

## Diet and Skin Cancer

HOMER S. BLACK

*Veterans Affairs Medical Center and Department of Dermatology  
Baylor College of Medicine  
Houston, Texas*

### INTRODUCTION

The skin represents one of the largest organ systems of the human body, constituting about one-twelfth of total body weight. Situated at the interface between the body and its environment, and acting as a barrier to the harmful effects of an expansive array of extrinsic agents, the skin consequently provides the foremost target for environmental insult (Thody and Friedmann, 1986). Consequently, skin cancer is the most frequently occurring malignant neoplasm in the United States, accounting for an estimated 900,000–1,200,000 new cases annually (Miller and Weinstock, 1994).

Major milestones in the study of cancer development have been achieved through investigations of the carcinogenic potential of various agents on skin (Berenblum, 1954, 1979; Boutwell, 1964), as this target tissue provides a model with obvious advantage for cancer studies.

Although Sir Percival Pott (1775) was the first to associate excessive exposure to an external agent (soot) and the unusually high skin cancer incidence of chimney sweeps, it was not until 1915 that Yamagiwa and Ichikawa (1918) first successfully produced cancer (skin) in experimental animals with coal tar—a study that helped launch the investigative era of carcinogenesis. Insight into the carcinogenic process was advanced with development of the two-stage theory, operationally defined as initiation and promotion (Berenblum, 1941; Rous and Kidd, 1941). Tumor initiation is generally regarded as a permanent alteration of the cell genotype that is brought about by a single or sequential exposure to a sub-threshold dose of a carcinogenic agent, while promotion has been described as “the process whereby an initiated tissue or organ develops focal proliferations, one or more which may act as precursors for subsequent steps in the carcinogenic process” (Farber, 1982). This factitious segmentation of the carcinogenic continuum has been invaluable in allowing dissection and definition of the biochemical steps in the cancer

process, and confirmation of the two stage theory with the so-called “reverse” experiment of Berenblum and Haran (1955) demonstrated that initiation and promotion stages were actually descriptive of the process occurring in mouse skin. It was from these early studies that the concept of a multistage carcinogenic process developed.

Even though the perception prevails that interest in environmental agents as causal factors in human cancer represents a more recent shift in emphasis (Higginson and Muir, 1976; Weisburger *et al.*, 1977), it should be clear from the foregoing that the study of cancer and the carcinogenic process has been driven by early recognition that environmental and occupational factors played a paramount role in the occurrence of cancer (Haagensen, 1931). Foremost among those factors are chemicals, viruses, radiation, and diet. Although there are over 200 different types of skin cancer, and much of our knowledge gleaned of the carcinogenic process has been obtained from studies with carcinogenic chemicals, exposure to ultraviolet radiation (UV) accounts for approximately 90% of nonmelanoma skin cancer incidence (Elmets and Mukhtar, 1996).

This chapter will deal primarily with two of the major extrinsic factors that can influence the development of skin cancer, namely, *ultraviolet radiation*, the primary causal agent, and *diet*, a potential modifier. The author will provide the reader with (1) a brief historical preface and an overview of the status of our current understanding of the relationship of how diet may influence skin cancer from both an experimental and clinical prospect; (2) suggestions for future research directions; and (3) general dietary guidelines, based upon our current knowledge, proposed for the prevention and/or management of skin cancer. The chapter is not intended to be a complete bibliographic reference source of skin cancer.

There are many major contributions that have been made to our understanding of the carcinogenic process in skin, as

already noted, through studies with an array of chemicals and even combined with some dietary factors. Only from an historical perspective are some of the early contributions recognized. But we focus on the carcinogenic agent, UV, with the knowledge that many of the chemical studies are irrelevant to the majority of human skin cancers. For example, UV involves no activation or detoxification of the presumed carcinogenic species; no competitive chemical inhibition; no binding to target molecules; and no transport to respective target sites. Changing the chemical milieu through dietary modification could impact any of these activities. Thus, it is fortuitous, in this respect, that the primary causal agent of skin cancer (UV) is a complete physical carcinogen, allowing examination of the *underlying* mechanisms of dietary modification of the skin cancer process.

## THE NATURE OF ULTRAVIOLET RADIATION

Solar radiant energy includes a broad region of the electromagnetic spectrum containing ultraviolet (UV), visible (light) and infrared radiation [International Agency for Research on Cancer (IARC), 1992]. UV radiation is generally considered to include wavelengths between 10 and 400 nm, with the Extreme UV extending from 10 to 100 nm; Far UV from 100 to 180 nm; Middle UV from 180 to 300 nm; and Near UV from 300 to 400 nm. Those wavelengths reaching the earth's surface are usually limited to 290 nm and greater, as shorter wavelengths are absorbed by stratospheric ozone. The photobiological designations (UV radiation of biological importance) of the Commission Internationale de l'Éclairage (CIE, International Commission on Illumination, Vienna, Austria) are reflected in Fig. 27.1, with the exceptions that 320 nm, rather than 315 nm, has been used to define the upper limit of UVB, and UVA has been further segmented into UVA1 and UVA2 based upon the recommendations of a Task Force empaneled at the first conference on the biological effects of UVA (Harber, 1986). Thus, UVC is defined as 100–280 nm; UVB as 280–320 nm; and UVA from 320 to 400 nm.

Although electromagnetic radiation is propagated in the form of waves, radiation may alternatively be considered as composed of a very large number of small packets of energy referred to as "quanta" or "photons" (Tarrant, 1989). The energy content of a photon is inversely proportional to the wavelength. Photons of the UVB band, at 280–320 nm, exhibit energies from 3.9 to 4.4 electron volts (eV), whereas those of the longer UVA band range from 3.1 to 3.9 eV (Grossweiner, 1989). In general, photon energy, or wavelength, determines the nature of the photochemical/photobiological process initiated, while the "exposure dose" (the energy falling upon a unit surface area of an object and ex-

pressed as joules per square meter) limits the rate at which the process takes place. Implicit in this is the requirement that photons be absorbed by a suitable target molecule (chromophore) before the process or response can occur—known as the First Law of Photochemistry. Thus, a photobiological response, per unit exposure of UV radiation, will vary with the wavelength of radiation and is dependent upon the efficacy of interaction between target molecules and the incident photons. A quantitative plot of this spectral variation is known as an "action spectrum."

When radiation strikes the skin, part of it may be reflected, part may be absorbed in outer layers of the skin, and part may be transmitted inward to deeper layers where the energy of the photon is absorbed (Morison, 1991). Depth of penetration is wavelength dependent. Many chromophores such as nucleic acids and proteins absorb the shorter wavelengths, and scattering of shorter wavelengths is normally more pronounced. In a fair-skinned individual, only about 15% of the UVB radiation reaches the dermis whereas about 50% of the longer UVA wavelengths penetrate to the dermis.

The more energetic UVB band is also the most biologically active portion of the solar spectrum, about 1,000 times more so than UVA with regard to erythema (sunburn). With regard to carcinogenesis, Forbes (1984) concluded that wavelengths greater than 330 nm had an average relative efficiency for carcinogenesis in mice of less than 0.002, relative to 1.0 at 297 nm. Using a similar animal model, van Weelden *et al.* (1986) found that in order to produce tumors in 1% of the animals, 1000 times more UVA exposure was required compared to UVB. The greater efficacy of UVB in carcinogenesis is readily apparent in Fig. 27.2, which represents an action spectrum for human nonmelanoma skin cancer, derived from experiments with hairless mice and adjusted for humans by correcting for optical differences between murine and human epidermis (deGruijl *et al.*, 1993; deGruijl and van der Leun, 1994). Nevertheless, there is approximately 20–30 times more UVA radiant energy in sunlight than UVB, and it is clear from the action spectrum that wavelengths greater than 340 nm may contribute, in no small part, to the carcinogenic action of UV radiation. Thus, the risks from additional UVA exposure, such as from tanning parlors or excessively prolonged sun exposure of individuals protected with effective UVB sunscreens, cannot be ignored, although the latter concern may be unfounded (Urbach, 1992–1993).

## THE ETIOLOGIC ROLE OF UV RADIATION IN SKIN CANCER

Over 100 years after Pott (Potter, 1962) had associated excessive exposure to soot with skin cancer occurrence, Unna

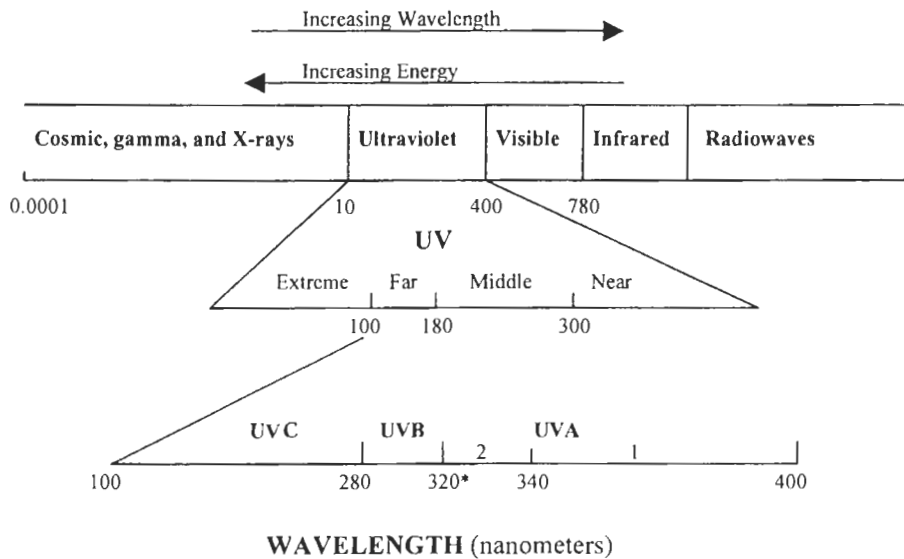


FIGURE 27.1 The electromagnetic spectrum with expanded scale of biological relevant ultraviolet wavelengths.

(1894) associated the severe degenerative changes of the sun-exposed areas of the skin of sailors with the development of skin cancer, “Carcinome der Seemannshaut” (Urbach, 1997).

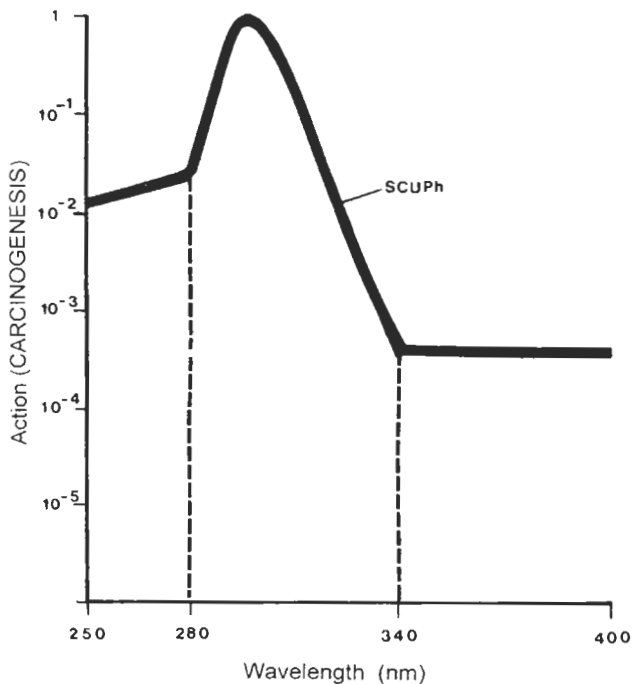


FIGURE 27.2 An action spectrum for UV-induced skin cancer in humans. This action spectrum, based upon currently available data and with qualifying caveats, is under consideration by Committee TC 6-32 for recommendation as a CIE standard.

Shortly thereafter, Dubreuilh (1896) confirmed the association of “la lumière solaire” (sunlight) exposure with keratoses and skin cancer exhibited by vineyard workers in southern France. The predisposition to skin cancer of light-skinned individuals, especially of Celtic origin, living in geographical areas of high insolation was also observed by Shield (1899).

Experimental proof of the causal role of UV irradiation in skin cancer was provided by Findlay (1928) when he demonstrated that UV radiation delivered daily from a quartz mercury-vapour lamp produced skin cancers in mice. Roffo (1939) demonstrated that skin cancer in rats could be induced by radiation from both a mercury arc lamp as well as *natural sunlight*. In addition, he showed that the principal offending UV wavelengths were excluded by clear window glass, thus setting an approximate limit of effectiveness in producing skin cancer to those wavelengths of  $\leq 320$  nm.

Between 1941 and 1975, Blum and his collaborators (1941, 1975; Blum, 1959) conducted important, extensive quantitative studies on the carcinogenic effects of UV radiation. They concluded that (1) repeated, but not single, doses of UV are required to produce tumors within the lifetime of an animal, and (2) tumor growth is accelerated by successive doses of UV radiation. Development time, a measure of tumor induction, was defined as the time from the application of the first dose of UV to the appearance of a tumor of defined volume. They also found that (3) differences in dose, intensity, or interval between doses did not alter the shape or the slope of the dose–time response, but only moved the relative position of the response curve along the dose axis, and (4) reciprocity of the carcinogenic response

held until doses of UV became too small to result in tumors during the lifetime of the animal. Other aspects of Blum's experimental model of UV carcinogenesis have been summarized (Blum, 1948; Urbach *et al.*, 1976; Black and Chan, 1977).

Roffo (1939) was the first to conduct an epidemiological study of skin cancer in humans, a study in which skin cancer occurrence was analyzed with respect to anatomical site, gender, nationality, and occupation. Whereas the question of an etiologic role of sunlight in human skin cancer does not lend itself to direct experimentation, it is nevertheless firmly based upon extensive observation and supported with animal experimentation. The evidence has been summarized as follows (Urbach, 1969; Urbach *et al.*, 1974; Emmett, 1973):

- Skin cancers occur most frequently on the head, neck, arms and hand—those parts of the body habitually exposed to sunlight.
- Members of pigmented races which sunburn less readily than light-skinned individuals have very much less skin cancer. When skin cancer does occur in pigmented races, it affects those areas exposed most frequently to sunlight (Quisenberry, 1963; Segi, 1963; Mulay, 1963).
- There appears to be much greater incidence of skin cancer among those Caucasians who spend more time outdoors than those who work predominantly indoors (Gellin *et al.*, 1966).
- Skin cancer is more common in light-skinned people living in areas of greatest insolation (Silverstone and Searle, 1970; Mason *et al.*, 1975).
- An exceptionally high risk of skin cancer exists among those individuals with genetic diseases characterized by intolerance to sunlight (Cleaver, 1968).
- Skin cancer is readily produced in mice and rats upon repeated exposure to UV radiation (Roffo, 1939, Blum *et al.*, 1941; Winkelmann *et al.*, 1963).

## EXPERIMENTAL DATA ON NUTRITIONAL EFFECTS

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### Background to Nutritional Aspects of Experimental Cancer

The fact that diet, and particularly food quantity, could influence cancer was recognized by early physicians who advocated "fames cura," or a starvation diet as treatment for cancer, as it was surmised that this disease, as others to which humans were subjected, proceeded from the food they ate (Garrison, 1929). Thus, many of the earlier experimental studies examined the growth-inhibiting effect of undernourishment observed on both development of neoplasms

and the effects on growth of existing tumors (Stern and Willheim, 1943). This growth-inhibiting effect was widely observed for numerous animal tumor transplants. For example, Bischoff *et al.* (1935) found that marked caloric restriction (50%), a caloric intake adequate for maintenance of the animals' general health, resulted in a 10-fold retardation in tumor growth of transplanted mouse sarcoma 180, whereas a 20% reduction resulted in no significant effect. In a carefully controlled experiment employing semipurified diets, Visscher *et al.* (1942) found the incidence of spontaneous mammary carcinoma dropped from 67% in control animals fed *ad libitum* to zero in animals fed a diet adequate in protein, vitamins, and minerals but in which carbohydrates and fat were each reduced to approximately one-third of the total calories ingested. Two important observations were noted around this period. First, animals on a restricted caloric diet exhibited greater longevity (Tannenbaum, 1940b) and second, short-term starvation was much less effective in restricting tumor growth than chronic undernourishment—a result that paralleled the clinical experience and undoubtedly tended to relegate dietary treatment of cancer as ineffective. Thus, the practical significance of caloric restriction appeared to lie in prevention, or at least a delay in time of appearance of neoplasms. Tannenbaum (1942a) demonstrated that underfeeding, again a 33–50% caloric restriction, resulted in both a marked delay in appearance of 3,4-benzpyrene-induced skin cancers as well as a decrease in total number of cancers. He also observed that caloric restriction exerted its main effect on the developmental (post-initiation) stage of carcinogenesis (Tannenbaum, 1944a). This influence of caloric restriction on *induced primary* tumor formation set the stage for a more analytical approach to the evaluation of the role of dietary factors in carcinogenesis. There seems little doubt that caloric restriction could play an important role in prevention of a wide range of human cancers (Albanes, 1987; Hocman, 1988; Weindruch *et al.*, 1991).

Early studies to determine the influence of dietary fat on cancer also began with observations on the development of transplanted tumors (Sugiura and Benedict, 1930). Mixed results were obtained, as exemplified by the finding that with Flexnor-Jobling rat carcinoma the percentage of positive tumor inoculations (takes) and tumor growth rates were diminished while the number of tumor regressions increased when the host animals were fed high-fat (butter fat) diets. However, the indictment of lipid as a dietary constituent that potentiates carcinogenesis resulted from the studies of Watson and Mellanby (1930) in which dietary fat (12.5–25% butterfat) was shown to enhance coal tar-induced skin tumors in mice. This observation was followed with intense investigation of the effect of dietary fat on carcinogenesis in the 1940s and 1950s (Tannenbaum, 1953, 1959). Lavik and Baumann (1941) made several intriguing

observations that provided early insight into the nature of the fat effect. First, the presence of lipid peroxides did not alter tumor-promoting power of fat. Both oxygenated and UV-irradiated samples, while exhibiting a high peroxide number, were relatively inactive in their influence on carcinogenesis. In their studies, heated (300°C for one hour) fat samples exhibiting lower peroxide numbers were most effective in promoting carcinogenesis. In this regard it is interesting to note that Haven (1936) found the growth rate of rat carcinoma 256 was lower in animals receiving a diet containing cod liver oil (Iodine number 145–180) than in those fed coconut oil (Iodine number 8–9.5). This was determined to be related to the presence of longer chain fatty acids in cod liver oil, no doubt the long chain *n*-3 fatty acids that are now known to exhibit anticarcinogenic effects. The second noteworthy observation in their studies was that mice seldom survived diets with 25% or more fat. A fat level of 15% (lard, butter, or vegetable oils) was adequate to demonstrate an effect on tumor formation and 10% gave a measurable response. Finally, they observed that the most effective period for enhancing skin carcinogenesis by feeding high fat was 1.5 to 3 months after the beginning of application of methyl chloranthane (MCA). These observations suggested that the degree of saturation of the dietary lipid was less important than the level and/or fatty acid composition of the dietary lipid source; that the percentage change in level of fat required to elicit a response was considerable less than the percentage of caloric restriction required to produce a similar response; and that the fat effect occurred in the post-initiation, or promotion stage of carcinogenesis. Indeed, Tannenbaum (1944b) clearly demonstrated that the dietary fat effect occurred during the postinitiation stage of chemical-induced carcinogenesis. Contemporary studies of that time (Tannenbaum, 1942b; Lavik and Baumann, 1943; Rusch *et al.*, 1945) suggested that although most of the accelerating action of fat on tumor formation could be explained on the basis of an increased caloric intake, fat *per se* increased the rate of tumor formation, particularly when the total intake of calories was restricted. Despite the many methodological problems suffered by the early experimental studies, they clearly pointed to caloric restriction and dietary fat reduction as two important dietary avenues to prevent or moderate the course of cancer for several organ sites and established fertile lines for future investigation. It is interesting to note that over 55 years ago, after examination of then available insurance statistics, Tannenbaum (1940a) observed that “*persons of average weight or less are not so likely to develop the disease [cancer] as those who are overweight*” and suggested “*that a caloric restricted and low-fat diet may aid in the prevention of human cancer, or at least delay its onset.*”

## UV-Induced Skin Cancer and Dietary Modification

Roffo (1929), who had provided early evidence for the role of UV-irradiation in the etiology of skin cancer, had also recognized the importance of lipids in cancer development. He had hypothesized that cholesterol was an “heliotropic” substance that migrated and accumulated at anatomical sites routinely exposed to UV rays of the sun. Subsequent degradation of cholesterol resulted in substances with carcinogenic activity (Roffo, 1933). This presented an attractive theory, as cholesterol is naturally occurring and widely distributed in biological tissues and thus could provide a basis for the biogenic origin of cancer. Indeed, a flurry of investigative activity continued through the 1950s in search of carcinogenic cholesterol derivatives and/or evidence of cholesterol involvement in cancer development (Fieser, 1954). It was just such an investigation that resulted in the observation that dietary fat had an influence on UV carcinogenesis (Baumann and Rusch, 1939). These investigators in an effort to examine the purported role of cholesterol in the carcinogenic process, used a fat-enhanced (5% hydrogenated cottonseed oil) diet to ensure sterol absorption. In addition, a second group of animals was fed a high-fat diet containing 30% cottonseed oil. Tumor latency of animals receiving cholesterol-supplemented diets was found to be no different from that of animals receiving a stock ration, whereas latency was shortened by about four weeks for animals receiving the high-fat diet. Thus, while failing to find supporting evidence for a role of cholesterol in UV-induced skin cancer, and despite the fact that their experimental design failed to control for the usual nutritional variables, as did many of the early investigations, they were the first to demonstrate the potential influence of dietary lipid upon UV-induced skin cancer.

Pursuant to the potential involvement of cholesterol in UV-induced carcinogenesis, a putative carcinogen, 5 $\alpha$ ,6 $\alpha$ -cholesterol epoxide, was identified in UV-irradiated skin from among several photooxidation products of the parent sterol (Black and Lo, 1971). Using the hairless mouse model (Black, 1983), cholesterol epoxide formation was shown to be UV dose-dependent, and levels of this compound increased eightfold in chronically irradiated animals (Black and Douglas, 1972, 1973). This increase preceded the appearance of squamous cell carcinomas. Although suggestive, no definitive evidence for the causal involvement of this compound in UV carcinogenesis was forthcoming. Nor did cholesterol feeding studies indicate a role for this sterol in UV carcinogenesis, although a slight, but statistically significant protective effect was observed (Black *et al.*, 1979).

As the formation of cholesterol epoxide was the result of photooxidative reactions, it seemed reasonable that these reactions might be inhibited by antioxidants. This concept was explored by feeding mice a closed formula ration containing a 2% (w/w) antioxidant mixture containing 1.2% ascorbic

acid, 0.5% butylated hydroxytoluene (BHT), 0.2% *dl*- $\alpha$ -tocopherol (acetate), and 0.1% reduced glutathione. At various time intervals, cutaneous antioxidant levels were determined. When skin at the various feeding intervals was irradiated with UV and cholesterol epoxide levels measured, an inverse relationship with antioxidant content was observed (Lo and Black, 1973). Thus, antioxidants, known to impede lipid peroxidation, were shown to inhibit the photochemical conversion of skin cholesterol to its epoxide and provided evidence for peroxidative involvement in carcinogenesis. These findings suggested possible prophylactic effects of systemic antioxidants not only on the formation of this putative carcinogen, but also on the subsequent pathological conditions that might result from, or concurrently with, its formation (Black, 1987). Indeed, when fed the same antioxidant mixture and chronically irradiated, animals demonstrated significantly fewer actinic lesions and tumors than control animals (Black, 1974; Black and Chan, 1975). Pauling *et al.* (1982) corroborated the observations concerning the inhibitory effect of the antioxidant mixture on UV carcinogenesis. Subsequent studies demonstrated that BHT, at concentrations in the antioxidant mixture, was the most active principal (Black *et al.*, 1978), although a second study from Pauling's group (Dunham *et al.*, 1982) found that higher levels of ascorbic acid, alone, could significantly inhibit UV carcinogenesis.

Other antioxidants and singlet oxygen quenchers have been shown to provide significant protection against UV carcinogenesis. Carotenoids, notably  $\beta$ -carotene, were shown to be photoprotective in dietary studies (Mathews-Roth, 1982). The protective effect is thought to be related to quenching of specific reactive species, although  $\beta$ -carotene may also act as an antioxidant (Krinsky, 1987). In this respect, strong indirect evidence for reactive oxygen species and radical involvement comes from studies in which UV carcinogenesis has been inhibited by a wide range of natural and synthetic agents exhibiting antioxidant properties (Black, 1974; Epstein, 1977; Dunham *et al.*, 1982; Wang *et al.*, 1991; Bissett *et al.*, 1991; Burke *et al.*, 1992; Gerrish and Gensler, 1993).

As a corollary to antioxidant-inhibited photocarcinogenesis, any condition that limits the level of radical susceptible targets should, likewise, modulate the UV carcinogenic process. Unsaturated fatty acids are a prime center for free radical attack and therefore prime candidates for manipulation of radical susceptible targets. Thus, it was nearly 45 years after Baumann and Rusch (1939) first reported that dietary lipid could influence UV carcinogenesis, that this seminal observation was to again receive attention, albeit from a somewhat different perspective (Black *et al.*, 1983).

Indeed, an approximate linear relationship between polyunsaturated lipid (corn or soybean oil) intake and UV carcinogenic expression was observed (Black *et al.*, 1985), with the lowest lipid level resulting in a significantly longer tumor latent period. In addition, with increased lipid intake, the number of tumors per animal (multiplicity) increased.

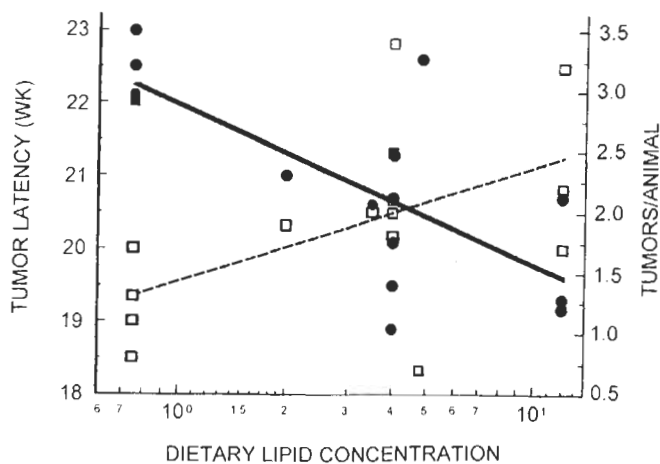


FIGURE 27.3 Relationship of UV-carcinogenic parameters, tumor latency, and multiplicity to lipid level intake (corn oil). Regression lines are derived from 15 observations from 6 experiments evaluated in an incomplete block design. Solid line and circles indicate the tumor latency period; dashed line and open squares indicate tumor multiplicity. Tumor latency period decreases and tumor multiplicity increases as the level of corn oil intake increases. Reprinted with permission from *The Cancer Bulletin*. Copyright 1993 The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

The relationship between level of dietary lipid intake and carcinogenic parameters is reflected in Fig. 27.3 (Black, 1993). Interestingly, dietary antioxidants produced an inhibitory effect almost equal to the degree of exacerbation of UV carcinogenesis evoked by increasing dietary lipid levels.

Reeve *et al.* (1988) found that feeding a diet supplying totally saturated sunflower oil (catalytically hydrogenated) completely abolished the UV carcinogenic response whereas those animals fed polyunsaturated sunflower oil exhibited 100% tumor incidence. When the diet of the animals receiving hydrogenated fat was reconstituted to a normal mixed fat diet, large numbers of skin tumors rapidly appeared, suggesting that tumor initiation had not been prevented by lack of polyunsaturated fat, but that an essential fatty acid deficiency held the tumors in abeyance, that is, at the promotion stage. It was subsequently shown that the principal effect of high dietary fat (corn oil) occurs at the promotion stage of UV carcinogenesis and that by replacing a high-fat diet with one of low-fat immediately after UV initiation, the exacerbating effect of high fat could be negated (Black *et al.*, 1992). Further support for a polyunsaturated fat requirement for UV carcinogenic expression was obtained when animals were fed constant levels of fat with graded proportions of polyunsaturated sunflower oil mixed with hydrogenated cottonseed oil (Reeve *et al.*, 1996). The UV-carcinogenic response was of increasing severity as the polyunsaturated content of the mixed dietary fat was increased.

That degree of dietary fatty acid saturation was an important determinant of carcinogenesis was suggested at an earlier period in nutritional carcinogenesis studies when Miller *et al.*

(1944) found that diets composed almost entirely of saturated fatty acids would retard chemically induced hepatomas in rats. Similarly, Carroll and Kohr (1971) and Carroll and Hopkins (1979) found that rats fed unsaturated lipids developed more mammary tumors than those fed the same levels of saturated lipid. The polyunsaturated fatty acid, linoleic acid, appears to be a requirement for mammary carcinogenesis (Ip *et al.*, 1985). In an earlier study of UV carcinogenesis, partially hydrogenated (60%) corn oil was found to inhibit UV carcinogenesis, compared to animals fed 4% or 12% corn oil diets (Black *et al.*, 1983). On careful inspection, those data suggest that a much more complex relationship exists between degree of lipid saturation and UV carcinogenesis. The 60% hydrogenated corn oil would have had approximately the same level of linoleic acid (18:2), the principal polyunsaturated fatty acid in corn oil, as that of the 4% corn oil diet, yet, by comparison, significantly inhibited UV carcinogenesis. Potential products of catalytic hydrogenation, such as *trans* fatty acids or conjugated linoleic acid, have not been examined for effect in UV carcinogenesis. Moreover, when animals were fed a diet employing menhaden oil as lipid source, a polyunsaturated lipid rich in eicosapentaenoic and other *n*-3 fatty acids, UV carcinogenic expression was not enhanced, but markedly inhibited (Orengo *et al.*, 1989). These observations would suggest that degree of dietary fatty acid saturation alone is not a determinant in modulation of UV carcinogenic expression.

#### Possible Mode of Action of Dietary Fatty Acids in Modulation of UV Carcinogenesis

From the foregoing, it should be apparent that both essential *n*-6 (particularly linoleic acid) and *n*-3 fatty acids are important modulators of the carcinogenic process. Both types of fatty acids are important determinants of prostanoid metabolism as well. Prostaglandins (PG), particularly of the 2-series, are recognized as important participants in the inflammatory response to UV and it has been shown that *n*-3 fatty acids markedly lower cutaneous PGE<sub>2</sub> levels and reduce the sunburn response (Rhodes *et al.*, 1995). They also act as physiological immunoregulators (Plescia and Racis, 1988). With respect to the latter, some studies suggest that the promotion stage of carcinogenesis, the point at which certain dietary lipids exert maximum influence, may be modulated immunologically (Vitale and Broitman, 1981). Indeed, it has been shown that suppressor T-cell function is PGE<sub>2</sub> dependent (Chung *et al.*, 1986). These investigators have demonstrated that UV-induced immune suppression is abrogated by treatment with an inhibitor (indomethacin) of PG synthesis. Indomethacin treatment has also been reported to convey a protective effect to UV carcinogenesis (Reeve *et al.*, 1995).

UV is not only immunosuppressive, but is known to activate epidermal enzymes responsible for facilitating PG synthesis from arachidonic acid (AA) through the cyclooxygenase pathway. Omega-3 fatty acids compete for reactive sites

on the cyclooxygenase enzyme and may shunt PG precursors through the lipoxygenase path, in effect reducing PG levels. PG synthesis may also be suppressed by reducing the level of hydroperoxide activator, possibly achieved by free radical scavengers or antioxidants that impede lipid peroxidation (Lands *et al.*, 1982). Thus, *n*-3 fatty acids not only act competitively with cyclooxygenase substrates to reduce PG levels, but *n*-3 fatty acids exhibit a high requirement for hydroperoxide activator, an *in vivo* level that may normally be insufficient to promote rapid PG synthesis. Indeed, Henderon *et al.* (1989) have shown that diets containing menhaden oil dramatically suppress plasma and cutaneous PGE<sub>2</sub> levels. Furthermore, plasma PGE<sub>2</sub> levels exhibit a near linear relationship to the log of corn oil intake, with lower levels of plasma PGE<sub>2</sub> present in animals receiving low-fat diets (Fischer and Black, 1991). Epidermal capacity to metabolize AA via the cyclooxygenase pathway is also potentiated by *n*-6 dietary fatty acid intake and is drastically inhibited in animals receiving dietary *n*-3 fatty acids.

It has been shown that dietary fat can suppress the T cell-mediated immune status in UV-irradiated mice, both with respect to contact (CH) and delayed-type hypersensitivity (DTH) (Black *et al.*, 1995a; Reeve *et al.*, 1996). Two questions arise with respect to the relevance of these findings to carcinogenesis. First, is the timing of these influences upon specific immune responses compatible with the time (i.e., postinitiation) at which high levels of dietary fat (*n*-6 fatty acids) are known to exacerbate UV carcinogenesis? Second, does dietary fat affect these specific immune responses *via* T-cell mediated immunologic pathways common with those related to carcinogenesis? Some evidence suggests that they do not, at least for DTH. High dietary fat intake results in DTH suppression, even before UV exposure (Black *et al.*, 1995a). UV irradiation hastens the complete suppression of this response in animals receiving high-fat diets. However, the DTH response rebounds by the time tumors appear in chronically-irradiated animals. Thus, the temporal profile of DTH response does not conform to the time at which dietary fat exerts its principal influence upon UV carcinogenesis. On the other hand, when tumor transplantation studies were undertaken, with animals receiving various periods of UV radiation, tumor rejection was significantly greater in animals fed low-fat diets—but only at a time when the complete tumor-initiating UV dose had been delivered. This, of course, is the time (postinitiation) when dietary fat *does* exert its influence on carcinogenesis.

In conclusion, it is clear that high levels of dietary fat exert profound influence (suppression) over specific immune responses, some of which occur when high dietary fat exacerbates UV carcinogenic expression. High dietary fat has been shown to elevate PGE<sub>2</sub> levels, the latter known to act as an immunoregulator of T-cell function and to modulate UV carcinogenesis. These observations make a strong circumstantial case that high dietary fat, especially those rich in es-

sential fatty acids, potentiates UV carcinogenesis *via* regulation of prostanoid metabolism in a manner that consequently suppresses immune responses that control the outgrowth of UV-induced tumors.

## CLINICAL STUDIES OF NUTRITIONAL EFFECTS

### Nonmelanoma Skin Cancer

The magnitude of the skin cancer problem is readily apparent upon comparison of its occurrence to that of other forms of cancer. As noted earlier, Miller and Weinstock (1994) estimated that the most common nonmelanoma skin cancers—basal and squamous cell carcinomas—account for 900,000–1,200,000 new cases annually in the United States. A recent estimate of new cases in the United States of all forms of cancer (exclusive of nonmelanoma skin cancer, which is usually not recorded in population-based registries) for 1997 is 1,400,000 (Parker *et al.*, 1997). Thus, the incidence of nonmelanoma skin cancer is approximately equal to the combined incidence of all other cancers! Alarming, population-based studies indicate that there has been a steady increase in incidence of nonmelanoma skin cancer over the past two decades (Glass and Hoover, 1989; Weinstock, 1989; Gallagher *et al.*, 1990). This increase occurs in regions of both high and low insolation, for both basal and squamous cell carcinomas, and appears to affect all age groups.

Epidemiologic studies indicate that at least 90% of basal and squamous cell carcinomas can be attributed to UV exposure (Mason *et al.*, 1975; Committee on Chemistry and Physics of Ozone Depletion, 1982; Scotto *et al.*, 1983). Koh *et al.* (1995) have updated and summarized the evidence linking solar exposure to nonmelanoma skin cancer. It is estimated that over 50% of the total lifetime dose of solar UV is received in childhood and adolescence (Marks *et al.*, 1990). In accord with this, it has also been estimated that the regular use of an SPF 15 sunscreen during the first 18 years of life would reduce the lifetime incidence of basal and squamous cell carcinomas by 78% (Stern *et al.*, 1986). About 95% of basal cell carcinomas in men occur after the age of 40, while squamous cell carcinoma primarily (75–80%) affects men over the age of 60 (Scotto *et al.*, 1983). These studies point to the relatively long latent period between time of exposure to solar UV adequate to induce nonmelanoma skin cancer and its actual appearance. Further, when prevention measures are ineffective or fail, it points to a need to develop intervention strategies, a potential role to be filled by dietary modification.

### The Role of Diet in Nonmelanoma Skin Cancer: Epidemiologic and Clinical Studies

Analytical epidemiologic studies have provided the principal evidence associating dietary factors with cancer (Arm-

strong and Doll, 1975). These associations, even when supported by experimental animal studies or clinical observations, have not always proved to be clinically pertinent (Rackett *et al.*, 1993), as noted from the following examples.

### $\beta$ -Carotene

Based upon existing epidemiologic data, it was suggested that individuals with an above average intake of  $\beta$ -carotene might experience a lower incidence of cancer (Peto *et al.*, 1981). A case-control study found that the incidence of skin cancer was inversely related to the level of serum  $\beta$ -carotene (Kune *et al.*, 1992). In addition, as previously noted,  $\beta$ -carotene had been shown to inhibit UV-induced skin cancer incidence in experimental animals (Mathews-Roth, 1982). Thus,  $\beta$ -carotene was examined as a skin cancer preventative agent in a controlled clinical trial. 1805 patients who were diagnosed with a recent nonmelanoma skin cancer were given either 50 mg of oral  $\beta$ -carotene daily or placebo (Greenberg *et al.*, 1990). Adherence to the prescribed treatment was good, determined by annual plasma  $\beta$ -carotene levels. However, after five years there was no significant difference between treatment and control groups in the mean number of new nonmelanoma skin cancers per patient nor with time delay before new tumor occurrence. Under the conditions of the clinical trial, the investigators concluded that  $\beta$ -carotene supplementation was inefficacious with respect to reducing the occurrence of nonmelanoma skin cancer.

### Isotretinoin

Despite reports of positive responses to treatment of basal and squamous cell carcinomas with oral retinoids, these agents have not proved to be efficacious in prevention of nonmelanoma skin cancer. 981 patients with two or more previously confirmed basal cell carcinomas were randomly assigned to receive either 10 mg of isotretinoin or a placebo daily. After three years of treatment, no statistically significant difference in either cumulative percent of patients with an occurrence of basal cell carcinoma or annual rate of basal cell carcinoma formation was observed between treatment and placebo groups (Tangrea *et al.*, 1992). There was, however, significant toxicity associated with the low-dose regimen of retinoid.

### Selenium

Selenium is another dietary factor that has been studied as a nonmelanoma skin cancer preventative. Clark *et al.* (1984), in a case-control study, examined the association between plasma selenium level and nonmelanoma skin cancer. Plasma selenium levels were significantly lower in the skin cancer patients. In a subsequent phase III, randomized study of 1300 skin cancer patients, supplemental yeast-based selenium was administered for up to ten years. Although there

was a significant reduction in new cases of colon cancer in the patients randomized to the selenium-supplemented group, there were no significant effects upon the occurrence of nonmelanoma skin cancer (Clark *et al.*, 1996).

### Dietary Fat

Results from epidemiologic and experimental studies regarding the influence of dietary fat on skin cancer have often been in conflict. Whereas experimental studies, previously discussed, clearly demonstrate a strong influence of dietary fat upon UV-induced skin cancer expression, both a case-control and prospective cohort study failed to find a relationship of skin cancer incidence with dietary fat intake or specific vitamin supplementation (Graham, 1983; Hunter *et al.*, 1992). The prospective study involved a cohort of 73,366 women during a four year follow-up. Thind (1986), in an international study, found a positive association of dietary fat with skin cancer incidence but was unaware of a biological basis for these findings and cautioned against the pitfalls of international data bases and broad correlation studies. Indeed, these types of studies are fraught with methodological difficulties due to (1) the complex nature of the human diet in a free-living population and (2) the difficulties in measuring food intake and analyzing dietary information. In particular, dietary history questionnaires and surveys, while availing epidemiologists with large sample sizes, lack validation procedures that would demonstrate that the method measures what it is intended to measure. (3) The nutritionist seeks methods that accurately reflect current food intake, as opposed to the epidemiologist who requires assessment of dietary patterns that are stable over long periods of time, usually years if cancer induction is under study (Lyon *et al.*, 1992). Some of the limitations of observational studies of diet and cancer can be circumvented by randomized intervention designs whereby direct answers to the question of dietary impact upon cancer incidence can be obtained (Henderson, 1992).

The rationale for undertaking a dietary intervention to modify nonmelanoma skin cancer occurrence rests upon several factors: (1) First, experimental animal studies had shown that high dietary fat intake exacerbated UV carcinogenesis, principally during the postinitiation period. (2) Further, changing from a high-fat to a low-fat diet, after a cancer-causing dose of UV had been administered, negated the exacerbating effect of high-fat intake (Black *et al.*, 1992). This suggested that dietary modification, even after one had been exposed to skin cancer-inducing doses of UV, could represent a potentially important intervention strategy. (3) Furthermore, the high prevalence of skin cancer and the identification of the relative risks of skin cancer patients developing subsequent skin cancers within two years (28% cumulative rate; Karagas, 1994) made it practical to make significant comparisons within a relatively short-term study. (4) In addition, an intervention design *creates* a dietary difference which, followed with frequent dietary assessment, averts many of the problems as-

sociated with epidemiologic studies and allows direct comparisons of dietary fat exposure and disease status.

Such an intervention trial has been undertaken by Black *et al.* (1994). Of 133 skin cancer patients (basal or squamous cell carcinomas) recruited for the two-year clinical intervention trial, 115 successfully completed the study. 58 patients were randomly assigned to the control arm in which no dietary changes were introduced. The 57 patients assigned to the intervention arm learned how to adapt low-fat eating habits to their food preferences and lifestyles, each patient given a "fat gram goal" that defined the grams of fat that would provide 20% of calories from fat. Baseline and follow-up dietary data were compiled from seven-day food records, from which four days were selected for analysis. Food records were verified for types of foods, amounts, and methods of preparation. Nutrient analyses were performed using the Minnesota Nutrition Data System. As the study was specifically designed to examine the influence of dietary fat on nonmelanoma skin cancer, stability of body weight and calorie intake was required in order to prevent any possible confounding effect due to these variables. Thus, patients in the intervention arm consumed higher levels of complex carbohydrate to compensate for the reduction in fat. The success of the dietary intervention protocol, with respect to meeting the goal of 20% of calories from fat, is reflected in Fig. 27.4. Patients in the intervention group had reduced their percentage of calories from fat from 39% to 21%, a level maintained during the remainder of the two-year study.

The potential of a low-fat intervention became apparent early in the study after only 76 patients had completed. A clear and significant difference in number of actinic keratoses (pre-malignant lesions) between groups occurred after 8–12 months, with patients in the control group diagnosed with new keratoses four times as often as those in the low fat group. Based on diet alone, patients in the control group consuming

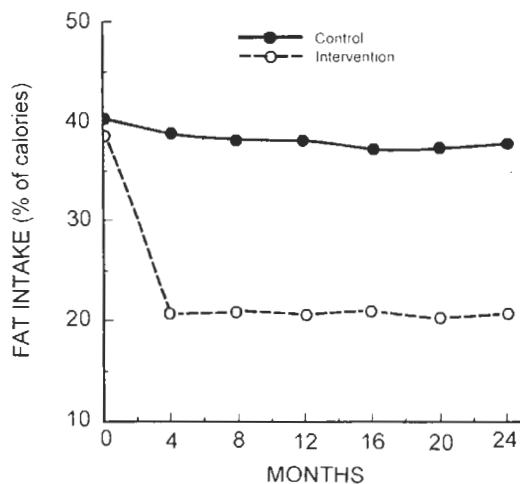


FIGURE 27.4 Dietary fat intake (fat as percent of calories) of skin cancer patients in the control group (solid circles) and of patients in a low-fat intervention group (open circles). Source: Jaax *et al.*, *Nutr. Cancer* 27, 150–156 (1997), with permission.

TABLE 27.1 Effect of Low-Fat Diet on Incidence and Occurrence of Nonmelanoma Skin Cancer\*

Treatment	N	NMSK/Patient	Patients with NMSK	Improvement
Control	58	0.26	9	9 → 9 NS
		$p < 0.01$	$p < 0.02$	
Intervention	57	0.02	1	9 → 1 $p < 0.05$

\*The control and intervention groups each had nine patients with NMSK in the first 8-month period. The control group also had nine patients with NMSK in the last 8-month period with only one patient with NMSK in the intervention group for this period.

high levels of fat were found to be at 4.7 times greater risk of having one or more actinic keratoses during the 2-year period than similar patients in the low-fat intervention group. The predisposing factors for actinic keratosis are similar to those for basal and squamous cell carcinomas (Marks *et al.*, 1988).

Indeed, the influence of reduction in the percent of calories as fat on nonmelanoma skin cancer occurrence (basal and squamous cell carcinomas) was observed after 101 patients had completed the study (Black *et al.*, 1995b) and became even stronger after all 115 patients had completed (Table 27.1). When skin cancer occurrence was examined in 8-month intervals across the 2-year study, occurrence in the control group did not change significantly from the baseline period. However, cancer occurrence in the intervention group was significantly lower ( $p < 0.02$ ) in the last 8-month evaluation period. The cumulative rate of occurrence of non-melanoma skin cancer (cumulative skin cancers/patient/time period) was 0.21 and 0.19 during the first 8-month period of the study and 0.26 and 0.02 during the last 8-month

period for control and intervention groups, respectively (Fig. 27.5).

With regard to diet, there were no significant differences in total caloric intake between the two groups, but there was a 47% reduction in the percent of calories consumed as fat in the intervention group. To compensate the total caloric intake of the intervention group, there was a 36% increase in carbohydrates compared to the control group. A small but significant increase in percent of calories from protein was observed. No differences in percent of calories from alcohol was observed between groups (Jaax *et al.*, 1997). Dietary parameters are shown in Table 27.2.

Overall, the methods for controlling fat intake permitted considerable flexibility in food choices since foods with little or no fat were emphasized, although higher-fat foods

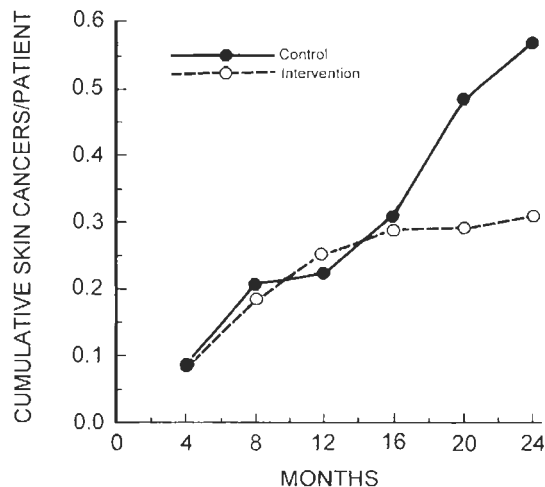


FIGURE 27.5 Influence of dietary intake on nonmelanoma skin cancer occurrence in control (solid circles) and low-fat dietary intervention (open circles) groups. Data points reflect cumulative numbers of nonmelanoma skin cancers per patient at each four month follow-up period. Source: Jaax *et al.*, *Nutr. Cancer* 27, 150–156 (1997), with permission.

TABLE 27.2 Major Dietary Variables of Control and Low-Fat Dietary Intervention Groups\*

Dietary variable	Baseline	Within study	p
Total Calories (kcal)			
Control	2265 ± 659	2196 ± 615	
Intervention	2400 ± 629	1995 ± 564	NS
Percentage of calories from			
Fat			
Control	39.9 ± 4.4	37.8 ± 4.1	
Intervention	38.9 ± 3.4	20.7 ± 5.5	0.0001
Carbohydrate			
Control	42.7 ± 8.1	44.6 ± 6.9	
Intervention	44.2 ± 5.4	60.3 ± 6.3	0.0001
Protein			
Control	15.5 ± 2.9	15.7 ± 2.4	
Intervention	15.6 ± 2.3	17.7 ± 2.2	0.0001
Alcohol			
Control	3.2 ± 4.5	3.2 ± 3.9	
Intervention	2.8 ± 3.8	3.2 ± 3.4	NS

\*Baseline values represent values ± S.D. of diets at time of randomization into study. Within study values are the mean values from 4 months through 24 months. There were no statistically significant differences in any of the parameters at time of randomization. *p* values are shown for the within study differences between groups.

Source: Jaax *et al.*, *Nutr. Cancer* 27, 150–156, 1997, with permission.

could be included as long as the fat gram goal was not exceeded. Thus, a singular strategy of reducing fat intake, with the goal of 20% of calories from fat, could be an effective aid in the management and prophylaxis of nonmelanoma skin cancer. Moreover, the influence of caloric restriction on cancer development should not be ignored. A diet in which the level of fat intake has been reduced, as in the study described, but in which no effort is made to maintain caloric intake or body weight, might be expected to convey even greater protection to nonmelanoma skin cancer and certainly to provide collateral health benefits, as well.

### Melanoma

It would be remiss not to consider melanoma in a discussion of skin cancer, although the etiology of this type of skin cancer is not clearly understood. Nor, until very recently, have there been animal models available to study the role of UV in the etiology of melanoma (Ley *et al.*, 1989; Setlow *et al.*, 1993), only one of which lends itself to dietary manipulation.

Cutaneous melanoma is a cancer of the pigment producing cells (melanocytes) that reside primarily in the basal layer of the epidermis (Koh, 1991). The incidence rate of malignant melanoma has nearly tripled in the past 40 years (Rigel *et al.*, 1987; Glass and Hoover, 1989; Grin-Jorgensen *et al.*, 1992), and currently ranks as the eighth most common cancer among whites in the United States (Koh *et al.*, 1995), where it is the most common cancer among whites between the ages of 25–29, although the median age of occurrence is 53. In 1993, approximately 32,000 new cases of melanoma were diagnosed in the United States (Boring *et al.*, 1993). That number is estimated to rise to 40,300 new cases in 1997 (Parker *et al.*, 1997), consistent with the 5% increase per annum observed earlier (Glass and Hoover, 1989). It has been estimated that by year 2000, malignant melanoma will afflict one in 90 white Americans (Rigel *et al.*, 1987).

Unlike nonmelanocytic skin cancer, the precise causal agent(s) of melanoma is unknown. Nevertheless, examination of worldwide latitude gradients, in association with melanoma rates, provided the first evidence that sunlight might be a causal agent of melanoma (Grin-Jorgensen *et al.*, 1992). Although cumulative UV exposure does not seem to explain the occurrence of melanoma as it does for nonmelanoma skin cancer, there is some evidence that frequent, intermittent UV exposure is involved. Nor does anatomical site of occurrence conform to those areas of the body habitually exposed to UV, although patients with malignant melanoma tend to have lighter complexions and spend more time outdoors (Gellin *et al.*, 1969). Koh *et al.* (1990) have summarized the evidence for UV involvement, as well as that which disputes such a role. Other potential etiologic factors, including an immunologic role, have been discussed (Lee and Merrill, 1970; Longstreth *et al.*, 1992). To date, little evidence supports a role for diet in development of melanoma (Lew *et al.*, 1985; Koh *et al.*, 1995), although a number of factors have been examined.

### Retinol, Vitamin E, Carotenoids, and Alcohol

In a clinic-based case-control study of nutritional factors and risk of malignant melanoma involving 204 patients and 248 controls, little or no evidence was found for a protective effect of increased plasma levels of retinol,  $\alpha$ -tocopherol (vitamin E), or carotenoids (Stryker *et al.*, 1990). Alcohol consumption (over 10g/day) exhibited a moderate trend of increasing risk. Even though vitamin E supplementation provided no association with decreased risk, there was a consistent increased risk in persons with low Vitamin E intake.

### Vitamin D

Speculation regarding the potential preventative effects of vitamin D on melanoma grew from laboratory studies that demonstrated that this vitamin inhibited the growth of cultured melanoma cells. Weinstock *et al.* (1992) examined the relationship between vitamin D and melanoma risk in a case-control study. Vitamin D intake was assessed by food-frequency questionnaires in 165 melanoma patients and 209 controls. They found no association of melanoma risk with total vitamin D intake, calorie-adjusted vitamin D intake, vitamin D intake from foods, or consumption of milk or vitamin D supplements. Thus, no evidence was found to support the contention that vitamin D protects against melanoma.

### Dietary Fat

In 1974, Mackie observed an unusual increase in incidence of melanoma (five patients over a 12-week period) in his clinical practice in Sydney. After interview with a dietician, it was determined that all five patients had altered their diets ten months or more before onset of their melanoma and had enthusiastically replaced saturated fat sources, such as butter, with polyunsaturated fat substitutes. Mackie suggested that the increased intake of polyunsaturated fat may have predisposed patients to the development of melanoma. In a subsequent study involving 142 melanoma patients and 82 controls, dietary questionnaires were administered to assess dietary habits, and fatty acid analysis of subcutaneous adipose tissue was employed as a marker for the percentage of linoleic acid ingestion in the preceding three years. No significant differences in linoleic acid intake, use of cooking oils, frequency of cooking habit, meals out, or intake of antioxidants were found (Mackie *et al.*, 1980). This study failed to control for racial differences in which dietary habits might have been influential, and a second study was undertaken with 100 melanoma patients and 100 matched controls. The polyunsaturated fat content of adipose tissue was significantly higher in melanoma patients than in controls and there were significantly more controls than patients who had a low percentage of linoleic acid in the triglyceride fraction of subcutaneous adipose tissue (Mackie *et al.*, 1987). Although the critical studies have not yet been undertaken, these prelimi-

nary findings suggest a potential role for diet in the prevention of melanoma (Mackie and Mackie, 1990).

## CONCLUSIONS

- Experimental animal data clearly demonstrate that dietary lipid, and certain antioxidants, can have significant influence on UV-induced carcinogenic expression.
- Degree of saturation, *per se*, appears not to have as important an influence on carcinogenic response in skin as level of the dietary fat and its fatty acid composition.
- A clinical dietary intervention trial indicates that a decrease in percentage of calories consumed as fat reduces the occurrence of premalignant actinic keratosis and non-melanoma skin cancer.
- Reduction in skin cancer occurrence was observed after one year of the low-fat dietary intervention.
- Reduction in dietary fat reduces the occurrence of basal cell carcinomas in humans, as well as reducing occurrence of squamous cell carcinomas in animals.
- Results from the clinical trial validate the relevancy of the hairless mouse/UV dietary model.
- *In toto*, these data suggest that implementation of a low-fat diet could play an important role in the management and prevention of this highly prevalent form of cancer.

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