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# TUMORS OF THE SKIN

## V. LOCAL ADMINISTRATION OF ANTI-TUMOR AGENTS TO MULTIPLE SUPERFICIAL BASAL CELL CARCINOMAS*

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In a previous double blind placebo-controlled study (1), topical administration of several anti-tumor agents was found to alter the natural course of solitary basal cell carcinoma, including complete regression in a statistically significant number of lesions. Several studies on the effects of local administration of chemotherapeutic agents to tumors in the skin and subcutaneous tissues, previously reported from this group (2–7) and other investigators (8–12), indicated that further investigation is warranted. This paper reports the effects of local administration of anti-tumor agents on multiple superficial basal cell epitheliomas.

Comparative studies on various agents, drug concentrations, durations of application, frequencies of application, methods of dressing and area sizes can be carried out in a single patient with multiple epitheliomas. The corresponding effects of various agents and drug concentrations upon the normal skin surrounding the tumors can be compared with each other and with control sites in the same patient.

In addition to being suitable for comparative studies of anti-tumor agents, multiple superficial epitheliomatosis is frequently a difficult therapeutic problem. Local chemotherapy was therefore explored in patients in whom the areas of the skin involved by tumor were large, thus making difficult the management by surgery or radiation. This study indicates that although the topical administration of anti-tumor agents to multiple epitheliomas is still an investigative technic, it is possible that topical administration of anti-tumor agents may become a practical approach to the management of multiple superficial epitheliomatosis.

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### METHODS

The seven patients in this study are quite dissimilar in regard to the number, distribution, and duration of tumors. The studies carried out in each patient were guided by the number, sizes, and anatomic sites of the tumors. Since the patients are dissimilar and since several agents and various drug concentrations were to be studied, the agents and their concentrations were varied among the patients. The agents were applied topically as ointments or were injected intracutaneously or subcutaneously in aqueous solution. The vehicles for topical application were Acid Mantle cream, Plastibase or aquaphor. The agents were administered daily or every other day. Some areas were covered with plastic occlusive dressing after each topical application while the other areas were not covered occlusively. Duration of the courses of application varied from three days to forty-three days. The response of the tumors was assessed by frequent inspection, photography, and microscopic examinations of serial biopsy specimens. Duration of observation following cessation of the applications varied from 6 months to more than 3 years.

Two groups of studies were carried out. In the first group of studies, multiple individual lesions were studied by administration of different agents or different concentrations of a selected agent to each individual lesion (Study Program I). In the second part of the study, multiple grouped or confluent lesions covering large portions of the skin were submitted to a single concentration of a single agent to an entire study area (Study Program II).

#### *Investigational*

*Study Program I*

In Study Program I the anti-tumor agents were administered by injection or inunction. The agents*

* The chemical agents were obtained as follows: 5-Fluorouracil through the cooperation of Dr. E. Miller, Hoffman-La Roche, Inc., Nutley, N. J., 5-Mercaptouracil and Dimethylurethimine through the cooperation of Dr. T. Bardos, School of Pharmacy, State University of New York at Buffalo and Dr. J. Ambrus, Department of Experimental

injected as aqueous solutions were: 0.5% 5-Flourouracil (5-FU), 5.0% 5-FU, 5.0% Dimethylurethimine (AB 132), 10.0% 5-Meraptouracil (AB 050), 0.05% Methotrexate, 0.2% Methyl-Glyoxal-bisguanylhydrazone HCl. The agents* administered as ointments by topical application were: 20.0% 5-FU, 0.02% Actinomycin D, 20.0% AB 050, 20.0% Methotrexate, 20.0% AB 132, 0.005% Nitrogen Mustard, 5.0% 5-iodo-2-deoxyuridine (IDUR) and 1.0% Cytosine arabinoside.

The reactions of the superficial basal cell carcinomas in this study were similar to those described in the study of the local administration of anti-tumor agents to single basal cell carcinomas (1). All of the agents studied produced some effects upon the tumors. The changes observed most often were erythema, followed by erosion of a part or all of the tumor surface. Necrosis of the tumor, superficial ulceration and crust formation were observed occasionally with most agents but regularly only with 5-FU. Eczematization (vesiculation and crusting) of the tumor and the skin surrounding the tumor sometimes occurred during the application of AB 132, AB 050, and IDUR.

As in the study of solitary basal cell epithelioma (1), 5-FU was the only agent which regularly produced tumor necrosis and regression. Under the conditions of this study, the agents other than 5-FU did not produce predictable or consistent tumor resolutions. Complete tumor resolution followed the application of AB 050, methotrexate, IDUR, and cytosine arabinoside in a small number of instances.

Although tumor regression following methotrexate was not consistent, the three superficial basal cell carcinomas which resolved after application of methotrexate cream reacted in a manner quite similarly to the reaction evoked by 5-FU: erythema and necrosis were sharply limited to the tumor; exfoliation of the firm adherent crust that formed following cessation of application of methotrexate left a smooth pink slightly atrophic scar (Figs. 1, 2).

Application of 5-FU cream or injection of aqueous solution of 5-FU was followed within 24 hours by erythema in most tumors (Fig. 3). Most tumors became raised slightly within 2 or 3 days (Fig. 4). Following the initial swelling superficial denudation appeared in portions of the tumor (Fig. 5). Necrosis of tumor was evidenced by ulceration and, after cessation of the administration, crust formation (Fig. 6). Exfoliation of the crust left a firm, erythematous atrophic scar (Fig. 7). Resolution of very superficial tumors left atrophy which was so slight as to be barely discernible.

*Study Program II*

Because application of 5-FU resulted in tumor regression more consistently than the other agents under the conditions of this study and because 5-FU produced no significant local or systemic morbidity, this agent was used in the patients studied in the second group of studies. In the second study program the concentrations of 5-FU, administered by topical application, were 0.5%, 1.0%, 2.0%, 5.0%, 10.0% and 20.0%. The various concentrations of 5-FU were applied daily for 10 to 43 days. Some areas were covered (daily) with occlusive plastic bandages; some areas were not occluded or covered. Because the epitheliomas were numerous and either in close proximity to each other or frankly confluent, the exact number of tumors in each study area was impossible to determine (Fig. 8). The number of lesions counted in each area studied was the minimum number present, since, as will be shown, some previously inapparent tumors became evident during the study. As the number of lesions studied was an approximation, so was the number of tumors that resolved an approximation. At the completion of the study of each area, the number of sites that appeared grossly to contain residual epithelioma was estimated and representative sites were examined by biopsy. The estimates of the number of residual tumors were probably quite accurate because all areas even slightly suspicious for tumor were counted as residual tumor and the representative specimens confirmed the clinical impressions in almost all instances.

The first patient studied was a 49 year old female with the basal cell nevus syndrome. The patient had a history of successive crops of skin tumors since the age of 14. She had been treated on numerous occasions with all the standard modalities (radiation, excision, electrosurgery). At the time of this study, she presented innumerable superficial, multiple basal cell carcinomas (for which she had refused standard therapy for the preceding four years) and scars of previous treatments on her head, trunk and extremities. Topical administration of 5-FU cream was carried out on several large areas including the chest, the back and the legs. The chest was covered by almost confluent superficial epitheliomas and scars of previous treatments such that the number of distinct lesions could not be counted. Cream containing 1% 5-FU was applied under occlusion for four days to the right chest and for 17 days to the left chest. Marked erythema and denudation appeared in the tumor areas. Six months after the administration of 5-FU had been stopped, approximately 10% of the treated area on the right chest

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Biology, Roswell Park Memorial Institute, Buffalo, New York; spiramycin through the cooperation of Dr. N. Back of the School of Pharmacy, State University of New York at Buffalo; Actinomycin D through the cooperation of Drs. J. Scigliano and A. Osterberg of the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Maryland; Methotrexate through the cooperation of Dr. J. Ruegsegger of the Lederle Laboratories, Pearl River, N. Y.; Nitrogen Mustard as Mustagen, Merck Sharp and Dohme, West Point, Pa.; IDUR through the cooperation of Dr. M. Boghosian, The Allergan Co., Santa Ana, Calif., and Cytosine Arabinoside through the cooperation of Dr. L. Rhuland of the Upjohn Co., Kalamazoo, Mich.

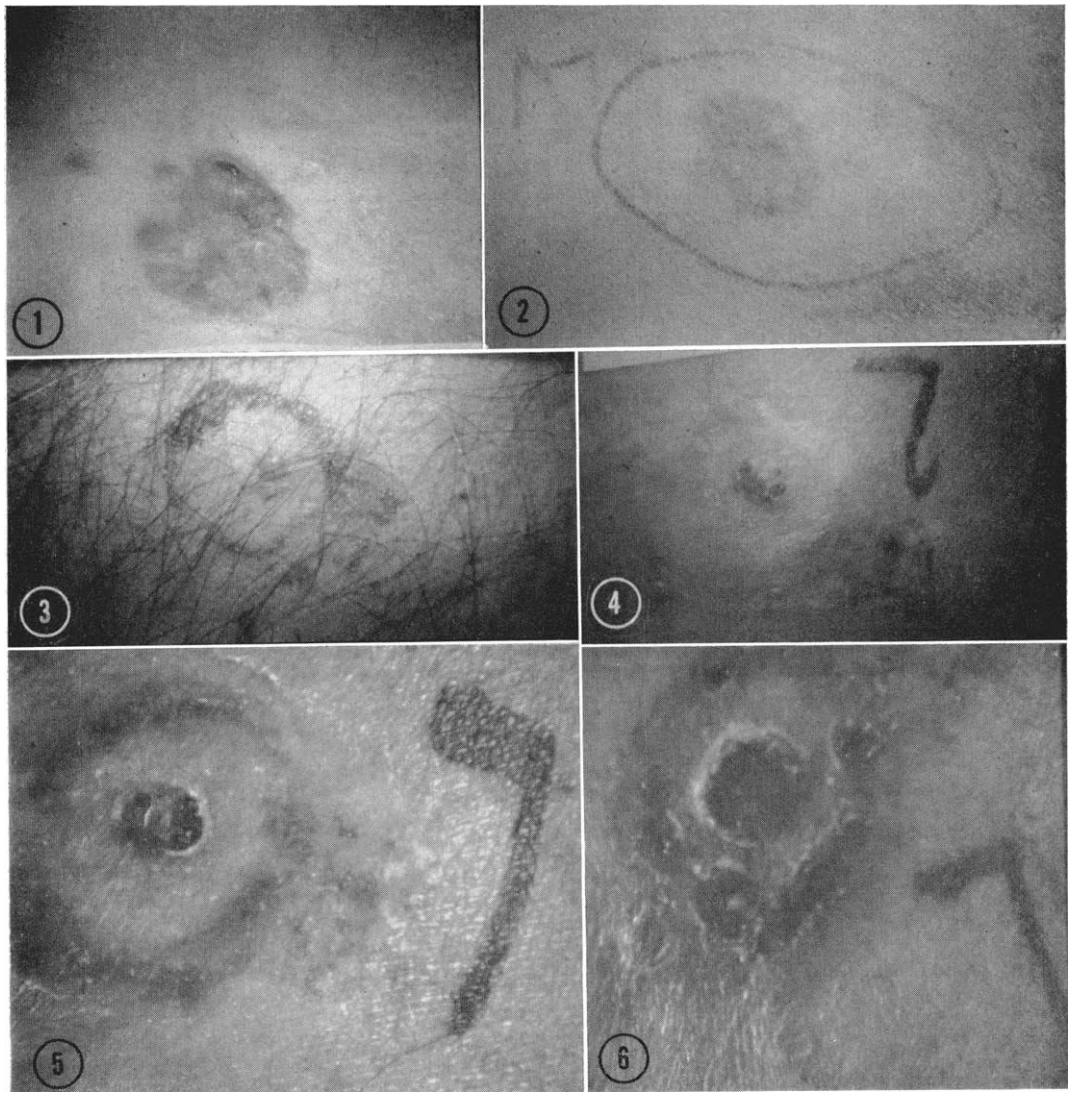


FIG. 1. Basal cell carcinoma prior to topical application of 20% Methotrexate in hydrophilic base.

FIG. 2. Site of lesions shown in Fig. 1 at 6 weeks following 4 week course of daily topical application of 20% Methotrexate in hydrophilic base.

FIG. 3. Superficial basal cell carcinoma prior to study.

FIG. 4. Same area as shown in Fig. 3 after 9 days of 5-FU application. Elevation of the tumor is evident.

FIG. 5. Same area as shown in Fig. 3 after 2 weeks of 5-FU application. Initial swelling with superficial denudation is evident.

FIG. 6. Same area as shown in Fig. 3 after completion of 4 weeks of 5-FU application. Necrosis and ulceration are quite pronounced.

and 20% of the treated areas on the left chest contained tumor.

During the courses of 5-FU application a number of areas that had not previously appeared to be epitheliomatous became erythematous and swollen. Biopsy examination of these sites showed superficial basal cell epitheliomas. Thus, areas which had no clinical evidence of neoplasm prior to application of 5-FU, reacted and the neoplasms became clinically apparent during the course of applications (Figs. 9, 10). The initially obvious lesions, as well as those which became apparent

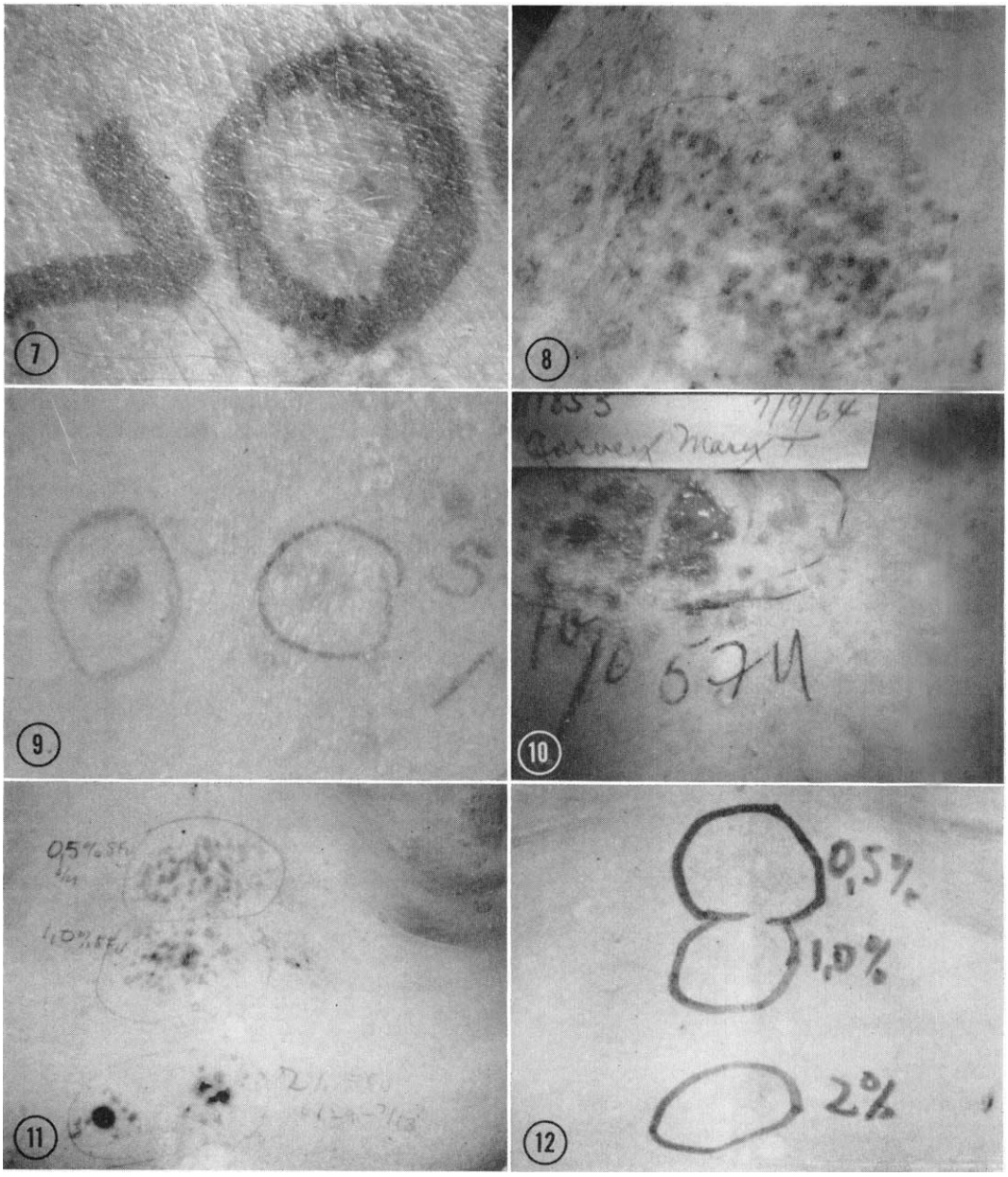


FIG. 7. Same area showing erythematous, atrophic scar 3½ months after completion of treatment.

FIG. 8. Extensive involvement by confluent and closely adjacent multiple superficial basal cell carcinoma prior to 5-FU application.

FIG. 9. Area prior to application of 5-FU with small number of lesions clinically evident.

FIG. 10. Same area during course of application of 5-FU. Reaction to 5-FU revealed numerous epitheliomatous lesions which were too small to be clinically evident prior to 5-FU application.

FIG. 11. 3 areas of superficial basal cell carcinoma during course of application of 5 FU including area shown in Figs. 8, 9 and 10.

FIG. 12. Same 3 areas as shown in Fig. 11, 12 months after completion of 5-FU application. No residual or recurrent tumors present.

during the course of 5-FU administration, subsequently underwent complete resolution (Figs. 11, 12).

The right and left legs contained numerous discrete basal cell epitheliomas. The diameters of the lesions varied from 2 to 5 mm except for one large tumor, which was 1.5 cm in diameter. 5% 5-FU cream was applied without occlusion 2 or 3 times daily for 43 days to the right leg. Very slight erythema appeared in some tumors, but there was virtually no tumor regression. 10% 5-FU cream was applied without occlusion 2 or 3 times daily for 38 days to the left leg. Erythema and swelling occurred in some tumors, but as with the right leg, tumor resolution was not seen.

The marked response observed on the chest was induced by 1% 5-FU cream. The very minimal response seen on the legs was obtained with 5% and 10% 5-FU cream, respectively. The contrast in response and degree of tumor resolution between the different sites studied on the chest and legs may have been due to the different modes of administration.

The second patient was an 86 year old female with multiple superficial basal cell epitheliomas of the trunk and lower extremities. The patient objected to further conventional methods of therapy. The areas studied, the concentrations of 5-FU in the cream, the use of occlusive dressing, the duration of the application, the number of tumors in each area, and the number of tumors which resolved is outlined in Table I. These areas have remained unchanged for eight to ten months after cessation of 5-FU application.

The third patient was a 58 year old male with multiple basal cell carcinomas of the trunk. Twenty years ago, he had received multiple increments of X-ray therapy to the face, neck, back and chest. The epitheliomas in this patient had been previously treated by radiation, surgery and electrosurgery.

The two areas studied were the left chest and the right chest. Each side of the chest contained about thirty superficial basal cell carcinomas varying from 3 to 10 mm in diameter.

A cream containing 5% 5-FU was applied to the left side (whole area) twice daily without occlusive dressing. The tumor became erythematous and swollen but did not show eczematization or ulceration. The erythema and swelling were sharply limited to the tumors. Following cessation of the applications the erythema gradually disappeared and the swollen tumors became progressively flatter. Two months after stopping treatment 6 basal cell carcinomas remained clinically evident in the study area.

To the right side of the chest 10% 5-FU cream was applied (to the whole area) twice daily without occlusive dressing. The tumors reacted with erythema and swelling similar to those treated with 5% 5-FU cream but the degree of erythema and swelling was more marked. Four months after stopping treatment there were four basal cell carcinomas clinically evident in the study area.*

TABLE I

*Effects of varying concentrations of topically applied 5-FU in hydrophilic base*

| Area | Concentration of 5-FU | Occlusive Dressing | Days of Application | Number of Tumors | No. of Tumors Resolved |
|---|---|---|---|---|---|
| Right upper back | 20% | No | 33 | 20 | 17 |
| Left upper back | 10% | No | 33 | 35 | 25 |
| Lower back | 5% | Yes | 7 | 44 | 41 |
| Right thigh | 10% | Yes | 10 | 21 | 18 |
| Left thigh | 5% | Yes | 12 | 10 | 10 |
| Right leg | 1% | Yes | 11 | 34 | 31 |
| Left leg | 1% | Yes | 17 | 53 | 49 |

## DISCUSSION

The effects of several concentrations of various anti-tumor agents upon multiple superficial basal cell epitheliomas were studied in the first part of this study for general orientation. Under the conditions of this study, all agents produced some effect upon the tumors although in a number of instances the effects were limited to barely perceptible erythema. Several agents produced gross tumor resolution, subsequently confirmed by biopsy examination. 5-FU produced tumor regression more consistently than any other agent. Comparative study of various concentration of a single anti-tumor agent has been shown to be feasible by simultaneous administration to multiple tumors in one patient. A systematic study of this type comparing four concentrations of 5-FU cream is now being conducted.

The observations described above have indicated, furthermore, that multiple superficial basal cell epitheliomatosis may provide a rapid, safe and practical screening system for exploratory assessment of anti-tumor activity in humans. In order to evaluate basal cell epitheliomatosis as a potential screening system, further studies are required to determine how anti-tumor

* This patient is presently still under study. Areas on his back are being studied with the concentrations of 5-FU which had been used on his chest but some areas are being dressed with occlusive plastic film in order to compare the results in areas treated with and without occlusion.

activity against basal cell carcinoma may be related to anti-tumor activity against other neoplasms. Continuing study in this direction may reveal the manner in which a skin tumor system may be applied to the investigation of other aspects of tumor biology and chemotherapy in man. These aspects would include the study of host defences against tumors (particularly as they undergo regression) without the depression of these defences, induced by systemic administration of most anti-tumor agents. The accessibility of skin tumors, furthermore, facilitates the study of mechanisms of anti-tumor action by the relative ease of serial procurement of specimens for histological, histochemical and biochemical investigation. The introduction of metabolites and antagonists of anti-tumor agents is also facilitated, as are studies on turnover rates, localization and determination of tissue levels of anti-tumor agents. Such studies may provide information on the requirements which permit eradication of skin tumors by chemical agents. This information may be of relevance to the chemotherapy of deep seated tumors.

While local chemotherapy in multiple discrete epitheliomas may be of value as an easily accessible system for studying anti-tumor drug activity, it may also provide an approach to the problem of removing large confluent areas of multiple basal cell epitheliomatosis, which present difficulties in clinical management by standard methods. The observations made in the second study program suggest that the topical application of 5-FU cream appears to justify further investigation in this regard. Although complete resolution of all epitheliomas did not occur in a number of study sites, the eradication of tumor in a large proportion of the involved area was of very considerable practical significance. Several months following cessation of application of 5-FU, small, discrete areas of residual epithelioma were easily amenable to excision, electrocoagulation or further local chemotherapy. Areas of epitheliomatosis as large as one half of the chest or back present virtually insurmountable problems in treatment when the tumor involvement is so confluent that no clearly definable margins are evident. Electrocoagulation and radiation are impractical because of the extensive field sizes. Although plastic surgery may present a possible approach to the removal of such large areas of tumor, provided large flaps can be successfully devised to resurface the excision areas, the problem of multicentricity of epitheliomatosis remains. The skin used to form flaps often itself develops multiple epitheliomas.

Several unknown factors must be evaluated before the possible clinical application of topical chemotherapy can be determined. Although large areas of epitheliomatosis have been followed up to 12 months after treatment, longer follow-up periods will provide a more meaningful estimate of the tumor regression rate. Furthermore, the optimum concentration of 5-FU for treating large areas has not been determined. The observations made in these studies suggest that the minimum effective dose may vary with the anatomical sites and with different patients. Such factors as frequency of administration and duration of course of administration have not been evaluated. Whether or not the large areas should be covered with occlusive film has not been definitively decided, although the observations in this study suggest that occlusion enhances the anti-tumor effect. Availability of 5-FU to the tumor may well vary with different ointment bases; a study is now being conducted to compare a number of ointment bases in regard to the efficacy of topical 5-FU administration. These and other clinical considerations indicate that considerable additional studies are warranted. This preliminary study, however, suggests that large areas of superficial basal cell epitheliomatosis can be favorably affected by topically applied 5-FU.

Previous studies had indicated that topical administration of 5-FU had minimal toxic effects on the normal skin and subcutaneous tissues adjacent to the tumor, while it induced necrosis in the neoplastic tissues at the same time. Lack of significant effects was also observed in normal skin at control sites. It therefore, did not appear necessary, nor was it feasible, to limit topical administration of 5-FU to tumor sites when large areas of the skin were involved by (nearly) confluent or closely adjacent basal cell carcinomas. Under these conditions, again, minimal adverse effects of 5-FU on the normal skin, intervening between or adjacent to the tumors, was observed, indicating differential effects on normal and neoplastic tissues respectively.

Diminutive lesions of basal cell carcinoma, however, became recognizable by their reaction

to topically applied 5-FU, although they had previously not been detectable by clinical examination. This may be of value for the early recognition and eradication of tumors, particularly in patients with multiple concurrent and frequently arising new crops of basal cell carcinomas.

Parallel investigations on solar and arsenical keratoses, on carcinoma *in situ* and on metastatic tumors in the skin indicate that these types of lesions are suitable for studies analogous to those reported here on basal cell carcinomas. These considerations suggest that additional studies of the effects of locally applied anti-tumor agents are warranted.

SUMMARY

The topical application and intralesional injection of several anti-tumor agents were accompanied by changes in the natural course of multiple basal cell carcinomas. Under the conditions of these studies 5-Fluorouracil produced tumor resolution more consistently than other anti-tumor agents. Topical application of 5-FU cream to large areas of confluent or closely adjacent multiple superficial basal cell epitheliomas resulted in tumor regression over large proportions of the involved areas. Minimal effects on normal skin adjacent to tumors were observed. Small lesions of basal cell carcinoma became recognizable by their reaction to topical 5-FU at a stage at which they were not otherwise clinically detectable. In view of the limited information available at present, local chemotherapy is an investigative procedure, and not indicated for the routine clinical management of skin cancer.

Further investigation of the effects of local administration of anti-tumor agents to cutaneous neoplasms are warranted in regard to studies on human tumor biology and mechanisms of chemical anti-tumor action, for screening of anti-tumor agents, and as a possible approach to the management of cutaneous tumors involving large areas of the skin.

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## DISCUSSION

DR. ROBERT AUERBACH, New York, N. Y.: I would like to suggest that in addition to therapy, which still remains to be developed, chemotherapeutic agents may be useful in delineating which areas of previously treated ulcers still contain the basal cell. In the occasional problem case where there is a large recurrent ulcerated basal cell it is sometimes difficult to know which edge is just not healing, which edge is infection and which is tumor. I think this is demonstrated in the patient with small superficial basal cell epitheliomas which were detected after the drug was put on. When Dr. Van Scott used intravenous methotrexate in the treatment of basal

cell epitheliomas, while it was not too effective in therapy, it served as a very efficient marker for the areas of the basal cell tumor.

DR. EUGENE J. VAN SCOTT, Bethesda, Md.: It seems quite probable that topically applied 5-Fluorouracil may be effective on superficial basal cell tumors because of increased permeability of the epidermis overlying such tumors. Possibly other agents, found to be ineffective, are ineffective because of their inefficient permeability through the epidermis. Could I ask the presenter's thoughts on this?

DR. WALTER F. LEVER, Boston, Mass.: I would like to ask Dr. Klein two questions in regard to his interesting presentation. In the first place, which method do you prefer, the open application or the occlusive application; and, if you use both methods, for which purpose do you use the one method and for which purpose the other? And, secondly, do you let the patient apply the preparation himself? You stated that the antimitotic agents were applied daily for a month or longer; do you regard it as safe for the patient to do it himself?

DR. ALFRED W. KOPF, New York, N. Y.: A word of caution should be expressed in the use of topically applied chemotherapeutic agents in the destruction of cutaneous carcinomas. This approach in its present stage should be considered a research tool which has not had sufficient clinical trial and follow-up to warrant suggesting it for general use. Furthermore, 5-Fluorouracil is not commercially available for this purpose. We have treated a small series of patients with histologically proven basal cell epitheliomas with 0.5% colchicine in Hydrophilic Ointment (USP) applied twice daily beneath Telfa gauze with some success. However, several lesions, even after four months of such treatment, failed to respond as indicated by persistence of tumor cells histologically.

I would like to ask Doctor Klein if he or his colleagues have encountered any complications such as delayed tumor response in their series.

DR. EDMUND KLEIN (in closing): Local chemotherapy is an investigative and not a routine clinical procedure at this stage of our studies. The main purpose was to explore it as an approach to the study of those aspects of tumor biology and chemotherapy which cannot be readily investigated by systemic administration of chemotherapeutic agents. The complications that were mentioned by Dr. Kopf in regard to topical colchemide derivatives are very real. With 5 FU we have not encountered submerged islands of tumor cells with apparent clinical cure, but with other agents we have had that experience. This phenomenon was described three or four years ago by Dr. Sullivan and co-workers. They had observed rather protracted disappearance of cutaneous tumors following local administration of podophyllin derivatives. An appreciable number of tumors, however, recurred. Recurrence was not necessarily accompanied by gross indications of the presence of tumor and might not have been recognized without repeated biopsy examinations. I think it should be clearly understood that 3 years is not an adequate observation period for definitive evaluations of a new approach to the control of cutaneous neoplasms.

In regard to Dr. Auerbach's statement, we believe that it might be feasible to use topical agents as markers for tumors. In this connection it is of interest, as Dr. Auerbach mentioned, that systemic administration of MTX "marked" the location of tumor involvement in patients with multiple superficial basal cell carcinomas by producing a differential inflammatory reaction at the tumor sites. This would indicate that this "marking" phenomenon is induced by the antitumor agent regardless of the route of administration. The differential interaction between anti-tumor agents and the tumor site, therefore, is not due entirely to preferential absorption of topically applied anti-tumor agents through the tumor surface, but appears to be related to a more general property.

We have had no reason to be concerned about superimposed infection, because most of the anti-tumor agents used in our studies inhibit bacterial growth; *i.e.*, the cultures that we have taken, were sterile. There are of course microorganisms which will not be inhibited by these agents.

As Dr. Van Scott pointed out, absorption through the tumor surface or skin is a prerequisite. For that reason MTX which is poorly absorbed, will not show much anti-tumor action on topical administration. We discontinued the exploration of methotrexate as a topical antitumor agent except for selected studies, because our results were not impressive, as Dr. Van Scott reported several years ago.

As far as the inhibition of epidermal growth by 5 FU is concerned, I would assume that any

regenerating tissue would incorporate 5 FU and would therefore be inhibited in this process. We have noticed some protracted inhibition of re-epithelialization in one patient. It was several months before epithelialization was complete. This delay in epithelialization, as well as observations on delayed regression of tumors, at some time after 5 FU administration had been discontinued, raises interesting questions of 5 FU transfer and economy during DNA production.

As far as Dr. Lever's question is concerned, we are in the process of evaluating occlusion versus non-occlusion as a mode of administration. I think from a practical point of view, our decision will likely depend on the area involved. If the area can be easily occluded, I feel almost sure that it will be preferable to do so, depending again on the conditions of the study which is being undertaken. If the area cannot be easily occluded, for instance the entire back, I would assume that it would be preferable to explore higher concentrations of the antitumor agent without occlusion.

I should mention in this connection that we are investigating agents which may alter the permeability characteristics of the barrier, keratolytic agents, agents of the adamantine series, and of the DMSO and dimethylacetamide series in the hope of detecting, by radioactively labeled compounds, the rate of absorption, turnover, retention and release in the areas to which the agent is applied.