SKIN MEDICATION

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In the previous paper by Dr. Ebling the normal anatomy and physiology of the skin and its appendages have been described. It is the object of this paper to discuss some of the ways in which skin function can become abnormal, and to evaluate critically the therapeutic means we have at our disposal to correct these pathological changes.

Abnormalities of the Epidermis

Ebling has already described how normal keratin is formed from epidermal cells by way of a granular layer, the stratum granulosum. This normal state of affairs can be interfered with in two ways. First there may be a failure to form a granular layer, and secondly this layer may become abnormally thickened. Both result in the production of abnormal keratin.

Absence of the Granular Layer

In this disorder there is a failure to form a granular layer and this is often associated with an increase in thickness of the epidermis; this combination occurs characteristically in psoriasis. It also occurs in other conditions in which there is increased or abnormal activity of the epidermal cells; thus it is seen in most types of cancerous and precancerous conditions of the skin. As already stated the keratin formed by this disordered epidermis is itself abnormal. It has different physical characteristics in that it forms large scales that flake off. It is this scaling that the patient sees, and is the reason for his consulting his doctor.

There are also changes in the keratin that are recognisable under the microscope. Nuclear remains are present in the substance of the keratin and this is known as parakeratosis to distinguish it from normal keratin. In addition there are histochemical alterations; for example, there is an increase of phospholipids and of protein bound sulphydryl groups (Braun-Falco, 1958, 1959; Jarrett, 1959).

In our discussion on treatment we will take psoriasis as the example of this type of disordered keratinization. The malignant conditions giving rise to this type of abnormal keratinization require special treatment either by surgery or by irradiation. The latter form of treatment will be briefly evaluated later in this paper.

Increase of the Granular Layer

This is much rarer than an absence of the granular layer. Nevertheless an abnormal keratin is produced which may also appear scaly, although the scales are not so large as in psoriasis. It is seen most often in lichenification of the skin caused by chronic irritation and rubbing. It is also

present in the relatively rare disease called lichen planus. The histochemical changes in the keratin and of the epidermal cells are not so well known as in psoriasis.

Blistering Diseases of the Skin

Many skin diseases are capable of producing blisters. These are formed either as a result of damage to the epidermal cells, or by the lifting up of the whole epidermis by an accumulation of fluid at the dermo-epidermal junction. The commonest condition causing vesiculation of the skin is eczema. Here the epidermal cells are damaged, break down, and form little microscopic collections of fluid which often rupture onto the surface and produce a weeping eczema. During the healing phase the epidermis regenerates, and there is an increase in the epidermal cell activity resulting in the formation of a parakeratotic keratin. This stage is often known clinically as scaly or dry eczema. This abnormal keratin is replaced later by normal keratin after the re-establishment of a granular layer.

There are several other diseases which give rise to blistering; among these are included pemphigus, dermatitis herpetiformis, and erythema multiformae. Pemphigus exists in several forms, and in the past was a fatal disease. Erythema multiformae is often a result of sensitisation to internal drug, or food allergen.

The Value of Therapy for these Epidermal Disorders

Psoriasis

I will take this disorder as a typical example of abnormal keratinization of the parakeratotic type.

Countless remedies have been recommended for its treatment. The genuine value of most of these is open to serious doubt. Of the more effective local applications one may list the following: crude coal tar 1–10 per cent, dithranol 0·05–0·5 per cent, and local irradiation with ultraviolet light either alone or combined with crude coal tar as in the Göeckerman régime (1931).

Those of more doubtful value include salicylic acid 0·5–5 per cent either alone or combined with other medicaments, ammoniated mercury ointment with and without solution of coal tar and numerous others. I think it is fair to say that none of these substances has any known rational basis for its effectiveness, or otherwise.

Recently we have been able to demonstrate the formation of a granular layer in mouse tails where none previously existed, after the local application of vitamin A. This vitamin therefore specifically generates a granular layer. We thought that this would be of great value in the treatment of psoriasis. Vitamin A, however, has another effect in that it induces hyperplasia of the epidermis. This is obviously undesirable in psoriasis as the epidermis is already active and greatly thickened. We were able to control this increase in activity caused by vitamin A by the use of local and systemic steroids. The most useful steroid was triamcinolone, and this had already been used alone with success in the treatment

of psoriasis (Shelley, Harum and Pillsbury, 1958). However, the dosage required was often great and the complications arising from its over-enthusiastic use caused it to fall into disrepute. The combination of the vitamin with triamcinolone in an oil-in-water emulsion proved successful in the treatment of psoriasis (Jarrett and Spearman, 1959b) and further clinical trials are still in progress.

It is of interest that the vitamin must be used in a water-solubilised form; the oil soluble preparations are of little or no value. This is an intriguing observation since there is some basis for the belief that oil soluble substances are better able to penetrate the epidermis than those dissolved in water.

Thickened Granular Layer

Lichenification. This is usually due to chronic pruritus, and is the result of constant scratching. The only really effective means of control are local corticosteroids, and either Grenz or X-irradiation. Other local treatments including menthol, camphor, phenol, and anaesthetic ointments such as benzocaine or cocaine are usually either useless or frankly dangerous because they may produce a contact dermatitis.

Lichen planus. I know of no specific treatment for this condition. Those suggested in most text books are valueless and only play for time until the patient makes a spontaneous recovery. In very severe cases it is worthwhile to give a course of systemic corticosteroids or ACTH, but there may be a relapse on discontinuing therapy.

Blistering Diseases

Eczema

This is one of the commonest skin diseases, and one for which endless remedies have been suggested. It can usually be taken that the number of treatments recommended for any particular condition is in the inverse ratio to the value of any one of them: eczema has more treatments than any other skin disease.

In the early stages of weeping eczema, soaks certainly make the patient more comfortable. These may be saline soaks, lead lotion, potassium permanganate, or even calamine. Probably the water is the most useful ingredient; because of its latent heat of vapourisation it cools the skin and reduces the vascular dilatation; it also prevents the dressing adhering to the affected area. Later in the dry scaly stage, zinc paste, zinc paste and ichthammol, tar ointments as for psoriasis, and of course the local corticosteroids can be employed.

At this point it is perhaps worthwhile to mention zinc paste. It is possible that zinc can substitute for magnesium in the epidermis. It appears that magnesium is required for proper keratin formation; it acts as a catalyst in the formation of disulphide linkages from the amino-acid cysteine (Neurath and Bailey, 1954). Further experimental work is required to ascertain whether zinc can substitute for magnesium and therefore act as a catalyst for the formation of disulphide linkages. If this is so then a rational role for the use of zinc in skin diseases can be substantiated.

Pemphigus

In the past this was a fatal skin disease. If the patient survived the first attack he usually succumbed to the second or the third. The advent of steroids has greatly changed this prognosis. A patient can be controlled with steroids during the acute phase of his disease; the dosage required at this stage is often very high. The dose can then be reduced during the succeeding remission. In this manner it is often possible to keep the patient alive through several attacks and in some cases until a natural cure has been attained. Supportive measures are also required in that protein loss must be made good, and skin sepsis controlled with antibiotics (Nelson and Brodey, 1955).

Dermatitis herpetiformis. This is an example of a disease the cause of which we do not know and one which we can control with therapeutic agents whose action we do not understand. It is a wonderful example of successful empirical therapy. This relatively rare disease is controlled with small doses of sulphapyridine (0·25–1·0 g. daily) or by dapsone given in doses of 25 to 100 mg. a day. The mode of action of these two drugs in this condition is entirely unknown (Alexander, 1955; Morgan, Marsden, Coburn and Mungavin, 1955).

Infective Conditions of the Skin

Pyococcal Diseases

During the past 25 years there have been enormous strides in the control of infective conditions of the skin. With the advent of sulphonamides and antibiotics the control of these conditions has become greatly improved. We are now able to deal adequately with such conditions as impetigo, ecthyma and secondary infected eczema.

Carbundles and boils are no longer the danger they were only a few years ago. Nevertheless these conditions may be recurrent and the general health of the patient has an important part to play in their permanent cure.

Tuberculosis of the Skin

This is another success story—calciferol, isonicotinic acid and streptomycin have greatly improved the prognosis of the once dreadfully mutilating diseases lupus vulgaris and scrofuloderma.

Fungus Infections

Until very recently microsporum ringworm of the scalp in children was a real problem and necessitated X-ray epilation, which occasionally caused permanent alopecia. Local therapy was virtually useless and the loss of time from school often serious.

Modern therapy with griseofulvin has given us a relatively safe method of oral treatment and requires only the simplest of local medication. This drug has also greatly improved the treatment of favus, ringworm of the skin and of the nails. Its precise mode of action is uncertain; it is fungistatic, not fungicidal. The drug is taken into keratinized structures such as hair, nails and epidermis making them resistant to invasion by the

fungus. The infected hair or nail keratin can be mechanically removed, and the new unaffected structures allowed to grow. With epidermal infections the infected keratin is removed by the normal shedding process (Williams, Marten and Sarkany, 1958; Hargreaves, 1960).

Tropical Diseases

Diseases like cutaneous leishmaniasis, and amoebiasis of the skin are amenable to modern antiprotozoal drugs, and therefore their treatment is much more successful.

Dermal Disorders

Under this heading I am including a small group of unrelated disorders which have become amenable, at least to some extent, to modern treatment whether or not the rational basis for their success is known.

We have reason to believe that the dermis exists in the living skin as a gel and not as a network of fibres and blood vessels surrounded by fluid. The fibres appear to be a fixation artefact; they are formed by the polymerisation of the parent monomer by chemical fixatives (Jarrett, 1958).

Urticaria

This is a common skin disorder and one which can be controlled by modern therapy. Although a cause for this type of vascular reaction should always be sought, we are often forced to control the condition empirically with antihistamine drugs. These substances act as blocking agents to the histamine produced by the abnormal vascular reaction. By the use of these substances cases can often be kept symptom free until a spontaneous recovery occurs.

Lupus Erythematosus

No specific treatment for this condition is available. Nevertheless certain of the modern antimalarial drugs such as mepacrine and chloroquin are of great value although their mode of action is unknown. In the disseminated form steroids are life saving.

Scleroderma

Again there is no known specific remedy. The hormones, relaxin and oestrogens have been tried on the rational basis of altering the physical state of the collagen.

Relaxin is a hormone obtained from the ovaries of pregnant sows. In late pregnancy this hormone causes softening of the pelvic ligaments and this allows greater pelvic mobility during delivery. It is reasonable to suppose that this hormone alters the physical state of connective tissues in that it causes depolymerisation. This would theoretically improve the state of the skin in scleroderma. The results obtained with this compound have been generally rather disappointing (Evans, 1959). Steroids are of doubtful value in this condition.

Granuloma annulare. This condition is often greatly helped by vitamin E and by local injections of hydrocortisone.

Disorders of the Sebaceous Glands

Under this heading the problems of acne vulgaris and rosacea will be considered. Acne is a common disease that occurs at puberty and is associated with increased activity of the sebaceous glands.

Sebaceous glands are stimulated by androgenic hormones such as testosterone and suppressed by oestrogenic hormones. These effects have been demonstrated in the rat (Ebling, 1948, 1955, 1957, 1961) and in human patients (Jarrett, 1955, 1959a).

It is therefore reasonable that oestrogenic hormones should be used to reduce the increased sebaceous activity in cases of acne. Systemic treatment with stilboestrol has proved most useful in the control of this condition. Courses of short duration with moderately heavy dosage (3 mg. daily for 21 days) often succeed in producing remarkable improvement. Local oestrogens can be used but their effect is generally not satisfactory. The mode of action of oestrogens is uncertain. It may have two sites of action, the pituitary, and the sebaceous glands themselves. Ebling (1955) has pointed out that it is possible to demonstrate the inhibitory effect of oestrogen in hypophysectomised animals. On the other hand, a pituitary hormone, or hormones, is necessary for the stimulating effect of androgens to be manifested (Lasher, Lorinez and Rothman, 1955; Ebling, 1957). It is therefore possible that oestrogens as well as acting locally on the sebaceous glands also have an inhibitory action on the pituitary.

Acne Rosacea

This is a similar condition to acne vulgaris occurring mainly in women at the menopause. There is a marked vascular dilatation in the disorder which is not present in common acne. Oestrogens are of value in rosacea, but they are nothing like so effective as with acne vulgaris.

Physical Methods of Therapy

Under this heading can be included surgical procedures, irradiation with X-rays, Grenz rays and ultra-violet rays, diathermy, cautery, and the local application of carbon dioxide snow. All these methods have their place in dermatological treatment. With the exception of the three types of irradiation all these methods cause destruction of the tissues. Irradiation of the skin with X-rays or Grenz rays (these are X-rays produced at very low kilovoltage) are used in the treatment of several benign skin disorders such as eczema, neurodermatitis, and chronic irritating conditions. They are of great value, but their mode of action is not well understood. X-rays are of course of paramount importance in the treatment of skin malignancies. These include the malignant reticuloses as well as squamous cell and basal cell carcinomas.

The other physical methods will not be discussed here as they are of little interest to the present appraisal.

Ointment Bases

The problem of ointment bases is difficult and complex, and little is known of the relative therapeutic values of the different bases available.

The nature and penetration of therapeutic substances from their ointment bases was reviewed by Goldsmith (1954). He points out the confusion between penetration, absorption, and drug release; these terms have been used indiscriminately. He suggests that "penetration" should mean entry into the skin, and "absorption" should mean systemic distribution through the blood stream. Whereas drug release from the ointment base although essential to enable either penetration or absorption of the active agent does not imply that either have actually taken place.

Penetration of normal skin probably has no relation to the penetration of diseased skin. Moreover each type of skin disorder probably alters the penetration in a different manner either making a particular medicament from a particular vehicle more or less easily available to the epidermal cells.

It has already been mentioned that in the case of vitamin A the water soluble form appears to be more active than the oil soluble form. It may be in this case that there is better skin penetration, or it may be that the vitamin is more active in its water soluble state. Much more work is required on the penetration of the skin and to this end the use of radio active isotopes are proving of great value.

The problem of the preparation of ointments, creams and lotions, and their relative merits is discussed by Hadgraft in another paper.

Conclusion

During the past three or four decades there has been considerable progress in the treatment of skin disorders, but this has been due to a relatively small number of new drugs. These modern powerful agents exert their effects on the epidermis itself or upon the organisms attacking the skin. In the past for all, and at the present time for many skin diseases, a galaxy of therapeutic remedies are suggested. Many of these are either completely valueless or of doubtful use.

Without doubt the main advances have been due to the introduction of antibiotics and corticosteroids. This has enabled the competent dermatologist using these compounds in reasonable dosage and with skill, to control and often cure conditions that were not amenable to therapy in the past.

The problem of ointment bases and the penetration of the active substances into the skin is complex. One, however, should not use a base in which the active principle is tightly held, and therefore is not released from its vehicle.

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