MORPHOLOGIC AND PHYSIOLOGIC EFFECTS OF CHEMOTHERAPEUTIC AGENTS IN PSORIASIS*

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Empirical use of countless remedies for psoriasis over the centuries has sorted out a relatively small number of drugs or agents that are recognized as having the worthwhile property of favorably affecting the disease. The most commonly utilized of these include ultraviolet light, X-radiation, derivatives of coal tar, and compounds of mercury and arsenic. The reason for the effectiveness of these agents is unknown, although various explanations have been conjectured. A rather popular and credible belief has been that the agents affect the lesion of psoriasis by virtue of their poisonous nature, inhibiting epidermal hyperplasia because of their general toxicity to cells. The observation of Gubner (1), later verified in many patients by Rees and Bennett (2), that aminopterin, a folic acid antagonist having anti-tumor properties, can cause clinical clearing of the cutaneous eruption of psoriasis seems to be compatible with this belief. One test of the hypothesis, however, would be to determine whether the histologic and cytologic changes occurring in the epidermis during healing of the lesion of psoriasis are similar following the different therapeutically effective agents.

Burks and Montgomery (3) studied the histologic changes of psoriasis in patients treated with topically-applied tar and ultraviolet light in specimens removed on the 10th–14th day of this treatment. In these specimens a stratum granulosum was present; the stratum corneum was normal or slightly thickened, with diminished parakeratosis.

Following the report of Sullivan and King (4) which called attention to the merits of topically-applied podophyllum resin in affecting the hyperplastic lesions of condylomata accuminata and verrucae vulgares, Ferrari (5) reported that podophyllin, as well as colchicine, could beneficially influence the lesion of psoriasis. King and Sullivan (6) made fundamental observations on epidermal changes in normal skin, condyloma accuminatum, and verruca vulgaris that occurred in response to podophyllin and also noted that similar changes occurred following topical application of colchicine. Twenty-four hours following the application of these drugs characteristic nuclear damage (arrested mitoses and dispersion of chromatin particles) of Malpighian cells was present and granules were found in cells of the upper Malpighian layer. At 7 days a prominent, broad granular layer was present. King (7) later described in detail epidermal changes in normal skin of mice following podophyllin and called attention to excessive production of tonofibrils by the cytoplasm of cells whose nuclei had been damaged by the drug.

Normal and abnormal growth of tissue present challenging problems to biology and medicine. The epidermis is a tissue particularly exploitable for study of these problems because it is accessible for experimental manipulative procedures. Furthermore, because of the unidirectional migration of its cells during their life span, succeeding generations of cells and products synthesized can be studied for changes resulting from such procedures.

The purpose of the present work was to study the effects of agents generally classified as poisons on epidermal hyperplasia of psoriasis, and to compare these with alterations following some newer chemotherapeutic anti-tumor agents having both known and unknown modes of biochemical action. The study was not undertaken as a therapeutic trial and was not designed to evaluate any of the agents used in regard to effectiveness, or indications for use, in the clinical management of psoriasis.

MATERIALS AND METHODS

Drugs were selected for systemic administration to patients with psoriasis because of the ability of these drugs or their analogues to interfere with the growth of hair (8). Patients were selected for systemic therapy from the following

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groups: adult males with severe, disabling psoriasis; women beyond the menopause with severe psoriasis; and patients with a 2–3 year history of repeated courses of aminopterin therapy referred for general evaluation, who were given one additional course of aminopterin while under our observation. A total of eighteen patients, 30–76 years of age, participated in this study. Seven received one or more drugs systemically. Sixteen were tested with topically-applied drugs.

The following drugs, with the exception of aminopterin, were administered in single intravenous doses: methotrexate* (6 patients), 0.5 mgm.–5 mgm./Kg.; actinomycin D† (3 patients), 25 *micro*grams/Kg.; 5-fluorouracil‡ (3 patients) 5, 7.5 and 10 mgm./Kg.; colchicine (1 patient), weekly intravenous doses, the largest of which was 5 mgm. Aminopterin was given to one patient in a dosage of 0.5 mgm. orally twice daily for 6 days; a second patient received 0.5 mgm. once daily for 12 days.

The following examinations were carried out prior to therapy: white blood cell count, hemoglobin, platelet count, blood urea nitrogen, liver function tests and skin biopsy. Spermatozoa counts were determined in two patients given aminopterin and in two patients given methotrexate. All procedures were repeated during and after therapy, with the exception of blood urea nitrogen determinations and liver function tests. Scalp hair roots were examined during therapy for presence of dysplasia, by a previously described technique (11).

Topical therapy was confined to localized areas of skin on the trunk, 2 x 2 inches in size or larger. Initially in each case the agent, in an appropriate solvent or vehicle (70% alcohol, water or Aquaphor®), was applied under an occlusive dressing for 18–24 hours. Subsequently, the agents were applied topically in different vehicles or solvents, on involved and uninvolved skin, for varying lengths of time.

The following agents were applied topically: methotrexate (9 patients), 5–50 mgm. in 2 cc H_2O, and as the pure powder; 5-fluorouracil (4 patients), 10 mgm./2 cc H_2O); actinomycin D (4 patients), 40 *micro*grams/2 cc H_2O; nitrogen mustard (3 patients), .04–0.5 mgm./2 cc H_2O; mercury (6 patients), 20% in aquaphor; podophyllum resin (15 patients), 0.5–1% in 70–95% alcohol, petrolatum, and tincture of benzoin; colcemide (3 patients), 0.5–1.0 mgm./2 cc 70% alcohol; trimethyl colchicinic acid (3 patients), 1 mgm./2 cc 70% alcohol; colchicine (5 patients), 0.1–3.6 mgm./2 cc 70–90% alcohol; undiluted liquor carbonis detergens (1 patient); 100% deuterium oxide (2 patients); 6-mercaptopurine (4 patients), 10 mgm./2 cc H_2O; triethylene thiophosphoramide 0.5 mgm./2 cc H_2O.

RESULTS

Clinical changes following drugs administered systemically. During the first week following a single intravenous dose of methotrexate, 5-fluorouracil, or actinomycin D the skin involved with psoriasis in most instances became somewhat more erythematous than usual, particularly at the margins of the lesions. In some patients a marked decrease in scales occurred during this time despite the more florid appearance of the underlying skin. At about the end of the first week the involved areas were less erythematous than before the day of therapy and marked reduction in scales was evident. In all cases lesions on the head and upper trunk were first to improve; last to improve were lesions on the forearms and lower extremities. In some patients improvement continued for varying lengths of time up to about three weeks (Figs. 1 & 2). In no case did all lesions disappear from the skin without further therapy, either topical or systemic. In most patients lesions ceased to improve within two weeks of the day of drug administration, relapsing thereafter to their pretreatment state.

In the one patient who received weekly intravenous doses of colchicine, involved areas of skin appeared less erythematous and scaly only after five weeks of therapy. The weekly dose had been increased to 5.0 mgms. by that time and although no signs of either clinical or hematological toxicity were detectable in the patient, the dose was lowered to 3.0 mgm. and was given twice weekly instead of weekly. The drug was continued at the latter dosage for two additional weeks and then discontinued, no further improvement of the skin having occurred.

The clinical response of psoriasis was not specifically followed in the two patients receiving

* 4-amino-N^{10}-methyl pteroylglutamic acid, a folic acid antagonist similar to aminopterin in chemical structure and anti-tumor properties.

† A compound having anti-bacterial and anti-tumor properties, isolated from cultures of *Streptomyces parvallus*. Its mechanism of action is unexplained. For bibliography see Reference (9).

‡ A pyrimidine analogue with a broad spectrum of activity against experimental tumors. Its action is considered to be due to inhibiting the 5-methylation of pyrimidines (10).

aminopterin in daily oral doses. These patients had been referred primarily for study of possible sequelae secondary to taking this drug for two and three years previously and were clinically observed only at occasional intervals when they reported for test procedures performed to evaluate systemic effects of the drug.

A number of signs of acute toxicity were observed in prtients receiving single doses of methotrexate, 5-fluorouracil, and actinomycin D. The signs included those indicative of bone marrow depression (lowering of the counts of white blood cells and platelets in the peripheral blood), signs of varying degrees of injury to the alimentary canal (nausea and/or ulcerations of the oral mucous membrane), and disturbance of hair growth (dysplasia of the roots of anagen hairs with or without hair loss). Evidence of depression of spermatogenesis was found in four patients studied for this. Two of these patients received methotrexate, the other two received aminopterin. The range of depression of spermatozoa counts (sperm/cc.) ranged from 49–90%; the range of depression of total spermatozoa per specimen varied from 63% to 97%. The lowered counts were detected 12–14 days from the day a single intravenous dose of methotrexate had been given, or from the first day of therapy with daily oral aminopterin. The time interval for the counts to return to normal was not determined. However, it is apparent that spermatogenesis is not permanently depressed since in the two patients who had taken repeated courses of aminopterin for 2 and 3 years previously the pretreatment control examinations revealed normal spermatozoa counts, both in total spermatozoa per specimen and in number per cc.

Clinical changes following topical application of drugs. Marked gross changes in lesions of psoriasis were evident following occlusive application of podophyllin, colchicine, mercury, nitrogen mustard, and liquor carbonis detergens. On the fourth day following the day of applcation the localized area of skin where each drug had been applied was, in most instances, free of scales (Fig. 3); erythema was either absent at this time or was only minimally visible. These changes were most pronounced when the drugs were used in the higher concentrations, although in a few patients, all of whom had inveterate localized patches of psoriasis, the treated areas did not develop the changes toward normal until as long as two weeks later. The areas remained as islands of clinically normal skin, located within a patch of involved skin, for variable lengths of time thereafter, from one week to approximately six weeks (Fig. 4). They were then re-involved with psoriasis by a process in which the cleared areas of skin were invaded by psoriasis from the periphery.

With the exception of colcemide and trimethyl colchicinic acid, both of which caused only questionable improvement of psoriatic skin within one week of the day of application, none of the other compounds tested topically had any observable effects on either lesions of psoriasis or on uninvolved skin.

Histologic changes. The healing process in psoriatic skin that occurred following each of the several drugs found to be clinically effective was basically similar in certain salient histologic features in all instances, although differences could be found to characterize the action of some drugs.

Twenty-four hours following occlusive application of either *podophyllin* or *colchicine* numerous cells in the lower two-thirds of the Malpighian layer showed various degrees of damage. Most obvious were cells with a markedly enlarged nucleus in which chromatin particles were either in clumps or scattered in rather random disorder (Fig. 5). In the uppermost level of the Malpighian layer was a zone in which the cells were quite distinct from those of the deeper Malpighian layer (Fig. 6). These cells were large and their walls appeared thick. Their nuclei were pyknotic. Numerous fine granules, which were morphologically indistinguishable from keratohyaline granules, studded a pale-staining cytoplasm. Such cells constituted a layer which was up to ten cells in thickness. The stratum corneum, at this time, was parakeratotic, in no way different from that of untreated control specimens.

Specimens removed 48 hours after the application of podophyllin or colchicine had changes similar to those found in the 24-hour specimens, although somewhat less in degree, and in addition contained other alterations later found to be maximal in the 96-hour specimens. The transitional nature of the changes in the 48-hour specimens becomes apparent when comparison is made with the histologic findings in the 96-hour specimens.

The state of the epidermis 96 hours following

podophyllin or colchicine was distinctive. The cells of the upper Malpighian layer now were flattened and made up a stratum granulosum that was up to 10–12 cell layers in thickness (Figs. 7, 8). Except for the extreme thickness of this layer, the cells and the granules contained therein appeared normal both in regard to morphology and staining properties. A thin stratum corneum, appearing to be normally keratinized, was present immediately distal to the thickened granular layer. Associated with this change was what may be interpreted as a sign of an exaggerated process of keratinization; in the upper portions of the Malpighian layer was a dense network of thickened tonofibrils with particularly prominent nodules of Bizzozero in the intercellular bridges (Fig. 9). The epidermis, although somewhat diminished in thickness as measured through an ocular micrometer, retained its acanthotic appearance at this time.

The above-described changes that took place in psoriatic epidermis in response to topically applied podophyllin and colchicine were also found in the epidermis of uninvolved skin of three patients tested. The magnitude of the changes was reduced, however.

Histologic alterations in epidermis affected with psoriasis can be correlated with the gross healing of lesions observed clinically. The action of these drugs appears to be a direct inhibition of epidermal hyperplasia, by arrest of mitosis, while allowing the process of keratinization to continue unimpeded in these otherwise damaged cells.

Changes occurring in psoriatic epidermis following topical application of *mercury*, *nitrogen mustard*, and *liquor carbonis detergens* were, at 96 hours, identical to those that were found 96 hours after application of podophyllin and colchicine. That is, clinical recovery of the lesion at this time was associated with a markedly thickened granular layer and a dense network of tonofibrils in the Malpighian layer (Fig. 10). No evidence of disturbed mitosis or nuclear damage was found at 24 hours or 48 hours following application of these drugs. However, very few mitotic figures were found in the epidermal cells at these times, suggesting that epidermal hyperplasia had been inhibited, but by a mechanism different from that with either podophyllin or colchicine.

Histologic changes in psoriatic epidermis following systemic administration of *methotrexate* and *5-fluorouracil* (biopsy specimens not obtained sufficiently early following actinomycin D) were indistinguishable from those following topical application of mercury, nitrogen mustard or liquor carbonis detergens. Because clinical improvement of lesions of psoriasis was most evident approximately one week following a single dose of these drugs, most biopsy specimens were obtained at this time and several days thereafter. In all specimens removed at these times the epidermis appeared to be quite normal except that it was somewhat acanthotic. Specimens were obtained earlier in two patients, one patient having received methotrexate and the other 5-fluorouracil. Although lesions showed little or no evidence of clinical improvement at these earlier times distinct histologic changes were present. Twenty-four hours following the time when methotrexate was given the epidermis did not contain a single cell in mitotic division. At 48 hours a few cells in mitosis could be found and at this time keratohyaline granules could be identified in cells of the upper Malpighian layer. Cells containing such granules constituted a zone 6–7 cell layers in thickness in the uppermost portion of the Malpighian layer. In a specimen obtained three days following 5-fluorouracil, and in another taken 5 days after administration of methotrexate, a well-formed granular layer, 5–6 cell diameters in thickness, had already formed (Fig. 11). A network of prominent tonofibrils was present in these specimens and, although the outermost stratum corneum was parakeratotic, a thin zone of normal-appearing stratum corneum lay immediately distal to the stratum granulosum.

DISCUSSION

Data from these studies indicate that the lesion of psoriasis is a result of hyperplasia of the epidermis in which cellular reproduction proceeds at a rate sufficiently rapid that maturation of epidermal cells and synthesis of tonofibrils is not completed, formation of a stratum granulosum does not occur, and the biologic and chemical processes of normal keratinization are not achieved. The remedial effects on psoriasis that are obtainable with topically-applied or systemically-administered agents, of the kind employed in this study, would seem to be due to their arresting or inhibiting the accelerated rate of epidermal hyperplasia, allowing adequate time and/or diversion of energy within cells for

morphologic changes and metabolic processes to occur normally.

It is clear that inhibition of epidermal hyperplasia is not dependent upon a single pathway or site of action common to all drugs causing this inhibition, since these drugs affect epidermal cells in several different ways. Further understanding of processes involved in maturation of epidermal cells and their synthesis of keratin may be derived from a consideration of the modes of action and morphologic effects of different chemical agents on the epidermis.

The effect of podophyllin and colchicine on cells of the Malpighian layer, and the further response of cells while under this effect, are particularly interesting and informative. Nuclear damage, identified as arrested mitoses and disintegration of nuclear material, is the primary effect of these drugs. When cells are so affected, however, production of tonofibrils continues. These phenomena occur in the epidermis of the mouse following application of podophyllin and have been identified and acutely described by King (7), who also pointedly emphasized that in epidermal cells affected by podophyllin "cytoplasmic activity concerned with fibril production continues unabated while the nucleus remains in a state of suspended mitosis". Since available evidence indicates that tonofibrils are keratinous in nature (12, 13, 14, 15) it seems rather important to recognize the fact that synthesis of keratin (or its precursor(s)) is a specialized function of the cytoplasm of epidermal cells and appears to be independent of the nucleus. Such a situation is compatible with a concept of cellular functions proposed by Rusch (16): "... all cellular functions are divided into two chief categories: one, the function of reduplication, and two, all other special functions not primarily concerned with cellular multiplication". Tonofibrils may be abundantly produced in mitotically arrested cells because more time is allowed for cytoplasmic production of tonofibrils before the cells reach the epidermal surface. On the other hand, tonofibrils may be produced so abundantly because additional cellular energy is now available for their synthesis, energy which would have been utilized for cellular division but now diverted because of nuclear damage and mitotic arrest. The latter possibility is compatible with the fore-mentioned concept of Rusch, which further states, "In addition to being mutually *dependent*, the various functions must also be recognized as mutually *competitive* with respect to the cellular nutrients required for their synthesis". Clinical clearing of the lesion of psoriasis following the action of podophyllin or colchicine on the epidermis may therefore result, at least in part, from a quantitative increase in keratin synthesis by each cell.

Although the modes of action of those chemical agents used in the present study which effectively restored the lesion of psoriasis toward normal may be different for each agent, the essential epidermal changes produced by each are similar. That is, all agents appear to inhibit cellular reduplication since within 24 hours following their use mitoses were either arrested, totally absent, or decreased in number. Regardless of the means by which cellular division had been restrained a marked increase of tonofibrils occurred and was associated with other morphological changes within the epidermis that indicated normal keratinization had resumed.

Topical application of methotrexate, 5-fluorouracil and actinomycin-D failed to influence the lesion of psoriasis. Repeated topical testings of methotrexate were made including its application as a pure powder, application in solutions at various levels of alkaline and acid pH, and application onto lesions after the stratum corneum was removed by means of cellulose tape. It is known that the drug can penetrate psoriatic epidermis since it has been detected in the urine following its topical application onto lesions (17). Failure of it to locally affect psoriasis therefore suggests that its pharmacologic action requires initiation at a distant systemic site.

How many of the newer chemotherapeutic drugs that are used systemically to treat cancer might be found to affect psoriasis is unknown. Rees and Bennett (2) reported that they found both 6-mercaptopurine and Daraprim® (2,4 diamino-5-*p*-chloropteroyl-6-ethyl-pyrimidine) to be ineffective. Blank (19) has observed psoriasis to improve in a patient with leukemia who received Myleran® (1,4,-dimethane sulfonoxy butane). Methotrexate, 5-fluorouracil and actinomycin-D were purposely selected for our study because they were known to interfere markedly with the growth of hair (8), an epidermal tissue.

It seems judicious to make some comment regarding the advisability of using anti-tumor chemotherapeutic agents in the general management of psoriasis. The serious acute toxic effects

that these agents can cause are well recognized. Possible carcinogenic properties of each for man have not been evaluated, nor does it seem that this can be done until a considerable period of time has elapsed. Until the necessary clinical data on each agent are obtained their general use in the treatment of psoriasis cannot be advocated. The chemotherapeutic agents are helpful tools for investigating the nature of the lesion of psoriasis and biologic processes of the epidermis. Data from such studies may be useful in a search for the cause and specific therapy of psoriasis, as well as contribute information to better understand malignant hyperplasia.

SUMMARY

1. Morphologic and physiological changes in psoriasis were studied by means of topically applied and systemically administered chemical agents. Clinical clearing of the lesion of psoriasis occurred following intravenous administration of methotrexate, 5-fluorouracil and actinomycin D, and following occlusive topical application of podophyllin, colchicine, mercury, nitrogen mustard, and liquor carbonis detergens.

2. The clinical effects on the lesion of psoriasis of both topically and systemically used therapeutic agents were directly correlated with depressed cellular reduplication of the epidermis. With systemically used agents depression of cellular reduplication in the epidermis paralleled a similar depression in other tissues of the body.

3. Independent functions of the nucleus and cytoplasm of epidermal cells were recognizable. The initial histological effect of the various agents on epidermal cells was nuclear damage, *i.e.* inhibition or arrest of mitosis. Cytoplasmic activity appeared undisturbed, however, since formation of tonofibrils and keratohyaline granules continued.

4. The morbid state of the epidermis in psoriasis can be defined in terms of excessive mitotic activity and incomplete cellular maturation.

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DISCUSSION

Dr. Jacob H. Swartz (Boston, Mass.): In 1945 I reported in the New England Journal of Medicine on the interrelation of *Streptococcus fecalis* and *psoriasis*. At that time I noticed that intracutaneous injections of *Streptococcus fecalis* obtained from stools of psoriatic patients produced a psoriatic papule clinically indistinguishable from typical psoriasis, on the normal skin of patients with psoriasis. Control studies with typhoid vaccine, staphylococcus toxoid and normal saline solution did not produce a similar phenomenon. The usual local reaction was ob-

tained with injections of autogenous vaccine of strept. fecalis in non-psoriatic subjects. As a result of such findings I began to treat psoriatic patients with *Streptococcus fecalis* vaccine. Not being familiar with the disage, I found that a number of those so treated grew worse and a few developed exfoliative dermatitis. In four patients I noted the development of psoriatic arthropathy which these patients did not have before treatment.

Dr. Peck reported to me a similar experience. A few patients did improve as a result of such treatment. Time does not permit a discussion of dosage.

I then began to use mandellic acid enemas, since mandellic acid has been used effectively by urologists in infections of the bladder caused by this microorganism. I chose enemas because of the greater contact of the chemotherapeutic agent with the microorganism.

The results have been gratifying in a fair number of patients. Coincidental with improvement there was a decrease in the colony count of *Streptococcus fecalis* in the stools. The local treatment was limited to petrolatum. These patients were treated during exacerbations.

I present this as another mode of therapy which has no serious sequelae. It is, I believe, more than just nonspecific therapy.

Histochemical studies of the upper epidermis before and during treatment have not been done. Such studies may be worth while.

Aminopterin is an antagonist to folic acid which in turn is essential for the metabolism of *Streptococcus fecalis*. The good effect of aminopterin may also therefore be due to its deterrent effect on *Streptococcus fecalis*.

Dr. Erwin P. Zeissiler (Winnetka, Ill.): I should like to congratulate the gentlemen from the National Cancer Institute on the results they have had in psoriasis.

One would judge from the list of chemotherapeutic agents presented to us here today that in treating psoriasis that the disease might have been a leukemia. These same compounds all have antileukemic properties. They are powerful protoplasmic poisons and their use must be carefully watched.

I would also like to say that in the treatment of psoriasis there is no substitute for sun light. Whether you use ultraviolet light of x-ray, or other actinic agents, the results will not be as good as when the entire body is exposed to the sun. I have always in my practice adhered to the principle of using sunlight where possible and I sent my patients to California or Florida, or Arizona for this purpose and I believe also that Dr. Goeckerman got along very nicely without the use of colchicine or any types of steroids in the treatment of psoriasis in which he advocated the use of coal tar and ultraviolet exposures according to a regular scheme. As intimated by my remarks I believe you are playing with fire in using these drugs except in exceptional cases where their use may be justified.

Dr. Rudolf Baer (New York, N.Y.): I would like to ask Dr. Van Scott whether he has any data as to how long the depression of the white count lasts after aminopterin has been discontinued? This question is of considerable importance because if the depression of the white count disappears within a few days one will not find any depression when doing a blood count a week after the drug has been stopped and thus one may overlook this undesirable effect on the hemopoietic system

Another important practical question was raised the other day when a small group of that vanishing species—the clinician—discussed the effect of aminopterin. Dr. Osborne stated—and I hope that I am quoting him correctly—that there is a greater tendency to depression of the white count in patients with psoriasis over 60 years of age treated with aminopterin than among younger persons and that therefore these are the patients in whom one has to be especially careful regarding hematologic side effects. I wonder whether Dr. Van Scott has any information on this point.

Dr. William B. Reed (Burbank, Calif.): I enjoyed the discussion very much. I would like to know whether Dr. Van Scott treated any patients with psoriatic arthritis with the chemotherapeutic agents? Did the treatment have any effect on the arthritis?

Dr. Frederick D. Malkinson (Chicago, Ill.): We too applied colchicine locally in the treatment of psoriasis with temporarily good results, using the same concentration that Dr. Van Scott used, 0.1 per cent. With continued treatment there is quite a risk of irritation of course.

Another important factor in the local application of colchicine is that this compound is an alkaloid which presumably may be very well

absorbed through the skin. To date no quantitative studies of percutaneous absorption of colchicine have been done. Widespread application of this material to the skin, then, is not indicated.

In one of our patients who had had long standing psoriasis and both rheumatoid and psoratic arthritis we saw some definite improvement in joint symptoms with the use of colchicine. Apparently this again confirms Gubner's original observation that antimitotic agents may be beneficial for joint involvement also.

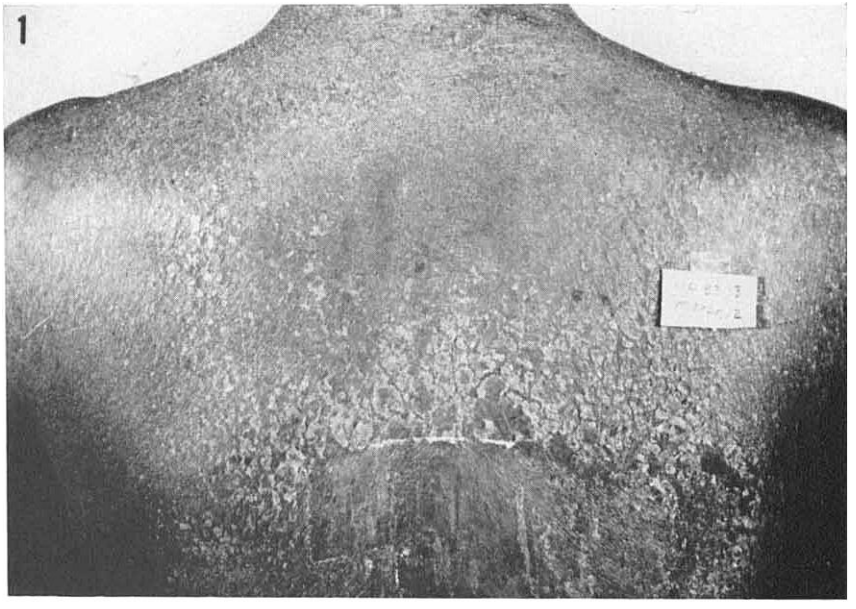
DR. EUGENE J. VAN SCOTT (in closing): The observations of Dr. Swartz are interesting but puzzling to me and I have no immediate explanation for them.

Dr. Zeissler, I hope that you have not misunderstood the objectives of this work. One of the reasons we undertook it was that it particularly related to the reservations you have expressed.

Aminopterin is being used in psoriasis and it is time we defined what these agents do, their immediate dangers and possible sequelae. We have wondered, for instance, whether the antimetabolites are carcinogenic. To date aminopterin has not been shown to be carcinogenic. This does not indicate that it is not, but it has not been demonstrated. Dietary starvation can beneficially influence psoriasis. Perhaps the effects on psoriasis that results from blocking the utilization of folic acid may be a chemical starvation similar to dietary starvation. Since this is unknown, however, the use of folic acid antagonists and other antimetabolites cannot be advocated for routine therapy of psoriasis. We have further used these agents experimentally in a few patients because we are interested in cancer. Psoriasis is a disease characterized by benign hyperplasia of cells. Because of this hyperplastic activity of psoriasis we have used it as a model to determine the biological effects of agents on the behavior of rapidly dividing cells. It seems interesting and important, for example, to single out a cytoplasmic function that is relatively independent of nuclear function, as the results of these studies indicate. I can only agree, however, that the therapeutic use of new agents in humans must be approached with caution.

In answer to Dr. Baer's question regarding depression of the white cell count, following the doses of the agents used, the white cell count returned to normal within a two week period. But this of course is proportionate to the dose. If the dose is large enough the white count would be irreversibly depressed, as would be a number of vital functions. I think you must be equally as careful with the young, middle aged and old aged persons regarding the depression of the white count.

Lastly, we have treated three patients with psoriasis who also had arthritis and have seen no definitive changes in the arthritis.



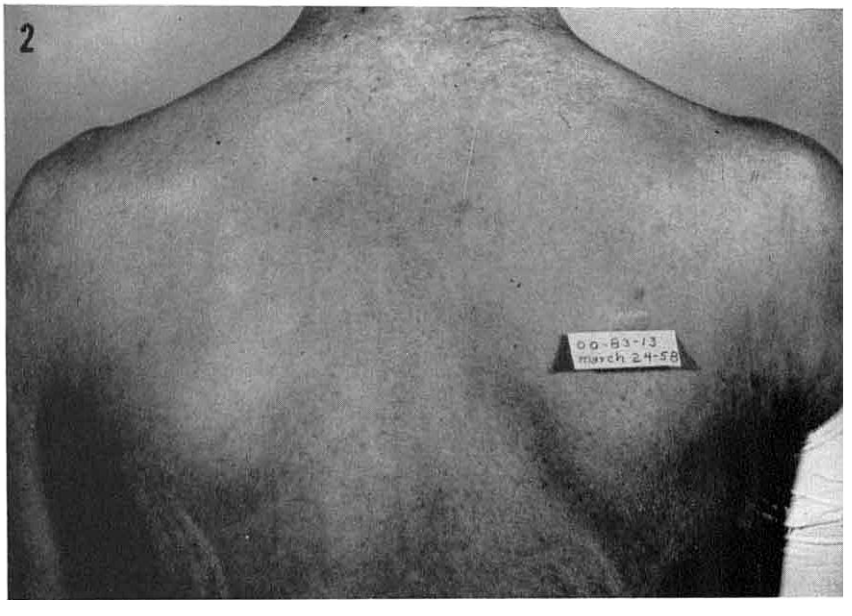


FIG. 1. Generalized psoriasis untreated. Thirty-five year-old man.
FIG. 2. Same patient as in Fig. 1, ten days following single I.V. injection of methotrexate.

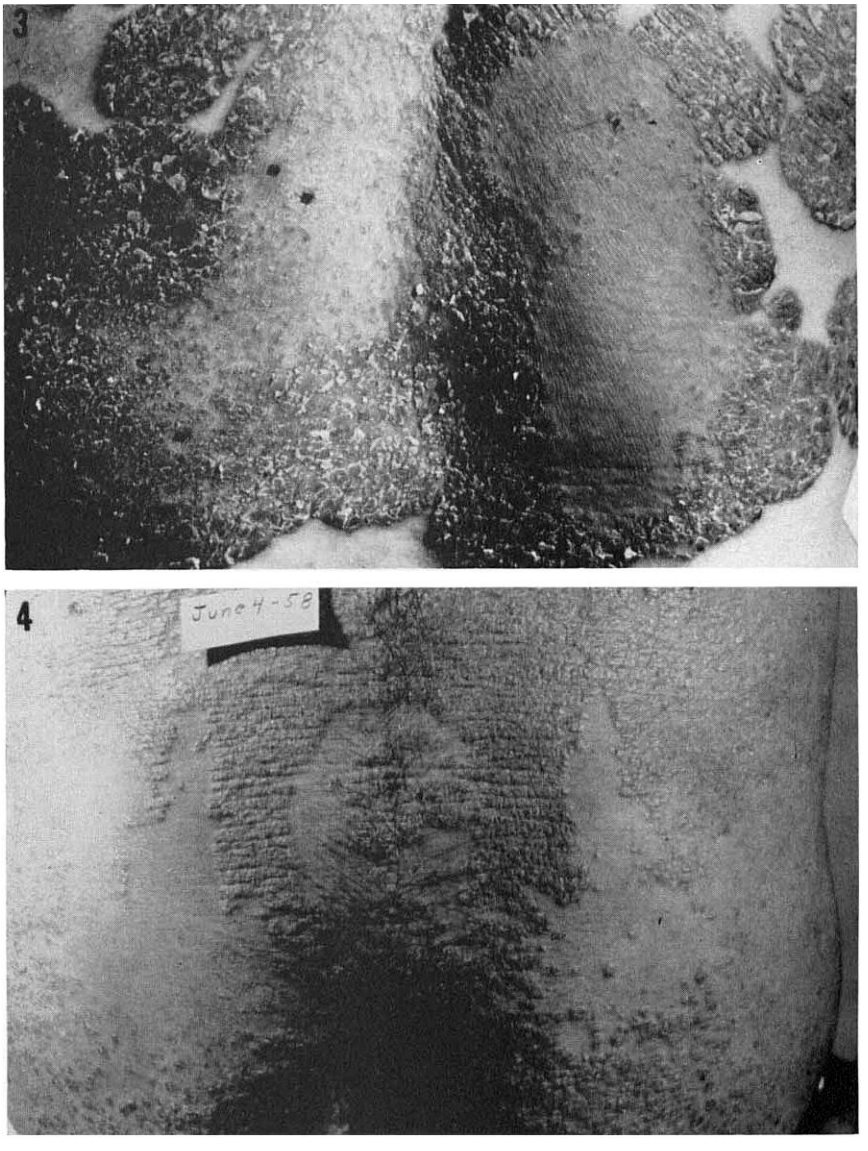


FIG. 3. Gross changes in psoriasis 4 days following occlusive application of colchicine on left, podophyllin on right. Back of 56-year-old man.

FIG. 4. Gross changes in psoriasis on abdomen of 35-year-old man 1 month following occlusive application of podophyllin. Alcoholic solution of the drug was applied in sponge rubber, cut in the form of letters of the alphabet.

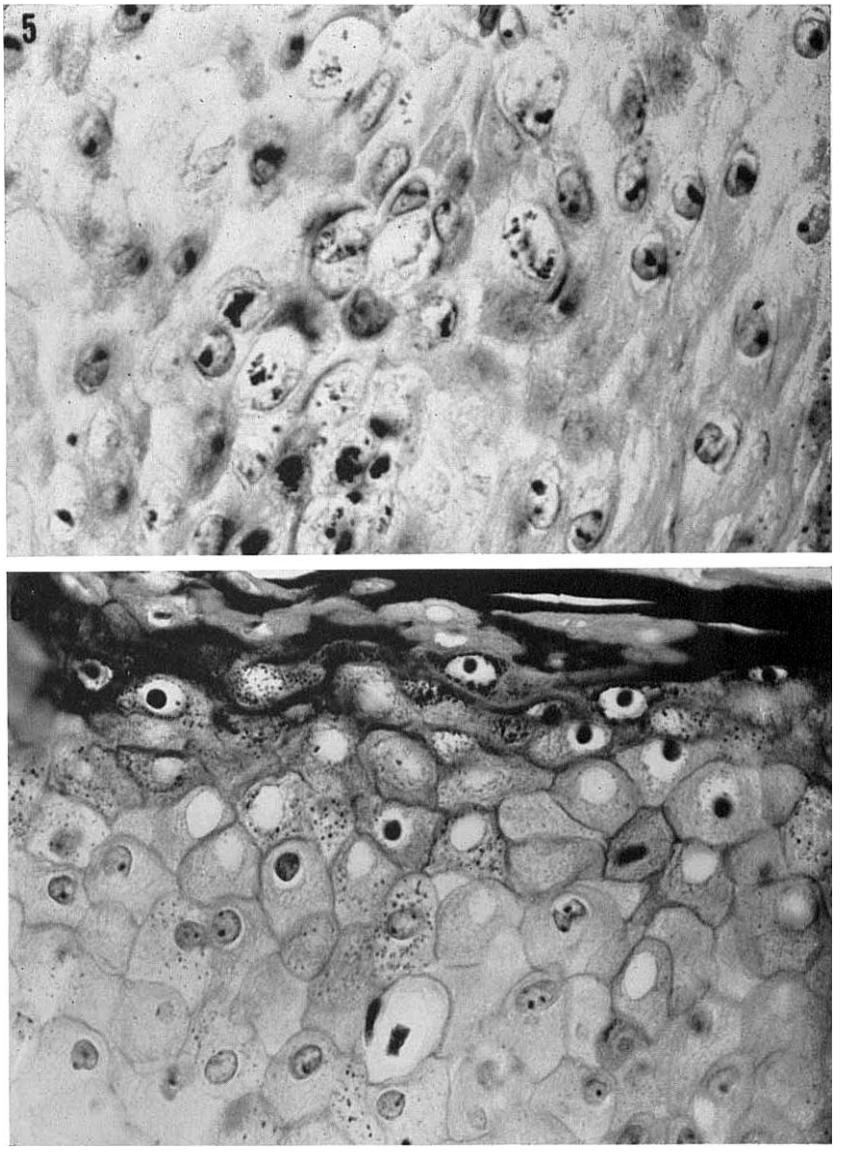


FIG. 5. Photomicrograph of Malpighian layer of epidermis from lesion of psoriasis, 24 hours following topical application of podophyllin. Characteristic enlarged nuclei with scattered or clumped chromatin granules are present. Gomori trichrome stain. ×680.

FIG. 6. Cells of upper Malpighian layer in psoriasis 24 hours following topical application of podophyllin. Note keratohyaline granules in cytoplasm. Gomori trichrome stain. ×530.

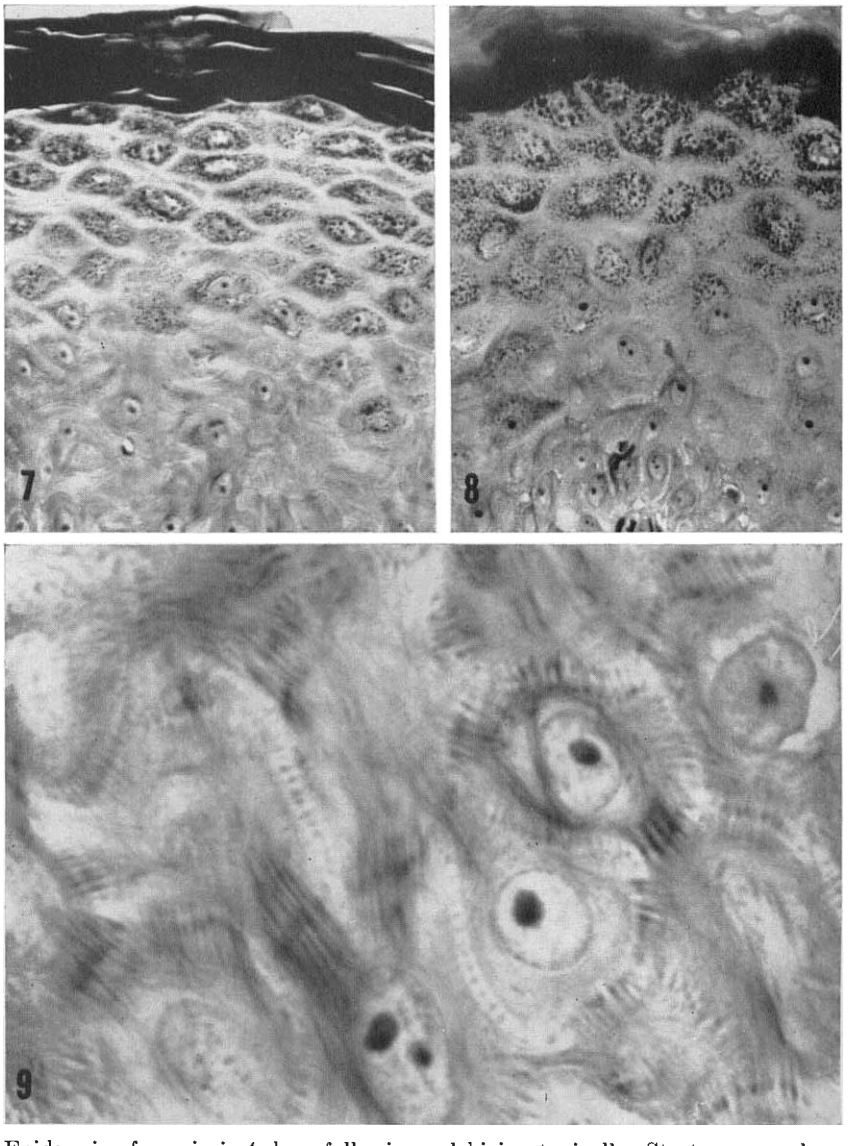


FIG. 7. Epidermis of psoriasis 4 days following colchicine topically. Stratum granulosum is much thicker than normal. Gomori trichrome stain. ×380.
FIG. 8. Epidermis of psoriasis 4 days following podophyllin topically. ×500.
FIG. 9. Excessive tonofibrils in epidermis of psoriasis 4 days following colchicine topically. Gomori trichrome stain. ×2000.

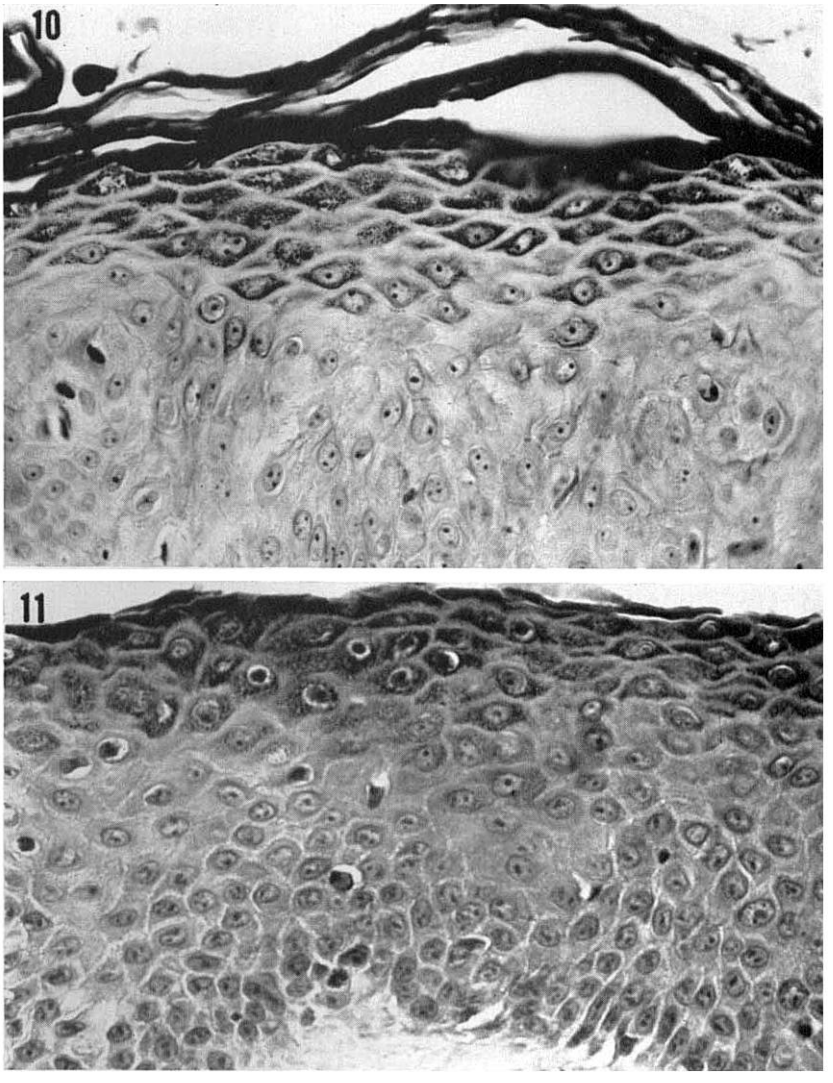


FIG. 10. Thickened granular layer in epidermis of psoriasis 4 days following occlusive topical application of liquor carbonis detergens. ×380.

FIG. 11. Similar thickening of granular layer in epidermis of psoriasis 3 days following single intravenous dose of 5-fluorouracil. ×380.