[CANCER RESEARCH 45, 6254–6259, December 1985]

Relation of Antioxidants and Level of Dietary Lipid to Epidermal Lipid Peroxidation and Ultraviolet Carcinogenesis[1]

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ABSTRACT

It has become increasingly evident that both quantity and quality of dietary lipid can influence the developmental course of several major forms of cancer in experimental animals. Using the hairless mouse-ultraviolet (UV) model, we had previously demonstrated that unsaturated lipid compared to equivalent levels of hydrogenated lipid enhanced photocarcinogenesis with respect to both tumor latency and multiplicity. In the present study using the same model, we have examined the effect of unsaturated lipid level and antioxidants upon epidermal lipid peroxidation and UV carcinogenesis. Sixteen groups of 45 animals each were used in the study, representing all combinations of three design variables: (*a*) a semipurified diet containing 4, 2, or 0.75% corn oil or 4% soybean oil; (*b*) 2% (w/w) antioxidant supplement or no supplementation; and (*c*) an escalating regimen of UV radiation to a cumulative dose of 70 J/cm^2 or no irradiation. The nonirradiated groups served as nutritional controls and as subjects for epidermal lipid peroxidation measurements. An approximate linear relationship between lipid level and tumor latency was observed, with 4% levels of unsaturated lipid producing maximum enhancement of photocarcinogenesis. Furthermore with increasing lipid level the numbers of tumors per animal increased. Antioxidants caused significant increases in tumor latency and decreases in tumor multiplicity but only at the highest lipid level used in these studies. Thiobarbituric acid values of epidermal homogenates also increased in relation to the level of dietary lipid intake. Epidermal thiobarbituric acid values from antioxidant supplemented animals were significantly lower regardless of lipid intake levels. From these data we conclude that (*a*) dietary lipid level has a direct effect upon the carcinogenic response to UV both in regard to tumor latency and tumor multiplicity; (*b*) antioxidants produce an inhibitory effect almost equal to the degree of exacerbation of carcinogenesis evoked by increasing lipid levels, at least for the range studied; and (*c*) dietarily administered antioxidants inhibit the formation of epidermal thiobarbituric acid reacting materials. These data strongly imply that free radical reactions, specifically lipid peroxidation, play a role in at least a part of the photocarcinogenic response.

INTRODUCTION

The influence of dietary lipid upon carcinogenesis first became apparent over 50 yr ago when Watson and Mellanby (3) observed that dietary fat enhanced the incidence of coal tar-induced skin tumors. This effect of dietary lipid upon chemical carcinogenesis was soon substantiated and numerous studies have since been conducted on the quantitative and qualitative composition of dietary lipids and their relationship to tumor enhancement (4–9). Generally, these studies have shown that animals fed high-fat diets develop tumors more readily than cohorts fed low-fat diets. Tumors of which this effect has been most often observed are those of the skin, mammae, and intestine. High levels of fat appear to exert maximum influence upon the promotional stages of carcinogenesis (10).

With regard to quality of fat, it is polyunsaturated lipids which generally enhance tumorigenesis. Recent studies indicate that small quantities of polyunsaturated fats when fed concomitantly with high levels of saturated fat enhance tumor formation as effectively as high levels of unsaturated lipid alone (7). These data suggest that polyunsaturated lipids are required for the most effective expression of specific chemically induced carcinogenesis.

The impact of these observations concerning the effect of lipid upon experimentally induced cancer has recently assumed greater significance with the collection of epidemiological data showing a positive correlation between dietary fat and human mortality rates resulting from certain types of cancer, notably mammary and colonic (11, 12). Although a considerable literature is accruing that suggests that etiologies of the main human cancers stem largely from our life-styles (13), it seems ironic that this potential relationship with respect to skin cancer has received so little attention, especially as both initiator (UV) and modifier (diet) so profoundly manifest life-style.

Previously the only direct study of the relationship of diet to UV carcinogenesis was that of Baumann and Rusch (14) published in 1939 in which they observed that animals fed high levels of fat formed UV-induced tumors more rapidly than animals fed low-fat diets. More recently, we observed that the degree of saturation of dietary lipids markedly influenced the UV carcinogenic response (15). Unsaturated lipid enhanced UV carcinogenesis both with respect to latency and multiplicity and it was suggested that unsaturated lipid might be required in photocarcinogenesis just as is the case for certain chemically induced cancers. In addition, the level of unsaturated lipid appeared to affect both the direction and magnitude of antioxidant-mediated modification of photocarcinogenesis (16). In the current study we have examined the influence of antioxidants and dietary lipid level upon UV carcinogenesis and epidermal lipid peroxidation.

MATERIALS AND METHODS

Animals and Diets. Three- to 4-mo-old female hairless (SKh-Hr-1) mice were obtained from the Skin and Cancer Animal Colony, Temple University, Philadelphia, PA. Upon receipt the animals were maintained on Wayne Lab-blox (Continental Grain Co., Chicago, IL) for a 2-wk

Received 4/22/85; revised 7/24/85; accepted 8/16/85.

[1] Supported in part by USPHS Grant CA-20907 from the National Cancer Institute and by Veterans Administration Medical Center Research Funds. Preliminary reports of this work were presented at the Annual Meetings of the American Society for Photobiology, June 1983, Madison, WI (1) and the American Association for Cancer Research, May 1984, Toronto, Canada (2).

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Table 1
Semipurified experimental diets of varying lipid composition

	Diets[a]			
	1	2	3	4
Casein (vitamin free)	27.40	27.40	27.40	27.40
Corn oil (tocopherol stripped)	4.00	2.00	0.75	
Soybean oil (cold pressed)				4.00
Corn starch	55.90	60.30	63.00	55.90
Mineral mix[b]	6.00	6.00	6.00	6.00
Vitamin mix[c]	2.20	2.20	2.20	2.20
Celufil (nonnutritive)	2.10	2.10	2.10	2.10

[a] Caloric density: Diets 1 and 4, 3.95 kcal/g; Diet 2, 3.86 kal/g; Diet 3, 3.80 kcal/g.
[b] United States Biochemical Corp.; Phillips and Hart salt mixture.
[c] United States Biochemical Corp.; vitamin mix minus ascorbic acid and tocopherol.

quarantine period after which they were divided into 16 groups of 45 animals each. Control (non-UV) and UV-irradiated groups received the powdered diets shown in Table 1. The custom diets were prepared by United States Biochemical Corp., Cleveland, OH. In addition, similar groups received these diets supplemented with a 2% (w/w) antioxidant mixture consisting of 1.2% ascorbic acid, 0.5% butylated hydroxytoluene, 0.2% DL-α-tocopheryl acetate, and 0.1% reduced glutathione. This antioxidant mixture had previously been shown to inhibit UV carcinogenesis, although the active principal is thought to be butylated hydroxytoluene (17). Antioxidant-supplemented diets were mixed in a twin-shell dry blender in our laboratory and all diets containing antioxidants were stored refrigerated under vacuum. Animals were fed *ad libitum* and housed 6–7 animals/cage under 12 h light-dark photoperiods at 21–23°C.

Animals were conditioned to the experimental diets for 2 wk prior to irradiation. During this period animals were identified by abdominal tattoo and initial body weights were determined. Thereafter individual body weights were determined every 2 wk.

Irradiation. Animals received irradiation 5 days/wk from nonfiltered General Electric UA-3 mercury arc lamps with principal emission lines at 254, 265, 280, 302, 313, and 365 nm. The mice were irradiated unrestrained in their cages in an irradiation chamber of special design (15). Total energy emitted from the lamps was mapped for five areas representing different sites within the 18.5- x 32.0-cm cages and the mean was used to calculate dose. The total energy was measured each week with a calibrated circular thermopile attached to a Keithley microvolt ampmeter. An initial suberythemic daily dose of 0.87 J/cm^2 was delivered. To compensate for epidermal thickening, the dose was increased every 2 wk by an average of 0.325 J/cm^2 until a daily dose of 2.18 J/cm^2 was attained. This level of irradiation was maintained until a cumulative dose of 70 J/cm^2 had been administered whereupon irradiation was discontinued.

Tumor Evaluation. Animals were examined at weekly intervals to evaluate actinic effects. Elevated lesions of 1 mm diameter were taken as end points for evaluation. Representative tumors of the type that occurred were histologically interpreted as papillomas or squamous cell carcinomas. Tumor development followed the usual progression from papillomas to squamous cell carcinomas as previously observed in UV-carcinogenesis studies using similar radiation sources and regimens.

Epidermal Lipid Peroxidation. Nonirradiated animals that had received the respective experimental diets for 35–40 wk were used for measurement of lipid peroxidation. Four animals from each experimental group were irradiated with a single 1.1 J/cm^2 UV dose, immediately sacrificed by cervical dislocation, and the dorsal skin excised. The epidermis was scraped from the dermis after brief (28-s) heat treatment (55°C) (18). Aliquots of epidermal homogenates prepared in 50 mM phosphate buffer, pH 7.2, were used for measurement of TBA[3]-reacting materials and peroxide value determinations (19, 20). For TBA tests, 1 ml of homogenate was incubated at 0° or 37°C, with shaking for the designated times. ADP and $FeSO_4$ were added to some aliquots to give final concentrations of 0.73 and 0.65 mM, respectively (21). The reaction was halted by addition of 15% trichloroacetic acid to give a final concentration of 5% trichloroacetic acid. The mixture was centrifuged at 2000 $\times$ *g* for 20 min, the supernatant was decanted, an equal volume of 0.67% 2-thiobarbituric acid was added, and the product was placed in a boiling water bath for 10 min. The sample was cooled to room temperature and made alkaline by addition of 200 μl of 5 M KOH (0.29 M, final concentration). Absorbance was read at 543 nm. Malonaldehyde bis(diethylacetal) was used as a standard for quantitation of TBA reacting materials.

Peroxide values were determined by the method of Swoboda and Lea (20). At designated incubation times 1-ml aliquots of epidermal homogenate were acidified with 0.1 ml acetic acid and extracted with 1.5 ml chloroform followed by a second extraction of 1.0 ml. The pooled lipid extract was dried under N_2, solubilized with 3 ml chloroform:acetic acid (3:2, v/v), and transferred to a tube fitted with sidearm and stopcock. After deaeration with bubbling CO_2, 80 μl of iodide reagent (1.2 g potassium iodide/ml H_2O, freshly prepared) was added and the tube was sealed under slight positive pressure of CO_2 and left standing for 1 h in the dark. The mixture was then diluted with 7 ml of 0.5% aqueous cadmium acetate solution, stoppered, vortexed for 15 s, and the biphasic system was separated by centrifugation (2000 $\times$ *g* for 15 min). Absorbance of the aqueous supernatant was determined at 350 nm. Calibration was accomplished using a series of reagent blanks consisting of various volumes of 0.2 mM potassium iodate in 0.5% cadmium acetate solution.

Protein was determined by the method of Lowry *et al.* (22).

Statistics. Cumulative tumor distributions (distribution of tumor onset in weeks) were estimated for each dietary group using the computer program SURVIVAL in the Statistical Package for the Social Sciences library. Comparisons of the distributions among groups were made in the same program using the *K*-sample test for censored data followed by pairwise comparisons between groups (23). This test is often considered to be a comparison of "median" times but is actually a test of overall shifting of distributions among groups.

Tumor multiplicity comparisons among groups were made at week 20 of the study using computer program NPAR1WAY in the Statistical Analysis System program library. Inferences were based on the Kruskal-Wallis and Wilcoxon rank sum tests with adjustments for tied observations.

In all of the comparisons, significance was based on two-tailed tests with *P*s of 0.05 or smaller. No further adjustments were made to compensate for possible inflation of type 1 errors when making multiple comparisons.

RESULTS

The experimental design allowed reasonable control over nutritional parameters that could complicate interpretation of data if nutritional imbalances among dietary groups had occurred. Although it seemed highly unlikely that the usual dietary nonutritives (*i.e.*, Celufil) would play a role in physical skin carcinogenesis, this question had been previously raised. Therefore to circumvent this criticism, we purposely introduced a caloric-density imbalance in the experimental diets in order to maintain nonnutritive equality. As seen in Table 1, the experimental diets used in this study varied from 3.80 to 3.95 kcal/g (4%; 6% in antioxidant-supplemented diets). It was assumed that by feeding the diets *ad libitum* the animals could easily compensate for their energy requirements by increasing food intake provided caloric-density inequality was no greater than that used in this study (24). Furthermore the paired group experimental design provided necessary information if dietary adjustments had been required. Evaluation of individual body weights revealed no significant

[3] The abbreviation used is: TBA, thiobarbituric acid.

differences in rate of weight gain between animals receiving any of the experimental diets (Chart 1). Thus the general nutritional status of animals on the respective dietary regimens remained comparable throughout the experimental period and any differences among the parameters investigated must have occurred as a result of varying lipid levels and/or antioxidants.

Previous studies had indicated that diets containing 4% corn oil enhanced UV carcinogenesis as much as those containing 12% (15). Thus to examine effects of lipid level upon photocarcinogenesis, we chose diets ranging from 0.75 to 4% in lipid. The lowest level, 0.75% corn oil, was determined to be the minimum that would provide an adequate amount of essential fatty acids. In addition, the 4% soybean oil-formulated diet was examined for the reasons that (*a*) soybean oil is the principal source of lipid for most commercial rodent rations and (*b*) we had noted that the photoprotective effects of antioxidants previously observed with commercial diets were diminished when semipurified diets containing corn oil were fed (25).

A comparison of the cumulative tumor probability plots for animals receiving the three levels of dietary corn oil is presented in Chart 2 (only the portion of the plot around the median tumor time is shown for the 2% lipid level). The relationship of dietary lipid levels to the cumulative tumor probabilities is emphasized by the lines connecting the evaluation periods on either side of the median tumor times. Animals receiving the diet containing 4% corn oil expressed the shortest tumor latent period, followed by the 2% lipid diet, with the 0.75% corn oil diet reflecting the longest latency. The cumulative tumor probability plot of animals receiving the 4% corn oil diet was significantly different from those of 2% and 0.75% diets, $P < 0.05$ and < 0.01, respectively.

The cumulative tumor probability plots of animals receiving the various lipid diets were compared to those receiving similar diets containing the antioxidant supplement (Chart 3). Whereas the effect of antioxidant supplementation on tumor latency is apparent with the 4% corn oil diet ($P < 0.05$; Chart 3*A*), this effect is absent with 2% (Chart 3*B*) and 0.75% corn oil diets (Chart 3*C*).

Although corn and soybean oils both consist of predominately unsaturated fatty acids, substantial differences in percentage of linolenic, linoleic, octadecanoic acids and ratios of total polyunsaturated to saturated fatty acids may occur, depending upon source and processing method (26). These differences could account for the more pronounced inhibitory effect of antioxidants on the cumulative tumor distribution of animals fed the 4% soybean oil diet compared to that of corn oil (Chart 3, *D versus A*). This may also partially explain why the magnitude of photocarcinogenesis inhibition by antioxidants has been observed to be greater in animals fed commercial rodent ratios compared to semipurified diets.

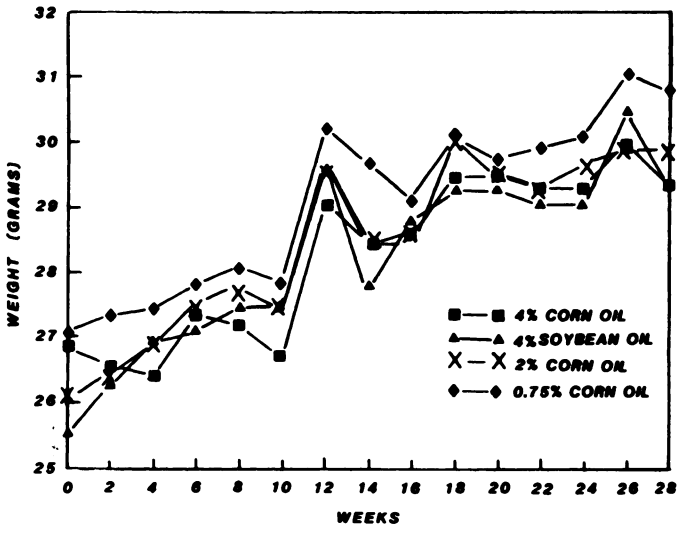

Chart 1. Comparison of rate of weight gain of animals receiving the experimental dietary regimens. Two-way analysis of variance was used to compare weight across time. There were no significant differences among groups, indicating an equivalent nutritional status for all dietary lipid levels.

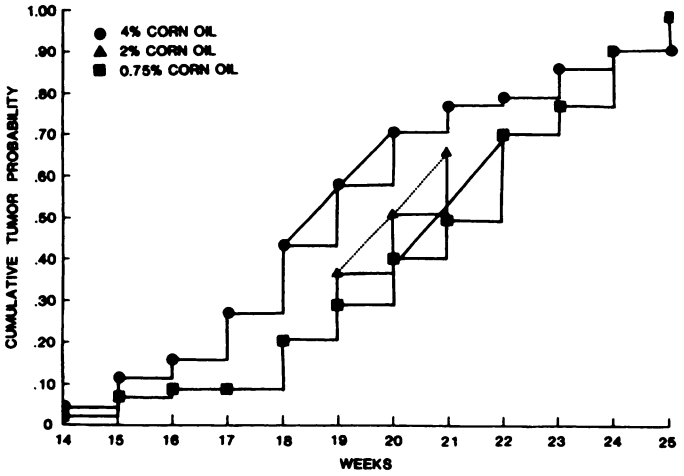

Chart 2. Relationship of cumulative tumor probabilities to dietary lipid level. All groups received 70 J/cm^2 of UV radiation. —— and ···· parallel lines are drawn across values on either side of the median tumor times to demonstrate the relationship to dietary lipid level. These values are the only *data points* plotted for the 2% lipid diet.

The median times for tumor formation for each of the respective lipid diets with and without antioxidants are represented in Table 2. It is clear that tumor latency increases with decreasing dietary lipid intake. Furthermore only with a shortened latent period do antioxidants affect an inhibitory response. This point is more dramatically reflected in tumor multiplicity (Table 3). The value of this parameter increased from 0.61 tumor/animal to 1.89 with 0.75 and 4% corn oil, respectively. Antioxidants had no effect at the lowest lipid level and indeed appeared to negate only that enhancement of tumor multiplicity elicited by having corn oil increased in the diet. It should be noted that all significant differences in tumor multiplicity observed at wk 20, the mean tumor latent period, had vanished by wk 30. It appears that antioxidants produce their inhibitory effects early on in the carcinogenic process and that unsaturated lipid is able to overcome such inhibition, perhaps by enhancing promotional events in the carcinogenic continuum.

Epidermal lipid peroxidation levels were measured in the animals serving as nonirradiated controls for the respective dietary groups. The typical rate of formation of TBA-reacting materials is represented in Chart 4. The reaction had usually plateaued at 60 min. Epidermal homogenates demonstrated no increases in TBA levels when incubated at 0°C. When incubated at 37°C the levels increased to 0.87, 1.72, and 1.99 nmol/mg protein for 0.75, 2, and 4.0% dietary lipid levels, respectively (Chart 5). Animals receiving the antioxidant-supplemented diets demonstrated relatively constant TBA levels of 0.45 nmol/mg protein at all dietary lipid levels when incubated at 37°C. TBA values for those homogenates containing iron and ADP were 1.5–2.0 times greater than those depicted in the chart. Peroxide values (not shown) of the lipid extracted from the individual homogenates

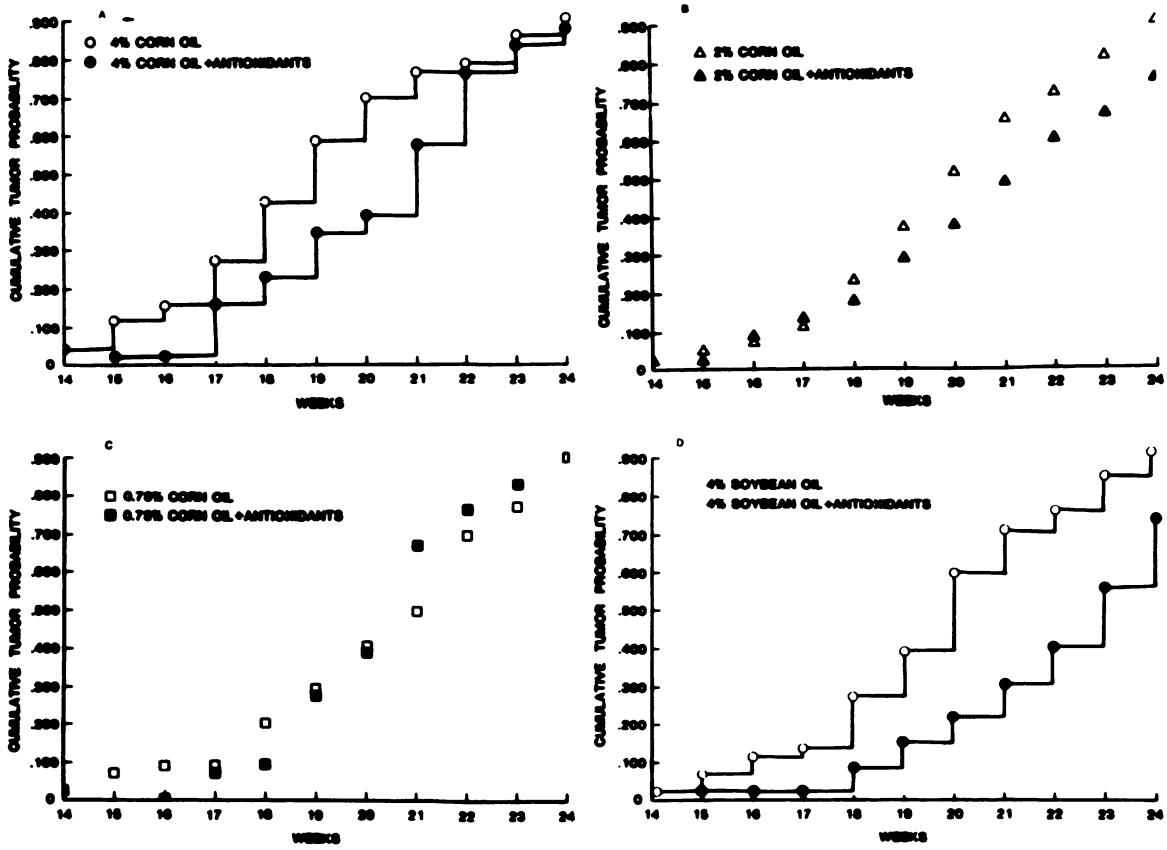

Chart 3. Effects of an antioxidant supplement upon the cumulative tumor probabilities of animals receiving diets of varying lipid composition. Antioxidants produced significant inhibition of tumorigenesis in diets containing 4% lipid (*A* and *D*) but this effect diminished in the 2% diet (*B*) and was absent in the 0.75% lipid diet (*C*). *D*, ○, 4% soybean oil; ●, 4% soybean oil plus antioxidants.

Table 2

Comparisons of the median latency times of tumor occurrence between groups of animals receiving diets of designated lipid composition with and without antioxidant supplementation.

*P*s were determined with the Statistical Package for the Social Sciences program SURVIVAL

Diet	Antioxidant	Time (wk)
4% corn oil	Without	18.4
	With	20.6[a]
2% corn oil	Without	19.9
	With	21.1[b]
0.75% corn oil	Without	21.00
	With	20.4[b]
4% soybean oil	Without	19.50
	With	22.6[c]

[a] $P < 0.05$.
[b] Not significant, at $P > 0.05$.
[c] $P < 0.001$.

increased with respect to the level of dietary lipid and albeit not quantitative were in general agreement with the trend observed for TBA values. These data indicate that the peroxidative reactions observed represent temperature-dependent enzymatic responses that are linearly related to the level of dietary lipid intake.

DISCUSSION

It is apparent from the present study that dietary lipid can influence the expression of UV-mediated carcinogenesis just as it has been shown to affect the progression of certain spontaneous and chemically induced cancers. Carroll (10, 11) and Carroll and Hopkins (27) have demonstrated that the enhancement of mammary tumorigenesis occurs only after a requirement for polyunsaturated fat has been met and have suggested that this effect is related to the requirements for essential fatty acids. Although our studies were not designed to address this interesting aspect of the influence of dietary lipid on carcinogenesis, the effects of antioxidants on tumor multiplicity suggest an analogous situation for UV-induced cutaneous cancer; *i.e.*, (*a*) antioxidants had no effect upon this parameter at the minimum dietary lipid level necessary to provide essential fatty acids and (*b*) antioxidants reduced tumor multiplicity at the higher lipid levels to essentially the same value as that which occurred for the minimum essential fatty acid diet (Table 3).

With respect to antioxidants, Horwitt's studies (28) imply that with increased intake of polyunsaturated fat an increased antioxidant requirement is incurred if tissue-specific lesions are to be prevented. McCay *et al.* (29) have demonstrated such a relationship for 7,12-dimethylbenz(*a*)anthracene-induced mammary carcinogenesis. The studies of Mathews-Roth and Krinsky (30) support such a relationship for UV carcinogenesis. These investigators found that the ability of β-carotene, an oxygen radical scavenger, to protect against UV-induced skin tumors declined as dietary fat was increased.

Whereas Hopkins *et al.* (31) and King *et al.* (9) have provided evidence that the enhancing effect of dietary lipid upon carcino-

Table 3

Effects of dietary lipid and antioxidants on UV-mediated tumor multiplicity. Data were analyzed with the Statistical Analysis System program NPAR1WAY at wk 20

	Mean no. tumors/animal						Significant comparisons				
	Control			Antioxidant			Lipid levels effect		Antioxidant effect		
Diet	1	2	3	1	2	3					
Group	1	2	3	4	5	6	1 *vs.* 2	1 *vs.* 3	1 *vs.* 4	2 *vs.* 5	3 *vs.* 6
	1.89	1.30	0.61	0.88	0.88	0.72	[a]	0.01[b]	0.02	[a]	[a]

[a] Not significant, at $P > 0.05$.
[b] Numerical values. $P <$ the designated values; Diet 1, 4% corn oil; Diet 2, 2% corn oil; Diet 3, 0.75% corn oil.

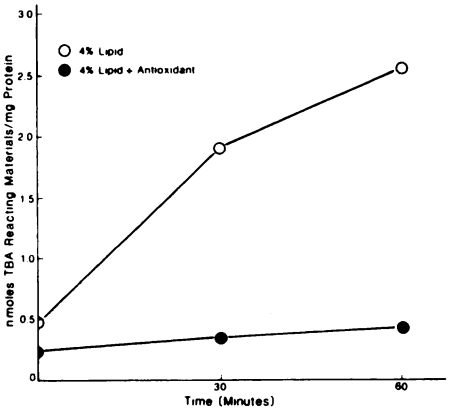

Chart 4. Typical epidermal lipid peroxidation reactions. TBA-reacting materials were measured in epidermal homogenates prepared from animals receiving diets containing 4% corn oil with or without antioxidants for 35 wk.

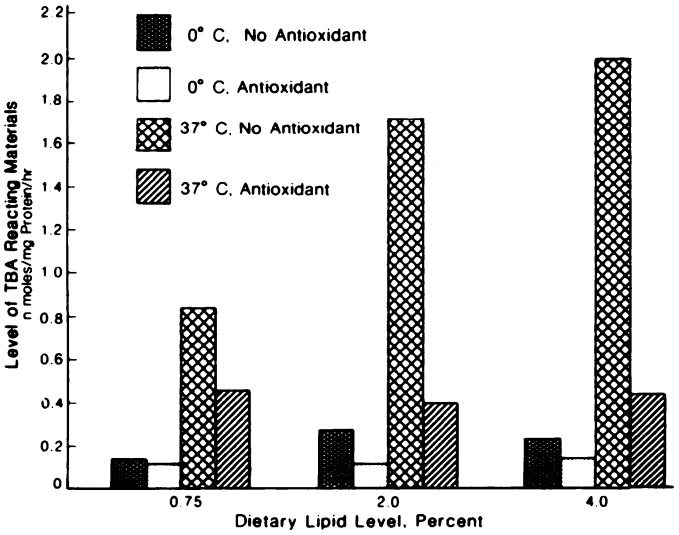

Chart 5. Effects of dietary lipid and antioxidants on epidermal lipid peroxidation. TBA reaction levels were determined in epidermal homogenates after 1 h incubation at 0° and 37°C. Homogenates were prepared from animals receiving the designated dietary levels of lipid with and without antioxidants. The reaction mixture contained no added iron or ADP. Values are the mean of three experiments.

genesis is partially mediated during the promotional stage in which the rate of tumor cell division is increased, Floyd *et al.* (32) suggest that peroxidized polyunsaturated fat may also be involved in the activation of carcinogens, thereby influencing initiation as well. The current studies may provide some insight into the potential mechanisms by which antioxidants act to inhibit carcinogenesis. Within the paradigm of current thought (33, 34), antioxidants are generally believed to act by (*a*) alteration of metabolism of the carcinogen, *i.e.*, by either decreased metabolic activation, increased detoxification, or increased clearance of the active carcinogenic species via glucuronic acid conjugation; (*b*) scavenging active species of carcinogens to prevent their reaching critical target sites; (*c*) acting directly with the carcinogenic species to prevent further reactions from occurring, either by competitive inhibition for critical target sites or indirectly through permeability alterations or transport of the carcinogen that results in less carcinogen reaching target sites; (*d*) scavenging oxygen radicals produced in prostaglandin synthesis or as products of normal metabolism; and (*e*) scavenging lipid radicals formed from peroxidation of cellular lipid constituents.

By eliminating manifestations of anticarcinogenic activities that are specific to individual carcinogens it may be possible to gain insight into more general underlying mechanism(s) of anticarcinogenic agents and as a corollary to the carcinogenic process itself. UV radiation is considered to be a complete carcinogen in that it acts as both initiator and promoter in skin (35). Whereas the use of a physical carcinogen such as UV may be disadvantageous in discerning the stage of carcinogenesis at which a modifier, *i.e.*, lipid and/or antioxidant might act, there is a distinct advantage in delimiting potential mechanisms of such modifiers. Of the five mechanisms previously listed, it is apparent that the first three would not apply to UV.

The remaining mechanisms both point to free-radical reaction involvement. The first, scavenging of active oxygen radicals produced from arachidonic acid oxidation suggests a potential link between dietary lipid, antioxidants, and immunocompetence. It is now clear that UV radiation induces systemic alterations in immune function which albeit a complex response is readily exemplified by decreased ability of a syngeneic host to reject transplanted UV-induced tumors, a type that is highly antigenic in comparison to other murine tumors (36). It is also known that increased polyunsaturated lipid intake, particularly those high in linoleic and arachidonic acids, is reflected in elevated cellular membrane arachidonic acid content (37). The oxidation of the latter results in formation of prostaglandins and a number of related immunopotentiators. UV radiation has recently been shown to activate epidermal phospholipase A_2 which releases membrane-bound arachidonic acid (38). The released arachidonic acid is subjected to cyclooxygenase attack that ultimately results in formation of an oxygen radical and elevated prostaglandin levels (39). Prostaglandin synthesis is presumed to be partially regulated by oxygen radical inhibition of cyclooxygenase. Nordlund (40) has recently demonstrated that para-substituted phenols and arachidonic acid markedly affect population

densities of Langerhans cells, immunocompetent dendritic cells that reside in the epidermis and that are readily destroyed by UV (41). The phenols are thought to act as oxygen radical scavengers thereby deregulating prostaglandin synthesis. Thus one can envision how the respective tumor-enhancing and inhibitory effects of lipids and antioxidants could be attributable in part to potentiation of the immune system.

Evidence supporting the involvement of lipid radicals and antioxidants in photocarcinogenesis has recently been summarized (42). The present data support such a contention, *i.e.*, (*a*) polyunsaturated lipid enhances the carcinogenic response to UV in a manner directly related to its dietary level; (*b*) antioxidants produce an inhibitory effect almost exactly equal to the degree of exacerbation of carcinogenesis evoked by increasing lipid levels; and (*c*) dietarily administered antioxidants inhibit an empirical measure of lipid peroxidation, the latter being a function of dietary lipid intake.

There appears to be a striking similarity between polyunsaturated lipid and antioxidant effects upon UV carcinogenesis and those evoked in certain chemically induced cancers. This suggests to us that these effects are germane to prominent biochemical mechanisms that underlie the carcinogenic process regardless of the specificity of initiating events. *In toto,* these data demonstrate a respective enhancement and inhibition of UV carcinogenesis by unsaturated dietary lipid and antioxidants, and strongly imply that free-radical reactions, particularly lipid peroxidation, play a role in at least part of the photocarcinogenic response.

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