Sociopolitical and economic climates between 1950 and 1975 favored the funding of cancer research, attracted imaginative policy makers, encouraged investigators, and generated new knowledge for clinical application. Important advances during this period include the discovery that DNA alteration is requisite for carcinogenesis and that DNA repair processes are important deterrents in the development of cancer. The better understanding of the histogenesis of epidermal cancer and melanoma has potential clinical value. More easily grasped is the progress made in the therapeutic control of mycosis fungoides and epidermal cancer. Complete control of epidermal cancer is now a foreseeable reality.

The quarter century from 1950 to 1975 had a propelling impact on biomedical science in general and, as a consequence, a comparable impact on dermatology and its related divisions. Sociopolitical and economic factors determined how much funding went into the biomedical research that accounted for the magnitude of this impact, but the positions of science and the states of knowledge at that time determined the progress of research and accounted for its quality. The period began with “free-wheeling” research which created new positions for science as new discoveries were generated from basic research. During the later years of the period, wider clinical applications of those discoveries for the control of disease were emphasized. The advances of the period can be judged by the brilliance of the discoveries themselves and the technologic sophistication behind them as well as by their contributions to the control of disease, the promotion of health and longevity, and the enhancement of the comforts of living. A physician probably sees scientific advancement mostly in terms of its impact on disease and health; certainly this bias is apparent in my assessments. However, other criteria are also important since to sustain our progress against disease, we must progress in the science of planning for research, both “basic” and “applied.” We are hopeful that biomedical discovery and development will be as valid and productive during the final quarter of this century as they were during the third quarter.

When Congress founded the National Cancer Institute in 1937, theories and hypotheses about the nature of cancer had already been formulated [1]. The importance of heredity in cancer susceptibility was recognized, but the interrelation between cancer cells and the host was not as fully appreciated as it is today. Hence the findings of the past 25 years which elucidated these relations are a very important component of oncologic progress.

A certain climate conducive to research in cutaneous oncology in 1950 was largely nurtured by the leadership of the National Cancer Institute. Its director, John R. Heller, was a dermatosyphilologist who had directed this country’s successful and intensive treatment program against syphilis during World War II and who quipped that he turned his attention to cancer after the attack on syphilis had knocked the “h” out of chancre. His firm endorsement of and encouragement to dermatologic research were later maintained and implemented by the perceptive policies of Kenneth M. Endicott, the Institute’s next director. C. Gordon Zubrod, the Institute’s director of intramural research during those years, recognized that the mechanisms which control the growth of integumental systems were relevant to neoplastic systems as well and fostered dermatologic research as part of the Institute’s intramural program. The visionary policies of these men were important to the progress of dermatologic research and cutaneous oncology during this period.

In this presentation, I shall limit my evaluation of the progress in cutaneous oncology to only a few of the events which changed the attitudes toward and direction of the three major categories of cutaneous cancer from 1950 to 1975: (1) epidermal cancer, the most common of all human cancers; (2) melanoma, the next most common skin cancer and probably the most dreaded; and (3) a cutaneous lymphoma, mycosis fungoides, relatively uncommon but always potentially lethal. This review can best be covered under the traditional headings of etiology, mechanisms of carcinogenesis, and therapy.

**ETIOLOGY**

The capability to alter DNA directly or indirectly is probably the common property of all carcinogenic agents. This realization is as impor-
tant to an understanding of the mechanisms of carcinogenesis as it is to characterizing etiologic agents. By 1950, the major etiologic agents responsible for epidermal cancer in man had already been identified. This was not and still is not true for melanoma and the lymphomas.

Ultraviolet radiation has long been recognized as the major cause of most epidermal skin cancers in man. However, although the anatomic sites of actinic keratoses, squamous cell carcinomas, and basal cell carcinomas are generally those areas most exposed to actinic radiation, some anatomic sites of basal cell carcinoma do not fit into such an association [2]. Therefore, etiologic factors other than actinic radiation appear to induce basal cell carcinoma, but what they are is still not known. This is also true in the hereditary forms of epidermal cancer. For example, in xeroderma pigmentosum the most frequent type of lesion is a squamous cell cancer which seems to result solely from exposure to ultraviolet radiation. In the nevoid basal cell carcinoma syndrome, however, the lesions appear on covered as well as on exposed body areas, but not so often.

Markedly diminished use of arsenic both in agricultural insecticides and in drug preparations has been associated with the virtual disappearance of clinically recognized new cases of arsenical cancers. In the past, exposure to tar and tar products has been associated with skin cancer, but the actual frequency of this association encountered clinically seems to have been and remains minimal.

Since 1950 no significant new etiologic factors in epidermal carcinogenesis have emerged; hence the incidence of epidermal cancer in the future should remain stable unless exposures to ultraviolet radiation change.

Although the carcinogenic stimulus which accounts for melanoma in man remains obscure, it is now reliably produced in guinea pigs by topical applications of chemical carcinogens (W. H. Clark, personal communication). Chronic trauma has been discounted as a causative event, but recent epidemiologic studies made in both the northern and southern hemispheres have suggested that light plays a role through its enigmatic influence on cutaneous melanocytes [3]. According to these studies, the frequency of melanomas increases sharply on exposed body areas. This increase is most marked in geographic areas towards the earth's equator.

The causative factors of cutaneous lymphoma remain unknown. An important first clue to its etiology is the association of its frequency with immunodeficiency states [4]. No such association has been made in regard to the lymphoma, mycosis fungoides, however.

MECHANISMS OF CARCINOGENESIS

Since carcinogenesis has been fully reviewed by Yuspa et al [5], the interpretation that follows is limited to some biologic parameters which seem important in defining the cellular and tissue reaction patterns which arise during the development of human skin tumors from microfocal beginnings to clinically definable diseases. After a carcinogenic stimulus impinges on a cell, the cell undergoes a neoplastic transformation and replicates into societal populations. A relation develops between these new cell populations and the host, which determines the quality and magnitude of the disease. All of these steps must be accurately defined before the pathologic events of carcinogenesis can be understood and a rational position for therapeutic management of the lesions can be formulated. During the past 25 years, important advances towards the attainment of these critical clinical objectives have been made.

Studies of epidermal tumors caused by actinic radiation have led to new theories on the molecular basis of carcinogenesis. In a series of epochal discoveries [6], Cleaver showed the importance of DNA repair in the control of epidermal cancer caused by ultraviolet light. What facilitates the emergence of malignant cells after DNA damage, however, is not yet known. Neither do we know why squamous cell cancers and basal cell cancers, two tumor types with distinct morphologic and behavioral differences, sometimes emerge after exposure to a common carcinogenic stimulus.

According to one hypothesis, basal cell cancers result when the normal epidermal cell loses its ability to mature and keratinize [7]. This hypothesis is compatible with the histologic finding of nonkeratinizing cysts within basal cell tumors and of nonkeratinizing palmar pits in the nevoid basal cell carcinoma syndrome. In such cases, tumor cells retain their normal germinative function but fail to mature. Otherwise they remain normal, that is, they depend upon the stromal elements of supportive cutaneous connective tissue for survival [8]. This may explain the nonaggressive character of basal cell tumors and their failure to metastasize to distant sites. The fact that keratinization occurs in basal cell tumors transplanted autologously to new cutaneous sites and in tumor explants grown in long-term culture [9] indicates that under certain conditions the dominant characteristic of the tumor cell, its failure to mature, is reversible. Thus far, however, these findings have not facilitated the development of new pharmacologic approaches to therapy, mainly because the conditions needed to induce keratinization have not been biochemically identified.

The studies of Clark on the histokinetics of melanoma evolution, first presented at the Symposium on the Biology of Skin in 1966 [10], are still the most important advance on the pathogenesis of this tumor. According to these studies, specific histologic patterns characterize the development of melanomas in the skin and help to determine the inherent malignancy of the lesions and the degree of containment that can be achieved by the host's immunoinflammatory systems. This knowledge, in turn, enables us to select the
most effective therapy. In a more recent publication [11], Clark et al apply specific histologic criteria to these interpretations.

Some recent findings on mycosis fungoides may help to improve our knowledge of how this lymphoma develops. The lymphocytoid cell with serpentine nucleus, identified by Lutzner and Jordan [12], apparently serves to identify the lymphoma as mycosis fungoides and to distinguish it from other lymphomas; but its precise nature has not been clarified. Found in inflammatory cellular infiltrates in various skin lesions [13] and in tissue cultures of normal skin [14], the lymphocytoid cell apparently is not a neoplasm. Its function and actual role in mycosis fungoides need to be explained.

The skin continues to be a popular medium for exploring carcinogenesis and the biologic mechanisms relating to it. Recognition that the cancerization process may be reversible was probably gained mostly from observations of the process in the integumental system. For example, the regulatory role of both the immune system on the development and course of cancers and to a lesser extent of the inflammatory system as a part of, or apart from, the immune system has been investigated in the skin. The roles of these systems can be studied in the clinical lesion of keratoacanthoma [15], which has been appropriately labeled a self-healing squamous cell cancer. Other areas are the lesions of early epidermal cancer, melanoma, and mycosis fungoides which can be reversed by the imposition of delayed hypersensitivity reactions [16–18].

**THERAPY**

Despite the distance to be covered before we can claim absolute control, I believe the most evident progress has been made in the improved clinical control of neoplasia in human skin. Goal-oriented efforts have been productive in cancer chemotherapy and have spin-off applicability to cancers of the skin. The lessons in cutaneous oncology learned through clinical experience have underscored the well-known rule, theoretically obvious but sometimes practically ignored, that effective therapeutic procedures must be carried out early and adequately.

The single formidable therapeutic weapon introduced against epidermal cancer has been topical chemotherapy with 5-fluorouracil [19,20]. Clinical experience has shown that if it is used early and adequately, precancerous keratoses and superficial epidermal cancers can be completely eradicated. This therapy, self-administered by the patients themselves, can be safely repeated as often as necessary to assure that microfoci of early epidermal cancers are obliterated even before clinical detection. If widely and consistently administered, this treatment, therefore, seems to be the means by which epidermal cancer can be reduced to an infrequently serious disease.

Although the potential of immunotherapy against melanoma has been widely explored in recent years, the mortality rates have not improved. Cure still depends entirely upon complete surgical removal of early lesions.

Therapeutic treatment of mycosis fungoides has substantially improved within the past 25 years. Before this, the disease was uniformly fatal, progressing from the skin and involving the lymph nodes and internal organs. Today, because of effective therapy applied early and sufficiently, the disease can be clinically obliterated, in most cases for extended periods. Whether it can be actually cured, however, is not yet known. Two treatments are responsible for the improved prognosis, whole-body topical administration of mechlorethamine [21] and whole-body administration of high-energy electrons [22]. Neither of these measures was developed specifically to treat this cutaneous malignancy. Rather, they applied existing knowledge and technology to treat a disease whose nature remains obscure.

**FEASIBILITY OF COMPLETE CONTROL**

It is important to realize that the most common of all cancers, epidermal cancer, is now almost completely controllable when certain requirements are met. Because of their appearance on highly visible integument, epidermal cancers as well as precancerous keratoses lend themselves to early diagnosis and eradication by adequate treatments. Moreover, lightly pigmented skin, which is prone to develop cancer after chronic exposure to ultraviolet light, is easily identified and, in fact, distinguishes whole genetic groups. Such people can be advised either to avoid exposure to the etiologic agent or to protect their skin by using topical preparations which effectively absorb those wavelengths of ultraviolet light that are responsible for causing skin cancer. Thus, epidermal cancer can be successfully treated, precancers can be eradicated before reaching more advanced states of malignancy, susceptible population groups can be identified, and since the means to avoid the impingement of the major carcinogenic stimulus are available, most epidermal cancers are now preventable. The achievement of this objective, which has been made possible by these measures, is not yet universal. But we can hope that the rate of progress against all forms of cutaneous cancers achieved within the last 25 years will be surpassed in the last quarter of the twentieth century.

**REFERENCES**