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The Rapid Induction of Cancers in the Hairless Mouse Utilizing the Principle of Photoaugmentation

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We report a method for rapidly inducing cancer in the hairless mouse utilizing regimen in which an exposure to highly erythemogenic, but otherwise clinically non-injurious, dose of broad spectrum (290–400 nm) ultraviolet light is increased by 20% every 6th day. Clinical and histological observations reveal the presence of squamous cell cancer after as little as 18 days of irradiation. The rate of cancer induction is enhanced by the 320–400 nm component and this enhancement is shown to be a photoaugmentative effect. The results support the idea that stratum corneum and/or malpighian layer thickening produced in early stages of tumor induction tends to protect against the detrimental effects of UV radiation. Strict monitoring of both the spectral distribution and output of the radiation source is imperative for reproducible rates of tumor induction.

Fluorescent sunlamps and hot quartz lamps have been the principal sources used in the past for tumor induction [1–4]. Fluorescent sunlamps emit primarily carcinogenic middle ultraviolet radiation (UVB). Hot quartz lamps emit UVA, UVB, and UVC radiation. Although the UVC contributes significantly to detrimental effects that result from exposure to these lamps, solar UVC does *not* reach the earth's surface. In the recent past, Urbach, Epstein, and Forbes [5] reported that the use UVA plus UVB from the solar simulating Xenon lamps may induce tumors more rapidly than UVB alone, although they later attributed this effect to differences in dose delivery [6].

In the above-cited references, tumor development required large time periods (up to 1 yr). An exception to this was revealed in the studies of Hsu et al [7] who were able to induce skin tumors in hairless mice as early as 7 weeks after a single exposure to 3–12 J/cm^2 of UVB/UVA (56%/28% respectively) using FS-20/40 T12 sunlamps. Most of these tumors were benign hyperplastic epithelial papillomas; 4 out of 96 were reported to be squamous cell carcinomas. The doses delivered resulted in severe crusting and ulceration prior to tumor development, leading one to suspect that nonspecific processes may play a role in tumor induction in this case. More recently, Strickland, Burns, and Albert [8] induced keratoacanthoma-like tumors in albino CD-1 rats single doses of 0.8–25.2 J/cm^2 using FS 20 lamps and 0.08 to 26 J/cm^2 of 254 nm radiation using a Westinghouse sterilamp. A linear dose-response curve was found for tumor production by 254 nm radiation, the dose-response relationship was similar but not as linear for broad-band UVA + UVB. Again, ulceration and scarring were accompanying acute effects of the higher doses broad-band irradiation, but did not occur with UVC at the same dose exposure.

We have endeavored to devise a method for rapidly inducing cancer in the hairless mouse which avoids concomitant severe injury which complicates interpreting the effects of UV light on tumor formation. Such a tumor model could be used to study the prophylaxis, mechanism and treatment of squamous cell cancer permitting rapid evaluation of these factors while animals are still in their youth.

In proceeding with this work, we were guided by 2 observations. *Firstly*, in chronic experiments with sub-blistering doses, the mice appeared to develop a tolerance to UV radiation resulting, perhaps, from stratum corneum thickening. *Secondly*, full spectrum (UVB + UVA) solar simulating UV radiation seemed to us to be more effective in inducing squamous cell cancer than did UVB radiation alone. Because of these observations, we felt it might be possible to rapidly produce squamous cell cancer by incrementally increasing the dosage of solar-stimulating UV radiation in such a way that little or no undesirable nonspecific injury occurs. We report here that such is the case and that the UVA component augments the effect of UVB.

MATERIALS AND METHODS

Energy Sources and Measurements

A Xenon solar-stimulating lamp [8] was used as the source. Its housing contains a 1600 w ozone-free Xenon bulb whose emission impinges upon 2 apertures through which light can emerge. In one case, (aperture 1) the light passes through a dichroic filter and a 2 mm Corning No. 9863 filter to obtain solar simulating UVA + UVB radiation from 290–400 nm. Light passing through the other aperture (aperture 2) impinges on a Bausch and Lomb grating monochromator (half value band width of 20 nm) set at 300 nm, which serves as a sophisticated "interference filter" of high light gathering power and photochemical stability, to produce UVB radiation. To avoid stray radiation below 295 nm, a l-mm Schott WG-320 cutoff filter was placed in front of the exit slit of the monochromator.

To obtain only UVA radiation, a 2.0 mm Schott WG-345 cutoff filter was employed in the aperture system in addition to the previous filters (1% transmission at 324 nm).

Energy output from this lamp system was measured by a calibrated thermopile in conjunction with a Keithley milli/microvolt meter (Model 149). The spectral distribution of light was measured utilizing an International Light Research Spectroradiometric System (Model IL 700). The total radiation output of the solar-simulator (UVA + UVB) was 230 ± 23 mw/cm^2. Of this, 16% was UVB and 84% was UVA radiation. The output of the monochromator-derived UVB radiation was 1.15 ± 0.01 mw/cm^2. The "effective" fluence rates of the solar simulator- and UVB sources (see below) were 2.89 and 1.02 mw/cm^2 respectively.

In order to effect a meaningful comparison between the experiments with the broad-band UVA + UVB and those with the UVB alone, it was necessary to calculate an "effective UVB dose," ED, ie., that fraction of the total dose which is effective in evoking a UV response for each system. This procedure allows an estimate of the degree to which the UVA component augments the UVB response by enabling comparison between the magnitude of the biological effects produced by the UVB and the solar-simulating UVA + UVB radiation at a given

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Abbreviations:
ED: effective dose—that fraction of total irradiation dose which is effective in producing a (pre) cancerous response (see text).
MED: minimal erythemal dose
UVA: long wavelength ultraviolet radiation (320–400 nm)
UVB: middle ultraviolet radiation (290–320 nm)
UVC: short wavelength ultraviolet radiation (< 290 nm)

ED. The ED was calculated as follows: The energies and spectral distribution of both sources were measured. These spectra were convoluted with our observed action spectrum for erythema/precancerous change in these mice (Willis et al., in preparation), in which the maximum response (which we set = 1.0) is at 307 nm. The convolution step results in an energy curve which reflects the relative probability that light of a certain wavelength will induce an erythema response. The area under these latter curves are then divided by the area under the respective total spectral output curves to yield a quantity, ϕ_{eff}, related to the fraction of emitted energy effective in producing an UVB-induced response. The ED is then obtained by multiplying the total dose by ϕ_{eff}. For the solar simulating (290–400 nm), ϕ_{eff} was 0.0126; for the monochromator, ϕ_{eff} was 0.886, and for the UVA source, it was close to zero. The "effective fluence rates" of each source referred to at the end of the previous paragraph, are obtained by multiplying the total fluence rate by the appropriate ϕ_{eff}.

Animals

Albino hairless mice which had been inbred in our laboratories (over 30 generations) from the outbred SK-I hairless or SK-II hairless strain obtained from Drs. F. Urbach and R. Davies (Philadelphia) and from Dr. J. Epstein (San Francisco) were used. (The latter strain contained some pigmentation on the ears). Each experiment involved 20 mice which were initially 6 weeks old. Previous experiments have established that their biological responses to light are essentially the same within ± 5% to obtain the minimal erythemal reaction, and that spontaneous tumor development is extremely low (< 2% after 1 yr of age). The animals were kept in a room with dim incandescent lighting, of constant temperature and humidity. They received standard laboratory food and drinking water.

Methods of Exposure

For radiation exposure, animals were affixed to a plastic mouse board and held in place with adhesive tape. The test site was approximately 1½ cm^2 in diameter and located in the mid-back. Exposures were delivered to the same site on 5 consecutive days each week. After 2 days of irradiation, a mild erythema extending to the margins of irradiation site could be seen, which provided a convenient method for assuring that same site was being repeatedly irradiated. Clinical observations were made on a daily basis. The animals were checked for general physical conditions and responses graded as follows:

E-1, mild-to-moderate macular erythema
E-2, intense macular erythema
1+, light scaling accompanying erythema
2+, firm scaling, palpable keratosis
3+, a raised palpable keratotic plaque (corresponding to early malignant development, as defined by Epstein, Fukuyama, and Dobson. [10].
4+, a papilloma or tumor corresponding to extensive malignant development (see below).

Four different observers made independent assays of the response in these animals. The 1+ through 4+ responses represent a continuum of (pre)cancerous changes. The E_1 and E_2 responses, in contrast, are not considered to be (pre)cancerous.

Irradiation times were determined from prior evaluation of minimal erythemal dose (MED). The doses were high enough to induce erythema without blistering. During the course of tumorogenesis, the doses were incrementally increased as described below.

Histology

Biopsy specimens were taken at varying times during the experiments and specimens were formalin fixed and prepared for routine hematoxylin and eosin staining. In addition, section were obtained for PAS observations.

RESULTS

a. Effect of Repeated UVB Radiation

1. Constant Dose: The daily total dosage of UVB (0.54 J/cm^2) was sufficient to induce initial erythema without blistering. The total dose at the end of 30 days was 1.62 J/cm^2 and the total ED was 1.44 J/cm^2. The clinical changes are noted on Table I. The first signs of change in texture of the skin occurred after 4 days. After 30 irradiation days, responses were as follows: 1+ in 75% of animals, 2+ in 20%, and 3+ in 5%. Early histopathologic changes were similar to those in actinic keratosis in human skin. At the 3+ stage, such changes were compatible with early squamous cell carcinoma or carcinoma *in situ*.

2. Incrementally increased dose: Starting with 0.061 J/cm^2, the daily dose was increased by 20% increments (based on the original dose) every 6th day so that 2.75 J/cm^2 (ED = 2.44 J/cm^2) were delivered in 30 irradiation days. (Table II). Under our conditions of irradiation this regimen maximized tumor formulation and minimized burning. Comparison between Tables I and II shows the expected increase in severity of response when the results are examined on a day-to-day basis. Interestingly, however, the responses are also more severe for equivalent effective doses. For example, at an effective dose of 1.24 J/cm^2 delivered in constant increments over 26 irradiation days (Table I) only 20% of the mice had 2+ and 5% had 3+ reactions, whereas when an effective dose of 1.23 J/cm^2 was delivered in increasing increments over 22 irradiation days (Table II), 50% had 2+ reactions and 20% had 3+ reactions. Histopathologic changes were qualitatively similar to those obtained under constant dosages.

b. Effects of UVA Radiation (320–400 nm)

Daily constant exposure of 62 J/cm^2 were given over the 30 irradiation day period, the total dose being 1860 J/cm^2. Twenty percent of animals showed 1+ reactivity by day 4, increasing to 65% by day 10. However, as the experiment proceeded, reactions became less apparent and by day 30, only minimal erythema (E_1) was present in all animals Table III). A persistent change in the texture of skin was not noted during the 30 irradiation day test period.

When the UVA daily dose was increased by 20% increments of the original dose (every 6th day), severe burning resulted. When this occurred, the experiment was terminated.

c. Effect of UVA + UVB Radiation (290–400 nm)

1. *Constant dose:* Table IV shows the results of irradiating 20 mice at a constant daily dose of 9.0 J/cm^2 (effective dose =

TABLE I. *Effects of constant daily dose of UVB (290–310 nm) radiation of hairless mice*[a]

Day Irr.	Total dose (J/cm^2)	ED (J/cm^2)	NR	E_1	E_2	1+	2+	3+
1	0.054	0.048	20					
2	0.108	0.096	3	17				
4	0.216	0.191			13	7		
6	0.324	0.287				18	2	
10	0.540	0.478				18	2	
14	0.756	0.670				14	6	
18	0.972	0.861				16	4	
22	1.188	1.05				16	4	
26	1.404	1.24				15	4	1
30	1.620	1.44				15	4	1

[a] ED = Total dose × ϕ_{eff} (ϕ_{eff} = 0.886). For explanation of responses, see text.

TABLE II. *Effects of escalating doses of UVB radiation (monochromator) of hairless mice*[a]

Day Irr.	Total dose (J/cm^2)	ED (J/cm^2)	NR	E_1	E_2	1+	2+	3+	4+
1	0.061	0.054	20						
2	0.122	0.108	3	17					
4	0.244	0.216				18	2		
6	0.378	0.335				18	2		
10	0.671	0.595				10	10		
14	1.01	0.895				9	11		
18	1.28	1.13				3	14	3	
22	1.59	1.23				4	12	4	
26	2.26	2.00				5	10	5	
30	2.75	2.44				4	9	7	

[a] ED = Total dose × ϕ_{eff} (ϕ_{eff} = 0.886). For explanation of responses, see text.

TABLE III. *Effect of constant daily doses of UVA (320–400 nm) radiation of hairless mice*[a]

Day Irr.	Total dose (J/cm²)	NR	E_1	1+	2+	3+	4+
1	62	20					
2	124	5	15				
4	248		6	10	4		
6	372		5	11	4		
10	620		7	0	13		
14	868		15	0	5		
18	1116		15	0	5		
22	1364		18	0	2		
26	1612		20	0	0		
30	1860		20	0	0		

[a] Initial dose = 62 J/cm². For explanation of responses, see text.

TABLE IV. *Effect of constant daily doses of UVA + UVB (290–400 nm) radiation of hairless mice*[a]

Day Irr.	Total dose (J/cm²)	ED (J/cm²)	NR	E_1	E_2	1+	2+	3+	4+
1	9.0	0.113	20						
2	18.0	0.226		20					
4	36.0	0.452			16	4			
6	54.0	0.679				14	6		
10	90.0	1.13				5	9	6	
14	126.0	1.59				2	4	14	
18	162.0	2.04				2	4	14	
22	198.0	2.49				2	4	14	
26	234.0	2.94				2	2	16	
30	270.0	3.40				2	2	16	

[a] ED = Total dose × ϕ_{eff} (ϕ_{eff} = 0.0126). Initial total dose was 9.0 J/cm². For explanation of responses, see text.

0.113 J/cm²). It is evident by comparison of Table IV with Tables I and III that UVA + UVB radiation induced a greater severity of response than either UVA or UVB alone. At the end of 30 days, 80% of the animals had developed early squamous cancer (3+) reactions as compared to 5% for the UVB alone.

The effect of UVA in augmenting precancerous and cancerous UVB induced changes under constant conditions of irradiation is further emphasized by comparing responses at equivalent effective doses. For example, at an effective dose of 1.44 J/cm² (30 days), 75% of the animals (irradiated with UVB alone) had 1+ response, whereas for 1.59 J/cm² UVA + UVB (day 14), 70% of the animals had already progressed to the 3+ stage.

Under these conditions, histopathologic results paralleled those occurring under UVB irradiation alone, except that the changes appeared somewhat more pronounced. The histopathological changes of the 3+ response are illustrated in Fig 1. There is a marked pseudoepitheliomatous hyperplasia of epidermal cells, and it can also be seen that some of the epidermal cells possess large atypical nuclei.

2. *Incrementally increased dose:* Doses were increased at 20% increments every 6th day, as described above. This was sufficient to maintain a brisk erythema without going to the point of ulceration. The total dose was 324 J/cm² (ED = 4.08 J/cm²). Observations (Table V) revealed changes in the texture of the skin by day 10, at which time more than 50% of animals showed scaling and slight thickening of the skin. As was true for UVB alone, the severity of response was greater, dose for dose, when the solar simulating radiation was incrementally increased than when it was held constant (Tables IV and V). Also, in analogy to the case for constant dosage, the response in the presence of the UVA component was clearly greater than it was for UVB alone (Tables II and V). In this case, 9 animals (45%) had 3+ reactions and 3 animals had developed 4+ responses after 18 days (effective dose 2.2 J/cm²) and the number of tumors continued to increase up to day 30. At equivalent

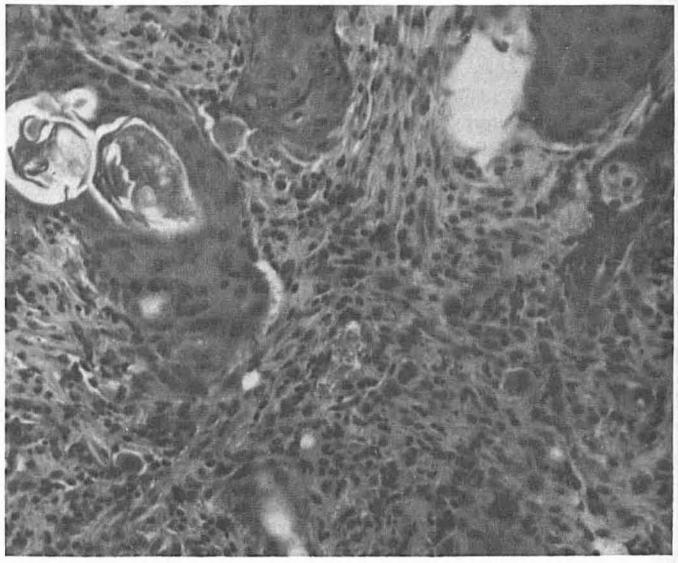

FIG 1. Histological section showing pseudoepitheliomatous hyperplasia of epidermal cells. Note the presence of large atypical nuclei. Normal epidermis in the hairless mouse is 1–2 cell layers thick.

TABLE V. *Effects of escalating doses of UVA + UVB (Solar simulator) radiation of hairless mice*[a]

Day Irr.	Total dose (J/cm²)	ED (J/cm²)	NR	E_1	E_2	1+	2+	3+	4+
1	8.6	0.108	20						
2	17.2	0.217	11	9					
4	34.4	0.433			10	10			
6	52.4	0.660			3	17			
10	90.0	1.13			6	14			
14	131.2	1.68				5	9	6	
18	175.1	2.21				2	6	9	3
22	221.7	2.79					3	8	9
26	271.0	3.42					3	9	8
30	323.9	4.08					2	10	8

[a] ED = Total dose × ϕ_{eff} (ϕ_{eff} = 0.0126.

doses of UVB, in the absence of UVA no animals had developed 4+ reactions and 7 animals (35%) had 3+ reactions.

Histopathologic changes in the 4+ animals showed atypical mitotic figures, hyperplasia and hyperchromasia of cellular nuclei, disintegration of intercellular bridges, and increasing variability in all sizes. Roughly 25% of the specimens obtained after 4 to 6 weeks of irradiation revealed so-called "spindle-celled" squamous cell carcinomas. This type of tumor closely resembled a fibrosarcoma with spindle-shaped cells extending from the epidermis to deep into the dermis (Fig 2*a* and 2*b*). This unexpected histopathologic finding is of extreme interest, since it is the type reported to occur in areas of radiodermatitis in humans and is regarded as a relatively rare Grade-4 malignant metastatizing form of squamous cell cancer

DISCUSSION

Irradiation of hairless mice with UVB or with broad band solar-simulating UVA + UVB radiation produced cancerous changes within 30 irradiation days. In both cases, the responses were much more severe, ED for ED, when doses were incrementally increased than they were when doses were kept constant. Moreover, the UVA + UVB combination appeared more effective than UVB alone in producing cancerous changes.

Comparison of Tables I and II, and IV and V for equivalent ED indicates lack of reciprocity in tumor production. Lack of time-dose reciprocity has been previously noted for photocar-

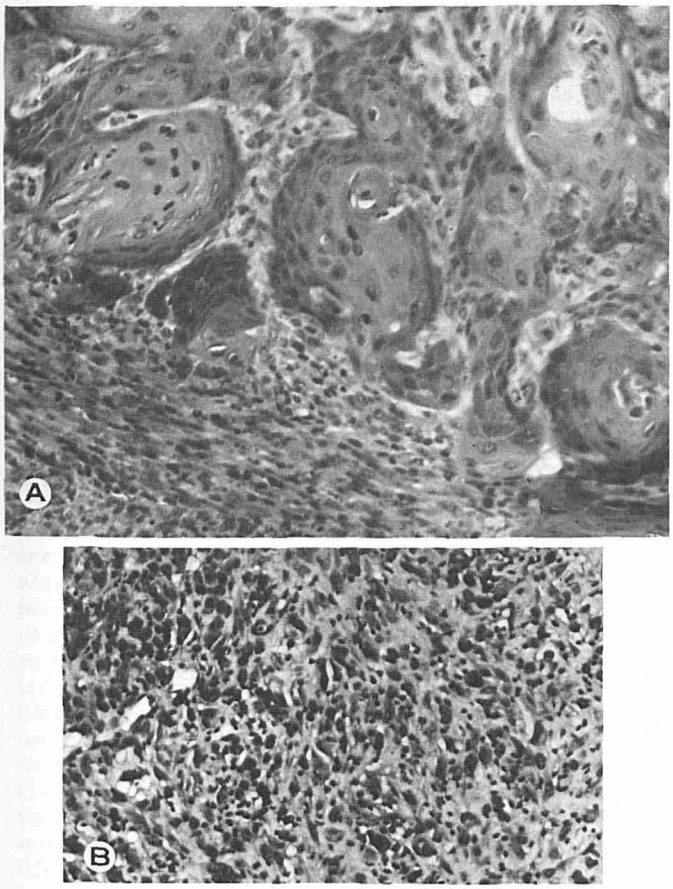

FIG 2. *a*, Pseudoepitheliomatous hyperplasia of 4+ reaction in hairless mice. Note the "streaming off" of epidermal spindle-shaped cells, resembling sarcomatous tumor, at the bottom of the epidermis. *b*, Extension of Figure 2*a* showing atypical cells extending deeper into the dermis. These cells are not as compacted into spindle-shaped cells as are those in figure 2*a*.

cinogenicity [11,12]. The significant role of DNA repair mechanism in the induction of skin cancer (see 13 and references therein) offers a ready explanation for such an observation. In addition, the epidermal changes themselves might also alter the optical and photochemical properties of the skin while tumor development ensues.

In view of the higher response of the UVA + UVB combination vis-a-vis that of the UVB alone, and the essentially different time course for UVA effect (in which there was actually a *regression*), it appears that although UVA is itself a poor carcinogen, it can augment the effect of UVB in promoting carcinogenesis. This idea is reinforced by the following preliminary experiment: two sets of mice were irradiated with 10 nm bands of "monochromatic" radiation in the 280–313 nm range (ca 7–15 mJ/cm^2). One set was immediately followed by 6.5 J/cm^2 of broad band solar-simulating UVA. The presence of the UVA component appeared to enhance the "action" of the UVB component in producing erythemal/precancerous response. These findings seem to argue in favor of a true photoaugmentation phenomenon [14] as opposed to simple photoaddition [15]. On the other hand, Forbes, Davies, and Urbach [6] observed that mice irradiated with the FS-40 sunlamp with and without the presence of additional solar-simulating radiation appeared to have *lower* tumor yields in the UVA-supplemented group. They attributed their previous results (obtained with different sources) in which the UVA appeared to enhance UVB-induced tumor formation [5] to differences in UVB dosage. This apparent discrepancy between our results and theirs is puzzling. One possible explanation may lie in the much higher intensities of the radiation (3 orders of magnitude) utilized in our system. In view of the observed lack of reciprocity, this factor could be very important. The slightly higher "effective" flux in the broad band UVA + UVB system (2.89 mw/cm^2 compared to 1.02 mw/cm^2 for the UVB system) might also have some effect, although we feel that this would not be very significant. Further study is needed to resolve this dilemma.

Of interest is the indication, implicit in our results, that photoaugmentation can be used to "advantage" in efficiently producing squamous cell carcinoma in hairless mice in a relatively short time. Evidently, the specificity for squamous cell cancer is also dose-dependent. Hsu et al., [7] produced most hyperplastic epithelial papillomas after single doses of UVA + UVB; more recently, Strickland, Burns, and Albert [8] produced "kerato-acanthomatoids" after single doses of UVA + UVB (see introduction). In both cases, these doses were different from each other, and were much larger than ours. In those studies, considerable burning and crusting was noted. In our system, little or no burning occurred and squamous cell carcinoma was the predominant lesion.

The histological data show that, as is well known, the stratum corneum thickens on exposure to UV radiation. It is possible that such behavior tends to protect against further UV damage by additional absorption, reflection, and scattering. Since little pigment is present in these mice, any such protective effect cannot be ascribed to either immediate or delayed tanning process. Because of such thickening, we suspected that it may be possible to incrementally increase the UVB dose without burning the skin as irradiation proceeds; this latter procedure would increase the probability of rapid tumor development. Our results bear out these conclusions, as can be seen by comparison between Tables I and II, and between Tables IV and V. The magnitude of the optimal incremental increase must be carefully empirically determined for each system.

The rapidity with which the tumors can be developed can minimize the effects of *physiologic aging* on the tumor induction process. Such effects are always superimposed on the environmental challenges, and are almost impossible to separate [13]. However, the development of a tumor in 6–8 weeks can allow at least a partial separation, since the hairless mice live for more than 1 yr and tumor induction can, in principle, be started at any time.

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