Hypersensitivity Reactions at Tumor Sites

Edmund Klein

Department of Dermatology, Roswell Park Memorial Institute, Buffalo, New York, 14203, and the Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

Summary

Induced cell-mediated immunity (hypersensitivity) resulted in selective injury and eradication of premalignant and malignant epidermal lesions in man with minimal or no adverse effects on normal tissues. Immune challenge produced resolution of more than 95% premalignant keratoses, superficial basal cell carcinomas, and squamous cell carcinomas in situ in 50 patients without recurrences for observation periods of up to 5 years. During the reaction to challenge, multiplication of normal cells and healing proceeded while their malignant and premalignant counterparts were being destroyed. Resistance did not develop on up to 7 successive courses of immunotherapy. The incidence of new lesions was decreased following immunotherapy in patients with otherwise persistent development of new lesions as compared to treatment with standard modalities. Systemic toxicity or generalized immune reactions did not occur. Immunity was transferred to nonsensitized patients by peripheral leukocytes from sensitized patients. Challenge reactions in patients with transferred immunity resulted in the same effects on epidermal neoplasms as in patients who had been sensitized by direct exposure to the sensitizer. The data demonstrate that specific cell-mediated hypersensitivity can be induced by simple chemicals in man which results in lasting involution of premalignant and malignant neoplasms. Studies are warranted to determine whether analogous principles can be extended to tumor biology in general.

Introduction

Specific tumor antigens capable of inducing a selective cytotoxic reaction which is confined to malignant cells were demonstrated by Foley (3) and confirmed by Prehn and Main (23). These authors found that syngeneic tumors more readily induce immunity in inbred animals than skin grafts. It was subsequently found that the level of immunity may be sufficient for rejecting small numbers of tumor cells while larger inocula result in tumor take (22). These studies were extended by Riggins and Pilch (25), who showed that some spontaneous tumors in animals contain antigens. Old et al. (21) showed that immunity to tumors can be transferred by peripheral leukocytes. Klein et al. (17) showed that tumor cells treated in vitro with leukocytes obtained from hosts sensitized against the tumor had lost their ability to grow on transplantation into syngeneic hosts. These observations indicated that specific cell-mediated immunity was an important factor in the relation between the host and the tumor (1).

Kaliss (9–11) and Hellstrom and Moller (5) showed that humoral antibodies can cause enhancement rather than inhibition of tumor growth. Law (18) demonstrated that thymectomy increases the susceptibility to both chemical and viral tumor induction. These observations indicated that humoral antibodies and cell-mediated immunity may have opposing actions on tumor development. Stimulation of the reticuloendothelial system, as shown by Weiss et al. (27) with a fraction of tubercle bacilli, increases resistance to a number of bacterial organisms as well as to mammary carcinoma. Exogenous leukocytes from syngeneic or allogeneic donors were shown by Delorme and Alexander (2) to complement the inadequate host defense mechanisms against primary tumors induced by chemical carcinogens in the rat. These studies suggest that cellular immunity can be activated against experimental tumors.

Studies in man by Nadler and Moore (19) have shown that peripheral leukocytes obtained from recipients of tumor homografts may induce tumor regression in the patient from whom the tumor graft was obtained. Nadler and Moore (20) have further shown that partial regressions following this procedure occurred in approximately 20% of 118 patients with a number of different malignant tumors. Three of these patients have been free of detectable disease for at least 2 years. Gerner and Moore (4) have found that in the course of transplants of homologous white blood cells, the recipient's differential white blood cell count is shifted to a relative lymphocytosis and granulopenia. The status of the relation of immunologic factors to tumors in man has recently been reviewed by Southam (26). It is apparent from the large amount of information which is becoming available in this area that further investigation is warranted.

Studies on Cutaneous Neoplasms

Tumors located in the skin provide considerable flexibility for the study of tumor biology and were, therefore, investi-
gated in regard to immunologic factors affecting premalignant and malignant epidermal neoplasms (7, 12). In the course of these studies it became apparent that delayed hypersensitivity reactions exerted profound effects on epidermal neoplasms in man which resulted in complete regressions. Immediate hypersensitivity reactions were difficult to induce under controlled conditions and did not appear to have selective effects on cutaneous neoplasms.

Studies on the relation of specific cell-mediated immunity to skin cancer were initiated several years ago (7, 12). A number of antitumor agents which were under study in a parallel program on local chemotherapy (14, 15) produced cutaneous hypersensitivity reactions on the skin of patients with epitheliomas (6, 7, 12, 16). One of these agents (2,3,5-tri-ethyleniminobenzoquinone, TEIB), provided through the cooperation of Dr. R. Goeswald of the Farbenfabriken Bayer AG, Leverkusen, Germany, was investigated further since it produced cutaneous neoplasms more intense challenge reaction at sites involved by cutaneous neoplasms than in the normal skin (6—8, 12, 13, 16). The reaction was a typical challenge response of the delayed hypersensitivity type. When the concentration of the challenging dose was reduced sufficiently, the reaction was almost entirely confined to the sites of neoplastic involvement with minimal or no reaction in the adjacent normal tissues (12, 13, 15). The intense reaction in cutaneous neoplasms resulted in resolution of superficial basal cell carcinomas, squamous cell carcinomas in situ, premalignant keratoses, and leukoplakia (7). The hypersensitivity could be transferred by peripheral leukocytes from sensitized to nonsensitized patients; the response of patients with transferred immunity to challenge was followed by tumor resolution (7).

Following studies with TEIB, dinitrochlorobenzene (DNCB) was investigated as a sensitizer in order to determine whether the hypersensitivity reaction resulting in tumor resolution required cytostatic activity or could be induced by chemicals which did not have specific antimitotic activities. The data indicated that cytostatic activity was not necessary.

Studies were initially carried out on a group of patients with advanced disseminated malignant diseases and then on patients with intractable multiple epitheliomas (7). The latter group was subsequently studied in greater detail and followed for observation periods of up to 6 years. This group included 6 patients with multiple superficial basal cell carcinoma syndromes, 7 patients with xeroderma pigmentosum, 5 patients with arsenical dermatoses and primary epidermal neoplasms, 3 patients with late radiation dermatitis associated with malignant degeneration, 18 patients with extensive solar keratoses and multiple squamous cell carcinomas in situ, and 10 patients with leukoplakia.

Studies on Basal Cell Carcinomas

The essential features of cell mediated immunity against epidermal neoplasms are demonstrated by the effects on basal cell carcinomas. Hypersensitivity was induced by topical application of a cream containing 0.05% TEIB. This preparation was applied daily under occlusion to an area of approximately 1 sq cm until hypersensitivity became apparent (Fig. 1). The concentration of the challenging sensitizer was then titrated over a concentration range of several orders of magnitude below the dose used for sensitization in order to determine the concentration of the sensitizer which would produce the minimal reaction required for tumor eradication (Fig. 2).

The procedure and effects of immune challenge will be described in a patient who had several hundred superficial basal cell carcinomas (Fig. 3). Hypersensitivity to topical application of 0.05% TEIB became apparent (Fig. 1) after approximately 3 weeks of daily administration. The preparation was then applied over the entire back of the patient. Within 24 hours the reaction to the challenging application started to become apparent by erythema, edema, and vesiculation (Fig. 4). After 24 hours, erosion became apparent, which led to exudation, necrosis (Fig. 5), and subsequent reepithelialization (Fig. 6). During an observation period of 5 years there was no recurrence of the lesions which had disappeared as a result of the immune response (Fig. 7). The patient subsequently developed new lesions at sites which had not previously been involved and responded in a similar manner to challenge with TEIB (Figs. 8, 9). This time the sensitizing agent had been titrated to a lower concentration (10^-3 % TEIB) which resulted in a considerably milder reaction. Resolution of the lesions and subsequent recovery, however, was similar although more rapid than it had been at the higher concentrations of the challenging dose (Fig. 8). In this as well as in other patients with multiple superficial basal cell carcinomas more than 98% of lesions were eradicated by immunologic challenge.

Before the first application of the challenging dose of TEIB, approximately 140 lesions had been counted on the patient’s back. The challenging application, however, resulted in reactions in well over 500 areas (Fig. 4). These areas included early lesions which could not be clinically detected prior to the onset of the hypersensitivity reaction. Biopsies of reactive lesions, not previously suspected, revealed these to be basal cell carcinomas. Thus, the hypersensitivity reaction unmasked clinically undetectable lesions. As a further result of the reaction, these early lesions underwent resolution. The areas between the lesions did not react to a significant extent. It therefore appears that the differential reactivity to immunologic challenge results in a permanent arrest of multiplication and in disappearance of malignant cells while temporary, reversible, or no effects occur in the corresponding normal tissues. This differential effect is further demonstrated by the observation that normal reepithelialization is proceeding while the necrotic exudate of tumors is forming in response to the challenge (Figs. 6, 10—14).

Systemic toxicity or other severe side reactions were not demonstrated. The discomfort resulting from the cutaneous reaction was adequately controlled by mild analgesics and topical or brief courses of systemic corticosteroids. Steroid administration did not interfere with the resolution of the neoplasms although the inflammatory component of the reaction was suppressed. This suggested that a protracted inflammatory reaction was not essential for resolution of the tumors.

Challenge reactions in malignant and premalignant lesions were induced by topical administration of concentrations of
10^{-6}\% \text{ TEIB or less although concentrations of } 10^{-2}\% \text{ to } 10^{-4}\% \text{ TEIB usually were employed. The concentration of the challenging dose was obtained by titrating the concentration of the agent on the normal skin by a series of patch tests to the lowest level at which a reaction occurs (Fig. 2). Advantage was then taken of the more intense reactivity of the neoplastic lesions.}

**Studies on Squamous Cell Carcinomas**

Studies on squamous cell carcinomas of the skin were limited to patients with advanced, disseminated malignant disease or patients with intractable multiple squamous cell carcinoma associated with arsenical dermatitis or xeroderma pigmentosum. Studies were confined to superficial lesions, unless advanced metastatic disease was present. In a number of patients with solar keratoses, carcinomas in situ were included in these studies. Squamous cell carcinoma in situ responded more intensely (Figs. 15—17) to topical challenge with TEIB or DNCB than the premalignant keratoses.

In general, the reaction to challenge in squamous cell carcinomas was similar to that of basal cell carcinomas; early, undetectable lesions of squamous cell carcinoma became apparent following challenge. The reaction at the proper concentration of the challenging agent was limited to the sites involved by lesions. At higher concentrations of the challenging agent, the reaction was markedly more intense in squamous cell carcinomas than in uninvolved skin. Recovery, healing, and reepithelialization occurred while the challenge was being continued and exerted a destructive effect on neoplastic lesions. This provided further indication of the selectivity of the reaction to challenge.

More than 90\% of squamous cell carcinomas in situ underwent regressions following immunologic challenge. Deeper lesions responded less favorably; those which did not regress completely became smaller and either responded to a second course of immunotherapy, topical chemotherapy, or to standard treatment. Residual lesions of squamous cell carcinomas in patients with xeroderma pigmentosum were submitted to a second course of immunotherapy to which topical 5-fluorouracil (5-FU) was added. While the reaction to the combination of chemotherapy and immunotherapy was considerably more intense than with topical 5-FU or topical challenge alone, the effects on the adjacent, apparently uninvolved skin were minimal. Resolution of 12 out of 15 lesions followed the combined topical chemotherapy and immunotherapy approach. This suggested a synergistic effect on malignant lesions without a concomitant increase in toxic effects. Lesions which had recurred following surgery or X-radiation gave unsatisfactory results; after 2—5 successive courses of immune challenge, less than 60% of these recurrent lesions regressed.

**Studies on Premalignant Epidermal Lesions**

Studies on premalignant keratoses were initiated in patients with arsenical keratoses. Challenge with TEIB at concentrations of 10^{-6}\% produced a reaction but did not eradicate arsenical keratoses. A concentration of 0.0005\% TEIB resulted in suppression of arsenical keratoses accompanied by erythema at the involved sites, without apparent effects on the adjacent normal skin. Increasing the concentration of TEIB up to 0.01% did not change the reaction. At a concentration of 0.1% the uninvolved skin also reacted although the reaction in the keratoses was more intense. Despite the more intense reaction at concentrations of 0.1% TEIB, arsenical keratoses did not undergo resolution.

Since immune challenge did not produce adverse effects in arsenical keratoses, solar keratoses were investigated. The effects in solar keratoses were essentially similar to those in superficial basal cell carcinomas. Following induction of delayed hypersensitivity to TEIB, the challenge response resulted in a reaction which was less severe but otherwise resembled the reaction of basal cell carcinomas. As had been observed in basal cell carcinomas, the reaction was usually limited to the lesions. At high concentrations of the challenging sensitizer, the intensity of the reaction was considerably more marked at sites involved by solar keratoses than in the adjacent normal skin. At the minimal concentration at which the lesions reacted, the normal tissues showed no gross changes. Keratoses which had not been clinically detectable became apparent as a result of the challenge reaction. The intensity of the reaction in these early lesions was less marked than in clinically obvious lesions. Following the challenge reaction, complete resolution (Figs. 18—21) occurred in more than 95% of the lesions.

**Studies on Leukoplakia**

Leukoplakia of the buccal mucosa and of the tongue, which was not suitable for standard treatment or had not responded adequately to topical chemotherapy (22), was studied by local immune challenge in a group of 10 patients. Hypersensitivity studies were limited to TEIB. The lowest concentration of TEIB at which a response to challenge was elicited on the skin was then applied under an occlusive dressing (Orahesive bandage) to the areas involved by leukoplakia. Within 24—48 hours a reaction occurred at the sites involved by leukoplakia. This reaction varied in intensity but was usually mild. As a rule adjacent areas of normal mucosa did not react. On several occasions the regional lymph glands became swollen and tender, without evidence of other pathologic changes.

Partial to complete remission of leukoplakia (Figs. 22, 23) resulted, but recurrences were observed within 4—6 weeks following discontinuation of immunotherapeutic challenge. Repeated challenge again resulted in resolution of lesions. Recurring lesions were less marked than those present before the initial challenge. Patients kept on intermittent challenge at intervals of 4—6 weeks were controlled without apparent recurrences for periods of up to 3 years.

**Intermittent Immune Challenge**

Intermittent administration of TEIB and DNCB was explored in patients with extensive, frequently recurring involvement by multiple superficial basal cell carcinomas, squamous cell
carcinomas in situ, or premalignant keratoses. Immune challenge reactions to TEIB or DNCB were induced at intervals ranging from 2 months to 2 years for periods of up to 5 years. Resolution of newly developed neoplasms as well as eradication of lesions which were clinically undetectable resulted from each course of immunotherapy. The incidence of new tumors was markedly reduced as determined by studies in which symmetrical sites were submitted to intermittent challenges to TEIB or DNCB, and standard therapeutic modalities respectively (Figs. 24–26). It therefore appeared that local immunotherapy is effective in eradicating established lesions, in aborting early lesions before they become clinically detectable, and in reducing the incidence of new lesions in patients with persistent development of new epitheliomas.

Studies on Transfer of Immunity

Studies were initiated to determine whether the effects of the hypersensitivity reaction on skin tumors were due to cell-mediated immunity or to humoral antibodies. Peripheral white blood cells were collected from each of three patients who had been sensitized to TEIB and DNCB respectively. The cells were separated and concentrated following leukopheresis of sensitized patients. The formed elements were further separated, and the WBC were concentrated. The concentrated WBC preparations (10^6 to 10^8 WBC per ml) were then injected subcutaneously into 8 patients who had been shown not to be hypersensitive to these agents and challenge was immediately initiated. Within 8–24 hours after administration of the cells, a hypersensitivity reaction to the respective sensitized agent was demonstrated in the recipients. The challenge response to TEIB or DNCB following cell-mediated transfer of immunity was shown to result in selective resolution of cutaneous neoplasms. The sequence of events following challenge was similar to the reactions in patients who had been sensitized by direct exposure to the sensitizer.

The challenge reaction was more marked and more rapid in onset at sites to which white cells had been injected than in other areas. It was evident, however, that the recipients' own cells had acquired reactivity to the sensitizer following the administration of white cells from sensitized donors. The acquired reactivity also was much more intense at sites involved by cutaneous neoplasms than in the normal skin when challenged by the same concentration of sensitizer. The reaction following WBC transfer which resulted in eradication of neoplasms was limited to superficial lesions.

Following direct induction of hypersensitivity, intravenous administration of the sensitizer 0.4 mg TEIB did not result in cutaneous or systemic hypersensitivity reactions. Since it is known that agents which produce specific cell-mediated hypersensitivity reactions are also capable of producing humoral antibodies (which may block the cell-mediated response), an attempt was made to utilize WBC-mediated transfer of immunity in order to avoid initial formation of humoral antibodies. In patients with mycosis fungoides to whom immunity had been transferred, a temporary reduction in the degree of infiltration at areas involved by plaques and nodules was observed following intravenous administration of TEIB. Plaques which had been injected with lymphocytes and to which challenging doses of the sensitizer were applied topically, underwent complete regression for observation periods of 6–8 months as indicated by clinical and microscopic examination. Topical application of challenging doses resulted in partial regression of lesions which had not been injected with lymphocytes. Partial regression consisted of a reduction in the size and the consistency of the infiltrate. Complete resolution of lesions which were challenged but had not been injected with WBC was not observed. These observations are in agreement with the work of Ratner et al. (24).

Effects of Combining Two Sensitizing Agents

Studies were carried out in five patients with multiple superficial epitheliomatosis (xeroderma pigmentosum, arsenical dermatitis, multiple basal cell carcinoma syndromes, and solar keratoses) to determine whether hypersensitivity reactions with two or more sensitizers produced a synergistic effect. Patients were sensitized simultaneously to TEIB and DNCB. Combinations of 2 sensitizing agents were shown to have synergistic effects in producing resolution of premalignant keratoses, superficial basal cell carcinomas, and squamous cell carcinoma in situ. The intensity of the reaction of neoplastic lesions to the combination of 2 or more sensitizers was markedly enhanced at concentrations at which the agents separately produced no apparent reaction. The effects on the adjacent normal skin, however, were not increased by the combination of the sensitizing agents.

Studies on Neoplasms of Nonepidermal Origin

Tumors other than those of epidermal origin showed either a challenge reaction to TEIB or DNCB which was the same as normal tissues or no reaction at all. These tumors included malignant melanoma, Kaposi's hemorrhagic sarcoma, adeno-carcinoma of the breast, mesothelioma, lymphosarcoma, Hodgkin's disease, other lymphomas, and infiltrates of leukemia.

Metastatic squamous cell carcinoma of the larynx was challenged with topical intralesional and parenteral administration of TEIB, following hypersensitization. Temporary, partial reduction in the size of some of the lesions was observed.

Discussion

The data obtained indicate that immune reactions of the delayed hypersensitivity type can result in eradication of superficial cutaneous premalignant and malignant lesions, with minimal or no effects on normal tissues. The effects of the immune reaction have at least some selectivity as indicated by the simultaneous occurrence of tumor involution and epitelialization. Since epithelialization has to be preceded by granulation tissue formation, it is evident that the immune reaction does not prevent connective tissue growth. Selectivity is further suggested by the marked difference in the intensity of the challenge reactions in normal and neoplastic epidermis respectively. The differences in the reactions are demonstrated...
by destruction of the neoplastic cells, but there is no significant alteration in the behavior and multiplication of normal cells. The selective nature of the effects is further indicated by the challenge response induced in clinically undetectable lesions. This reaction demonstrates the presence of early lesions as shown by histologic examination. Although this reaction was considerably less severe than in clinically overt lesions, the reactions were essentially the same.

The process of unmasking clinically undetected lesions by immune challenge resembles an analogous effect of topical cytostatic therapy. The reduced incidence of new lesions in patients who had persistently developed new skin tumors in the past, as well as in patients in whom symmetrical sites were submitted to immune challenge and standard treatment modalities respectively, suggests that immunotherapy also results in destruction of lesions which are too small to become apparent by their reaction to the hypersensitivity-inducing agent. The response to challenge of a lesion consisting of a few cells would produce a reaction which would not be grossly apparent. Nevertheless, the neoplastic cells would undergo involution. Thus, neoplastic lesions of microscopic size would be eradicated without any indication of their presence or destruction. If these lesions had remained viable, they would have developed into clinically significant neoplasms. Their removal by immune challenge would account for the reduced incidence of tumors following one or more courses of immunotherapy.

The resolution of premalignant keratoses in patients with arsenical dermatitis, xeroderma pigmentosum, or solar keratoses also indicated the selective nature and the potentially prophylactic value of immunotherapy since the involution of premalignant lesions prevents their transformation to squamous cell carcinomas. Again, the removal of clinically undetectable lesions by immunotherapy would reduce the subsequent incidence of premalignant and malignant neoplasms. The removal of neoplastic cells by immune challenge reactions appears to be related to qualitative or quantitative differences in the antigenic composition of normal cells and their premalignant and malignant counterparts. The antitumor effects of the immune reaction may, therefore, be exerted at the earliest stages of malignant transformations at which differences in antigenic composition are elaborated. These differences may be present in neoplastic cells before their premalignant or malignant state can be recognized by morphologic criteria.

Further indications of the differential nature of the effects of delayed hypersensitivity reactions on neoplastic and normal cutaneous tissues are provided by the results of titration of the challenging dose. It was thus established that challenge reactions can be elicited in the neoplasms at concentrations of the sensitizing agent one or more orders of magnitude below those required for evoking a response in normal skin. The extension of the reactivity to mucosal premalignant lesions when the primary hypersensitivity reaction is produced in the skin further suggests the presence of a factor which is common to neoplasms arising from epidermal structures.

It appears from the studies on transferring immunity by peripheral leukocytes that the reaction is associated with cell-mediated specific immune mechanisms. Presumably the sensitizing agent interacts with components of both normal and neoplastic epidermal cells, which elicit an immune response on the part of the host. Since a reaction can be obtained in normal skin at sufficiently high concentrations of the challenging dose, the sensitizing agent affects normal as well as neoplastic elements. The reasons for the more marked intensity of the reaction at the sites involved by premalignant and malignant lesions may indicate that proportionately larger amounts of the sensitizing agent have access to the neoplastic cells than to the normal cells. This in itself would constitute an important difference between normal cells and their malignant counterparts. A quantitative difference in the amount of sensitizing agent which reaches the normal and malignant cells may occur on the basis of a mechanism similar to that of the Koch phenomenon. This may account for the qualitative difference in the effects. On the other hand, the possibility of the formation of different antigens in normal and neoplastic cells, under the influence of the same sensitizing agent, has not been excluded. The sensitizing agent acting as a hapten may combine with or otherwise alter components of normal and malignant cells, which in their natural states do not differ sufficiently from each other to provide a basis for immunologic incompatibility. Following interaction with an appropriate hapten, however, the changes in the reactive component of the neoplastic cells may be sufficient to stimulate an effective immune response. Cell-mediated immune reactions are usually more specifically directed towards the carrier protein than the hapten while humoral antibodies are more responsive to the hapten. Therefore, the observations that effects of challenge reactions on cutaneous neoplasms following sensitization with a potential hapten are associated with cell-mediated immune mechanisms appear to be consistent with these considerations.

Studies on the effects of combining two or more sensitizers indicate a synergistic effect at concentrations of the challenging doses which are orders of magnitude below the levels at which each sensitizing agent alone elicits a reaction in normal cells or their neoplastic counterparts. The enhancement of the effects of topical cytostatic agents on tumors of the skin which have been challenged following induction of hypersensitivity further suggests a selective action of the immune response. The increased effects of cytostatic agents may be the result of altered absorption of the cytostatic agent due to increased permeability as a result of the delayed hypersensitivity reaction at the sites involved by neoplasia.

The effects of local challenge were largely limited to superficial lesions. This may be due to the fact that the sensitizing agent produces immunologic reactions which are mediated both by cells and humoral antibodies. In the avascular environment of the epidermis, the cellular immune reaction would predominate since it depends on actively migrating cells rather than on passively diffusing macromolecules. In lesions which have penetrated into the dermis, both the humoral antibodies and the cellular elements would be available to react to the challenging sensitizing agent. Therefore, the humoral antibodies could more readily combine with the sensitizing agent and reduce the intensity of the cellular reaction. These considerations may explain the lack of effects of intravenous administration of TEIB following the induction of hyper-
sensitivity by direct application of the agent. The limited number of observations on intravenous administration of the sensitizer following the induction of transferred immunity suggests that the effects noted may be due to the lack of humoral antibodies while the recipient was generating sensitized cells. Humoral antibodies may, therefore, interfere with the cellular immune response.

Topical immunotherapy, with or without concurrent topical cytostatic therapy, appears to offer promise in the management of extensive superficial premalignant keratoses, multiple basal cell carcinomas, and multiple squamous cell carcinomas in situ. Immunotherapy, particularly when it includes two or more suitable sensitizing agents and when combined with topical cytostatic therapy, may offer a well-tolerated and efficient approach to the management of these types of clinical problems. Present studies suggest that preserved lymphocytes, or components of lymphocytes, may transmit the selective reactivity of hypersensitization from one individual to another.

The effects following induction of specific cell-mediated hypersensitivity by the chemical agents which we have studied differ in epidermal neoplasms and in those arising from other tissues. This suggests that these agents behave differently towards cells of different origin, as might have been expected in view of the high degree of specificity of cell-mediated immunity and hypersensitivity-inducing agents for specific target cells. It also indicates that agents which induce cutaneous hypersensitivity have some selectivity for cutaneous neoplasms. Studies appear warranted, however, to explore agents which produce hypersensitivity in other tissues with a view towards eliciting delayed hypersensitivity reactions which may be utilized for producing effects in neoplasms arising from them, analogous to those in tumors of epidermal origin.

The utilization of delayed hypersensitivity evoked by a simple chemical in the management of clinical problems, particularly as related to neoplastic lesions, presents a new approach to the management of disease. This approach exploits the therapeutic potential of delayed hypersensitivity reactions which, until recently, have been considered primarily as causes of diseases or as obstacles to therapy. Further work in this area may result in extending the principles of immunotherapy to other types of neoplasm or to other types of disease.

REFERENCES

Hypersensitivity Reactions

Figs. 1–26. DNCB, dinitrochlorobenzene; TEIB, 2,3,5-triethyleneiminobenzoquinone.

Fig. 1. Initial reaction in normal skin to TEIB (0.05%) following induction of hypersensitivity.

Fig. 2. Reactions of normal skin to challenge with decreasing concentration (0.05%, 0.005%, 0.0005%) of TEIB. Minimal reaction to challenge with TEIB at concentrations of 5 parts per 10 million.

Fig. 3. Patient with multiple superficial basal cell carcinomas. Approximately 140 lesions were clinically detectable prior to immune challenge with TEIB.

Fig. 4. Reaction to challenge with 0.05% TEIB in same patient as in Fig. 3. More than 500 lesions have become apparent by their response. The majority of the reacting lesions could not be recognized clinically prior to challenge. Intervening normal skin does not show reaction.

Fig. 5. Necrosis limited to sites involved by tumors in patient shown in Fig. 3.

Fig. 6. Same patient as in Fig. 3. Simultaneous growth of normal cells and destruction of malignant cells during challenge reaction to TEIB. Normal epidermis and connective tissue is multiplying to resurface sites as tumors disappear, while other tumors are undergoing necrosis as challenge reaction is being continued.

Fig. 7. Same patient as in Fig. 3 following recovery from challenge reaction to TEIB (approximately 4 weeks after discontinuing topical administration of TEIB). More than 98% of lesions have been eradicated without recurrence for observation period of 5 years. Healing has occurred with minimal or no scarring.

Fig. 8. Same patient as shown in Fig. 3. Second course of immunotherapy with TEIB (1 part per 10 million) one year after completing initial course. Considerably fewer lesions than prior to immunotherapy have arisen de novo during the intervening period. Majority of lesions showing reaction to challenge were not clinically detected prior to TEIB administration.

Fig. 9. Same patient as in Fig. 3 following recovery from second course of immunotherapy. Patient has remained free of clinically detectable lesions with intermittent courses of immunotherapy.

Fig. 10. Close-up of basal cell carcinoma in patient with late radiation dermatitis accompanied by malignant degeneration prior to challenge with DNCB.

Fig. 11. Same lesion as in Fig. 10 twenty-four hours after challenge with topical DNCB (1 part per million). Edema, erythema, and vesiculation are limited to site involved by lesion, with minimal effects on adjacent normal skin.

Fig. 12. Same lesion as in Fig. 10 at 72 hours of challenge with 1 part DNCB per million. Lesion shows erosion and exudate.

Fig. 13. Same lesion as in Fig. 10 at 96 hours of challenge with 1 part of DNCB per million; necrotic exudate has formed in center of lesion. Marginal reepithelialization and requisite granulation tissue formation is proceeding as tumor is being destroyed by continued challenge reaction.

Fig. 14. Same area as in Fig. 10 at tenth day of challenge with 1 part DNCB per million. Despite continued challenge at therapeutic level of sensitizer, complete healing with minimal or no scar formation has occurred.

Fig. 15. Patient with arsenic-induced dermatitis showing numerous premalignant keratoses and squamous cell carcinomas.

Fig. 16. Same patient as in Fig. 15 after 72 hours of challenge with DNCB (1 part per 1,000) showing erythema multiforme-like reaction. In the center of each circular erythema a neoplastic lesion is undergoing necrosis. Selectivity of reaction to challenge is indicated by reversible temporary reaction of normal skin as contrasted to permanent destructive action on tumors.

Fig. 17. Same patient as in Fig. 15 at 4 weeks after discontinuing challenge with DNCB. Except for preexisting scars from previous surgery, complete healing has taken place.

Fig. 18. Patient with premalignant (solar) keratoses prior to immunotherapy.

Fig. 19. Same patient as in Fig. 18 following 48 hours of topical challenge with TEIB (5 parts per 10,000). Overt lesions as well as lesions which were initially not clinically apparent have reacted.

Fig. 20. Same patient as in Fig. 18 showing reaction limited to lesions with minimal or no adverse effects on normal skin.

Fig. 21. Same patient as in Fig. 18 at 4 weeks after discontinuing challenge. Complete recovery without scar formation has occurred.

Fig. 22. Extensive leukoplakia of buccal mucosa prior to immunotherapy.

Fig. 23. Same area as in Fig. 22 after 72 hours of challenge with TEIB (5 parts per 10 million). Complete ablation of leukoplakia without injury to normal mucosa is seen. Mucosa subjacent to leukoplakia is normal on gross and microscopic examination.

Fig. 24. Patient with xeroderma pigmentosum prior to immunotherapy. Numerous premalignant keratoses, squamous cell carcinomas in situ, and superficial basal cell carcinomas are present.

Fig. 25. Same patient as in Fig. 24. Left side of face shows effects of challenge with TEIB (5 parts per 100,000) limited to sites of lesions. Topical TEIB was applied intermittently for 12 months to left side of face while lesions on right side were treated with standard modalities. During this period the patient developed approximately 50 lesions and numerous premalignant keratoses on the right side while one basal cell carcinoma and no clinically detectable keratoses appeared on the left side.

Fig. 26. Same patient as in Fig. 24 following course of intermittent TEIB administration. Patient has remained free of clinically detectable lesions.
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