The Influence of Photoreactivating Light on the Type and Frequency of Tumors Induced by Ultraviolet Radiation

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One advantage of ultraviolet light as a carcinogen is that its effect on cells is fairly well understood. For example, when ultraviolet radiation induces mutation, inhibition of growth, or death, the cellular compound first affected is almost certainly nucleic acid, and the organelle probably the nucleus ([7], [8]; and see Hollaender [15] for bibliography). In addition, at least one of the physiological results of irradiation with λ 2537 Å in *Escherichia coli* is a specific inhibition of deoxyribonucleic acid synthesis (18). Moreover, ultraviolet carcinogenesis lends itself to excellent kinetic analysis (2).

There is, however, little agreement on the cellular substance whose absorption of radiation initiates the series of reactions culminating in a cancer cell. The action spectrum for ultraviolet carcinogenesis has been difficult to interpret. As Rusch and his co-workers have shown (25), the most effective wave lengths for inducing tumors in mouse skin lie between 2,900 and 3,341 Å. Wave length 2,537 Å, strongly absorbed by nucleic acids and a potent mutagen, is ineffective (25, 11) or weakly effective (6) for induction of tumors in albino mice.1 Blum and Lippincott (6) ascribe this lack of effect to the absorption of radiation of this wave length by superficial epidermal cells. Rogers (24) found λ 2537 to be carcinogenic when used to irradiate fetal mouse lung in vitrō.

A study of photoreactivation (16) or photo-reversal of ultraviolet carcinogenesis may help clarify the problem. Von Borstell and Wolff (8) have given direct, and others (7) indirect, evidence that only ultraviolet-caused damage to the cell nucleus is reversible by reactivating light. This suggests that, if ultraviolet carcinogenesis is reversed by reactivating light, the initial damage is to the cell nucleus.

A working hypothesis for ultraviolet carcinogenesis is thus: the first step in the change from a normal to a tumor cell is some alteration in the nucleic acid in the cell nucleus, resulting in change of some nuclear function.

Griffin and co-workers (18) studied the effect of visible light on carcinogenesis caused by a mixed spectrum of ultraviolet light.2 Simultaneous irradiation with visible and ultraviolet light reduced the incidence of tumors; visible light following ultraviolet increased the incidence. Both effects were small but consistent. That ultraviolet damage to albino mouse skin is photoreversible was shown by Rieck and Carlson (83).

The general subject of ultraviolet carcinogenesis is reviewed by Blum (3) and that of photoreactivation by Dulbecco (10).

**MATERIALS AND METHODS**

Since we wished to test the effect of photoreactivating light on carcinogenesis by ultraviolet radiation, it was desirable to use as the carcinogenic radiation a restricted spectral band, λ 2500–3100 Å, eliminating as far as possible the longer wave lengths, which are photoreactivating. Such a band was obtained by the use of an 85-watt G.E. C-H3 mercury arc, in conjunction with the filter system suggested by Bain and Rusch (1). It was calculated from the known emission of the lamp and the transmission of the filter that 98 per cent of the energy emerging from the filter lay between λ 2504 and 3548 Å.

Despite the questionable carcinogenicity of λ 2537 Å, we included a series of animals irradiated with this wave length, because much of the data on ultraviolet effects and photoreactivation in bacteria had been obtained with λ 2537 Å. The source was two 50-watt G.E. 4" germicidal" lamps (low-pressure mercury arcs) emitting chiefly the line λ 2537 Å.

For photoreactivation the methodology developed for bacteria was adapted for mice: after each daily ultraviolet dose, the animals to be photoreactivated were immediately subjected for an hour to as intense reactivating light as they could tolerate.

1 Rusch (personal communication) later found that a sufficiently high dose of λ 2537 Å was carcinogenic and induced carcinomas and papillomas only.

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1 After our experiments were under way, we learned of the experiments of Griffin and his co-workers then in progress. They generously agreed to exchange data with us before publication. Fortunately, the design of the experiments differed so much that there was little duplication of effort.
Between irradiations animals were kept in complete darkness or illuminated with nonreactivating yellow light (17).

The reactivating light source was a G.E. AH-5 mercury arc supplemented by three 15-watt "blue" fluorescent bulbs and two 500-watt tungsten lamps. The radiation was passed through 6 mm. of window glass, 12 mm. of pyrex glass, and 54 mm. of 0.08 N CuCl₂ solution. The most serious technical problem in reactivation was overheating the mice. By cooling the animals with a fan during reactivation and using the tungsten bulbs only during the first 10 minutes of irradiation, the temperature in the vicinity of the mice was kept below 38°C.

Male and female CA-F1 hybrid albino mice (BALB/c × A) were used. The mice were divided into five groups: (a) 2537-dark, given a daily dose of λ 2537 A alone; (b) 2537-light, given a daily dose of λ 2537 A followed by reactivating light; (c) and (d), the corresponding λ 2800-3100 A groups; and (e), nonirradiated controls. These groups will be referred to in the rest of the paper as 2537-D, 2537-L, 2800-3100-D, 2800-3100-L, and control. Ultraviolet will be abbreviated to UV.

The animals were individually caged for exposure to various radiations, substantially as described by Blum and Lippincott (6). The mice were irradiated 6 times a week, except for a few holidays, for a total of 189-197 days. This period included days with no irradiation. They were then observed for 144-157 days longer, without further irradiation (see Tables 2 and 3). The technic for irradiation with UV was adapted from Blum et al. (6).

The total dose of λ 2537 A given the animals over the entire experiment was approximately 8.8 x 10⁸ ergs/sq cm, estimated from published tables of the emission of this type of lamp. For the first 24 weeks, the intensity was approximately 1.5 x 10⁴ ergs/sq cm/sec, for a weekly dose of 1 x 10⁸ ergs/sq cm.

This dose was less than the carcinogenic dose of UV reported by Blum and Lippincott (6). On considering their experiment, we had thought that the weak carcinogenicity of λ 2537 A was in part due to uncontrolled photoreactivating light in their laboratory and the short duration of their experiment (8 months). A minimal dose of UV was felt to be desirable for the most clear-cut demonstration of photoreactivation (16, 18; see also 4). When, however, no sign of tumors had appeared after the first 24 weeks, the intensity of the radiation was increased to approximately 8 x 10⁴ ergs/sq cm/sec, and the weekly dose to approximately 5.55 x 10⁸ ergs/sq cm, for the remainder of the irradiation period. This was about the maximum dosage used by Blum and Lippincott (3) in their experiment.

In the 2800-3100 group, as with the 2537 group, a minimal intensity and weekly dosage was again used in the beginning. After 142 days, when the animals had received a total of 5.7 x 10⁵ ergs/sq cm, no tumors had appeared. For the remainder of the experiment the dose was increased to 1.75

RESULTS

Early effects of λ 2537 A.—Soon after irradiation was begun, ears of the mice reddened, and the eyes became irritated. The corneas became dull; conjunctivitis developed, then ulcérations, and later opacities were apparent. Both 2537-D and -L animals appeared similar, except that eye defects in the L animals were less severe.

The differences between the D and L mice were most marked in the Swiss albino, and in general these mice were more sensitive to λ 2537 than were the CA-F1 hybrids.

With continued irradiation the ears in all the mice became inflamed and puffy. At the time the dosage was increased, there were no tumors, except for a papilloma on the tail of one of the Swiss mice. With increased dosage, eye damage became more severe.

As soon as the daily irradiations were halted, the animals quickly recovered their general vigor, and some of the surface irritations healed. Tumors appeared continually during the postirradiation...
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period and were scored with relative ease, since other lesions were minimal.

Early effects of $\lambda$ 2500–3100 A.—Ear reactions were more and eye reactions less severe than in the 2537 groups, and there was little obvious difference between the D and L groups. The typical ocular lesion in the 2500–3100 group was a tightly closed eye with serous exudation; in the 2537 group the eyes remained open and often had corneal opacities. Eye damage, and especially differences between the D and L groups, was looked for, since the mouse eye was known to be especially sensitive to UV (21).

As the irradiation continued, reactions were somewhat worse in the L than in the D groups, except for the eye lesions, which were similar in both. With increased dosage of UV, eye lesions became worse and were definitely worse in the L group. Ears became thickened unevenly; some

In six additional mice the spleen was completely autolyzed so that, although it was enlarged grossly, no microscopic diagnosis could be made. Similar leukemic infiltrations were found in addition in the liver and/or lungs in six animals. There was no apparent effect of the radiation on the incidence of leukemia.

The skin lesions were classified into five groups as noted in Table 1. A certain number of lesions which grossly resembled tumors, especially those of the eyelid, on microscopic examination proved to be inflammatory in nature. The inflammatory changes varied but usually were chronic, with evidence of ulceration, granulation tissue, and attempts at repair. Similar changes were often seen in the surroundings of frank tumors, especially the sarcomas. In several instances, there was partial or complete destruction of the ocular bulb.

### TABLE 1

<table>
<thead>
<tr>
<th>Microscopic diagnosis</th>
<th>Tumor of left ear</th>
<th>Tumor of right ear</th>
<th>Tumor of left eyelid</th>
<th>Tumor of right eyelid</th>
<th>Tumor of tail</th>
<th>Ulcer of tail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer and/or inflammation</td>
<td>48</td>
<td>41</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Papilloma</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>14*</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>20†</td>
<td>12</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>2</td>
<td>17</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* One of these resembled Bowen's disease (carcinoma in situ).
† One of these partly chondrosarcoma; one unclassified sarcoma.
‡ One of these questionable—perhaps only proliferation of epithelium near an ulcer.

The tumors were classified into four general categories. No metastases were observed. The fibrosarcomas (Figs. 4 and 5) frequently extended widely through the subcutaneous tissues of the skull and thorax, occasionally forming enormous hornlike projections from the heads of the animals. This was a particularly prominent feature in those sarcomas which had ulcerated and become infected with abscess formation. The carcinomas (Figs. 2 and 3) were typically squamous-cell in nature. In many instances epithelial pearls were prominent (Fig. 3). The papillomas (Fig. 1) were superficial and showed changes similar to those characteristic of senile keratosis in humans. The lesions characterized as hemangiomas are of less certain identity and may represent merely discrete telangiectases or masses of granulation tissue. However, in each of the four instances, the vascular lesion was quite localized and unassociated with ulceration or more than minimal inflammation. There were no mammary tumors or pulmonary adenomas.

**Tumor incidence.**—Tables 2 and 3 show the
frequency of tumors at various stages of the experiment. The frequency of tumors is the total number of tumors divided by the number of animals living at 233 days for the 2537 group, and at 189 days for the 2800–3100 group. Two histologically distinct tumors in the same animal were scored as two tumors. Several animals had multiple tumors on one or both ears, but when such tumors were clustered closely together they were scored as one. Such multiple tumors, in one case five on one ear, occurred in two 2537-D Swiss mice, in one 2800–3100-D Swiss, and in one 2800–3100-D CA-F1 male; none occurred in an L group. The bias introduced by scoring these as one would be to diminish the actual frequency of tumors in the nonphotoreactivated mice.

All tumors occurred in the ear except for the following eye tumors, which are included in Tables 2 and 3: a carcinoma in a 2537-D CA-F1 female, one in a 2800–3100-D CA-F1 male, and one tumor, analyzed grossly only, in a 2800–3100-D CA-F1 female. It is noteworthy that no eye tumors were found in an L group.

Several animals with tumors were not examined histologically. These animals had died spontaneously and were found unfit for autopsy. In all cases they had large tumors which resembled tumors in other animals which upon examination proved to be malignant. The bias introduced, if any, by including these, would be to increase the apparent incidence in the 2800–3100-D group. All other tumors in Tables 2 and 3 were proved malignant by histological examination. No tumors appeared in any control animals.

Tumors first appeared after 233 days of irradiation in the 2537 group, and after 189 days in the 2800–3100 group. When irradiation was stopped, very few tumors had appeared in either group. Only during the remaining period did tumors appear abundantly and regularly, and most of our data are therefore concerned with delayed, postirradiation tumors.

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### Table 2

**Cumulative Frequency of Tumors in Mice Irradiated with \( \lambda = 2537 \) A**

<table>
<thead>
<tr>
<th>Stage of Experiment</th>
<th>No. Mice</th>
<th>STRAIN</th>
<th>CA-F1</th>
<th>Swiss</th>
<th>Total</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>233 days, first appearance of a tumor</td>
<td>12</td>
<td>8</td>
<td>9</td>
<td>29</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>297 days, irradiation stopped</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>369 days, Swiss mice sacrificed</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>12</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>454 days, remaining mice sacrificed</td>
<td>4</td>
<td>5</td>
<td>9*</td>
<td>0.53*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CA-F1 only.

### Table 3

**Cumulative Frequency of Tumors in Mice Irradiated with \( \lambda = 2800-3100 \) A**

<table>
<thead>
<tr>
<th>Stage of Experiment</th>
<th>No. Mice</th>
<th>STRAIN</th>
<th>CA-F1</th>
<th>Swiss</th>
<th>Total</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>369 days, first appearance of a tumor</td>
<td>14</td>
<td>19</td>
<td>17</td>
<td>50</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>280 days, irradiation stopped</td>
<td>3</td>
<td>8(3)*</td>
<td>11</td>
<td>24(5)*</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>424 days, remaining mice sacrificed</td>
<td>15(5)*</td>
<td>15(1)*</td>
<td>28(6)*</td>
<td>0.56*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 454 days, additional tumors disclosed only on histological examination</td>
<td>15(5)*</td>
<td>15(1)*</td>
<td>28(6)*</td>
<td>0.56*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figures in parentheses are tumors, included in the total, in animals not autopsied and in which there was only gross examination, hence no proof that the tumors were malignant.

† CA-F1 only.
The data show a reduction in the frequency of tumors in the visible light-treated animals. This reduction is most marked in the 2537 group, which had a frequency of 0.41 in the D and 0.19 in the L animals, at 369 days; and less marked in the 2800–3100 group, which had a frequency of 0.48 in the D and 0.30 in the L animals at the comparable stage. For the small numbers of animals in these experiments, however, neither result is statistically significant.

Why cancer induction by λ 2800–3100 A should be apparently less photoreversible than induction by λ 2537 A was of some theoretical interest. Effects such as growth inhibition and lethality caused by wave lengths near 2800–3100 A in sea-urchin gametes (26) and in paramecia (19), and nucleolar changes in grasshopper neuroblasts (9) are quite photoreactivable.

Table 4, in which all lesions diagnosed by histological examination are listed, may indicate some actual photoreactivation of carcinoma induction in the 2800–3100 group. Wave length 2537 A induced carcinomas only, while λ 2900–3100 A induced both types of malignant tumors. In 2800–3100 L there is a distinct reduction in the incidence of carcinomas, the carcinoma-sarcoma ratio in 2800–3100 D being 0.32, and in L, 0.10, a difference as marked at least as in the 2537 D and L animals.

**DISCUSSION**

These experiments clearly show the carcinogenicity of λ 2537 A for the skin of albino mice. Rogers' report (24) on the carcinogenicity of λ 2537 A in embryonic mouse lung, and Blum and Lippincott's suggestion (6) that λ 2537 A is carcinogenic, are confirmed.

The experiments of Griffin et al. (13) in which visible light following UV increased carcinogenesis may perhaps best be compared with our studies.

**TABLE 4**

<table>
<thead>
<tr>
<th>No. animals examined</th>
<th>Strain</th>
<th>Carcinoma</th>
<th>Sarcoma</th>
<th>Papilloma</th>
<th>Hemangiomas</th>
<th>Ulceration, surface infection</th>
<th>Total no. of lesions</th>
<th>Fraction of total malignant tumors which are carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2537-D</td>
<td>2800-3100-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Swiss</td>
<td>6</td>
<td>4</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>CA-F1♂♂</td>
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<tr>
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<td>1</td>
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</tr>
<tr>
<td>7</td>
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<td>0.15</td>
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<tr>
<td>Total 33</td>
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<td>20</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**FIG. 1.**—Benign papilloma of left ear of CA-F1 male mouse irradiated with λ 2537 A and treated with reactivating light. The superficial noninvasive nature of the lesion is apparent. H & E, × 15 (approx.).

**FIG. 2.**—Squamous-cell carcinoma, grade 1, of ear (both ears had similar tumors) of Swiss male mouse irradiated with λ 2537 A and kept in the dark. Note the deformation of the ear by the invasive tumor which extends down to the cartilage and in areas invades the connective tissue of the other side of the ear. H & E, × 15 (approx.).

**FIG. 3.**—Squamous-cell carcinoma, grade 2, of right ear of CA-F1 male mouse irradiated with λ 2537 A and treated with reactivating light. Note the epithelial "pearl" in upper right corner. Numerous malignant epithelial cells intermingled with stromal cells can be seen as well as two mitotic figures. H & E, × 200 (approx.).

**FIG. 4.**—Fibrosarcoma of left ear of CA-F1 female mouse irradiated with λ 2800–3100 A and kept in the dark. Note the almost complete replacement and tremendous enlargement of the connective tissue of the ear by tumor. The cartilage is preserved. The skin laterally is ulcerated, and on one side the ulcer is covered by a thick crust of fibrino-purulent exudate. H & E, × 15 (approx.).

**FIG. 5.**—Same tumor as Figure 4. Note the pleomorphism with giant cells, multinucleated cells, and numerous mitoses. H & E, × 200 (approx.).
with $\lambda$ 2800–3100 A. The disparity in results may not be significant, since the effect of reactivating light on the over-all incidence of tumors in our 2800–3100 group was small at best.

The specific induction of carcinomas by $\lambda$ 2537 A was predicted by Blum and Lippincott (6) but not found by them in their experiments (in which, however, only three, or possibly six, tumors were induced). They suggested that the poor penetrability of $\lambda$ 2537 A confined its action to the upper layers of skin cells (see also [11, 20]).

The fact that photoreversibility of UV carcinogenesis was not statistically convincing makes discussion speculative. One may wonder, nevertheless, why carcinoma induction by $\lambda$ 2800–3100 A should be photoreversible, and not sarcoma induction. One possible explanation is that, as suggested by Blum, potential carcinoma cells can recover from the effects of UV more readily than sarcoma cells. Hence, photoreactivating light stimulates a natural ability for recovery. This hypothesis is partly based on the experimental finding that, for a given total UV dose, the longer the interval between each repeated subdose, the longer the latent period, and the smaller the carcinoma/sarcoma ratio (3).

Some support is given to the idea that carcinoma induction by UV starts with some damage to the cell nucleus. Further studies seem justifiable, and, should the experimental findings in this paper be confirmed, investigation of the post-irradiation physiology of irradiated cells, as has been done with bacteria, might be helpful for the solution of the problem of carcinogenesis.

SUMMARY

Ultraviolet light, $\lambda$ 2537 A, is a potent inducer of skin neoplasms in albino mice. This finding is contrary to reports in the literature that $\lambda$ 2537 A is not, or is only weakly, carcinogenic for the skin of albino mice.

Wave length 2537 A induced only carcinomas, in contrast to $\lambda$ 2800–3100, which induced both carcinomas and sarcomas, with sarcomas predominating. Reactivating light (ca. 3600–4000 A) apparently reduced the carcinogenic action of $\lambda$ 2537 A, but not that of $\lambda$ 2800–3100 A. It did, however, possibly lower the incidence of carcinomas induced by $\lambda$ 2800–3100 A. It is suggested that reactivating light may reduce carcinoma induction, by either $\lambda$ 2537 or 2800–3100 A, but not sarcoma induction.

The exploratory experiments reported here were handicapped by the small number of animals.

While the evidence for the carcinogenicity of $\lambda$ 2537 A is convincing, that for the photoreactivating phenomena is not statistically significant, and conclusions on the photoreversibility of carcinogenesis are therefore only tentative.

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REFERENCES


The Influence of Photoreactivating Light on the Type and Frequency of Tumors Induced by Ultraviolet Radiation

Albert Kelner and Edgar B. Taft


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