# SYMPOSIUM

## TOPICAL MEDICATION IN RELATION TO SKIN PHYSIOLOGY

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THE human skin has withstood topical medication from unknown antiquity to known adrenocorticosteroids. In the face of such a tradition it is no easy thing to make a critical assessment of the current situation, still less to look into the future.

The rationality of topical therapy requires not only that the medicament should be effective, but that local application of it should be better than systemic administration. For example, the local elimination of animal ectoparasites, by the use of benzyl benzoate or tetraethylthiuram monosulphide for scabies or DDT for head lice, is unquestionably effective. On the other hand, topical therapy of some fungal diseases of the skin is becoming superseded by griseofulvin, a systemic fungicide which may be taken orally (see, for example, Martin, 1959; Blank and Roth, 1959; Reiss, Kornblee and Gordon, 1960; Blank, 1960). The best mode of attack on bacterial infections of the skin is more open to debate. Pillsbury, Shelley and Kligman (1956) believe that topical therapy is preferable to systemic only in very superficial infections. Several antibiotics, such as neomycin and bacitracin, are effective, but they council strongly against all topical use of sulphonamides, penicillin, streptomycin, organic mercurial compounds and time-honoured tincture of iodine; this is, however, more because of the likelihood of induced hypersensitivity than for lack of effectiveness.

Though the variety of other traditional topical medicaments is large, I think we must admit that their efficacy is usually questionable and their mode of action, if any, unknown. Indeed, many preparations would probably be more beneficial as bland dressings with their supposed "active" ingredients left out. The necessity of water, though not too much of it, to the cornified epithelium is undoubted (Blank, 1952), particularly if the water absorbing properties are reduced in skin disorders (Flesch and Jackson Esoda, 1957).

Adrenocorticoids have within the last 10 years proved to be the most effective group of substances yet discovered for the treatment of skin disorders. Stoughton (1959) lists more than seventeen skin diseases in which oral or intracutaneous administration of such compounds was effective. In only three, namely, atopic dermatitis, nummular eczema and anogenital pruritis was topical application equally good, though there were also variable responses in other "eczematous" disorders. Nevertheless, such conditions account for about half of all cases of skin disease. Though cortisone is without significant action (Goldman, Thomson and Trice, 1952), hydrocortisone is effective as a topical agent (Sulzberger, Witten and Smith, 1953; Malkinson and Wells, 1954; Witten, 1955). Fluorohydrocortisone, in one-tenth of the concentration,

is as effective as hydrocortisone (Sulzberger, 1955). More recently other synthetic corticoids, of which triamcinolone (Rein, Fleischmajer and Rosenthal, 1957) appears to be the most potent, have been introduced for topical therapy.

Since steroids, including cortisone and hydrocortisone, are readily absorbed by intact skin (Malkinson and Ferguson, 1955; Malkinson, Ferguson and Wang, 1957; Goldzieher and Baker, 1960), the difference between the effects of cortisone and hydrocortisone is surprising. One possible explanation is suggested by the finding of Malkinson (1958) that, at skin sites from which the barrier is removed, the absorption of hydrocortisone free alcohol but not of cortisone is greatly increased. Hence hydrocortisone may more readily pass into skin in which the barrier has been damaged by inflammation. Other possibilities are that cortisone is metabolically inactivated more quickly than hydrocortisone, or that the action of the hormone may depend upon intermediate metabolic products which are readily formed in the skin from hydrocortisone but not from cortisone (Malkinson, Lee and Cutukovic, 1959; Malkinson, 1960).

How do these substances work? On a biochemical basis we do not know. But there are many experimental results indicating how various substances including steroids, may affect skin and I am going to try and review this field. I shall do so not in relation to particular chemical compounds, about which as a zoologist I know little, nor specifically in relation to skin diseases, about which I know less, but in relation to the structure and function of some of the components of the skin. I omit the apocrine glands and the condition hidradenitis, which may in part have an endocrine cause (Brunsting, 1952) and which has been systemically treated with both testosterone (Cornbleet, 1952) and hydrocortisone (Danto, 1958), and also the eccrine sweat glands. The condition miliaria or "prickly heat", according to Pillsbury and others (1956) has borne the brunt of a full pharmacopeia and the only specific treatment is to eliminate sweating. Neither shall I deal with the melanocyte nor the hair follicle, a structure of great fascination for study, but from the viewpoint of topical application unyielding, though not perhaps unrewarding.

*The Epidermis*

Cells are formed in the basal layers of the *stratum Malpighi* and move outwards. In the region known as the *stratum granulosum* keratin begins to be synthesised within them; the cells eventually lose their nuclei as they pass to form the *stratum corneum.*

There seems little reason to doubt that the intermediate metabolism of carbohydrates by the epidermis involves the Krebs cycle (Griesemer and Gould, 1954, 1955; Cruickshank, Hershey and Lewis, 1958), and the distribution of relevant enzymes has been investigated by, for example, Ellis and Montagna (1958) and Goltz, Fusaro, Blazejovsky and Jarvis (1959).

The metabolic processes uniquely associated with epidermis, such as keratinisation, have been reviewed by Lorincz and Stoughton (1958).

Keratins are composed of long polypeptide chains held together by cross linkages. The most important of these is the disulphide bond, formed by the oxidation of two sulphydryl groups belonging to two cysteine residues in adjacent polypeptide chains. The result is a molecule of cystine to which both polypeptide chains contribute; this reaction does not require energy but releases it. Nevertheless, according to Jarrett, Spearman and Hardy (1959), the *stratum granulosum* contains a high energy system on the evidence supplied by the distribution of enzymes. They suggest that in this region there is an active breakdown and re-synthesis of polypeptide chains, before keratinisation by cross-bonding takes place.

In the skin condition *psoriasis* there is no granular layer and the cells of the *stratum corneum* retain nuclei. Keratinisation is abnormal; there is an unusually high concentration of sulphydryl groups, suggesting that the breakdown and resynthesis of unfolded polypeptide chains has been incomplete, and the high amount of phospholipid probably is evidence of incomplete utilisation of the high energy system. The most obvious explanation of parakeratosis would appear to be a specific enzyme defect. Roe (1959) concluded that an abnormal glycoprotein accumulates in psoriatic epidermis. Because of a systemic error in sulphur metabolism this incorporates sulphur which thus becomes unavailable for keratin synthesis. Flesch and Jackson Esoda (1961) believe that a mucopolysaccharide builds up in the pathologic horny layer instead of becoming decomposed as in normal keratinisation. A similar view is held by Tickner (1961), who suggests that the psoriatic lesion arises from a failure of the union of tonofibrin fibrils due to the presence, in abnormally large quantity, of a substance produced by some metabolic block. Jarrett and others (1959) and Van Scott and Reinertson (1959), on the other hand, incline to the view that the lesion involves excessive cellular proliferation, with the result that there is insufficient time for breakdown and re-synthesis of the polypeptides, tonofibril formation is not completed, formation of the stratum granulosum does not occur, and normal keratinisation is not achieved. The question of what factors control epidermal mitosis and what substances influence it is therefore of importance.

Bullough (1946, 1950a, b) and Allen (1956) have presented evidence that oestrogens stimulate mitosis in the epidermis of the mouse. Bullough (1953) put forward the view that cell division requires energy derived from carbohydrate metabolism and that oestrogens facilitate a stage, possibly the hexokinase reaction, which is normally rate-limited. Gelfant (1959a, b, 1960a, b, c) has challenged these conclusions, maintaining that there is no concrete evidence that glucose is actually used as a source of energy for mitosis and that oestrogens have no effect. Oestrogens do not seem to affect epidermal mitosis in the rat (Carter, 1953; Ebling, 1954, 1955); it is interesting, however, that they seem to reduce epidermal thickness, suggesting that cell life is diminished and the rate of cell loss is increased. Hypophysectomy results in significant thickening of the epidermis, producing a well marked granular layer, in both female and male rats (Ebling,

1955, 1957a); this thickened epidermis can be reduced by oestrogens. Androgens, also, have been shown to stimulate epidermal mitosis in the mouse and rat (Bullough and Van Oordt, 1950; Ebling, 1957a, b).

Vitamin A causes hypertrophy of the epidermis in rats (Studer and Frey, 1952; Bern, Elias, Pickett, Powers and Harkness, 1955; Sobel, Parnell, Sherman and Bradley, 1958) and in guinea-pigs (Montagna, 1954), though Fisher and Herrmann (1957) could find no such effect after topical application to human skin. Lawrence and Bern (1958), in a very careful study of the effects of topically applied vitamin A on mouse skin, showed that the epidermal thickness was linearly related to the log of the dose, and that the increased thickness was the result of rapid epidermal proliferation.

Many agents inhibit epidermal cell division; prominent are adrenaline (Bullough, 1955; Ghadially and Green, 1957; Gelfant, 1960) and adrenal steroids such as cortisone (Ghadially and Green, 1957) and desoxycorticosterone acetate (Gelfant, 1960).

Attempts to treat psoriasis by systemic or topical application of adrenocortical steroids were not initially crowned with unqualified success. Fergusson and Dewar (1957), for example, reported inconsistent results with ACTH or prednisolone. The synthetic corticoid triamcinolone seems to show more promise. Shelley, Harun and Pillsbury (1958) reported that 36 out of 60 patients given oral triamcinolone showed an unquestionable response within a week. Symptoms were erased by 2 to 4 weeks, but reappeared when treatment was stopped. Jarrett and Witham (1961) have reported that such treatment causes reappearance of a granular layer in the psoriatic areas. Cohen and Baer (1960) found that oral triamcinolone was more effective than methyl prednisolone or prednisolone; others, while agreeing that triamcinolone is a potent drug for systemic treatment of psoriasis, point out that undesirable side effects are common and it is unsuitable for general use (Greenlee and Epstein, 1959). However, effective results from topical medication have been achieved with triamcinolone acetonide in lotion (Crowe, Fitzpatrick, Walker and Olson, 1958) or given into the lesions (Cohen and Baer, 1960; James, 1960; Readett, 1961) and by subdermal infiltration with triamcinolone diacetate (Gerard, 1960).

Jarrett and Spearman (1959) confirmed the observation of Lawrence and Bern (1958) that topical application of vitamin A to mouse tail epidermis causes formation of a granular layer and conversion of "parakeratotic" scales to flexible keratin. They concluded that it would be worthwhile treating psoriasis with a combination of local vitamin A, to promote formation of a granular layer, and systemic or topical triamcinolone to reduce epidermal mitosis. Such treatment was successful, though a full report is awaited.

Corticoid-like steroids, such as triamcinolone, clearly show promise for the treatment of psoriasis, especially if undesirable side effects can be avoided by topical application. Though histological evidence supports its rationality, it may still be premature to regard the treatment as specific. A whole range of unrelated compounds may act in a similar way. Burks and Montgomery (1943), for example, achieved formation of a stratum

granulosum and diminished parakeratosis in psoriatic lesions by the use of old-fashioned tar and ultra-violet light. It is interesting that Läuppi and Studer (1959) have been able, by means of a phenanthrene derivative, to inhibit the proliferation of the epidermis of rats which is induced by testosterone. Van Scott and Reinertson (1959) reported clearing of psoriatic lesions, with a thickened granular layer and inhibited epidermal hyperplasia, after topical application of mitotic inhibitors such as podophyllin and colchicine, mercury (20 per cent in "aquaphor"), nitrogen mustard, and liquor carbonis detergens. Methotrexate (a folic acid antagonist), 5-fluorouracil and actinomycin D were effective when given intravenously but not topically; this suggested that they may have an indirect action.

*Sebaceous Glands*

The sebaceous glands are truly holocrine; the cells are replaced around the periphery and the sebum is formed by the breakdown of the whole cell as it moves towards the duct. Many factors have been alleged to affect sebaceous activity, but the overriding importance of steroid hormones has been shown both in animal experiments and in human trials.

Androgens, systemically administered or topically applied, cause enlargement of the sebaceous glands of animals (de Graaf, 1943; Ebling, 1948; Montagna and Kenyon, 1949; Hamilton and Montagna, 1950; Haskin, Lasher and Rothman, 1953; Lapière, 1953). The effect seems to involve an increase in cell size as well as in cell division (Ebling, 1957). Though Shelley and Hurley (1957) failed to observe any enlargement of the sebaceous glands after implantation of testosterone into the human axilla, Jarrett (1959) showed clearly that intramuscular injection of 25 mg./day of testosterone caused a marked increase in the surface sebum in adolescent boys. Enlargement of the sebaceous glands by testosterone requires the presence of the pituitary (Lasher, Lorincz and Rothman, 1955; Ebling, 1957). It has been proposed by Lorincz and Lancaster (1957) that the pituitary contains a "sebotropic" factor.

The possible effects of progesterone are subject to some dispute. Haskin, Lasher and Rothman (1953) and Lasher, Lorincz and Rothman (1954) found that doses of 1–10 mg. daily stimulated the sebaceous glands in spayed adult rats, and stated that this effect was comparable with that of testosterone. Hodgson-Jones, MacKenna and Wheatley (1952) have shown that in man the sebum level fluctuates during the menstrual cycle, being highest in the luteal phase, and rises during pregnancy. Zeligman and Hubener (1957) have claimed that progesterone produces mild to moderate acne in women, involving slight but not statistically significant enlargement of the sebaceous glands, and Smith (1959) showed that progesterone increased the surface sebum in senile women. On the other hand, Ebling (1961), using doses of 0·1–0·2 mg. of progesterone per day for 3 weeks could find no effect in either intact or spayed, immature or adult, female rats, and Jarrett (1959) found that the amount of surface sebum was unaltered by treating adolescent men and women with progesterone.

Adrenocorticoids have been reported by Castor and Baker (1950) to reduce the size of sebaceous glands when applied locally, though Haskin and others (1953) achieved only a slight effect by the injection of cortisone. Systemic administration of ACTH, similarly suppresses the glands, according to Baker, Ingle, Li and Evans (1948), but Haskin and others (1953) found that this treatment caused glandular enlargement. In man, Strauss and Kligman (1959) found that enlargement of sebaceous glands was induced by ACTH in a proportion of males and females, though only 2 out of 6 treated with hydrocortisone showed such a response. It is difficult to reconcile all these results, though the suggestion of Haskin and others (1953) that ACTH causes production of adrenal androgens could explain a difference between its effect and that of corticoids.

Oestrogens, by general agreement, cause a reduction in the size of sebaceous glands (Hooker and Pfeiffer, 1943; Ebling, 1948, 1951). In rats, the effect of oestradiol-17$\beta$ appears to be brought about by a more rapid disintegration of the sebaceous cells, and a reduced cell production is not necessarily involved (Ebling, 1954, 1955). Indeed, by combining oestradiol and testosterone, the incidence of mitoses can be raised without increasing gland size (Ebling, 1957). The overall effect of oestrogens is one of reduced sebum production, as demonstrated clearly by Jarrett (1955) in human patients given stilboestrol. It seems likely that the sebaceous cells have no time to differentiate fully before they are shed.

The effect of oestrogens is independent of the presence of the pituitary (Ebling, 1955), and it can be produced locally (Lapière, 1953). Natural oestrogens such as oestrone and oestriol are also effective, as are a number of synthetic steroids of low oestrogenic potency such as 16-epi-oestriol and oestradiol-17$\alpha$ (Bullough and Laurence, 1960).

These facts might suggest a clear endocrine etiology for skin disorders such as acne vulgaris and seborrhoea, which involve enlargement of the sebaceous glands, as well as a rational approach to systemic or topical therapy. Lipman Cohen (1941) drew attention to the probable endocrine background of acne, and Hamilton (1941) stated clearly that male hormone was a prime factor, a view endorsed by Rony and Zakon (1943). But the idea that acne results solely from a high production of androgens may be too simple. Some authors, for example Aron-Brunetière (1953), have proposed that the essential cause is an increased androgen : oestrogen ratio. Moreover, the demonstration that androgens are without effect in the absence of the pituitary suggests that a hypophyseal hormone may be involved in the etiology of acne. The condition may perhaps occur in the male because a rising production of androgens during adolescence overlaps some hypophyseal activity which later abates. Lorincz and Lancaster (1957) believe that the hypophyseal factor has a separate identity from known pituitary hormones.

Haskin and others (1953) have suggested that adolescent seborrhea and acne in the female is the result of luteal progesterone and not of adrenal androgens. Since in experimental animals progesterone has been shown to enlarge the sebaceous glands only in relatively large doses, we cannot be sure that its action is not dependent on prior conversion to androgens.

Such a process might also explain its effect in senile women reported by Smith (1959). If this were so, a direct role of progesterone in the etiology of female acne would be precluded.

Amelioration of acne after treatment with oestrogens has been reported by a number of authors. Lawrence and Werthessen (1942) successfully used orally administered oestrogens, and Jarrett (1955) found that 3–5 mg. of oral stilboestrol per day had a beneficial but temporary effect. The question arises of how far topical application is of equal value. Whitelaw (1951) applied 1·25 mg. of sodium oestrone sulphate daily in an ointment to adolescent males and females and noticed great improvement in more than half of them within 6 months, without any side effects in the males. More recently, Peterkin (1959) has reported that application of a lotion base containing 1 mg./ml. of epioestriol improved 73 per cent of acne patients within 2 months, compared with only 45 per cent when the base alone was used.

*The Dermis*

The connective tissue of the dermis consists mainly of a complex association of a metabolically inert protein, called collagen, and mucopolysaccharide. The collagen is traditionally observed as bundles of fibres and the mucopolysaccharide as the semifluid amorphous ground substance, though Jarrett (1958) suggests that the histological appearance of fibres and spaces may be an artefact of fixation. In addition the dermis contains elastic fibres, vascular beds at various levels, fibroblasts which secrete the unpolymerised tropocollagen from which the collagen is formed, mast cells, melanocytes, macrophages, lymphocytes and other leucocytes (Montagna, 1956).

In many skin diseases inflammation occurs in the dermis, and similar changes can be brought about by such diverse stimuli as bacterial invasion, thermal injury and frostbite. "Inflammation" is an overworked word and an undefined process though two features seem to be of special importance in its pathology, namely increased capillary permeability to protein and the emigration of leucocytes. A number of endogenous substances will increase capillary permeability. Histamine is produced by the mast cells in man and most other mammals; 5-hydroxytryptamine (serotonin) appears to be produced by mast cells in rodents, but by blood platelets in man (Spector, 1958; Schachter, 1960). Bradykinin and kallidin are polypeptides which are released from a plasma globulin by an enzyme kallikrein (Cormia and Dougherty, 1960), and there are other similar substances, for example, "leukotaxine" prepared by Menkin (1951a).

The release of histamine, which can be induced in man by intradermal injection of various specific histamine liberators, produces "flare" and "wheal"; subcutaneous injection of such substances produces erythema, pruritis and oedema. But how histamine is held in the cell or released cannot be satisfactorily explained; antihistamine drugs are mostly synthetic analogues of histamine which do not affect histamine release but act by competitive inhibition. Histamine release after injury of skin is

almost immediate and of brief duration, and there is evidence that inflammation is maintained and sustained by a mechanism insensitive to antihistamine measures (Spector, 1960). Nevertheless, abnormally large amounts of excreted histamine have been shown in some diseases, for example, urticaria pigmentosa (Demis, Walton and Higdon, 1961). In atopic dermatitis, also, skin histamine levels have been shown to be above normal, though Johnson De Oreo, Lascheid and Mitchell (1960) concluded that this did not justify the conclusion that histamine was responsible for or of major significance in the cutaneous alterations.

Though steroids have been reported to have many different dermal effects, there is little precise information on their mode of action. In a careful paper on "Histological effects of hydrocortisone in the skin of man", Goldman (1955) had to conclude that these studies "do not suggest any mechanism for the local suppression of inflammation. Our techniques are at present too crude. . . ." It may be of value, nevertheless, to try and summarise the existing clues.

Steroids may act on the collagen-mucopolysaccharide complex. Oestrogens have been shown to increase the amount of intracellular water in the skin of mice, probably by increasing the amount of ground substance (Cooper and Schmidt, 1957a, b). Corticoids appear to have an opposite effect. Hydrocortisone ointment applied to man (1 per cent twice daily for 1–8 months) or oral cortisone or prednisone, or ACTH, caused progressive atrophy of collagen fibres as well as disappearance of interfibrillar mucopolysaccharides, dissociation of elastic fibres and atrophy of fibroblasts (Mancini, Stringa and Canepa, 1960). A decrease in the ratio of hexosamine (derived from mucopolysaccharide) to collagen in biopsies from the buttocks after 2 weeks systemic medication with prednisone, methylprednisone or triamcinolone has been reported by Wright, Sobel and Nelson (1960). In the rat, the uptake of $^{14}C$ and $^{35}S$ by mucopolysaccharide constituents is inhibited by cortisone or hydrocortisone (Schiller and Dorfman, 1957).

The "anti-inflammatory" action of adrenocortical steroids is undisputed, but the mechanism is debatable. There is evidence that the mast cells themselves are inhibited; according to Asboe-Hansen (1957, 1958) adrenocortical compounds cause clumping of the granules, a slower uptake of $^{35}S$ and reduced histamine secretion. Vacuolation and disruption of mast cells with release of granules, as well as an increase in the number of binucleate cells, is induced in human tissue by cortisone (Bloom, 1958). ACTH reduces the number of circulating blood mast cells in the rabbit (Boseila, 1958).

On the other hand, Menkin (1951a, b) states that cortisone suppresses the increase of permeability due to the liberation of polypeptides ("leukotaxine"). Dougherty and Schneebeli (1955) and Scott and Kalz (1956) consider that adrenocorticoids act, not by inhibiting the production of the inflammatory stimulus, but by interfering with its action. Dougherty and Schneebeli (1955) produced inflammation in the skin of adrenalectomised mice by a variety of methods, and showed that antiphlogistic steroids prevent destruction of the fibroblasts and reduce the numbers of

invading leucocytes and macrophages, as seen in loose connective tissue spreads. By the use of $^{14}C$-labelled hydrocortisone and autoradiography they showed that the steroid actually accumulates within the fibroblasts; such cells resist destruction.

Spector (1958) has pointed out that there are two hypotheses about the mode of action of cortisone and hydrocortisone on capillary permeability. Either they prevent the antigen-antibody combination from exerting its effect on the capillary wall, or they cause a general depression of the reactivity of the capillary wall to stimuli which increase permeability. The evidence suggests that there is some truth in both hypotheses. Marks, Smith and Cunliffe (1961) have suggested that salicylates, also, act by preventing antigen-antibody combinations from exerting their effects on the capillary wall.

An effect on the blood supply in experimental chambers made in rabbit ears has been observed by Ebert and Barclay (1952). Cortisone brought about increased vascular tone in the arterioles and reduced sticking of leucocytes to the arteriolar endothelium.

The anti-inflammatory action of cortisone is inhibited by desoxycorticosterone (Dougherty, 1954). It is interesting to note that, in tissues which are specially sensitive to them, such as the uterus and vagina, oestrogens produce all the features of inflammation, including leucocyte emigration.

Corticoids are usually regarded as effective antipruritic agents, though experimental evidence to support such an action is sometimes conflicting. Cormia and Kuykendall (1953) found that, though antihistamines, analgesics such as aspirin and codeine, and sedatives all raised the threshold concentration of histamine needed to produce a recognisable pruritis, intramuscular cortisone had only a very little effect. Frank (1958) found that neither hydrocortisone free alcohol nor hydrocortisone diethylaminoacetate had any effect when applied after histamine, but both steroids shortened the duration of pruritis when applied 2 hours previously. They also had a significant antipruritic effect, as compared with a blank vehicle, in patients, though less than half benefited even with the highest concentration (0·5 per cent) used. Macris, Blank and Beecher (1959) trained investigators to record the duration of experimental pruritis after the application of cowhage (pods of *Macuna pruriens*). They reported that calamine lotion, ointments of menthol, xylocaine, nupercaine or hydrocortisone, together with various vehicles and placebos had no effect on the duration of pruritis.

## Conclusions

Some traditional topical medicaments are becoming discarded as valueless or are being superseded by more effective systemic remedies. In addition, the use of steroids, especially those of the adrenal cortex or their synthetic analogues, is opening up new possibilities of local therapy. In spite of the development of some preparations that are "anti-inflammatory and antipruritic" we do not know exactly how such substances work, any more than we understand the pathogenesis of most

skin diseases. Steroids may affect the epidermis and its appendages as well as the dermis.

A decade or so ago the skin could reasonably have been regarded as a neglected organ. This is no longer true; skin physiology and experimental dermatology, as well as steroid chemistry are developing rapidly and we may expect further improvements in skin therapy.

In conclusion I turn again to antiquity. Moses (1451 B.C.) reported that, for disobedience of the commandments, "The Lord will smite thee with the botch of Egypt, and with the emerods, and with the scab, and with the itch, whereof thou canst not be healed". Later we learn the reason for the lack of therapeutic measures: "thou shalt not anoint thyself with oil; for the olive shall cast his fruit".

Without wishing to imply that I accept the given reasons, I observe that the scab, itch and botch are still with us. But the olive does not cast his fruit; we have oil, and we have discovered even better things than oil with which to anoint ourselves. In case the opening of my paper should have appeared too sceptical, I end it by making clear that I think it proper and profitable for the search to continue.

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