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RADIATION CARCINOGENESIS: RADIOPROTECTORS AND PHOTOSENSITIZERS

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ABBREVIATIONS

AET	2-β-Aminoethylisothiouronium-Br-HBr
GLH	Glutathione
5-HT	5-Hydroxytryptamine creatinine sulfate
MEA	Mercaptoethylamine
CYST	Cysteine
PAPP	Para-aminopropriophenone
MEG	Mercaptoethylguanidine
BHT	Butylated hydroxytoluene

INTRODUCTION

Absorption of energy from electromagnetic radiation of a broad wavelength spectrum results in a number of different types of DNA damage (1, 2). No single DNA lesion is induced by any one specific radiation quality but the frequency of certain types of lesions and their repair is dependent on the type of radiation. For example, low linear energy transfer (LET) radiation such as gamma and x-rays results in repairable lesions such as single strand breaks (3), and ultraviolet radiation (UVR) induces pyrimidine dimers (4). Although the different radiation qualities produce different amounts of the various types of DNA damage wavelengths below about 320 nm, are considered carcinogenic (5).

It appears that while the number of types of DNA lesions that lead to cancer may be limited, there is no single specific carcinogenic lesion. The fact that different forms of DNA damage may set in motion the changes that result in neoplasia suggests that the different initial lesions could have a common or a very limited number of pathways. The hypothesis that DNA damage induces repair with some probability of error (6) would be consistent with the idea of a common pathway being induced in a number of ways. Similarly, the idea of transposons set in motion by DNA damage might be the process (7). There is no absolute reason that a single pathway exists but it is intellectually satisfying, tidy and fun to look for.

It is known that the spatial distribution of the damage influences the outcome since high-LET radiation, such as neutrons and heavy ions, are more effective than low-LET radiation (8, 9). A statement that one radiation quality is more carcinogenic than another assumes that doses of the different radiations can be equated. In terms of the amount of energy

deposited this may be so but the density of ionization will determine, for example, the probability of scission of both strands of DNA which in turn may determine the nature of the sequelae such as chromosome aberrations and the modes of repair (10). In other words, the relative biological effectiveness (RBE) is greater for the densely ionizing high-LET radiation than low-LET radiation. At low doses the RBE values for late effects, such as cancer, may reach high values - very much higher than for acute effects (11).

There are many common features between radiation-induced cell killing, mutagenesis and carcinogenesis. For example, the form of the dose-response curves for cell killing and for the induction of some tumors mimic each other (12), if only in an inverse manner but the identification of the critical differences between the biological processes have not been made. It is still a matter of opinion, rather than documented fact, what are the precise mechanisms of radiation-induced cell killing and mutagenesis. If the initial events involved in cell killing, mutagenesis and carcinogenesis have common features such as the physio-chemical changes that lead to DNA damage one would expect some comminality of effect of radioprotectors and radiosensitizers on these biological end points.

Since radiation-induced cancers involve more biological processes than the initial events there are a number of points along the neoplastic pathway at which the final outcome can be modulated.

This paper will outline 1) some of the salient features of radiation carcinogenesis that are pertinent to the questions of how the carcinogenic effects might be influenced, 2) the effects of radioprotectors on ionizing

radiation-induced cancer, and 3) the effect of photosensitizers on UVR-induced skin cancer.

Radiation Carcinogenesis

Since the deposition of energy during exposure to radiation can be quantitated reasonably in physical terms, and to a lesser extent in biological terms, radiation should provide a very useful tool for probing the mechanisms of carcinogenesis. In the case of ionizing radiation there is the advantage that graded single doses result in a graded response. In other words with the appropriate test tissue radiation acts as a complete carcinogen. Under certain conditions radiation may also only initiate cells that may remain capable of expressing the phenotypic changes characteristic of neoplasia for long periods of time (13, 14), or radiation may induce either direct or indirect changes that result in the expression of the initial neoplastic change. In the terms of the current jargon used to describe the multistage nature of carcinogenesis radiation is a complete carcinogen, an initiator and a promoter. Both the human experience and the experimental data relate mainly to radiation as a complete carcinogen, however, it is not known whether risks presented by the properties of initiation and promotion are less or more important than radiation as a complete carcinogen.

In the case of UVR, multiple exposures are characteristically required to produce overt skin cancers (15) and in this sense UVR is not a complete carcinogen or is a weak carcinogen. It is now clear that UVR fits the description of an initiator (16–18) and the findings of Blum and his colleagues have long suggested the promotional properties of UVR (15).

The reason for describing radiation carcinogenesis in terms of a multistage or multifactorial process is to underline that it is theoretically possible to influence the outcome of the long process of cancer at different stages.

It is not possible to describe precisely either the events that are generated by the exposure to radiation that result in neoplastic change or their timing but some of the facets of the complex process are understood. In experimental radiation carcingenesis the mechanisms might be considered in three categories (Table I). These differences in mechanism explain why the dose-response curves for different target tissues are not simple or singular in form (19, 20). The differences in the shape of the dose response curves noted for different tissues probably are due to differences in the factors influencing expression rather than a marked difference in the responses for initial events (21).

TABLE I

MECHANISMS OF RADIATION CARCINOGENESIS (MOUSE)

DIRECT EFFECT ON TARGET CELL	INDIRECT EFFECT	COMBINED DIRECT AND INDIRECT
DNA DAMAGE	CELL KILLING	TARGET CELL CHANGE plus EFFECTS OF ENDOGENOUS FACTORS
?EXPRESSION OF ONCOGENE	ALTERED HORMONAL BALANCE	
INTRODUCTION OF "ERROR"		
EXAMPLE:	EXAMPLE:	EXAMPLE:
?MYELOID LEUKEMIA	OVARIAN TUMORS	THYMIC LYMPHOMA ?MAMMARY CANCER

It is not surprising that exposure to whole-body irradiation may induce cancer by a number of different mechanisms since the radiation-induced damage causes a cascade of events, some of them involving complicated restoration processes as well as disturbances in homeostasis in a number of systems. What is still puzzling is the large variation in susceptibility between tissues in any one strain or species and between the same tissue in different strains or species. It is evident that the genetic background is a predominant feature and may explain strain- and species-dependent differences but why some tissues are quite resistant and others are exquisitely sensitive in a particular strain is far from fully understood.

In the three somewhat arbitrary groups of mechanisms shown in Table I, it is possible to identify particular aspects that appear to be associated

with particular cancers within the group. For example, in the "Direct Effect on Target Cell" group the importance of specific chromosome aberrations in myeloid leukemia may be as important in murine myeloid leukemia as appears to be the case for some human leukemias (22). Mechanisms involving "Indirect Effect" mechanisms are probably much more important in mice than man but are a good example of an abscopal effect. The marked sensitivity of the mouse oocyte to radiation damage with the subsequent imbalance of the ovary-pituitary feedback mechanism affects a lot of tissues. This hormonal imbalance unfortunately results in a clear lack of independence in the genesis of certain hormone-dependent tumors following irradiation. In the third group, "Combined Direct and Indirect", thymic lymphoma is the example that has been the most studied (23). An important aspect of the mechanism appears to be damage to the bone marrow and other hematopoietic tissue (24).

In epithelial tissues, especially skin, the relative resistance to cancer induction may well be due to either the lack of expression or suppression of initiated cells and not a lack of initiation.

The possibilities for modulating radiation carcinogenesis are presumably almost as numerous as the number of different factors that determine whether or not an overt tumor occurs after exposure to radiation.

Modulation of Radiation-induced Cancer

Reduction in the instantaneous dose rate of the exposure to radiation is the most thoroughly studied of the factors that alter the incidence of radiation-induced cancer (25). It is assumed that reduction of the rate of induction of the initial lesions allows the repair mechanisms to be effective in reducing the interaction of two sublesions. But of course

reducing the dose rate must also alter spatial and temporal aspects of the sublesions and reduce their interaction, and therefore the number of biologically effective lesions (11). It has not been shown unequivocally that reduction in the dose rate influences only the initial lesions and not the expression of those lesions. Attempts to influence the repair mechanisms of ionizing radiation-induced damage have not been very useful in probing mechanisms of carcinogenesis. However, Zajdela and Latarjet (26) have suggested that caffeine treatment of mice exposed to UVR reduced the tumor incidence because post replication repair, the so-called error-prone form of repair, was inhibited and excision repair, error-free repair, took a more predominant role. Since these changes in repair could result in reduced cell survival and a concommitant reduction in tumors the picture is confounded.

When the total dose of low-LET ionizing radiation is given in two or more fractions the carcinogenic effect is reduced in some tissues (27–34). Reduction in the carcinogenic effect will not be seen if the total dose is small.

In the case of high-LET radiation neither lowering the dose rate nor fractionating the total dose reduces the carcinogenic effect. In fact in some tissues and some total doses fractionation may be more effective (35) as is certainly the case for life shortening in mice (36–37).

Radioprotectors Radiation Carcinogenesis

When it was shown in the 1950's that thiol compounds were effective in protecting against the acute effects of low-LET radiation (38; also see Monograph by J. F. Thomson, 39) experiments on late effects followed, especially on radiation-induced life shortening.

Since it is considered that in most strains the major fraction of radiation-induced life shortening is due to an increase in mortality from either a higher frequency of tumors or earlier death from tumors any effect on life shortening may be interpreted, at least in part, in terms of effects on tumors (40, 41).

A dose-reduction effect on life shortening was found in C3HF mice with cysteine and anoxia (42). The effectivenesses of AET for protection against life shortening in 101 x C3H F_1 mice was considered equivocal (43). Storer (44) tested a number of agents in A/J and C57BL/6J male and female mice and found that agents (AET, MEA, PAPP 5-HT) that were known to provide a comparable amount of protection against marrow damage, differed considerably in their efficacy in protecting against life shortening. These findings suggested that protection against life-shortening is quite different from protection against acute radiation effects. The most effective protection was obtained in C57BL/6J males and no protection was found in A/J males. Clearly protection against radiation-induced life shortening is a complex matter influenced by sex and strain of the experimental mouse, as well as the radiation dose and the protective drug or combination of drugs that are used. Autopsies were not carried out in this study but it is known that C57BL/6 mice are very susceptible to radiation-induced thymic lymphoma so it is reasonable to assume that a major contribution to the life shortening observed in the irradiated C57BL/6J mice was due to thymic lymphoma. Thus, the protection found in this strain may have been due to a reduction in thymic lymphoma as has been found by other workers. It is also clear from this study that some of the causes of life shortening were not influenced by radioprotectors.

Maisin et al. (45) compared the protective effects of combinations of agents with that obtained with individual drugs. It was found that a combination of AET, GSH, 5-HT, MEA, CYST was very effective in protecting against life shortening in BALB/c and but individual agents varied in effectiveness in C57BL/6J mice (see Table II). The protective effect in BALB/c mice was comparable to that found for acute effects, with a dose reduction factor (DRF), at about 2.8. A DRF is the ratio of the radiation dose in treated mice to the radiation dose required in control mice to produce an equal level of effect.

TABLE II

DOSE REDUCTION FACTORS*: PROTECTION AGAINST LIFE SHORTENING TREATMENT

Strain and Sex	AET	PAPP	MEA	5-HT	Source
Mouse C57BL/6J Males	1.2	2.7	1.5	1.3	Storer, 1971
Mouse C57BL/6J Females	1.1	1.5	1.7	1.2	Storer, 1971
	Combination of :				
	AET	MEA	GSH	5-HT	CYST
Mouse BALB/c Male			2.8		Maisin, 1977

*The DRF varies with dose and the maximum DRF reported has been used.

In a large study involving over 7,000 mice Maisin et al. (46) found that the mixture of agents that had protected against life shortening was effective in protecting against thymic lymphoma (Fig. 2). When the data

for all carcinomas in C57BL/6 mice were pooled a protection was noted. The only carcinomas examined individually in C57BL/6 mice were liver tumors and protection was questionable. In BALB/c mice, which have a much higher natural incidence of cancer, the mixture of radioprotectors was effective in protecting against thymic lymphoma and appeared to protect against myeloid leukemia.

In the case of lung tumors, which in some strains occur naturally at a high incidence and are advanced in time of appearance by irradiation, the evidence for protection is equivocal. Maisin et al. ( ) found that the pattern of time of appearance and incidence of lung carcinomas in BALB/c mice was similar after the mixture of radioprotective agents and 350 R x-rays to that after 100 R x-rays alone. Yuhas could not show a clear cut protection in mice given WR 2177 (47).

Because of the multiplicity of factors that influence the tumorigenic response to radiation, it is not surprising that the literature on protection against radiation-induced tumors appears contradictory. For example, there are reports of either no protection or increased tumor response after exposure to radiation and protective agents (48–51). This appears paradoxical at first sight but can presumably be explained by the fact that high doses of radiation cause both considerable cell killing and life shortening. A reduction in potential tumor cells and a loss of time in which late-life tumors can be expressed will reduce the incidence of some tumors after irradiation. After radioprotective agents the incidence of certain tumors could be higher than after high doses of radiation alone.

There has been a consistency in the reports about the effectiveness of various radioprotective agents against thymic lymphomas (43–46, 52, 53).

The radioprotection, even after high radiation doses, appears to support evidence that radiation-induced damage to hematopoietic cells other than thymocytes plays an important role in the mechanism of radiation-induced thymic lymphoma. Therefore, the protection against radiation-induced tumorigenesis by radioprotectors is clear for a tumor involving cell killing of other than the target cells. Since similar abscopal effects are thought to be involved in the genesis of radiation-induced ovarian tumors radioprotectors should be effective in protecting against such tumors, but published results are not conclusive (43, 48).

There is no reason to believe that the initial chemical changes that occur in cells after irradiation and that result in cell killing are any different from those that lead to the changes that cause cancer and therefore one would expect radioprotectors that are effective against cell killing to be effective in reducing the tumorigenic effect by reducing the initial events. As yet, there is no completely satisfactory set of data that demonstrate protection against radiation-induced carcinomas. Perhaps there are difficulties in getting an adequate concentration of radioprotectors in the target cells of tissues that are susceptible to radiation-induction of carcinomas even when levels are sufficient to protect bone marrow cells. Whatever the reason may be, it would be interesting to establish whether radioprotectors clearly reduced carcinoma induction. For example, a test of radioprotection by WR 2721 against breast cancer in BALB/c mice might provide a definitive answer to the question of whether or not there is a differential effect of radioprotectors on cell killing and induction of carcinomas.

Oxygen and Radiation-induced Cancer

Holman (54) and Warburg et al. (55) proposed that H_2O_2 was responsible for neoplastic transforamtion irrespective of the type of initial change caused by the particular carcinogen. While there have been no definitive experiments that remove that idea from the roster of hypotheses on the origin of cancer, there has been little supporting evidence produced. Feinstein developed the acatalesemic mice to provide a model system for investigating the role of catalase in carcinogenesis and radiation effects (56). Acatalasemic mice mice that are sensitive to H_2O_2 were not found to be unduly susceptible to naturally occurring tumors (57). Since mice with acatalasemia are not completely devoid of tissue catalase (unlike humans with this genetic defect) 3-amino-1H-1, 2,4-triazole (AT) was used to inhibit the low levels of tissue catalase in these mutants. The effect of AT was also studied in normal mice. The use of AT in the diet is complicated by the fact that it can reduce intake of food. However, naturally occurring liver tumors in C3H mice appeared earlier and at a higher incidence in AT treated acatalasemic mice than in the AT treated normal catalase mice. On the other hand, the susceptibility to radiation induced thymic lymphoma did not appear to be different in acatalasemic C57BL/6 and mice of the same strain with normal catalase levels (57).

Acatalasic humans have been identified but, to my knowledge, have not been reported to have high cancer rates; nor do I know of any in vitro studies of cells from such humans. The role of forms of oxygen such as OH radicals and singlet oxygen has been not only shown to be important in radiation-induced damage but it has also been suggested that active forms of O_2 can also result from normal metabolism and play a part in naturally

occurring cancer (58). Recently there has been considerable interest in the role of superoxide radical anions in cancer induction (59) and the role of free radicals in promotion (60). If different events are involved in initiation and promotion but can be caused by free radicals perhaps the fact that ionizing radiation is an effective complete carcinogen is related to its capability in generating free radicals (61).

Dietary antioxidants have been shown to protect against chemical carcinogenesis and UVR-induced skin cancer. There has been no systematic study of the effects of antioxidants, such as BHT, on ionizing radiation-induced carcinogenesis.

Photosensitizers and Carcinogenesis

When we come to the obverse of the protection coin, namely sensitization, the account has even less to its credit, at least in the case of ionizing radiation. However, there are a large number of compounds that extend the UVR wavelength spectrum for a number of biological effects. Photosensitizers in general are low molecular weight, usually planar, structures often with alternate single and double bonds. The majority of these compounds produce a phototoxic response, a few induce an immune or photoallergic reaction. Photosensitized reactions involve absorption of UVR usually UVA (320–400 nm) in a chromophore. The events that result from the absorption of specific wavelength(s) are complex and follow different paths. For example, electron transfer from a sensitizer, such as certain dyes, or to the system via free radicals. Some sensitizers act in an indirect manner through a triplet-triplet transfer. The question of a carcinogenic effect of photosensitizers is confounded in the case of photosensitizers such as polycyclic hydrocarbons which are themselves

carcinogenic. The most interesting form of photosensitized reaction for the study of carcinogenesis, involves the photochemical interaction of a photosensitizer such as psoralen with the system forming psoralen-DNA adducts. The structure of some of the furocoumarins or psoralens that have been studied is shown in Fig. 3. Furocoumarins are a group of compounds some of which occur naturally and others have been synthesized (62). Some of the naturally occurring psoralens such as 8-methoxypsoralen (8-MOP) have been used for perhaps thousands of years to treat areas of skin with abnormally little pigment and recently exposure to 8-MOP and UVA (PUVA) has been introduced as a treatment for psoriasis (63). Exposure to planar furocoumarins such as psoralen and some of its derivatives and UVA results in the formation of both mono and difunctional adducts with pyrimidine bases; thus, DNA interstrand links are induced. 4,5'-dimethylangelicin because of its angular form results in exclusively mono-functional adducts (64). These DNA lesions involving one DNA strand are much less biologically effective. Appropriate side chains as occur in 3-cabethoxypsoralen also prevent the formation of the di-functional adduct (65).

Since the two forms of adducts that are the predominate lesions after exposure to PUVA can be assayed, it is possible to investigate the quantitative relationship of induction of these lesions with the induction of cancer. Latarjet and coworkers found that 3-carbethoxypsoralen which forms only mono-functional adducts did not induce tumors (66). We have restricted our studies to 8-MOP (67, 68). It can be seen from Fig. 4 that the incidence of epidermal carcinomas is dependent on the number of exposures to PUVA (and the total number of induced psoralen-DNA

crosslinks). We have also found that the incidence of squamous cell carcinoma increases when the number of exposures is kept constant but the dose of UVA, and therefore the number of psoralen-DNA crosslinks increases. It can be seen in Fig. 5 that with low total doses no skin cancers may be seen unless the PUVA regimen is followed by the promoter 12-O-tetradecanoyl-phorbol-13 acetate (TPA) (Fig. 6). These results indicate that a small number of PUVA exposures can initiate cells that in some way are prevented from being expressed unless there are further exposures to PUVA or treatments with TPA are given.

SUMMARY

Although the mechanisms of radiation carcinogenesis are far from understood, we are at least beginning to understand some aspects of the processes and how they may be studied. Perhaps the current molecular studies that implicate inherent oncogenes will establish the common pathway by which different initial lesions, lead to neoplasia. A major unsolved problem is the untangling of the skein of interactions that are involved in both suppression and expression of the initial changes induced by radiation.

There has been no impetus from the clinic for the study of protection with chemicals against radiation-induced cancer and in recent years only Maisin's group has carried out major experimental studies in the field. As more is known about possible mechanisms of radiation injury, repair and carcinogenesis, there appear to be ways in which radioprotectors could be used to probe mechanisms. Free radical scavengers protect against radiation-induced thymic lymphoma but this protection may be due to

protection against bone marrow cell killing rather than blocking initial lesions in the thymocytes. It should be possible to determine whether protection against oocyte killing protects against ovarian tumors. Such a finding would be good evidence of the role of the oocyte in the mechanism of radiation-induced tumors arising from granulosa cells.

Photosensitizers have proven useful in experimental skin carcinogenesis. Since the induction of psoralen-DNA crosslinks appear to be an effective way to initiate cancer, the use of different psoralens and exposure to UVA should prove very useful in studying the subsequent steps that must occur before the neoplastic changes are expressed. The introduction of PUVA treatment for such a common disease as psoriasis raises questions about the risk of the use of photosensitizers.

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FIGURE LEGENDS

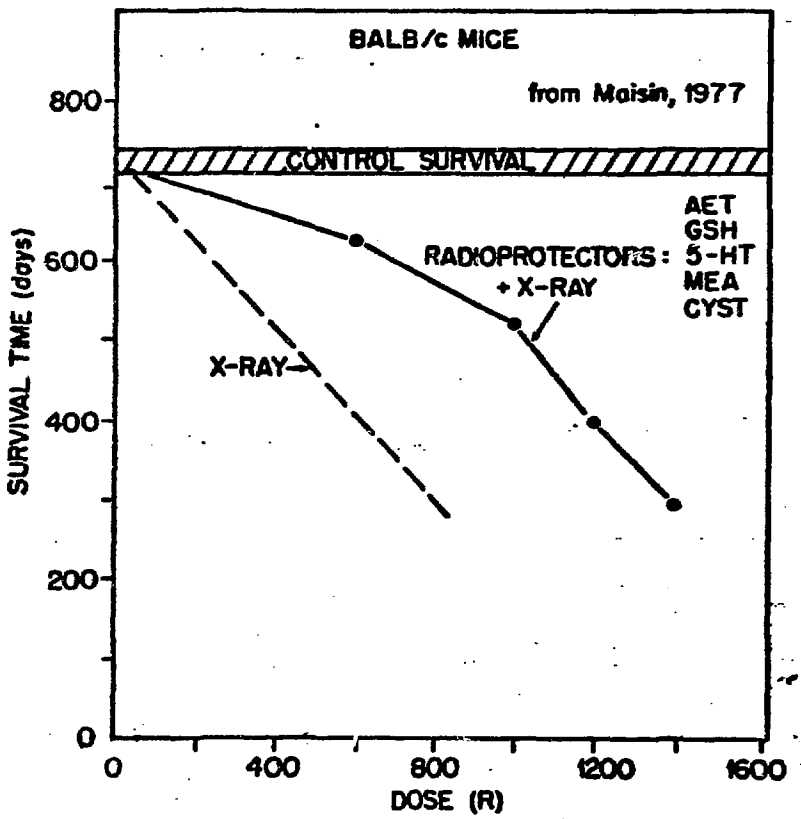
Fig. 1. Survival time as a function of dose of x-rays: ----, and x-rays plus radioprotectors: ●—●, in BALB/c mice.

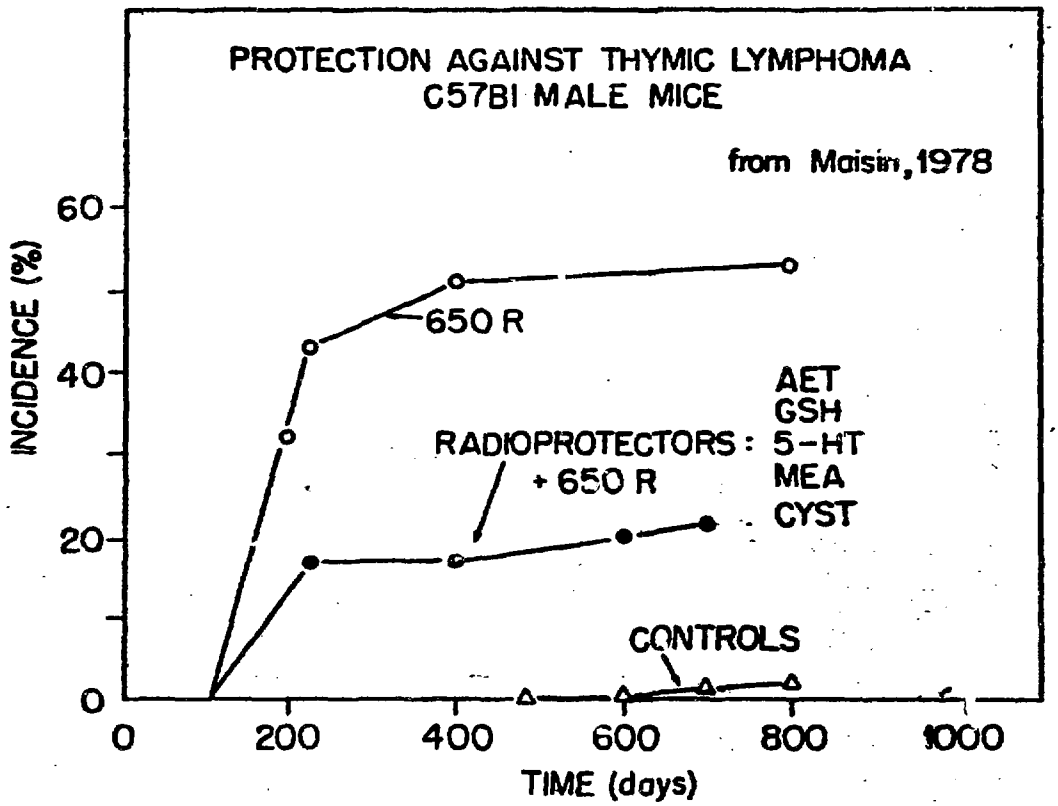
Fig. 2. Incidence of thymic lymphomas in C57BL male mice as a function of time after irradiation: ○—○, irradiation plus radioprotectors: ●—●, and controls: △—△.

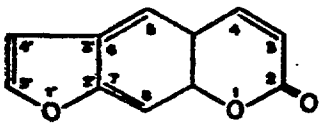
Fig. 3. Structure of psoralen and related furocoumarin.

Fig. 4. Skin cancer incidence as a function of time in SKH:hairless-1 mice treated with 18 exposures (3/week) of 250 μg 8-MOP and 1.25×10^3 J/m^2 UVA (320–400 nm): ——, 36 exposures: △—△, and 72 exposures: ○—○.

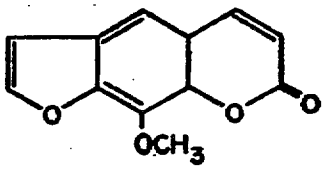
Fig. 5. Skin cancer incidence as a function of time after 18 exposures (3/week) of 250 μg 8-MOP and 1.25×10^3 J/m^2 UVA (320–400 nm): and the same regimen followed by 5 μg TPA 3/week for 50 weeks.


BALB/c MICE
from Maisin, 1977
CONTROL SURVIVAL
AET
GSH
5-HT
MEA
CYST
RADIOPROTECTORS :
+ X-RAY
X-RAY
SURVIVAL TIME (days)
800
600
400
200
0
0
400
800
1200
1600
DOSE (R)

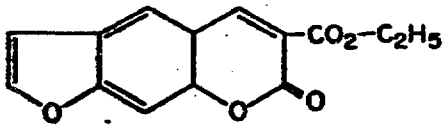

PROTECTION AGAINST THYMIC LYMPHOMA
C57BI MALE MICE
from Maisin, 1978
INCIDENCE (%)
60
40
20
0
650 R
RADIOPROTECTORS : AET
GSH
5-HT
MEA
CYST
+ 650 R
CONTROLS
0
200
400
600
800
1000
TIME (days)



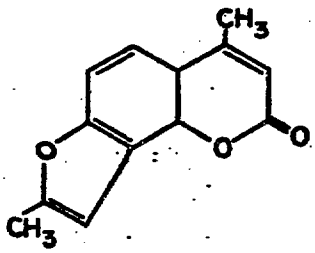
PSORALEN



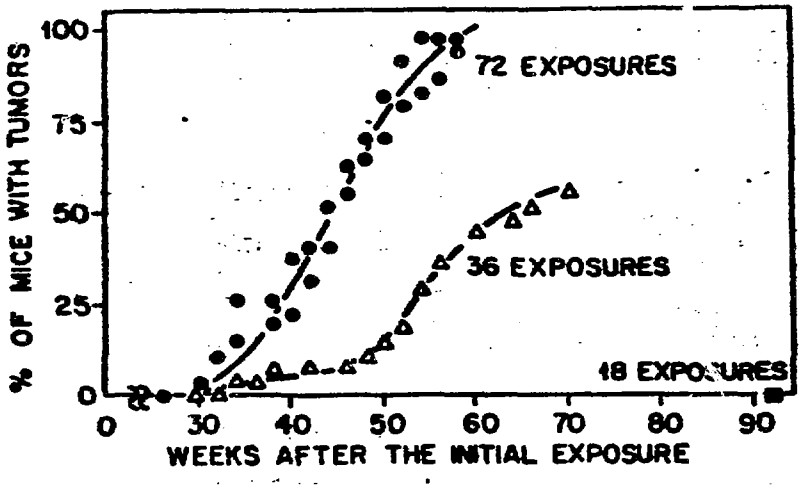
8-METHOXYPSORALEN

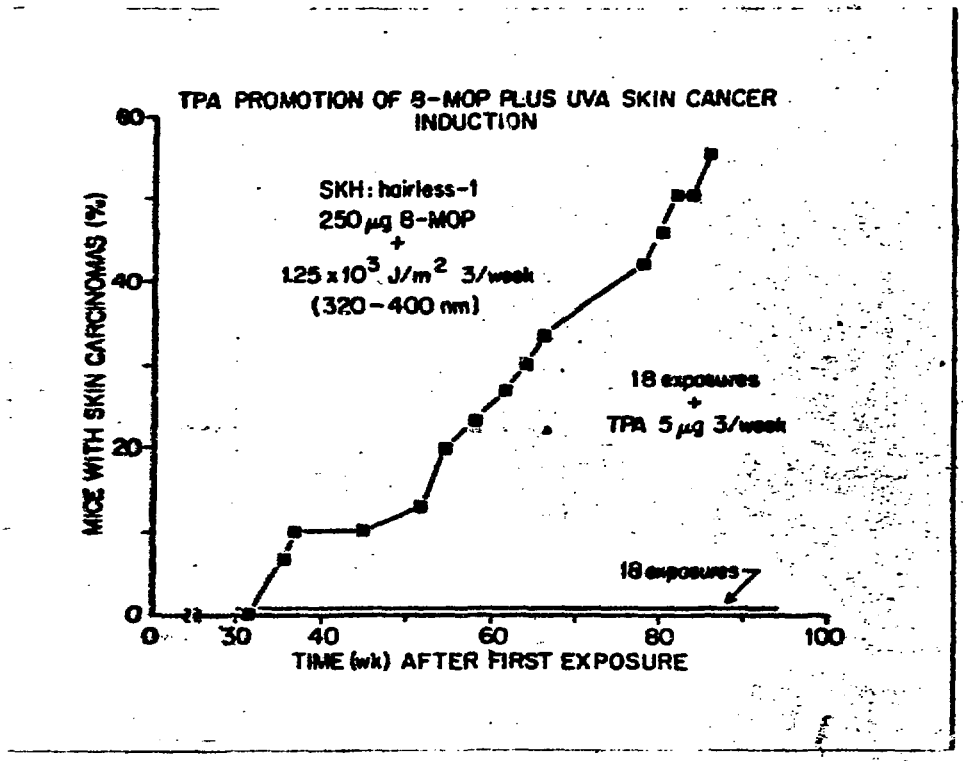


3-CARBETHOXYPSORALEN



4, 5'-DIMETHYLANGELICIN


% OF MICE WITH TUMORS
100
75
50
25
0
72 EXPOSURES
36 EXPOSURES
18 EXPOSURES
0
30
40
50
60
70
80
90
WEEKS AFTER THE INITIAL EXPOSURE


TPA PROMOTION OF 8-MOP PLUS UVA SKIN CANCER INDUCTION
SKH: hairless-1
250 μg 8-MOP
+
1.25 x 10³ J/m² 3/week
(320-400 nm)
18 exposures
+
TPA 5 μg 3/week
18 exposures
MICE WITH SKIN CARCINOMAS (%)
0
20
40
60
0
30
40
60
80
100
TIME (wk) AFTER FIRST EXPOSURE