3. The action spectrum for affecting DNA compared to sunlight through two stratospheric thicknesses of ozone. As a result of absorption by the epidermis the presumptive carcinogenic spectrum decreases appreciably but has a similar shape to the DNA one above 300 nm. The different symbols represent different microbial, viral or molecular end points. See ref. 11 for details.