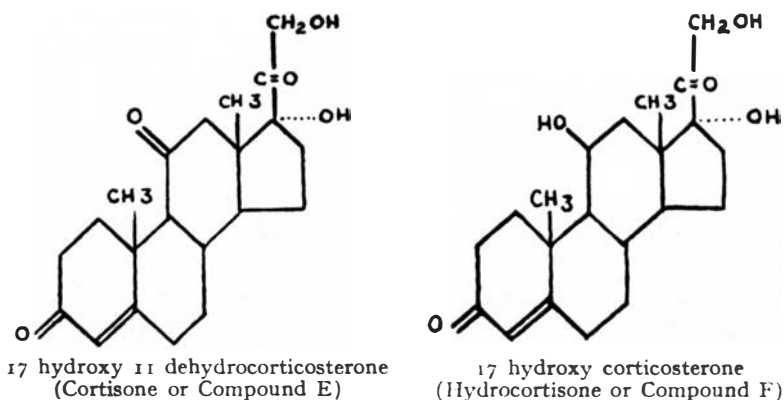


THE PLACE OF CORTISONE AND CORTICOTROPHIN IN THE TREATMENT OF CERTAIN ACUTE PHASES OF LEPROSY

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In 1936 a steroid was isolated from the adrenal cortex¹ which became known as compound E, and in 1949 its name was changed to cortisone. It is converted in the body into a closely allied substance, hydrocortisone, which is being continuously produced by the normal adrenal cortex as a result of stimulation exerted by the anterior pituitary gland via corticotrophin (ACTH). Although the average amount of hydrocortisone produced daily is 25-40 mg., larger supplies are required by the body when subjected to strain and stress such as trauma or major surgery. Both cortisone and hydrocortisone can be synthesized for therapeutic use, the former as the acetate and the latter either as the free alcohol or as the acetate. It is generally agreed that cortisone is preferable for systematic use and hydrocortisone for local application or for injection into joints.²



Corticotrophin (ACTH) is the adrenocorticotrophic hormone of the anterior pituitary gland, and its function is to stimulate production of hydrocortisone by the adrenal cortex. It is obtained for therapeutic use from the anterior pituitary glands of mammals, and has to be administered by injection.

Among the disorders in which cortisone and ACTH have a beneficial effect are certain allergic states, but their exact mode of action in suppressing or counteracting tissue reaction is as yet unknown. The physician who undertakes to treat leprosy must be prepared to treat a number of allergic complications as well, and it is important for him to know which of these will respond to

steroid therapy in order that he may relieve pain and prevent serious sequelae. These are: (1) Severe erythema nodosum leprosum; (2) Allergic reactions in the eyes; (3) Severe or persisting neuritis; (4) Acute sulphone sensitization.

Erythema Nodosum Leprosum. This is an allergic phenomenon which may occur in lepromatous leprosy (or in dimorphous leprosy which is passing into the lepromatous type) during the stage of the disease when the bacilli are becoming granular; it is not an exacerbation of the underlying disease. Thus it need not be considered an unfavourable development and will not require special treatment so long as it takes a mild form. If severe, however, and associated with complications such as high fever, prostration, mental depression, neuritis, iridocyclitis, lymphadenitis, orchitis, arthralgia and bone pains, steps must be taken to bring it under control. Some cases will respond to analgesics, antimony injections and immediate stoppage of sulphone therapy, but all will respond rapidly to cortisone or ACTH. Cortisone is put up in tablets of 5 and 25 mg., and dosage is 100 mg., on the first day (divided into three 8-hourly doses) reducing each day so long as the reaction is being controlled; e.g. 100 mg.—75 mg.—50 mg.—25 mg.—12.5 mg. Such a 5-day course will often prove adequate but can be repeated as required. Sulphone treatment must be continued throughout, but it may prove desirable to make a reduction in dosage. One of us (R.G.C.) has had success with the less orthodox method of commencing with small doses of cortisone and increasing daily until the reaction is controlled. If ACTH is used the daily dosage will be 30-40% that of cortisone, and we would recommend a long-acting preparation which need not be injected more often than once daily (ACTH gel), the scheme for a 5-day course being 40 mg.—30 mg.—20 mg.—10 mg. 5 mg. Should the reaction not be controlled by a short course of cortisone or ACTH, then treatment must be continued for as long as required, using the smallest effective daily dosage and persevering with sulphone. The fact that sulphone treatment need not be stopped is one of the great advantages accruing from the use of these hormones, and our experience, together with a study of the literature, satisfies us that early fears of aggravating the underlying leprosy have proved unfounded. Many clinicians have reported successful results with short courses of cortisone or ACTH,³⁻¹⁷ and some have used prolonged courses without ill effect.^{18, 19} We have given cortisone to two patients for periods of 11 and 15 months respectively, with no adverse effect, and one

of Sir George McRobert's patients required three courses each of 4½ months. In all but short courses it is advisable to give 3-5 grammes of potassium chloride by mouth daily, to restrict salt intake if oedema develops and to treat with mercurial diuretics those in whom oedema persists. Withdrawal symptoms may occur if large doses of cortisone are stopped abruptly; these include headache, anorexia, nausea, vomiting, restlessness and joint pains, but will subside in 2-5 days.²⁰ Such symptoms are due to temporary cortical atrophy, and in order to prevent them it is necessary to make a gradual and progressive reduction in dosage towards the end of the course of treatment in order to allow time for the patient's adrenal cortex to recover. Should a situation arise in which cortisone had to be stopped abruptly it would be advisable to give a few injections of ACTH to stimulate endogenous cortisone production. If major surgery has to be carried out while a patient is having prolonged treatment it is important to give additional cortisone to cover the immediate post-operative period, for the patient's adrenals will not be able to produce the extra hydrocortisone which is normally secreted at this time and dangerous adrenal insufficiency may arise. The patient's requirements will be covered by 300 mg. of cortisone on the day of operation and on the first postoperative day, dosage being gradually reduced thereafter to the preoperative level. On the day of operation it is best administered as a continuous intravenous drip of 100 mg. in 1500 ml. of 5 per cent dextrose in water every eight hours. If ACTH gel is given over a long period it will be found possible to reduce the frequency of injections from once daily to once every other day and even to twice a week, and, unlike cortisone, it will not produce cortical atrophy. As it depends for its effect on the functioning capacity of the patient's adrenal cortex a poor response is likely if the latter be damaged or diseased, and this is important in lepromatous leprosy for the adrenal glands may undergo amyloid change²¹ with subsequent inability to respond fully to stimulation by ACTH.²² In addition, it tends to cause greater salt and water retention than cortisone, has more marked androgenic effects, and in rare instances may give rise to serious sensitivity reactions.²³

There is no evidence of acquired drug resistance or of addiction to cortisone or ACTH,²⁴ and contra-indication to their use are few. Active tuberculosis is one, but we know of a patient with pulmonary tuberculosis and lepromatous leprosy in whom the lung lesion healed radiologically during a 6-month course of cortisone which was given to control severe erythema nodosum

leprosum. The patient received streptomycin and isoniazid throughout this period. Another contraindication is said to be present or past mental illness, but doubt has been cast on this view.²⁵ Caution should be observed in severe hypertension and in congestive cardiac failure (sodium and water retention), in peptic ulceration and diverticulitis (silent perforation), in a patient who gives a history of previous thrombo-embolic episodes (decreased clotting time), in diabetes (increased glycosuria) and in severe osteoporosis (increased protein catabolism). In osteoporosis it would be wise to prescribe testosterone and a high-protein diet.

Recently two new synthetic steroids have been marketed, namely, prednisone and prednisolone, which are analogues of cortisone and hydrocortisone respectively and are 3-5 times more potent. They are put up by various manufacturing chemists in 5 mg. tablets, and the maximum daily dose should not exceed 40 mg. They have the advantage of not causing sodium retention or potassium depletion, but other side-effects are not lessened and gastric disturbance is more likely to occur. Dosage during a 5-day course would be: 20 mg.—15 mg.—10 mg.—5 mg.—2.5 mg.

Iritis, Iridocyclitis and Scleritis. Any or all of these allergic reactions may occur in lepromatous leprosy either during an erythema nodosum reaction or independently, and require energetic treatment with eye-drops of 1% hydrocortisone acetate or cortisone acetate. The drops should be instilled hourly in the acute stage, gradually decreasing to a maintenance dose of thrice daily, and a 2½% ointment is useful for application at night. Atropine drops may be required in addition. Systemic treatment with cortisone or ACTH will rarely be required but should be instituted if the drops fail to control the attack within 24-48 hours.

Severe or Persisting Neuritis. Unlike eye reactions, neuritis is not confined to lepromatous leprosy for it is not uncommon in dimorphous and tuberculoid leprosy under sulphone treatment. In the lepromatous type it is usually associated with erythema nodosum reaction but may occur independently. Oedema is the factor responsible for nerve swelling and pain, and, if unrelieved, will cause ischaemia and other pressure effects owing to the limited expansile capacity of the nerve sheath. This situation calls for speedy action, particularly when the common peroneal or ulnar nerves are involved, in order to prevent complications such as dropped foot or claw hand. The first line of action is to stop sulphone and to give an intraneural injection of 1-2 ml. of

equal parts of 2% procaine and a suspension of hydrocortisone 25 mg. per ml. Such injections should be repeated as often as required for they combine the analgesic action of procaine with hydrocortisone's function of relieving oedema and inhibiting fibrosis. Garrett²⁶ has advocated a combination of hyalase with procaine and injects 5-6 ml. at a sitting, and on the strength of his results it would be worthwhile assessing the value of hyalase combined with hydrocortisone and procaine, but it is possible that the spreading action of hyalase will be nullified by hydrocortisone's anti-hyaluronidase effect. Treatment by intraneural injections may in some cases require to be supplemented by systematic cortisone or ACTH, but surgical treatment should be instituted without delay if progress is not satisfactory and the function of a vital nerve is threatened. Nerve swelling in tuberculoid leprosy may be due to caseation, and, if this is suspected, surgical treatment should be carried out and hormone treatment avoided.

Acute Sulphone Sensitization. Cortisone and ACTH have a very important place in the treatment of severe sulphone sensitization and have radically improved the prognosis in this dangerous and even fatal complication. Dosage will depend on response, but the following daily dosage scheme is suggested as a basis: **cortisone**, 200 mg.—175 mg.—150 mg.—125 mg.—100 mg.—75 mg.—50 mg.—25 mg.—12.5 mg.; **prednisole or prednisolone**, 40 mg.—35 mg.—30 mg.—25 mg.—20 mg.—15 mg.—10 mg.—5 mg.—2.5 mg.; **ACTH**, 80 mg.—70 mg.—60 mg.—50 mg.—40 mg.—30 mg.—20 mg.—5 mg.

In mild cases, where systematic treatment is not required, dermatitis and associated pruritus can be treated by an ointment containing hydrocortisone or prednisolone at strengths of 1 or 2½ per cent.

Summary and Conclusions

We have given a short account of cortisone and corticotrophin (ACTH), together with their side effects, and have described their important role in the treatment of certain allergic complications of leprosy. Severe erythema nodosum responds dramatically to these hormones, and one or two short courses are often sufficient to bring the reaction under control. Prolonged courses may be necessary in some cases, even up to twelve months or more, and have the great advantage of enabling sulphone treatment to be continued without interruption. We are satisfied that patients who have been so treated have not suffered any aggravation of their underlying

leprosy. Details of management are given and mention is made of the new synthetic steroids prednisone and prednisolone. An account has also been given of the importance of steroid therapy in the management of acute ophthalmic and neural reactions, and, lastly, of severe sulphone sensitization.

It is concluded, therefore, that there is a definite place for the use of cortisone and corticotrophin in certain acute complications of leprosy and of sulphone therapy, not only for the relief of distressing symptoms but also for the prevention of lasting disability.

Acknowledgements

Grateful thanks are due to Sir John Taylor of the Medical Research Council for supplies of cortisone and ACTH for use at the Jordan Hospital, and to Dr. Gladys L. Hobby of Messrs. Chas. Pfizer & Co. Inc. for supplies of "deltacortril". We would also like to thank Sir George McRobert for permission to include details of one of his patients.

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