CORTISONE AND ITS ANALOGUES IN DERMATOLOGY

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Dermatology is one of the branches of medicine in which the usefulness of cortisone and its analogues is most appreciated. These steroids are vitally important in the most serious skin diseases, such as pemphigus vulgaris and acute lupus erythematosus, and they are helpful in many others, such as exfoliative dermatitis and lichen planus. With systemic therapy it should be realized that large doses of steroids are needed in order to suppress inflammation in the skin and it is seldom worth while using less than 100 mg. of cortisone daily, and often very much more is required. The other great difficulty is the rebound which is likely to occur in many skin diseases some days after stopping steroid therapy, and sometimes the relapse results in a worse state of the disease than existed before treatment. In some cases large doses of cortisone have to be continued over many months with all the attendant dangers of serious complications such as intercurrent infection, peptic ulceration, psychotic illness, thrombosis, glycosuria, disturbance of fluid and electrolyte balance and osteoporosis.

On the other hand, hydrocortisone locally applied to the skin is free from the dangers of systemic effects if used in reasonable amounts, and it is used to suppress inflammation and itching in some common skin conditions which will be briefly discussed. The objections to this use of hydrocortisone are its high cost and the occasional aggravation of surface infection if it is wrongly used, as in impetigo; or that an important diagnosis should be overlooked while symptoms are being suppressed with topical hydrocortisone.

A brief account will be given of some important applications of systemic steroid therapy in dermatology, but the so-called connective tissue diseases (systemic lupus erythematosus, dermatomyositis, scleroderma and polyarteritis nodosa) will not be discussed. This will be followed by some notes on local application of hydrocortisone as an ointment or cream and by intradermal injection. Finally, the effects of these steroids on skin reactions will be discussed.

Pemphigus Vulgaris

It is in true pemphigus that we have the greatest need for long-term steroid therapy. In this disease of unknown cause, blisters appear widely over the skin surface and in the mouth, leading to large erosions. The blister forms within the epithelium, apparently by loss of cohesion between epithelial cells, and it is by study of the cytology and histology of the blisters that pemphigus may be separated from all the other bullous eruptions. Before cortisone became available, patients with pemphigus would usually die within about two years, and those last months of their lives were fraught with pain and misery. With steroid therapy, blistering can be suppressed and life prolonged and, indeed, there are sometimes remissions in which the treatment can be suspended for a year or more. Very large doses of steroids are often needed to bring the blistering under control, whereupon the dose is gradually reduced to that which will maintain a patient almost free of blistering. During the first two or three weeks of treatment, dosage of the order of 400 or 500 mg. cortisone daily must usually be given, and sometimes 1 or 2 g. daily are necessary to bring the disease under control. For maintenance, it may be necessary to continue with 150 or 200 mg. daily for many months, though gradual further reduction must be attempted from time to time. Naturally these patients run the gauntlet of complications from cortisone, but at present there is no other satisfactory approach to control of the blistering.

I prefer to start treatment with cortisone and perhaps change to prednisone when the maintenance dose has been established and when the patient is ready to leave hospital. In my experience, rapid build-up of prednisone to very large dosage at the start of treatment has led to peptic ulceration and even to perforation; of course this can happen with comparable dosage of cortisone, but possibly it is less likely. Measures to combat salt and water retention with these large doses of cortisone must be taken promptly and it is

FIG. 1.—Pemphigoid of seven months' duration in a woman of 58.

advisable to check the patient's weight daily. When diuretics are used to reduce oedema, close check must be kept on the electrolyte balance

Pemphigoid

The commonest of these major bullous diseases lacks a satisfactory label, and under the term 'pemphigoid' there may lurk more than one clinical entity; but at least we must keep true pemphigus and dermatitis herpetiformis separate from it. Pemphigoid is usually met with in old people, and while the ultimate prognosis is good, extensive blistering may endanger life in the aged or debilitated. The blisters are densely packed on the limbs (Fig. 1) and are often set in plaques of erythema which may extend onto the abdomen and chest, but the mucous membranes are seldom affected. Another distinction from pemphigus is the histopathology of the blister which in pemphigoid is subepidermal. Pemphigoid, unlike dermatitis herpetiformis, does not respond to empirical treatment with sulphapyridine or with diamino diphenyl sulphone, nor is it as chronic, nor as itchy.

Pemphigoid responds satisfactorily to treatment with cortisone or to parenteral ACTH, and the

FIG. 2.—The same after three weeks of treatment with prednisone (40 mg. daily).

dosage does not need to be as high as in pemphigus. While some patients relapse when the steroid therapy is stopped, there is, after some months, a fair chance of complete recovery, so that attempts should be made from time to time to withdraw cortisone. Fig. 2 shows the effect of giving prednisone mg., 40 daily, for three weeks.

Bullous Erythema Multiforme

Typical erythema multiforme is transient and not very distressing, and it is, therefore, not in need of steroid therapy. Severe erythema multiforme with predilection for mucous membranes (Stevens Johnson Syndrome) demands symptomatic relief, and cortisone is effective. After a few weeks the cortisone may be withdrawn without likelihood of relapse. Antibiotic cover for secondary infection may be needed.

Drug Eruptions

Many drug eruptions will subside quickly enough when the offending drug has been stopped. Occasionally the reaction is so severe as to endanger life or to cause great discomfort. For instance, sulphonamide sensitivity may have been induced

by previous skin applications, whereafter even a small amount by mouth may provoke a widespread and distressing eruption which would take six or seven weeks to disappear. We have recently treated two such cases with slow intravenous infusions of 20 mg. ACTH daily with rapid relief, and undoubtedly the period of illness was curtailed. In both cases it was possible to stop treatment after two weeks, without relapse.

Two kinds of drug reaction are liable to be severe and very prolonged. These are generalized exfoliative erythrodermia and lichenoid eruptions, and they may be produced by gold salts, arsenicals, mercurials and by mepacrine.

A useful degree of suppression can be effected by steroids, though for many months there is a tendency for relapse on withdrawal. Doses of the order of 100 to 200 mg. cortisone daily are likely to be needed.

Therapeutic Reactions

Rapid destruction of infecting organisms at the start of chemotherapy may result in toxic or allergic reactions on the part of the host. The Herxheimer reaction, which occurs when syphilis is treated, is an example of this kind. The reaction may be blanketed by giving cortisone concurrently with penicillin during the first few days of anti-syphilitic treatment. Again, during the treatment of lepromatous leprosy with sulphones, rather violent lepra reactions may occur with fever and erythema nodosum. It is sometimes justifiable to give cortisone to suppress this kind of reaction, in order to press on with effective doses of diamino-diphenyl sulphone.

Generalized Exfoliative Erythrodermia

Exfoliative dermatitis, once it has become universal, is liable to persist for many months or even years and carries with it, besides discomfort and disability, considerable danger from surface infection and protein depletion. Consideration of aetiology is important. Those cases that can be related to a specific *drug eruption* are usually much helped by steroids, and eventually there will be full recovery. The commonest type of case, however, is that which has started *with eczema*, and the eczema has generalized. These cases usually need steroid treatment under which control is adequate, but treatment usually needs to be carried over many months, and relapse on withdrawal of cortisone is the rule.

Psoriasis sometimes generalizes in this way. While universal psoriasis undoubtedly responds to large doses of steroids, there is a tendency for the erythrodermia to break through even though cortisone is continued, and for suppression cortisone dosage has to be very large, for example, 200 mg.

daily. On withdrawal of cortisone the psoriasis relapses fully, and usually one is left with the feeling that nothing has been gained or harm has been done. In my opinion the temptation to use steroids for psoriasis should be altogether resisted.

The rare type of generalized erythrodermia that sometimes accompanies a reticulosis or lymphoma may be bedevilled by severe itching, in which case it may be justifiable to use sufficient cortisone to suppress symptoms, while realizing that there will be no curative effect on the underlying disease.

Lichen Planus

Lichen planus usually resolves spontaneously within a year, and while the itching may be troublesome, the disease is usually not serious enough to justify systemic steroid therapy. Sometimes the disease drags on so long, and itching is so distressing that treatment with slow intravenous infusion of ACTH or with cortisone is given. The results are excellent. Relief from itching occurs within 48 hr. and resolution of the lichen papules is well under way within three weeks. Often, after treatment has stopped, relapse is only moderate or slight and there is no particular tendency to bad rebound as in eczema. Lichen planus may severely damage the scalp and, in cases where active damage is apparent, it may be reasonable to give steroids to prevent further extension of permanent bald patches. Of all the cutaneous diseases, lichen planus is the one upon which cortisone has the most distinct effect in the removal of pathological infiltrate, besides suppressing symptoms.

Atopic Eczema

While the clinical manifestations of the eczema-asthma syndrome can be effectively suppressed by cortisone or ACTH, it is seldom justifiable to use this kind of treatment for what is a labile constitutional disease. All too often a casual term of treatment is undertaken to get the patient over a difficult episode, but withdrawal often results in severe relapse so that it becomes difficult to stop the cortisone.

Occasionally the eczema is so severe that life is almost insupportable outside of hospital, and then one has to decide whether to embark upon a course of steroid therapy with no likelihood of being able to discontinue it. In most of these patients it requires at least 100 mg. of cortisone daily to suppress the eczema or prurigo, though there are fluctuations in the requirement. Children require almost the full adult dose, and only the most severe and intractable childhood eczema or Besnier's prurigo should be treated with cortisone.

Eczema

In the general run of eczemas, whether constitu-

tional, nummular, seborrheic, contact or varicose, steroid therapy should not be undertaken without very careful consideration. Only if the eczema is very widespread and unresponsive to conventional therapy and to hospitalization should steroids be used. All too often on stopping the treatment the relapse is severe, and the ultimate state of the patient may be worse than the first.

Valuable information has been gained by the study of the effects of short courses of steroid therapy on severe eczema, and this experience has been recorded by Dowling (1953) and is included in the first report of the Medical Research Council Panel on the dermatological applications of ACTH and cortisone (1954).

Alopecia Areata

In cases of extensive or long-standing alopecia areata, Dillaha and Rothman (1952) showed that large doses of cortisone would produce growth of hair. As soon as the cortisone was stopped the hair fell out again and there was no long-term advantage. This effect of cortisone remains as a point of interest in a totally obscure disease, but it is of no practical therapeutic value.

TOPICAL APPLICATION OF HYDROCORTISONE

Hydrocortisone acetate or free alcohol in strength of $\frac{1}{2}$ to 1 per cent. is effective in an ointment base, cream or lotion. A small amount gently rubbed into the skin for about a minute twice daily is usually sufficient. Suppression of the exudative phase of inflammation is seen, as for example, in eczema, and itching is reduced. Treatment with topical hydrocortisone is only suitable for eczema of quite limited extent, as the cost of treating large areas is prohibitive. Hydrocortisone is particularly valuable in relieving anogenital pruritus. Response is good in seborrheic eczema, atopic eczema, contact eczema and discoid eczema. In lichenification there may be some relief of itching, but resolution is unusual. On the other hand, psoriasis is quite unresponsive to these applications (except for genital lesions) and chronic discoid lupus erythematosus, lichen planus and many other dermatoses are unaffected by local hydrocortisone. The ease of application and cleanliness of these preparations has added greatly to their popularity, particularly for those parts of the body where they are most effective (the face and the flexures and genital region). Sometimes through faulty diagnosis an infective condition such as impetigo has been treated with hydrocortisone and it may be aggravated thereby, but, on the whole, exacerbation of local infection has been less than one might have expected. It is clear that most of these conditions are relieved by hydro-

cortisone rather than cured, and it is usually necessary to proceed to more active treatment once the inflammation has been brought under control. A summary of the experience of the staff of St John's Hospital for Diseases of the Skin with topical hydrocortisone has recently been published (1957).

Injection of Hydrocortisone

Intradermal injection of hydrocortisone has so far proved to be of little importance in dermatology, though there are a few interesting applications. In alopecia areata for instance, regrowth of a tuft of hair at the site of injection of hydrocortisone is academically interesting rather than cosmetically satisfactory. Small plaques or nodules of lichen simplex or lichen planus may respond to injection and individual nodules of sarcoid may be influenced in this way. The results from injecting hydrocortisone into keloids have not been very encouraging, but undoubtedly some keloids have been reduced by this method and it is a form of treatment which does not seem to do harm. The usual technique has been to inject 10 mg. of hydrocortisone, suspended in the usual diluting fluid, together with hyaluronidase and novocaine. It is difficult to get a good dispersion of hydrocortisone crystals, and it is not unusual for the steroid to remain visible in the skin for a few months. The crystals may provoke a foreign body kind of cutaneous reaction, together with a depressed 'scar' which is, however, not permanent. This reaction (investigated in detail by Goldman *et al.* 1953) has discouraged the use of hydrocortisone injections about the face.

The Effect of Steroids on Skin Reactions

Objective tests for the local action of hydrocortisone in the skin are less easy to arrange than might be imagined, and most of our information comes from treating areas of eczema. Effective penetration of the hydrocortisone preparation into the skin is important and may be the main factor in regional differences of response. For example, eczema of the face is more responsive than eczema on the extremity, and presumably the hydrocortisone penetrates better into areas with thin epithelium and numerous pilosebaceous units.

It is worth considering the known reactions of the skin and the effects of steroids upon them.

Immediate Wealing Response

The urticarial weal may be produced by pharmacological agents such as histamine, or indirectly by allergic reactions to foreign proteins, introduced into the dermis by prick, scratch or injection. The effect of local hydrocortisone or of systemic cortisone or ACTH on the immediate urticarial skin

response is minimal. This may be correlated with the fact that the steroids exert little or no beneficial effect in clinical urticaria.

Sunburn

If hydrocortisone is applied to the skin immediately after exposure to ultra-violet light or sunlight, the subsequent erythema is no different from controls. Both the urticarial response and erythema of ultra-violet light are not obviously reduced if the test subject has been given prior cortisone or ACTH, but with careful measurements Holti (1956) has shown slight reduction of these reactions experimentally. The effect of prior cortisone and locally applied hydrocortisone in reducing subsequent X-ray erythema is worthy of further study (Scott and Kalz, 1956).

Delayed Allergic Responses in the Skin

The Mantoux reaction may be altered when the patient is receiving cortisone, or if cortisone acetate is injected with the tuberculin. While the reactions in tuberculin-sensitive patients are reduced, Citron and Scadding (1957) have shown increased reactions in some patients with sarcoidosis. Apparently suppression by cortisone of the vascular component of tuberculin allergy may enhance the reaction by allowing the tuberculin to remain at the site of injection.

Eczematous reactions to allergens applied as patch tests do not lend themselves well to combination with local applications of hydrocortisone and usually no effect is demonstrable. Haxthausen (1956), choosing nickel-sensitive patients, improved the technique by introducing the allergen into the skin by iontophoresis. It was then possible to show suppression of the eczematous response in some cases when fluorohydrocortisone was applied. Again, some reduction of eczematous response to allergens applied as patch tests can be demonstrated when the patient is under the influence of systemic steroid therapy, but the results of such tests are often equivocal.

Surface Damage

The effect of hydrocortisone on experimental burns and on chemical damage has been difficult to assess, owing to difficulty in controlling the degree of damage, and because of variation of effect depending on the time of applications of the hydrocortisone relative to the damage. Controlled injury may be done to the skin surface by removing its keratin by repeatedly stripping an area with cellophane tape. After 20 or 30 strippings the area becomes red and shiny, and the erythema persists for several days and is confined to the denuded area. Hydrocortisone ointment applied to part of such a uniformly-stripped area causes

reduction or suppression of the erythema. It takes about 4 hr. to effect this (Wells, 1957) and the hydrocortisone exerts its effect for several hours, after which the erythema returns. Biopsies showed suppression of the perivascular lymphocytic infiltrate in the upper dermis in the hydrocortisone treated area, as compared with the control area.

Thus, perhaps the most clearly demonstrable effect of locally-applied hydrocortisone in damaged skin is its suppression of vasodilatation in the subpapillary vascular plexus of the skin, together with reduction of small round cell perivascular infiltrate. This effect is reversible, if hydrocortisone applications are stopped. There appears to be slight delay in reconstitution of the skin surface under the influence of hydrocortisone.

Healing

Under the influence of systemic steroids, certain experimental animals and man show a delay in the vascular and fibroblastic components of cutaneous repair. Reference to this aspect of connective tissue repair will be found in Rothman (1954). Delay in wound-healing may add to the post-operative difficulties of cortisone-treated patients who have to undergo surgery.

Summary

1. An outline is given of the use of systemic steroids in the bullous diseases, drug eruptions, exfoliative erythrodermias, lichen planus and the eczemas.
2. The scope of topical therapy with hydrocortisone is reviewed, and mention is made of intradermal hydrocortisone injection.
3. The effect of cortisone and hydrocortisone on skin reactions is discussed.

Acknowledgment

I am indebted to the Institute of Dermatology for the photographs. (Photographer, R. J. Lunnon, Esq.)

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