Skin Cancer: Its Causes, Prevention, and Treatment

Frederick D. Malkinson, M.D., and Stephen Rothman, M.D.

The accessibility of cutaneous cancers offers two unique opportunities: 1) the laboratory and clinical investigation of factors important to the predisposition and development of malignant cutaneous neoplasms, and 2) the early diagnosis and adequate treatment of these tumors.

Perhaps the earliest contribution to our knowledge of carcinogenesis was Percivall Pott's observation in 1775 that scrotal cancer in chimney sweeps resulted from chronic soot exposure. In the 19th and 20th centuries clinical observations revealed that skin cancers also arise from long-standing contact with tars, pitch, and petroleum products (lubricating oils, etc.). Experimentally, repeated applications of tar and later on of single polycyclic hydrocarbons to the skin of mice and rabbits have reproduced these malignant growths.

Although chemical carcinogenesis was perhaps the first important observation in the pathogenesis of skin cancer, other significant predisposing or "irritant" factors are now recognized.

Clinical studies long ago suggested a relationship between the development of skin cancers and chronic exposure to sunlight. In a review of our own patient material,[3] for example, it was found that 91.1 per cent of all skin cancers occurred on uncovered parts such as the face, ears, neck, and dorsa of hands (Table I). In many individuals exposure to excessive amounts of sunlight over the years results in a severe form of senile atrophy of the skin. The skin becomes thin, sallow, dry, wrinkled, slightly scaling, and inelastic; often freckles, lentigines, and telangiectases are present. Such changes are frequently seen in sailors, farmers, fishermen, habitual sunbathers, etc., and

Table I

Distribution of Skin Cancers According to Site*

Exposed		Partially exposed		Nonexposed	
Site	%	Site	%	Site	%
Face	87.0	Arm	1.2	Back	3.2
Ear	1.6	Scalp	0.9	Chest	1.2
Neck	1.6			Abdomen	1.2
Hand	0.9			Thigh	0.9
	91.1		2.1		6.5

* Based on 246 cases seen in the Dermatology Clinic of the University of Chicago from 1930 to 1946.

Department of Medicine, Section of Dermatology, University of Chicago Clinics: Stephen Rothman, Chairman.

[For references see p. 205]

are more common in blonde or red-headed persons. The frequency of precancerous keratoses and carcinomas in these individuals is exceedingly high. To substantiate further the role of chronic sun exposure Public Health Service statistics[1] have shown that precancerous keratoses occur six times as frequently in the southern section of the United States as in the northern, and that the incidence of skin and lip cancers is about two and one-half times as great in the southern states (at 32° latitude) as in the central states (at 38° latitude). Experimentally, too, it has been demonstrated in mice that chronic exposure to intense ultraviolet light produces both cutaneous keratoses and malignant tumors. It is now established that the carcinogenic rays of sunlight are the same as those responsible for sunburn (2800-3100 Å in the ultraviolet part of the spectrum).

A dramatic association of sunlight exposure with malignant cutaneous tumors is seen in the rare syndrome, xeroderma pigmentosum, where extreme sensitivity to sunlight in infancy or early childhood results in severe atrophy or "farmer's skin" after only a few brief exposures. Individuals with xeroderma pigmentosum seldom survive to adulthood because of the early development of multiple malignant cutaneous neoplasms. Since this disorder is inherited as a recessive trait, it illustrates a link to genetic factors, as well as to sunlight exposure, in the pathogenesis of skin cancers.

Another factor related to the role of sun exposure concerns the low incidence of carcinoma in dark-skinned races. The assumption is that this is the result of resistance to the sunburn-producing rays, and it indicates that racial factors are also of some importance in the predisposition to skin cancer.

In addition to specific chemicals and to part of the ultraviolet-light spectrum, other forms of chronic irritation such as heat, physical trauma, and ionizing radiation may be followed by malignant change in the skin. Almost eighty years ago Kangri cancers were first described in Kashmir as arising on the thighs or abdomen at the point of contact with the Kangri jar, a brazier of hot coals carried under the clothing for warmth in cold weather. The frequent occurrence of leukoplakia and oral cancer in tea-tasters after repeated exposures to very hot tea has also long been recognized. Mechanical trauma has preceded skin cancers in such well-known cases as the "collar-button" lesions seen in males during the stiff-collar era. Another example still encountered at the present time is the occasional occurrence of carcinoma under the nose-piece of eyeglasses.

Chronic radiodermatitis occurs as a late change following several relatively small exposures or after acute radiodermatitis resulting from one or more massive exposures. The dosage levels of roentgen ray tolerated by the skin are well established but after excessive exposures from accidents and other causes the skin ultimately shows chronic changes of dryness, atrophy, hyper- and hypopigmentation, and telangiectases. Keratoses which may become malignant, basal-cell carcinomas, and squamous-cell carcinomas, as well as other tumors, not infrequently develop in such altered skin.

So far the observations recorded have indicated that the most significant factor in the pathogenesis of skin cancer is that of exposure to chronic chemical, actinic, thermal, or mechanical injury. Some importance may also be attributed to racial and genetic factors. In the consideration of chronic injury as the foremost etiologic agent it seems almost certain that all of the diverse forms of trauma mentioned produce analogous physiological and pathological disturbances in the skin. Normally skin keratin is continuously desquamated as ultramicroscopic particles, but after repeated ultraviolet-light irradiation or simple mechanical rubbing the keratin layer becomes greatly thickened as a result of inhibition of physiologic peeling. This "superkeratinization" with formation of a harder, thicker keratin represents the initial biologic alterations in epidermal cells resulting from repeated minor traumata. It is the first step in malignant degeneration and is followed later by cellular anaplasia and invasion of the under-

Fig. 1. Basal-cell carcinoma, left inner canthus.

Fig. 2. Mixed-cell carcinoma, successfully treated with roentgen rays.

lying dermis. Undoubtedly, at least in the development of the two most common precanceroses of the skin and mucous membranes—senile keratosis and leukoplakia—chronic trauma and superkeratinization are the principal factors.

Senile keratoses are seen in older, and occasionally younger, individuals, occurring on light-exposed areas principally in those who have been exposed to sunlight and the elements for many years. The lesions may be single or multiple and usually accompany changes of senile atrophy in the skin. Senile keratoses vary in size from a few millimeters to a centimeter or more, range from red to brown in color, and present a dry, gray-white, adherent scale which is the only palpable element of the uncomplicated lesion. In themselves they are benign and may persist unchanged for many years. Eventually, however, carcinoma, usually of the squamous-cell type, develops in about 20 per cent of untreated lesions.

Leukoplakia may be regarded as the counterpart of senile keratosis as it occurs on the mucous membranes. The lips and the mouth—particularly the buccal mucosa and the anterior dorsal surface of the tongue—are the sites most frequently involved, but vulvar leukoplakia is not uncommon after the menopause. The condition is characterized by opalescent spots which later become milky white. These lesions are sharply circumscribed and in time the surface becomes rough, thickened, verrucous, and fissured. Subjective symptoms are nil unless fissures are present or secondary infection occurs. The early, flat, opalescent lesions are almost invariably benign, but when the patches become hyperkeratotic and fissured, malignant degeneration may be found. As with keratoses, leukoplakia may remain benign and show little change for many years, but ultimately squamous-cell carcinoma develops in 20 to 30 per cent of untreated patients.

The principal etiological factor in the development of leukoplakia is chronic local irritation. Mechanical irritation may result from ill-fitting dentures, faulty occlusion, carious teeth, improperly constructed crowns and bridges, and habitual chewing (inner surface of lip or buccal mucosa). Leukoplakia is not uncommon in smokers and may result from chronic exposure to heat (as on the lip at the contact spot of a pipe stem) or, perhaps, from the chemical carcinogenic action of tobacco. Chronic exposure to sunlight is also an important factor in leukoplakia of the lips and in its predilection for the lower lip. Leukoplakia has often been observed in syphilitics, too, although the reason for the association of the two conditions remains unknown. Leukoplakia is more common in men than in women by a ratio of almost 10 to 1, and like senile keratoses, is found most frequently

in middle-aged and older individuals.

Skin cancers arise predominantly on exposed areas from precancerous conditions or from normal skin. There are two principal types of carcinoma and these are classified definitively on the basis of histopathological changes: basal-cell carcinoma, showing proliferation, anaplasia, and invasion of the underlying dermis by cells of the basal-layer type, and squamous-cell carcinoma, in which tumor growth derives from similar changes in the cells of the malpighian or prickle-cell layer of the epidermis. Occasionally two variants of the microscopic features of these fundamental forms of carcinoma are found: either the tumor cells present are a type intermediate between basal and squamous cells, or the two cell types maintain their identity but are found together in the same tumor (mixed-cell tumor).

Skin cancers occur principally in middle-aged and older individuals; less than 2 per cent occur in patients less than thirty years of age. Men outnumber women 2 to 1. Carcinomas are usually single but are multiple in up to 20 per cent of cases, and both types of carcinoma may be found in the same patient. A survey taken in 1952 showed that skin carcinomas accounted for only 2.2 per cent of all cancer fatalities in the United States.[4]

Basal-Cell Carcinoma

Approximately 65 per cent of all malignant skin tumors are of the basal-cell type. These lesions are characteristically slow growing and respond most satisfactorily to adequate therapy if the tumor is not far advanced. Metastases are almost never seen, occurring only rarely after extension to underlying bone. The course of the untreated lesion, however, is one of slow but persistent local peripheral and invasive growth. In the late stages with deep invasion of bone, and particularly with involvement of structures such as the orbit or the cranial cavity, it may be impossible to save the patient.

Basal-cell carcinomas vary considerably in their clinical appearance. Often the lesion first appears as a firm, waxy papule or nodule with telangiectasia. Following enlargement of the tumor the center usually becomes depressed leaving a pearly border. Erosion with crusting and bleeding may occur and eventually, as tumor cells invade more deeply, a frank central ulceration with a rolled, raised border is seen (rodent ulcer). Occasionally central healing with atrophic scar formation occurs as the tumor spreads peripherally in a rather superficial manner. Globular forms of basal-cell carcinoma are also not uncommon. Infrequently increased amounts of melanin pigment occur in these tumors leading to some difficulty in differential diagnosis from melanoma. An uncommon but distinctive clinical variant is the morphea-like basal-cell carcinoma. This is a flat, yellow to white, indurated, and rarely ulcerated lesion characterized by considerable fibrosis following a determined but unsuccessful attempt by the tissues to eradicate tumor cells.

A more benign form of basal-cell tumor is the superficial erythematous basal-cell carcinoma. This lesion usually occurs in multiple numbers rather than singly and in contrast to the other clinical types has a predilection for the covered areas of the body. Superficial basal-cell carcinomas appear as flat, red, slightly scaling patches which sometimes enlarge to several centimeters in diameter and often show a fine threadlike, raised border. Other characteristics may include traumatic bleeding, crust formation, erosion or ulceration, and central scarring. Although histologically these lesions show buds of proliferating basal cells still attached to the overlying epidermis, invasion of the dermis and underlying structures by detached tumor cells may occasionally occur, as it does in other varieties of basal-cell carcinoma.

Squamous-Cell Carcinoma

Squamous-cell carcinoma of the skin is a common entity, although it is seen less frequently than basal-cell carcinoma. It is by far the more dangerous of the two lesions, however, since it is faster growing and may metastasize to regional lymph

nodes and beyond to other tissues and organs. The tumors may be slow growing and remain localized for many years, but often they grow swiftly either from the onset or after periods of quiescence. In 95 per cent of cases they are found on the head or dorsa of the hands, arising from normal skin or precancerous lesions such as senile keratosis or leukoplakia. Squamous-cell carcinoma also occurs occasionally in areas of radiodermatitis, at the edge of long-standing ulcerations, or in old scars due to thermal or chemical injury.

The clinical appearance of this tumor varies considerably. Often it appears as a crusted ulcer surrounded by a firm, wide, indurated border with undermined edges. Some lesions present as flat, raised, infiltrated papules or nodules without a central depression. Occasionally verrucous and vegetative lesions are seen. Although frequently it is possible to distinguish basal-cell carcinomas from squamous-cell lesions clinically, often the most experienced observers may err. Biopsy should always be performed to substantiate the suspicion of carcinoma and to establish the specific type.

Prevention and Treatment

It is obvious that prevention of cancer means essentially removal of those factors producing chronic skin or mucous membrane irritation. It may be advisable, for example, to acquaint young individuals, who have outdoor occupations but as yet show little skin change, with the consequences of long-term sunlight exposure. Where feasible, the older patient with "farmer's skin" should be persuaded to change his outdoor occupation and to avoid sunlight. An effective sunscreen preparation such as a 15 per cent para-aminobenzoic acid ointment can be prescribed for times when sun exposure is unavoidable. In patients with leukoplakia appropriate dental restorations or cessation of smoking may suffice to induce remission. Those exposed to occupational carcinogens (tar, pitch, petroleum derivatives) may be forced at length to change their jobs, although industrial control methods in this country at the present time are excellent. In addition, the physician must realize that prolonged regular observation is most important for those patients subject to occupational cancer, for persons with persistent or recurrent leukoplakia, and for those with multiple, senile keratoses. Any lesions showing suspicious changes (redness and induration at the base of a keratosis, sudden thickening of a patch of leukoplakia) should be examined by biopsy as should all new lesions suspected of being malignant. Persons working with radioactive materials or roentgen rays should also have periodical medical examinations.

Measures suitable for the treatment of senile keratoses depend on the history and appearance of specific lesions. The small keratosis which has shown no growth or surface change may be left untreated provided the patient returns regularly for observation. Often a keratolytic ointment, such as 2 per cent salicylic acid in unguentum aqua rosae applied two or three times daily, keeps the keratinization satisfactorily controlled. When a keratosis persists and particularly when it enlarges, becomes widely erythematous, or begins to show infiltrative changes, biopsy followed by electrocoagulation and curettage is indicated. If malignant change has occurred further treatment is carried out as described.

Biopsy is advisable for all patients with leukoplakia. If the patches are flat and opalescent, correction of local irritant factors and continued observation suffice. Persistent leukoplakia or lesions which become rough and thickened should be biopsied at sites which appear to be most advanced and then treated by thorough electrodesiccation. For larger lesions surgical removal is also satisfactory. Where squamous-cell carcinoma is found histologically, surgery or radiation therapy with removal of possibly involved lymph nodes is indicated. For persistent widespread leukoplakia of the lip, with or without carcinoma, a satisfactory surgical procedure is a wedge or horizontal resection with extension of the mucous mem-

brane of the inner lip to produce a new vermilion border.

There are two main forms of therapy for previously untreated skin carcinoma: irradiation (roentgen rays or radium) and surgical removal.

Radical surgical excision is chosen by many, and according to some statistics its results are satisfactory. However, radical surgery is difficult or has disfiguring effects in many sites about the face such as eye canthi, ala nasi, etc. Furthermore, one of us (S.R.) has observed relatively frequent relapses after surgery even when wide excision was carried out.

Electrocoagulation with curettage is unreliable and is best restricted to the treatment of recurrent carcinomas at sites where further roentgen-ray therapy or surgery is not practical. The local use of caustics is to be condemned except, in expert hands, for the rarely indicated special technique developed by Mohs.[2]

Our own preference is for roentgen-ray therapy. With competent techniques this treatment is without significant trauma or discomfort to the patient and is the only satisfactory method for lesions which are difficult to remove surgically. Cosmetic results, too, are usually quite satisfactory. Cure rates in excess of 95 per cent for basal-cell carcinomas are obtainable with irradiation. When roentgen-ray therapy is used a margin of at least 4 to 6 mm. of seemingly uninvolved skin should be included about the circumference of the irradiated area. Fractional dosages are routinely used, the amount of radiation given at each treatment depending on the size and location of the tumor. Since 1947 our method of treatment has been to give 5400 r in equal fractional doses administered three times weekly until a total of nine treatments has been given (i.e., 9 x 600 r). Small lesions over ample subcutaneous tissue are sometimes treated in five sessions. For lesions on thin skin (such as the ear) and for those over 2 cm. in diameter 15 x 360 r are given. The factors for the radiation administered are TSD 20 cm., 80 kv, 10 ma (inherent filtration 0.71 mm Al).

The case records of sixty-eight patients with all types of skin carcinomas treated with roentgen rays or radium at the University of Chicago Clinics from 1945 to 1950 have been reviewed. To these were added the case histories of six patients treated between 1938 and 1945. In all, seventy-eight carcinomas were treated in this group of seventy-four patients. There were thirty-six basal-cell carcinomas, eleven squamous-cell carcinomas, eight intermediate-cell carcinomas, five mixed-cell carcinomas, eleven squamous-cell carcinomas in situ, and seven superficial, erythematous, basal-cell carcinomas. In all patients the diagnosis was confirmed or established by biopsy and all cases were followed for at least five years. Seventy-one of these tumors were treated successfully without recurrence, although many received therapeutic dosages now recognized as frequently inadequate. Of the seven recurrences noted (all basal-cell carcinomas) six occurred in patients receiving insufficient treatment (1800-3600 r). One recurrence was seen in a patient who had received 4500 r (radium). Of forty-six patients treated with the modern dosage schedule of 5400 r or an approximately equivalent dose of radium, this last individual was the only one to show recurrent tumor growth.

In general, roentgen-ray or radium therapy is effective in the treatment of squamous-cell carcinomas. In large, rapidly growing tumors, however, and for those complicated by regional lymph-node metastases radical surgical removal remains the treatment of choice.

Superficial, erythematous, basal-cell carcinomas present slightly different treatment problems. Because the lesions are superficial electrodesiccation with curettage is a suitable form of therapy and even larger lesions can be treated in stages by this method. Surgical removal can also be recommended for these carcinomas. Although "standard" dermatologic roentgen-ray therapy is successful considerable radiation penetrates to normal tissue below the tumor. Good treatment results, however, may be obtained with very soft (Grenz) rays largely absorbed by the epidermis and the attached tumor cells.