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THE BIOLOGY OF PSORIASIS

EUGENE M. FARBER, M.D. AND ALVIN J. COX, M.D.

INTRODUCTION

Psoriasis is characterized by a variety of changes in the skin, but the fundamental defect that is responsible for the development of the psoriatic lesion is still obscure, even though the literature is full of announcements of findings that are said to be specific. These supposedly specific features have been of many different types and have pointed at one time or another toward every conceivable kind of possible etiological mechanism. As time has passed, however, every recognized attribute of the disease has been found to be lacking in absolute specificity.

Because of this lack of a definite feature, or of a known etiological agent, psoriasis can be defined only in terms of its usual manifestations: clinical, histological, physiological and chemical. In other words, its recognition is based upon probability. If enough of the attributes usually exhibited by psoriatic lesions are present, the probability reaches almost 100 percent.

Most studies of psoriasis have as their ultimate goal the identification of the cause or causes of the disease. From this knowledge, an understanding of the pathogenesis and the development of rational treatment would follow almost automatically. Intermediate goals are: improvement of our understanding of the conditions that lead to aggravation of the disease, improvement of our means of recognizing atypical cases, the discovery of means of identification of individuals with latent psoriasis or with the potential to develop psoriasis, and the deveelopment of improved methods of managing the disease.

The following observations, many of them drawn from the experiences of the Psoriasis Research Group in the Department of Dermatology at Stanford University, may serve to clarify the position that we occupy today with respect to the ultimate goal. We should not be surprised that the goal is not in sight. After all, the amount of study of psoriasis is infinitesimal compared with that already directed toward the solution of another growth disturbance, cancer.

There have been a number of major approaches to the analysis of the psoriasis problem, each of which has permitted some specific conclusions about the disease. Some of these will be considered below.

NATURAL HISTORY STUDY

Studies of the natural history of psoriasis have been most important in the formulation of the concept of psoriasis as a clinical entity. One might think that this approach, utilizing simple observation and correlation, might have been exhausted long ago, but such is not the case, for the reason that newer developments have made possible much more accurate and effective evaluation of data than was employed prior to the introduction of computer techniques. Furthermore, the disease is continually presenting itself under new conditions. For example, rebound phenomena have followed adrenal cortical suppression, and exfoliation has been induced by chloroquine and other substances. Also, more data are becoming available concerning special groups of cases, such as those in particular racial categories or under special natural environmental conditions.

In order to provide our research group with facts, a detailed questionnaire was distributed through our clinical group and by many cooperating dermatologists in the United States. Forty queries, relating to five broad areas included: (1) characteristics of the psoriatic participant and his family; (2) sites affected by psoriasis; (3) the influence of various physical factors; (4) relationships to other diseases; and (5) the incidence and nature of spontaneous remissions. In 1966, when the number of respondents reached 2144, the questionnaires were coded by Dr. Ross Bright, and a statistical analysis utilizing the IBM 7090 computer and the Harvard-developed

Department of Dermatology, Stanford University School of Medicine, Palo Alto, California.
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Data/Text System produced 700 cross-tabulated arrays. With the aid of the computer, our analyst has performed in minutes what formerly took months to do with a desk calculator. We respect the shortcomings of the questionnaire as a measuring device; nonetheless, it provides quantitative data on a large scale to give us guidelines for channeling research efforts. The complete study is being published elsewhere (1).

An example of a contribution of this study is the interesting observation that in 37 percent of the participants in our survey psoriasis had begun before the age of 20. In 12 percent the onset was prior to the age of 9. An additional 24 percent reported the beginning of the psoriasis between the ages of 20 and 29. This indicates, in contrast to the impression created by some reports, that psoriasis occurs frequently in the pre-adult age group. This is illustrated graphically in Fig. 1. At the same time, however, it is clear that many patients do not experience their first psoriatic plaque until middle age or later, so estimates of the incidence of psoriasis must take into account the age of the individuals who are surveyed.

We plan to continue the questionnaire program and initiate follow-up studies. Pursuit of more detailed information should answer a number of important questions. One is concerned with whether there are familial patterns of distribution of psoriasis. We have already noted a family in which three brothers and two nephews presented psoriatic lesions on the hands only.

GENETIC FACTORS

The genetic aspect of psoriasis is one of great importance. Most students of this disease have no doubt that a genetic influence exists in many cases, and presumably in all.

The results of racial studies of psoriasis, such as those indicating that the disease is infrequent in Negroes and in American Indians (2), while it is apparently absent among Indians of the undeveloped portions of Venezuela (3), are best explained on a genetic basis, although it is clear that the role of environmental factors, such as climate, diet and group habits has not been adequately examined in relation to differences of incidence of psoriasis in racial groups. Our questionnaire has not provided significant information regarding racial incidence because more than 98% of the patients studied were Caucasian.

The strikingly increased incidence of psoriasis in the progeny when both parents are psoriatic as compared with that when only one parent is affected (4), is practically impossible to explain on any basis other than a genetic one.

Our data indicate a strong familial incidence of the disease, illustrated in Fig. 2. Eighteen percent of the respondents to our questionnaire reported a parent with psoriasis, 11% reported a sibling, and 13% iden-

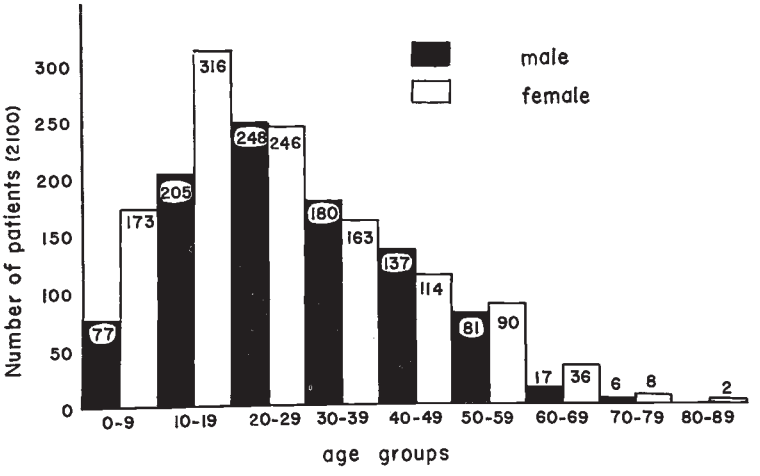


FIG. 1. Age of onset of psoriasis among 2100 patients surveyed by our questionnaire

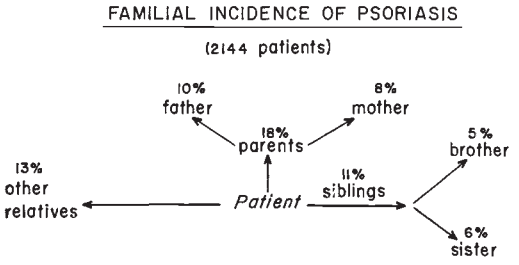


FIG. 2. Familial incidence of psoriasis related by 2144 patients with this disease.

tified more distant affected relatives. The incidence of psoriasis in the children of the respondents was only 3%, but this figure is misleadingly low because many of the children in this group have not reached the age at which psoriasis would be expected to appear. In 1956 a family that we studied presented only one case of psoriasis among five siblings. By 1961, three of five had lesions of psoriasis.

We should like very much to find a specific test for latent psoriasis, as this would be of great value in making a genetic survey, and indeed, without such a test, precise genetic studies are not possible. Conclusions as to the exact genetic mechanism, therefore, must remain tentative, although the evidence now available satisfies us that psoriasis is an inheritable disease.

INDUCTION OF LESIONS

Whatever the exact genetic relationship, we should remember that there are other substantial factors that produce lesions of psoriasis, and that these may be as important or even more important than the genetic predisposition.

The most clear-cut inciting factor in psoriasis is injury to the skin. The isomorphic response, originally described by Heinrich Koebner in 1877, could be produced by intentionally injuring the skin in 23 of 25 selected patients with active psoriasis studied in our laboratories (5). Fourteen percent of the respondents to our questionnaire said that their psoriatic lesions originally began at a site of injury. These figures are doubtless low inasmuch as certain types of injury might not have been recognized by the patients. Any kind of pre-existing skin lesion or minor trauma to regions such as the elbows or knees, may represent the initiator of an isomorphic response. Several examples are shown in Fig. 3.

A clear-cut deleterious effect upon the course of psoriasis may be expected as a consequence of systematically-administered steroid therapy, and it is probable that many other chemical substances excite or exaggerate the psoriatic process, perhaps through some alteration in the skin with a result comparable to a Koebner reaction. Further experience is necessary to evaluate the hazard of antimalarial treatment reported by Ziprkowski et al (6). We suspect that a large proportion of lesions of psoriasis are initiated by some kind of local injury to the skin.

With all of the assembled knowledge of this isomorphic reaction, we are still in ignorance of its fundamental nature. We do not even know whether the first change in the skin is epidermal or dermal, or both, since it is so very difficult to produce an alteration on one side of the basement membrane without damaging elements on the other side. There is need for further analysis of this response. In the absence of this or any other manifestation of psoriasis in animals, the induced isomorphic response in man represents a valuable model with which the evolution of the psoriatic lesion can be studied under controlled conditions.

Some other possible environmental factors in the evolution of psoriatic lesions are suggested from responses to our questionnaire. Seventy-seven percent of the patients reported that they were improved in hot weather and 88 percent noted that they were worse in cold weather. Seventy-eight percent specifically stated that sunlight caused improvement, while 15 percent reported exacerbation on exposure to sunlight. Forty percent listed worry as a factor in the exacerbation of psoriatic lesions. Of 362 women who had been pregnant since the onset of psoriasis, 50 percent reported an improvement in their skin lesions during pregnancy. The significance of this is not clear, particularly since 27 percent noted exacerbation during pregnancy.

REMISSIONS OF PSORIASIS

As a counterpart to the induction of lesions of psoriasis, we should consider the re-

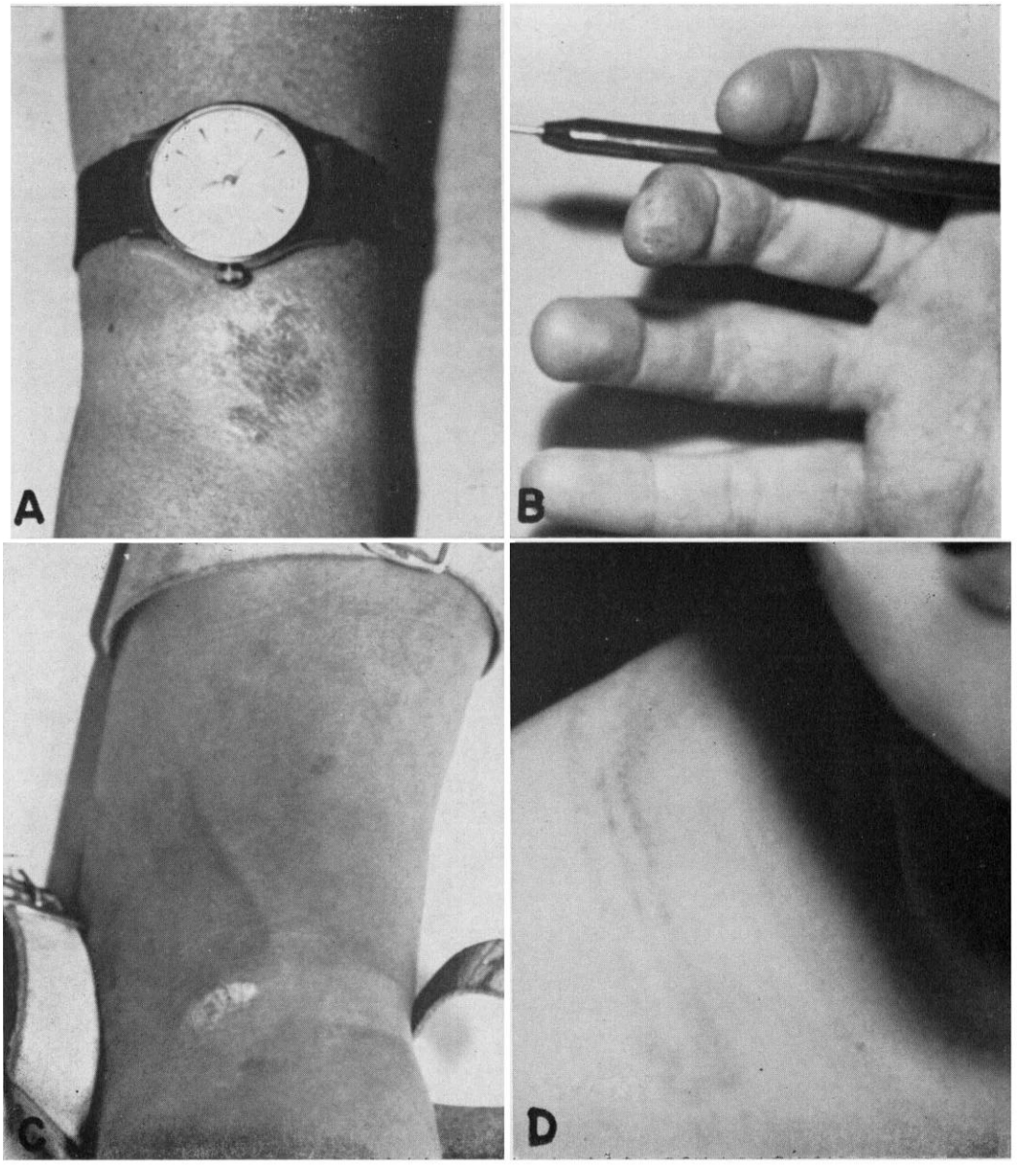


FIG. 3. Induced psoriatic lesions. A. At the site of contact with a wrist watch. B. At the site of repeated pressure of a pen on the hand of a student. C. Corresponding to the zone of pressure and rubbing beneath the strap of a sandal. D. Beneath a brassiere strap, apparently as a result of trauma.

mission of lesions. This may be spontaneous or may be brought about by therapy.

38.5 percent of all individuals responding to our inquiry reported that their psoriasis had "disappeared completely" at some time during the course of the disease. (Fig. 4) This incidence includes both spontaneous and induced remissions. Remission occurred with almost equal frequency in the two sexes. Several correlations are interesting. Among individuals who reported that sunlight improved their lesions, 81 percent reported "disappearance" of

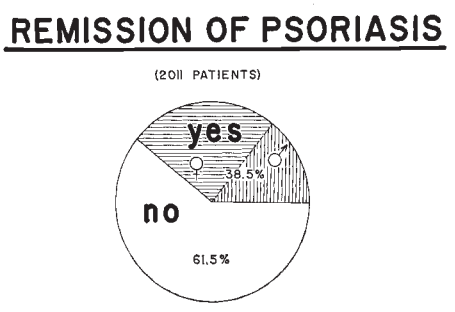


FIG. 4. Occurrence of complete remission reported by 2011 patients with psoriasis.

the disease at some time, while among those in whom sunlight made the condition worse, there was only a 15 percent incidence of "disappearance" of lesions. In patients who had reported the development of psoriasis at the site of an injury, only 14 percent noted that the disease had ever "disappeared". Women who indicated that they were better during pregnancy, however, experienced no greater incidence of complete remission than did the total respondent group.

This phenomenon of complete remission, even though in most patients it is only temporary, tells something about the basic nature of the disease, and its analysis may lead toward the understanding of psoriasis. It is likely, however, that it represents some altered balance brought about, as in other diseases, by external or internal changes that do not modify the causal factors in any fundamental way.

Complete remission of psoriatic lesions can often be induced by therapy, but of all forms of therapy known to us, none is a real cure. Some or all lesions can be resolved with treatment, such as application of tar and the use of ultraviolet light, but plaques usually recur at various intervals after treatment has been discontinued. In spite of the new methods of therapy involving topical application of steroids or the administration of anti-metabolites, the longest remissions still follow the well-known Goeckerman regime, utilizing tar and ultraviolet light. This failure of any therapy to effect a permanent cure emphasizes the fact that the known therapeutic agents achieve their success by inhibiting epidermal growth, but not by removing the predisposition of the skin to develop psoriatic plaques.

In view of the widening interest in the low taurine diet for psoriasis as advocated originally by Roe (7), a report of the experience of Zackheim (8), in our group, is pertinent. Taurine powder in gelatin capsules in a dose of 330 mg twice daily was given to each of ten patients, for two to four weeks. This total daily dosage of 660 mg is from five to ten times the average daily ingestion of taurine which is present mainly in meat and sea food. The psoriasis in these selected patients had been relatively stable for several weeks. Only mild local therapy such as weak coal tar or steroid creams, or simple lubricating preparations had been used, and these were continued unchanged during the taurine administration. Each of seven patients ingested 660 mg daily for four weeks and three others received the same dose for two weeks. One of the patients on taurine for four weeks became distinctly worse. No significant change was noted in the other nine patients. None of the patients experienced any marked pruritus.

The occurrence of worsening in one of ten patients receiving a high dosage of taurine in a two to four week period is probably not significant. These findings, therefore, throw doubt upon the hypothesis that taurine is of etiological importance in psoriasis.

The relationship between psoriasis and arthritis is a clear indication of the presence of a systemic component to psoriasis even though there is no other recognized internal manifestation of the disease. Most investigators believe that "psoriatic arthritis" differs from other forms of rheumatoid arthritis (9) but the distinction is not sharp (10). It might be hoped that something about the nature of the associated arthritis would add to the understanding of the nature of psoriasis, but this prospect has not been realized either by past studies or by our own analysis, which does no more than support the view that the relationship between psoriasis and arthritis is more than incidental.

LABORATORY INVESTIGATIONS

A vast number of different measurements have been made of tissues and fluids from patients with psoriasis. Certain measurable abnormalities are conspicuous, and over the years there have been large numbers of re-

ports suggesting that one or another finding is specific for psoriasis, but with the passage of time the alleged specificity of such changes has been proven wanting.

Without enumerating the more recent publications which claim specific changes in psoriasis, most of which have not yet been adequately tested for their validity, we predict that their fate will be the same as that of the many comparable claims that have preceded them.

An example of difficulties that have confused investigators in psoriasis is afforded by the problems involved in the study of skin lipids. Many workers have attributed special significance to various changes that they identified in skin surface lipids from psoriatic patients, and some have concluded that there is a specific disturbance of lipid metabolism in psoriasis (11). Wilkinson (12), in our laboratories, (who has done meticulous work for several years) has demonstrated that errors relating to the collection of samples of surface lipids are very difficult to avoid, and that when standard cleansing procedures and standard time intervals for lipid accumulation precede the collection, no significant abnormalities are found in lipids from the uninvolved skin of patients with psoriasis.

I should like to mention one study in our laboratory by Dr. Marvin Karasek (13) that was designed to serve as an indicator (Fig. 5) of a wide variety of possible metabolic changes that might characterize the psoriatic patient, through preparing what has been called a "metabolic profile" of the major constituents of the blood in psoriatic patients.

Four classes of substances were separated by a method based upon differences in the ionic charge of the constituents. Each of the groups was further resolved by gas chromatography and paper chromatography for the separation of the compounds indicated in Fig. 5. From these data, he constructed a metabolic profile for the steady state metabolism of the normal control subject, and compared it with that obtained from patients with psoriasis. The psoriatic subjects used for this study were in the basal state, ranged in age from 20 to 50, and had moderate to severe psoriasis not under treatment.

The normal profiles could not be distinguished from psoriatic profiles. From these findings and from all other observations we conclude that there is no major imbalance in the overall metabolism of the psoriatic patient.

Another substantial negative effort by Karasek and associates (13) was an attempt to identify a possible viral etiology of psoriasis. A large-scale screening process was initiated, examining the scales, the feces, the blood, and the urine of twenty patients with active psoriasis. 100 ml. samples of blood were drawn from each patient and concentrated by ultracentrifugation; 1000 ml. samples of 24 hour urine were similarly treated. Samples were assayed for possible virus activity by multiple passages in chick embryos (up to six). The samples were screened in three cell lines for cytopathic effects, and were inoculated intracerebrally and intraperitoneally into newborn mice. There was no cytopathic effect that could not be attributed to occasional contaminating infections in the cultures, including two instances of contamination by influenza virus. In addition, a labeled antibody to inoculated embryonic tissue applied to histological sections of frozen-dried psoriatic tissue, failed to become localized in any element of skin in lesions of psoriasis.

Karasek's group is still reluctant to conclude that viruses do not play a role in psoriasis. They point out that had they worked with cases of hepatitis with the same techniques, their results would also have been negative. They are satisfied that they have not missed a readily identified virus in psoriasis, but feel that as more sophisticated approaches become available from the massive screening

SERUM PROFILES — STEADY STATE

Metabolites	Psoriasis
Amino acids	N
Amines	N
Sugars	N
$PO_4^{\equiv}$	N
Nucleotides	N
Sulfur compounds	N

(11 Psoriasis, 10 Control)

FIG. 5. Result of a study of the serum "metabolic profile" in psoriasis.

HISTOCHEMISTRY – PSORIASIS EPIDERMIS

glycogen
amino acids
proteins
complex proteins
nucleic acids
phosphatases
dehydrogenases
DPN and TPN dependent diaphorases

Different from normal but not specific to psoriasis – thus far

FIG. 6. Summary of studies by histochemical staining of psoriatic plaques.

programs currently used for the possible viral etiology of leukemia, another and more extensive search should be made applying these new techniques.

Histochemical changes in psoriasis have been the subject of a large number of published reports, and these will not be reviewed here. Our own group (14) has made an extensive effort to confirm the presence of specific enzymatic or other histochemical changes suggested by other workers. The result of our studies, utilizing sections of quick-frozen or frozen-dried psoriatic skin is stated briefly in Fig. 6. In this area more than in most others, published reports have suffered from the lack of adequate controls. When hyperplastic epidermis resulting from other causes has been compared to psoriatic epidermis, we have found without exception that similar deviations from the normal histochemical pattern were present.

No discussion of psoriasis should be concluded without a consideration of the significance of the histological findings in the affected skin. Changes in microscopical structure of the skin in psoriasis are like the gross manifestations of the disease: if they are characteristic enough clinically, a diagnosis carries a high degree of reliability. At the same time, the histological structure of psoriatic plaques lacks any absolutely distinctive quality. Not only are there differences in pattern in different patients, but there may be differences within the same patient or changes in a single lesion from one time to another. We have seen many cases in which, following the removal of a specimen presenting non-specific changes, a subsequent biopsy yielded a fully characteristic lesion. We have also obtained "typical" and "atypical" lesions from the same patient at the same time (15). In agreement with the conclusion of Lagerholm (16), based upon electron microscopical studies, we have found that early lesions of psoriasis in general possess a less characteristic appearance on light microscopy than do older lesions. In our experience a large number of psoriatic lesions lack the fully characteristic histological appearance usually attributed to this disease.

Atypical lesions frequently present less epidermal thickening than do well-developed, classical psoriatic plaques (Fig. 7). Furthermore, they frequently do not contain the greatly increased numbers of mitotic figures, described in the specimens studied by Van Scott (17), which led to an estimation of a turnover time for psoriatic epidermis of about four days. (Fig. 8) The fact that many psoriatic plaques show significantly less histological evidence of rapid epidermal growth should warn us not to assume that all psoriatic epi-

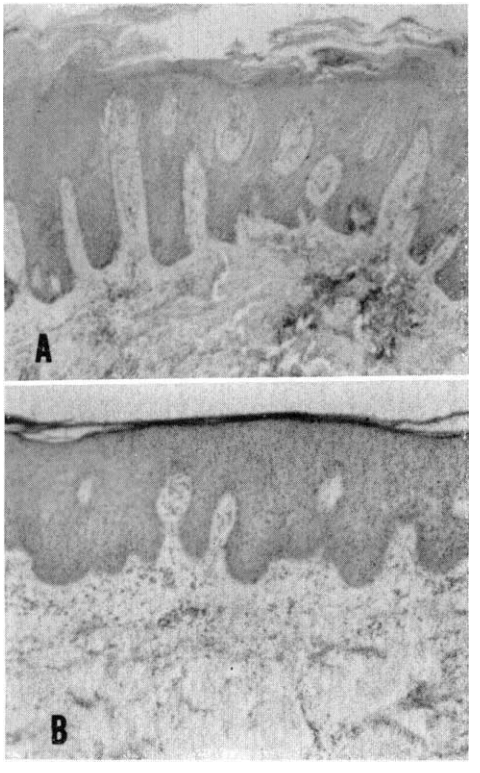
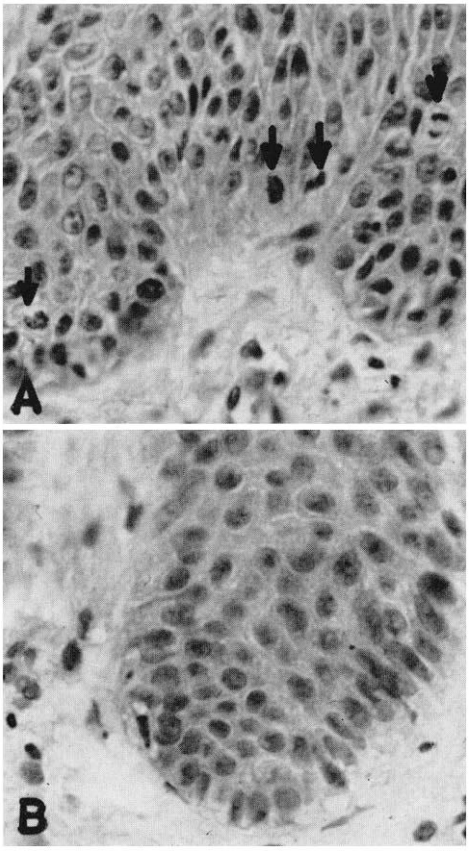


FIG. 7. Variation in histological pattern in different lesions of psoriasis (× 45).



dermis possesses the degree of growth activity estimated by Van Scott from the study of "typical" lesions.

As a result of these observations, we believe that the degree of growth alteration may be different in different psoriatic lesions, even when these are in the skin of a single individual. That the character of the epidermal maturation in a single psoriatic lesion may undergo rapid variation is suggested by the sometimes striking alternation of parakeratotic and orthokeratotic layers in the stratum corneum over psoriatic plaques (Fig. 9). This indicates qualitative differences in maturation of the epidermis during successive time periods corresponding to the formation of these layers.

It should be recognized, however, that changes in growth activity of the epidermis in a psoriatic plaque need not represent a fluctuating causal mechanism for the local manifestation of the disease. Indeed, it seems likely that the rapidly proliferating epidermis in psoriasis is subject to superimposed controlling factors that may change from time to time. This concept provides an explana-

FIG. 8. Difference in frequency of mitotic figures (arrows) in different lesions of psoriasis (× 250).

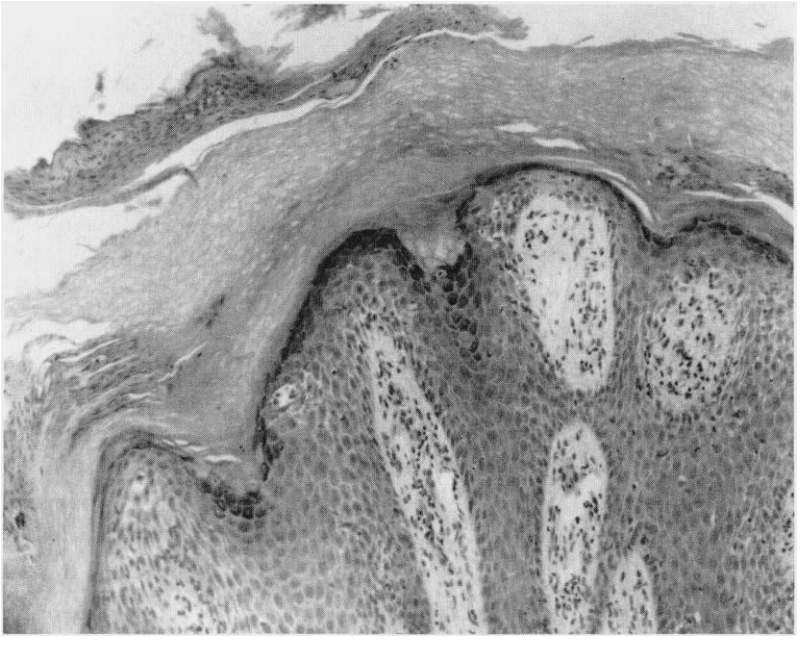


FIG. 9. Alternation of orthokeratotic and parakeratotic portions of a psoriatic scale (× 85)

tion for the success of a variety of therapeutic agents in causing regression of lesions without effecting a complete cure. We still believe that the evidence of variability in the growth activity of psoriatic lesions need not detract in any way from the concept that the psoriatic plaque is a result of a defect in normal epidermal growth control.

One further matter that should occupy our attention is the question of whether any abnormality can be identified in uninvolved skin of patients with psoriasis. That there is something different in such skin is proved by the occurence of the isomorphic reaction.

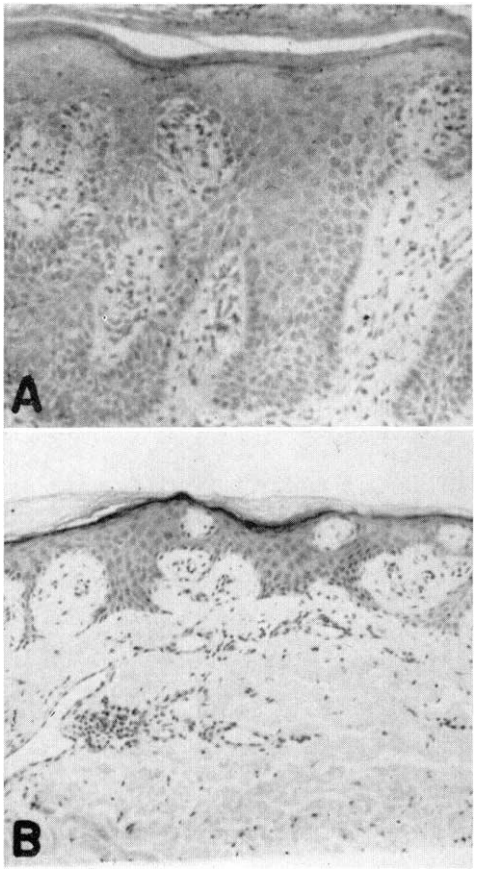


FIG. 10. Result of 0.2% fluocinolone acetonide cream applied topically to a psoriatic plaque. A. Appearance before treatment. B. Appearance after 12 days of continuous topical therapy under an occlusive dressing. The epidermis has been much reduced in thickness but the skin is not entirely normal, exhibiting bulbous papillae that contain unusually prominent capillaries (× 95).

Structural differences have been reported in such skin (Braun-Falco) (18), and our own studies have shown minor histological changes in clinically uninvolved skin of some psoriatic patients.

We have made an effort to determine whether skin that has never been affected with visible lesions has been altered. This is difficult because the memory of patients is often faulty. When we have been sure that psoriasis has never affected the area of clinically uninvolved skin we have not found any histological abnormalities. It is our conclusion that when recognizable structural changes have been present in clinically uninvolved skin, they have represented residual changes due to prior active lesions comparable to those after resolution of psoriatic lesions following topical fluocinolone application (Fig. 10) or after triamcinolone injection (Komisaruk, et al.) (19).

A PROBABLE PATHOGENIC MECHANISM IN PSORIASIS

There is widespread agreement that the process leading to the appearance of a psoriatic plaque is epidermal hyperplasia, and that without this, the plaque would not appear. A fundamental aspect of the pathogenesis, therefore, is the cause of this abnormal growth. Based upon the lack of identification of any constant difference between psoriatic epidermis and other kinds of hyperplastic epidermis, we conclude that the epidermal growth in psoriasis is not in itself distinctive, but that a modification of growth control is probably the underlying mechanism. The growth rate in psoriatic epidermis appears to be no greater than that which can be achieved in a healing wound or in cell culture.

It should be kept in mind that normal epidermal cells have a capacity for rapid growth, that is displayed quickly after the epidermis is injured. The normal epidermis, therefore, represents a state of great restriction of growth potential. It is possible that there are growth stimulating substances that act even in the presence of the normal inhibitors, but none has been identified in psoriatic plaques, and it appears probable that the hyperplasia comes about largely through the reduction or loss of the normal control mechanism.

CONCLUSIONS

Clinical and laboratory studies have reached almost complete agreement supporting the following conclusions:

1. That there is no specific morphologic or physiologic marker which by itself can identify psoriasis. It is possible, of course, that further study will disclose a distinctive change but it is more likely that the nature of the tissue reaction is non-specific, suggesting that the basic abnormality lies not in the nature of the growing cells, but in an alteration of the mechanism of epidermal growth control.
2. That no metabolic change in the patient or chemical peculiarity of the growing epidermis in psoriasis distinguishes it from other types of actively growing epidermis. This is in accord with morphological and physiological findings. It seems likely, however, that some significant chemical change may still be identified, particularly one that relates to growth control rather than to the growth process itself. By chemical change, one includes enzymatic processes, hormonal influences, and effects of undiscovered infectious agents.

It is a normal stage in the evolution of understanding a disease for many conflicting views to be promoted. This simply means that many people are thinking about a problem that has been with us for a long time. We should remember the confusion concerning leprosy that existed before the *Mycobacterium leprae* was discovered, or the uncertainty related to systemic lupus erythematosus before the concept of hypersensitivity was applied, or the number of suggested causes of pellagra before this was recognized as a vitamin deficiency disease!

There is encouraging progress in the study of psoriasis, and if we join our forces there will be a much better chance to solve the problem of this challenging disease.

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