Adrenocortical Steroids, Their Derivatives, and Corticotropin

Pharmacologic Aspects, Uses, and Contraindications in Dermatology

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Adrenocortical hormones and corticotropin (ACTH) may yield rapid and beneficial results in specific skin disorders. However, the diversity of hormonal and metabolic effects produced by these agents imposes certain limitations to their use. Consequently, the beneficial results which may accrue must be weighed against the possible ill effects of hormone overdosage. The over-all effects of the hormone must be considered before therapy is undertaken for the purpose of producing a specific action in a specific tissue or organ system.

The purpose of this paper is to review some of the basic pharmacology of the adrenocortical hormones, their new derivatives, and corticotropin, with particular emphasis on potential side-effects and employment in diseases of the skin.

PHARMACOLOGY

The adrenocortical hormones are steroids. Over a period of 20 years, 29 compounds have been isolated, culminating in large-scale synthesis for practical use.

In man the adrenal secretory products are mainly hydrocortisone (Compound F) and corticosterone (Compound B); in addition, other steroids have been isolated from adrenal extracts in smaller amounts; these consist of cortisone (Compound E), desoxycorticosterone (DOC), 11-dehydrocorticosterone (Compound A), 11-desoxy-17-hydroxycorticosterone (Compound S), androgens, estrone, and progestrone.* Recently a new adrenal steroid has been isolated from adrenal extracts and synthesized. This new steroid is of significant importance because of its tremendous potency in the regulation of electrolyte metabolism. It is aldosterone (electrocortin), which, in all likelihood, largely accounts for the marked potency of the amorphous fraction of adrenal extracts in maintaining life of adrenalectomized animals.[5] Aldosterone has less powerful effects on organic metabolism.[6] It may be of importance in edematous states.† It is potentially of considerable significance in states of altered adrenal function; Conn[9] recently described a new syndrome associated with an adrenal tumor apparently the result of aldosterone hypersecretion.

Recent developments in steroid chemistry may herald a new era in steroid therapy. Derivatives produced are highly active and exhibit specific proportionate changes in metabolic actions, suggesting that in the future much more selectivity of therapeutic agents for specific patients will be feasible; e. g., fludrocortisone (9-α-fluorohydrocor-

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* References 1 to 4.

† References 7 and 8.

tisone) is long-acting, combines many potent hydrocortisone and desoxycorticosterone properties, and is active both orally and locally.‡ Prednisone (Δ-1-dehydrocortisone) is four to five times as potent as cortisone (mg/mg.) without electrolyte changes. (11). Hydrocortisone is qualitatively comparable to cortisone, but quantitatively its effects are more intense (the activity being 1.3 to 1).§ Table 1 presents a comparison of the metabolic effects of the hormones listed.

Electrolyte metabolism revolves around the increased excretion of potassium and the retention of sodium. Therefore, varying degrees of hypokalemia, hypochloremia, and metabolic alkalosis can result during adrenocortical therapy.[14]

The adrenocortical hormones influence water metabolism by virtue of their effect on electrolytes and also by their diuretic or antidiuretic effects.[15]

Carbohydrate metabolism is also influenced by these hormones. Gluconeogenesis is increased.[16] The conversion of proteins and other noncarbohydrates to glucose is thereby increased. In diabetics moderate aggravation of their diabetes can occur during the administration of these hormones. The functional reserve of the normal pancreas is sufficient to compensate for this diabetogenic action.[17]

Inhibition of anabolism and increased protein catabolism are the resultant effects of these hormones on protein metabolism.[18] Therefore, varying degrees of a negative nitrogen balance can occur.

The interpretation of the results of the adrenocortical hormones on lipid metabolism is difficult, for studies in this field have been few.[19]

The influence of these hormones on the enzyme systems has been widely investigated. There has been demonstrated both in animals and in man an inhibitory effect of cortisone on the activity of hyaluronidase. Hyaluronidase-inhibitor levels were increased under corticotropin therapy.‖

A deficiency or excess of adrenocortical hormones modifies the capacity of the organism to respond to stress. A deficiency of these hormones, as in Addison's disease, is characterized by the organism's vulnerability to exogenous stress.[14]

The adrenocortical hormones can produce androgenic effects such as acne or hirsutism, and in females minor menstrual irregularities (amenorrhea) can occur.[14] The degree of androgenic effects produced is dependent upon the hormone secreted.

Administration of adrenocortical hormones leads to suppression of endogenous adrenocortical secretion, with atrophy of the adrenal glands and suppression of the anterior pituitary. Therefore, under the administration of these hormones, there is an inhibition of both the anterior pituitary and the adrenal glands.¶

Acute adrenal insufficiency may occur if adrenocortical therapy is suddenly stopped. Clinically this is manifested by varying degrees of weakness, fatigability, hypotension, and collapse. Fraser [22] has reported irreversible shock with resultant death under these circumstances.

TABLE 1.—*Comparison of Hormone Effectiveness on a Milligram per Milligram Basis*

	Hormone Effectiveness				
Metabolic Effect	Corticotropin	Fludrocortisone	Hydrocortisone	Cortisone	Prednisone
Electrolyte metabolism	++	++++	+	+	±
Organic metabolism: carbohydrate, protein, & fat	++	++++	++	++	+++
Anti-inflammatory	++	++++	++	++	+++
Cutaneous pigmentation	++++	–	–	–	–
Stress	++	+++	++	++	++
Androgenic	+++	±	++	++	+

‡ References 6 and 10.

§ References 12 and 13.

‖ References 20 and 21.

¶ References 14 and 19.

The prolonged use of large doses of adrenocortical hormones can result in changes in the skin comparable to those seen in Cushing's syndrome—moon facies, fat pad deposition, thin skin, and violaceous striae.[19]

Histopathological studies on integument treated by both local and systemic cortisone have been carried out by numerous investigators.# Large doses in animals produced [23] (1) reduction in the number of epithelial cells resulting in a thinning of the epidermis; (2) inhibition of hair growth, and (3) atrophy of the sebaceous glands. In the dermis, there was a decrease in thickness due to condensation of the collagen fibers into a compact, homogeneous mass. This may be described as a "melting down" process of the collagen. There was an absolute reduction in the number of fibroblasts with nuclear changes (pyknosis and shrinkage). The elastic fibers were apparently not affected. Regarding the atrophy of the sebaceous glands, Brunsting [26] pointed out that seborrhea is not associated with the acne produced under cortisone administration. Similar changes occur locally with topical and systemic therapy.[25]

A careful investigation on certain diseases of the skin was performed by Sauer and his associates [27] after corticotropin administration. Their results can be summarized as follows: Skin temperature, taken at room temperature, showed a distinct tendency toward elevation; absorption time of intracutaneous saline was shortened; sweating was augmented both during and after corticotropin adminstration; sebum and other ether-soluble materials delivered at the skin surface were diminished. The results were interpreted as evidence of an accelerated peripheral circulation.

Osteoporosis may result when administration of adrenocortical hormones is long continued,[28] and one must be aware of this important physiologic effect. Cortisone interferes with protein synthesis, thereby decreasing formation of osteoid matrix. Diminished calcium deposition occurs and probably accounts for increased calcium and phosphorus loss.*

During adrenocortical therapy there is increased fragility of blood vessels and an increased tendency toward thrombotic phenomena.[19]

The anti-inflammatory effects of the adrenocortical hormones are not limited to the local processes of inflammation. Systemic symptoms may be masked. Fever and signs of toxemia can be suppressed, thereby making the dissemination of infection a dangerous sequela. Perforation of a viscus and resultant peritonitis can occur without the usual symptoms. The exacerbation of tuberculosis during cortisone administration deserves special emphasis, which will be discussed subsequently.

Adrenocortical therapy suppresses both local and systemic allergic responses of the organism. The mechanism involved is similar to the anti-inflammatory response of connective tissue under cortisone administration.†

There is a pituitary-adrenal relationship. Corticotropin produces a specific stimulus on the adrenal glands, causing a secretion of hydrocortisone, aldosterone, corticosterone, and other adrenal hormones. Corticotropin is the only known substance capable of producing this specific adrenal response. In the absence of corticotropin there is an atrophy of the adrenal glands. There is an autonomous balance whereby an excessive production of adrenocortical hormones can lead to a suppression (or inhibition) of the adrenocorticotropic hormone (ACTH). This suppression is significant, as an iatrogenic adrenal insufficiency may occur upon the sudden withdrawal of corticotropin or under severe stress.

Corticotropin is a polypeptide which is prepared by extraction from the pituitary tissue of animals. The pituitaries of hogs are the chief source of the commercial preparation, although pituitary extracts from beef, sheep, and whales are available. The

References 23 to 25.

* References 29 and 30.

† References 31 and 32.

source of the pituitary tissue that is used is important, for allergies to the particular animal tissue that is used can occur and cause a severe hypersensitivity reaction in the patient.[33] This reaction to corticotropin may be of a species-specific type; it is a true allergy to the animal pituitary tissue used for the corticotropin preparation.

The physiologic actions of corticotropin are best described by its effect on the adrenal cortex and on the body as a whole. Corticotropin causes a stimulation for the secretion of hormones of the adrenal cortex, and their physiologic actions have been described. The effect on the organism as a whole again depends on the amount of stimulation of the adrenal cortex and the organism's response to the adrenal hormones. Increased pigmentation can occur with corticotropin therapy. Question arises as to whether the stimulus for pigmentation is due to the melanin-stimulating hormone (MSH) found in the corticotropin preparations or whether corticotropin itself can cause pigmentation. Even highly purified preparations of corticotropin have produced increased pigmentation.[14]

The action of corticotropin is dependent upon an intact adrenal gland. Its use causes both a hypertrophy of the adrenal cortex and an inhibition of the anterior pituitary.

ROUTES OF ADMINISTRATION

Table 2 presents the various routes of administration, the responses obtained by the routes used, and the hormones that can be used via the particular route.

Orally there is an initial high blood level with rapid response (important when quick effect is desired) but the duration of action is short—6 to 10 hours; consequently, divided doses are necessary in order to maintain a sustained effect. Fludrocortisone has a prolonged effect, while cortisone, hydrocortisone, and prednisone are of shorter duration.

Oral doses of cortisone are divided so as to maintain as constant a blood level as possible. The methods for determining the dose for effective therapy are two. One can start with as low a dose as possible and work up to the therapeutic dose or start with a high dose for immediate effect and gradually taper down to the lowest dose which will give a therapeutic effect.

TABLE 2.—*Routes of Administration and the Expected Response with the Hormones Employed*

Routes of Administration	Pharmacologic Basis	Hormone Employed
Oral	Initial high blood level	Hydrocortisone
	Rapid response	Cortisone
	Duration of action is short (6 to 10 hr.)	Fludrocortisone
		Prednisone
Parenteral		
	Almost no initial blood level rise	Cortisone
Intramuscular	Slow response	Corticotropin
	Prolonged action (up to 24 hr.)	
Intravenous	Rapid response	Corticotropin
	Short duration of action	Hydrocortisone
Local		
Intraocular	.....	.....
		Hydrocortisone
Intra-articular	Little or no systemic effects	Prednisone (?)
Percutaneous	Potential systemic effects	Fludrocortisone

The intramuscular route gives almost no initial rise in blood level and very slow response, but the duration of effect is prolonged up to 24 hours. A single dose (120 mg.) of cortisone given intramuscularly has an effect for about 24 hours. Hydrocortisone acetate should not be used via the intramuscular route, for it is absorbed irregularly and produces too slowly a noticeable metabolic or therapeutic effect.

Corticotropin may be given by either the intravenous or the intramuscular route. The intravenous route is a highly effective and economical method of producing an adrenocortical response.[34] Renold and associates [35]

RESPONSE OF 17-KETOSTEROID EXCRETION TO INCREASING DOSES OF ACTH INFUSED INTRAVENOUSLY OVER A PERIOD OF 8 HOURS

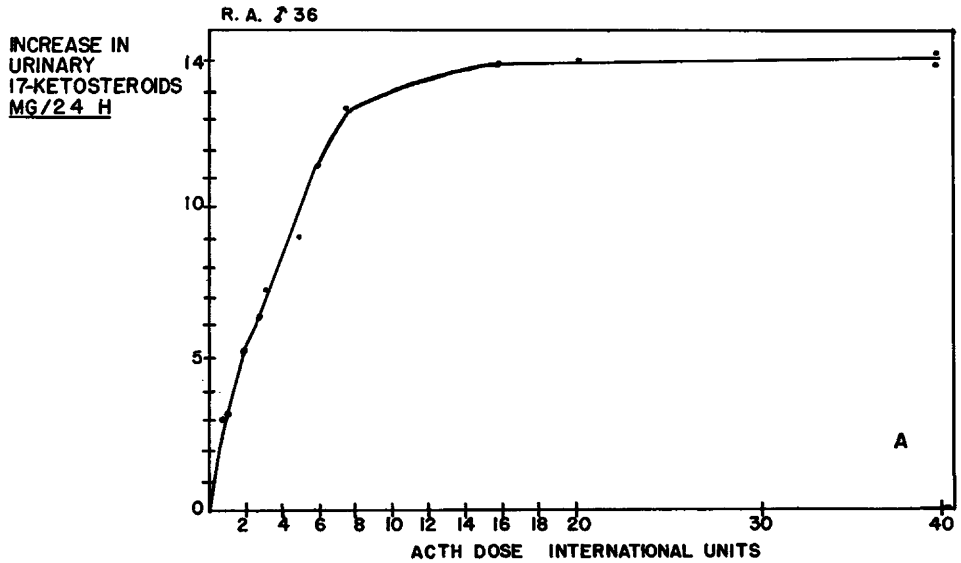

Chart 1.—Dose response curve. (Reproduced with permission from Renold, Jenkins, Forsham, and Thorn: The Use of Intravenous ACTH: A Study in Quantitative Adrenocortical Stimulation, *Journal of Clinical Endocrinology and Metabolism,* Charles C Thomas, Publisher, Springfield, Ill.)

INCREASE IN ADRENOCORTICAL RESPONSE WITH LENGTHENING PERIODS OF INFUSION OF A STANDARD DOSE (20 MG LA-I-A) OF ACTH

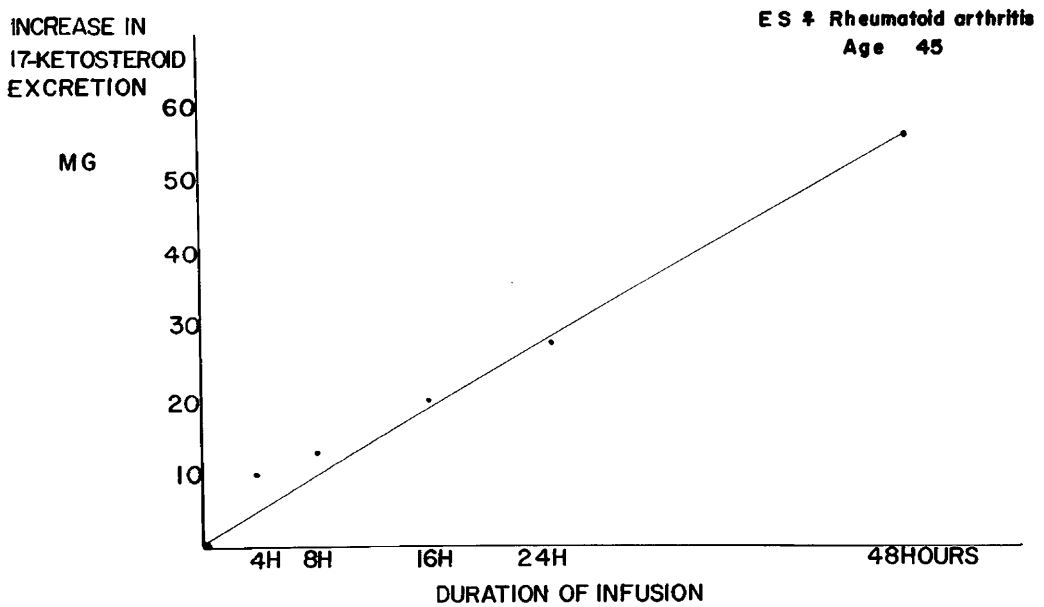

Chart 2.—Time response graph. (Reproduced with permission from Renold, Jenkins, Forsham, and Thorn: The Use of Intravenous ACTH: A Study in Quantitative Adrenocortical Stimulation, *Journal of Clinical Endocrinology and Metabolism,* Charles C Thomas, Publisher, Springfield, Ill.)

found that as long as the duration of infusion was constant the intensity of response produced increased with the amount of corticotropin used, up to a "critical dosage," over and above which little or no additional response was elicited. In subjects with normal adrenocortical function, this critical dosage level was approximately 20 units of corticotropin infused over an eight-hour period (Chart 1).

With a constant dose of 20 units, it was demonstrated that an extension of the period of infusion from 30 seconds to 48 hours resulted in a linear increase in the intensity of adrenocortical activation. The intensity of the stimulus varies directly with the duration of stimulation (Chart 2).[35]

Therefore, the total output of adrenocortical steroids is directly proportional to the duration of the intravenous infusion. However, small doses of corticotropin (10-20 units) given in an intravenous infusion over periods of 18 to 20 hours can yield a maximal response with a minimal dose.

The use of an intramuscular repository corticotropin in the form of corticotropin gel offers the advantage of prolonged stimulation with one injection. Thereby, the patient can be ambulatory and yet receive a constant adrenal stimulation with maximal response. The intramuscular route has its advantage in rendering the patient ambulatory, as compared with the intravenous route, which necessitates prolonged bed rest. The newer gel preparations contain a highly purified corticotropin, so that little intramuscular inactivation occurs. Therefore, fewer U. S. P. units are needed.

Local application refers to percutaneous, intraocular, and intra-articular usage. Locally, hydrocortisone is much more effective than cortisone. Fludrocortisone is quite effective locally and in smaller concentrations by virtue of its high potency. To date no information is available regarding local application of prednisone. Corticotropin is ineffective via local application. These hormones have very good anti-inflammatory and antipruritic properties. They offer the dermatologist a valuable medicament for the treatment of specific skin disorders. Advantage of this route lies in the fact that there is a lack of systemic and overdosage side-effects from hydrocortisone.[36] However, with fludrocortisone, because of its tremendous potency, significant systemic effects may occur from the percutaneous absorption of this hormone. The following cases illustrate this important point.

CLINICAL STUDIES PERFORMED ON THE PERCUTANEOUS ABSORPTION OF FLUDROCORTISONE

Procedure.—A 0.25% concentration of fludrocortisone was incorporated in an oxycholesterol-petrolatum ointment (Aquaphor) base. This concentration was selected, for it is a concentration available for commercial use. Fifteen grams of the ointment was rubbed into the skin every 24 hours in four divided doses. A total of 37.5 mg. of fludrocortisone was therefore rubbed into the skin every 24 hours. Areas of skin used were the extensor surfaces of both forearms and the dorsal surfaces of the hands. The type of skin in this area had an inflammatory (erythematous) appearance, but was intact, with no broken surfaces. Patients were instructed to rub the ointment into the skin for approximately five minutes under supervision of a nurse. Patients were at rest, but not complete bed rest, in the hospital. Regular type diet was used. Daily eosinophile counts and daily weights were obtained at the same time each day. Ointment therapy was begun after controls on the patients were first obtained.

REPORT OF CASES

CASE 1.—A 56-year-old white woman was admitted to the Colorado General Hospital because of an acute flare-up of a chronic generalized neurodermatitis. Involvement was primarily limited to the flexural surfaces, but she also had periorbital edema and generalized erythema. On the gluteal region and thighs she had evidence of an urticarial eruption. Other physical findings reported by the cardiology department were as follows: heart—slight enlargement to the left on percussion; normal sinus rhythm; second aortic sound was greater than the second pulmonic sound. There was a Grade 2 to Grade 3 systolic murmur at the aortic area, and a

Grade 1 aortic diastolic blow. Liver and spleen were not palpable. There was no pretibial edema. Fluoroscopy of the chest revealed mild left ventricular and left auricular hypertrophy. The ECG was within normal limits. A diagnosis of rheumatic heart disease was made from the above findings. The patient had good compensation, for she had never been in cardiac failure and had neither exertional dyspnea nor ankle swelling.

After laboratory controls were obtained on two consecutive days, use of the prepared ointment was started. Table 3 presents the pertinent findings. A weight gain was noted after the second day of treatment. On the sixth day, patient was in acute respiratory distress; there were moist rales in the base of each lung, and she had a 1+ pitting pretibial edema. Chest x-ray revealed increased vascular markings and a questionable pleural effusion on the left side. The ECG revealed auricular fibrillation with a moderately rapid ventricular response. The diagnosis was acute heart failure. The fludrocortisone ointment was stopped; digitalis therapy was instituted, and mercaptomerin (Thiomerin) was given to produce diuresis. On the following day the ECG revealed signs of hypokalemia, and the serum potassium was 3.2 mEq. After diuresis compensation was again good, and digitalis was no longer necessary. There was a decrease in the total eosinophile count on the sixth day, which continued for three days after the ointment was stopped. The treated area of skin showed no residual inflammation.

TABLE 3.—*Cutaneous Absorption Study Using 0.25% Fludrocortisone Ointment*

	Control														
Days	1	2	1	2	3	4	5	6	7	8	9	10	11	12	13
Total Eosin. Ct.	726	440	....	....	....	....	....	110	44	22	44	110	....	....	165
Daily wt. in kg.	70.1	69.2	70.0	70.8	71.0	72.2	72.3	77.8	78.8	68.9	67.8	68.2	68.2	67.9	...
Serum sodium	....	....	151.2	....	....	....	....	....	142.5	....	....	....	....	....	...
Serum potassium	....	....	5.6	....	....	....	....	....	3.2	....	....	....	....	....	...
Ointment applied	....	....	X	X	X	X	X	....	....	....	....	....	....	....	...

Case 1 in the text. Fludrocortisone ointment was stopped after five days of therapy because of the sudden onset of dyspnea, excessive weight gain, and ankle edema. Patient was given a digitalis preparation for digitalization along with an antidiuretic on the sixth day.

CASE 2.—A 72-year-old white man was admitted to Colorado General Hospital because of an eczematoid dermatitis on his legs and generalized erythema. After the eczematous eruption on his legs had cleared, the patient was started on the fludrocortisone ointment. The area to which the ointment was applied (extensor surfaces of the forearms and the dorsal surfaces of the hands) did have some residual erythema, but the entire skin was intact. The patient had pigmentation from a previous stasis dermatitis, but no pretibial edema. After two days' application of the ointment, he began to develop pretibial pitting edema (1+) of both legs and gained 1 kg. On the sixth day, a total of 4.5 kg. had been gained, and 2+ to 3+ pitting pretibial edema occurred, with color changes and bluish congestive appearance on both legs. The ointment was discontinued after six days of application, in order to prevent any permanent hemostatic damage to his legs. The patient continued to gain weight for three more days after the ointment was stopped. A total of 5 kg. was gained before his weight started to decrease. The average total eosinophile count, taken as a control on this patient, was 473 per cubic millimeter. On the sixth day of treatment the total eosinophile count was 242 per cubic millimeter. The eosinophile count began to rise again about 24 hours after the ointment was stopped. Elastic bandages were applied to his legs, and the foot of his bed was elevated to reduce his edematous legs. When the patient was discharged, he had minimal pretibial edema and the area of skin that was treated with the ointment showed no residual erythema.

COMMENT ON CASES AND INTERPRETATION OF RESULTS

From these studies it became obvious that the hormone was absorbed in amounts sufficient to cause such systemic effects as fluid retention (weight gain) and eosinophile fall, and after cessation of the drug an eosinophile rise and weight loss occurred. Case 1, a patient with an organic heart lesion, but one which was compensated, was thrown into acute heart failure. In Case 2, the patient had a predisposition to stasis dermatitis and developed marked pitting pretibial edema, with obvious vascular stasis of his legs. Both patients demonstrate the rapidity of systemic effects after application of the fludrocortisone to approximately 8% of the body surface. The drug had to be stopped in order to prevent permanent damage. Since fludrocortisone is a very potent hormone, small amounts absorbed through the skin may cause severe systemic reactions, and

in patients with an underlying organic lesion great care must be exercised to prevent aggravation of this lesion and resultant permanent damage. Therefore the amount, concentration, and the size of the area to be treated must all be considered before one proceeds to use fludrocortisone locally.

DERMATOLOGIC USES OF THE ADRENOCORTICAL HORMONES

The type of skin disease to be considered for adrenocortical or corticotropin therapy should be weighed against the possible side-effects that can result from its usage.

The systemic use of the adrenocortical hormones in dermatology has its greatest benefit in those diseases that are of the inflammatory type. The effects exerted by these hormones are temporary and palliative in nature. The symptom complex of the disease process is altered, but the basic disease is not changed, as is evidenced by the return of symptoms after discontinuance of the hormone.[37]

The sudden cessation of systemic adrenocortical hormones can result in a rebound phenomenon exemplified by a recurrence of the disease in a similar or a severer form than was originally treated.

The side-effects of systemic therapy with these hormones are particularly important when prolonged therapy is considered.

The indications for the systemic administration of the adrenocortical hormones or corticotropin in skin diseases are considered under three headings [38]:

1. Those diseases that are fatal
2. Those that are acute but self-limiting inflammatory or allergic disorders
3. Diseases that are chronic in nature but do not alter life expectancy

Fatal skin diseases in which hormonal therapy is indicated are those such as pemphigus,[39] acute generalized exfoliative dermatitis,[40] and disseminated lupus erythematosus.‡ In these diseases hormonal therapy is beneficial and sometimes life-saving. The dosage required for treatment of these conditions is sometimes extremely high, as in pemphigus, where 300 to 500 mg. of cortisone every day is occasionally required to control the disease. Since the medications used for treatment are life-saving in nature, side-effects that occur must be weighed against the cessation of the drug and possible recurrence of the disease. Therefore, any side-effects due to the hormone should be anticipated and proper steps taken to prevent them from causing increased harm to the patient. In these instances, large doses and long maintenance courses in hormonal therapy are justified, despite the side-effects, because of the fatal prognosis without their use.[38]

In diseases that are acute but self-limiting in nature, the use of hormonal therapy depends on the severity of the attack and the comfort of the patient. In this category fall the acute allergic reactions to drugs or contactants.[44] The manifestations of these reactions can be protean—angioedema, erythema multiforme, and anaphylactoid purpura.§

If after a trial of conservative measures the disease process continues, hormonal therapy is indicated. If a threat to life exists, as in acute, progressive, allergic reactions, hormonal therapy is justified. In allergic reactions where hormonal therapy will permit more rapid recovery and return the patient to his job, the economic factor and the comfort of the patient are then considerations. Since these are self-limiting diseases, if the patient is not reexposed to the offending allergen, the use of short-term hormonal therapy is consonant with good therapeutics, for the patient will be over his acute illness and off of the drug before side-effects can occur.

In diseases that are chronic in nature but do not alter life expectancy, the justification for hormonal therapy should be thoroughly scrutinized. It is true that the diseases in this group may make the patient quite uncomfortable, but the side-effects from the prolonged use of the hormones may outweigh the temporary relief obtained from

‡ References 41 to 43.

§ References 37 and 42.

their use. If life is unbearable and the patient is prevented from working or carrying out his normal functions in life, the side-effects would probably be justified; but the use of these hormones must definitely be restricted to specific cases. Considerations should also be given to the anticipated favorable response of the disease to hormonal therapy on the basis of past experience. Examples of the chronic skin diseases in which the adrenocortical steroids or corticotropin are not indicated are chronic psoriasis, chronic phases of scleroderma, alopecia areata, and chronic lichenified lesions such as lichen simplex chronicus.||

In the treatment of atopic eczemas, both the infantile and the adult form, the side-effects definitely must be weighed against the temporary beneficial results. Before resorting to adrenocortical steroids other types of therapy must be utilized to their fullest extent, for the relapse after cessation of these hormones can be severer than the original disorder. Systemic hormonal therapy is usually reserved for very resistant and unmanageable cases that have failed to respond to other measures. And if hormonal therapy is decided upon for these patients, the dose used should be one that achieves relief of symptoms without causing marked side-effects. A smaller dose is indicated even if mild symptoms persist. In other words, one should not strive for complete relief of symptoms in these patients, for the side-effects of the therapy may preclude the usage of these hormones.

Topical adrenocortical steroids have proved to be a successful addition to the dermatological armamentarium. The indications for topical therapy are dependent on those disorders that are benefited by its use.[45] With this type of therapy rapid and beneficial results may be anticipated in the acute inflammatory dermatoses. Lesions that are chronic and lichenified show less response, as was shown in our clinic with use of both hydrocortisone and fludrocortisone. Through clinical observation it was found that the topical use of fludrocortisone was highly effective in the treatment of the following skin diseases: nummular eczema, contact dermatitis, dyshidrotic hand eczema (acute and subacute), and sunburn (used for clinical evaluation only). Chronic lichenified lesions responded better to other modes of therapy.

The preparation of fludrocortisone ointment is similar in its actions and indications to hydrocortisone ointment,[46] the difference being in their effectiveness with the lower dosages, and the time element in their response (slightly faster response with fludrocortisone than with hydrocortisone). However, fludrocortisone is absorbed in such significant amounts that systemic complications can occur.

In the Dermatology Clinic at the Colorado General Hospital, it was found that the fludrocortisone is very effective, and a rapid response occurs with the concentration of 0.25%. After control of the acute phase one can use a lower concentration, such as 0.1%, for limited maintenance. The preparations containing only 0.05% were not of adequate concentration to induce remissions, although for tapering-off purposes this concentration usually sufficed.

REBOUND RELAPSE

In the use of topical hormones one must realize that the sudden cessation of the drug results in a "rebound relapse" similar to that with the systemically administered hormones. If the topical hormone is abruptly stopped as soon as beneficial results occur, the "rebound relapse" of the skin condition is usually worse than the original manifestations and much more difficult to control, often requiring a longer course of therapy. In one instance systemic cortisone was required to cause a remission. To avoid this, we have continued the use of the topical hormone (hydrocortisone) for at least 7 to 10 days after complete cessation of symptoms of remission has occurred and then weaned the patient from the topical hormone either by decreasing the concentration of the hor-

|| References 24, 27, 37, and 38.

mone in the ointment base or by fewer applications.

Rebound relapse is often encountered when systemic corticosteroid is discontinued and has been generally attributed to inhibition of the pituitary-adrenal axis. This theory seems hardly applicable in cases when local hydrocortisone preparations are used because, as previously noted, insufficient hormone is ordinarily absorbed to produce systemic metabolic effects.[36]

However, cellular changes must occur after local application of hydrocortisone. These changes are obviously due to a local increased action of adrenocortical steroid on the cellular structure. It would appear that these cells may in time become accommodated to a higher concentration of adrenocortical steroid. Therefore, when the local hormone is suddenly stopped, the cells may not respond to the lower dose of systemically produced adrenocortical steroids that is being constantly delivered to them by way of the cutaneous vessels. A local adrenocortical insufficiency probably results, and cellular changes occur, thereby bringing about a reversion to the original diseased state.

SIDE-EFFECTS

The undesirable reactions that occur after the systemic use of these hormones are of two general types: (1) those due to overdosage of the hormone, representing an exaggeration of its physiologic actions (and occurring during intensive and prolonged administration), and (2) those occurring chiefly after hormonal withdrawal, reflecting a state of adrenal insufficiency, induced by normal suppression of adrenocortical function.

These undesirable reactions may be exemplified by the following:

1. Osteoporosis and resultant spontaneous fractures in patients receiving systemic cortisone. It is known that osteoporosis due to disuse atrophy may occur in normal patients under prolonged bed rest. The administration of adrenocortical hormones or corticotropin to an immobilized patient can exaggerate osteoporosis and lead to spontaneous fractures. The postmenopausal female patient either has osteoporosis or is susceptible to its development. The use of the adrenal cortical hormones in this type of patient predisposes her to spontaneous fractures. The consequences resultant from immobilizing such a patient and giving her adenocortical hormones are obvious.

2. Portions of, or the entire picture of, Cushing's syndrome, which may be pronounced in some patients. This may be characterized by moon facies, fat pad deposition, striae, and the production of frank diabetes in a latent diabetic.

3. The exacerbation of a quiescent peptic ulcer, which can lead to perforation.

4. Dissemination of tuberculosis in an active tuberculous patient. The activation of tuberculosis in a latent or inactive patient can occur but is infrequent.¶

5. Abnormal salt and water retention resulting in edema or various degrees of congestive failure or aggravation of hypertension in the presence of renal damage.

6. Increased susceptibility to infection, especially tuberculosis.

The important side-effects to be recognized as being due to drug withdrawal are as follows:

1. Rebound relapse. This is significant both in the systemically treated patient and one that is treated locally only.

2. Occlusive vascular accidents, such as coronary thrombosis. These are significant during treatment but especially after withdrawal.

3. Relative adrenal insufficiency due to superimposed stress. This can occur even during hormone administration.

CONTRAINDICATIONS

The contraindications to the use of systemic adrenocortical steroids and corticotropin should be recognized by all who undertake to treat patients with these hormones.

Systemic diseases in which there are strong contraindications to the use of these hormones are peptic ulcer and active tuberculosis.

Only a relative contraindication exists in patients with diabetes, for they can be controlled with slightly increased insulin dosages.

In patients with other systemic diseases, such as hypertension and occlusive vascular and renal disease, considerable caution must

¶ References 47 to 49.

be exercised to prevent progression of their disease.

Changes in the mental picture, resulting in psychotic episodes are usually temporary and reversible upon cessation of the drug. No correlation necessarily exists in patients having and those not having a history of psychotic episodes regarding the incidence of psychotic breakdowns during adrenocortical therapy.[19]

SUMMARY AND CONCLUSIONS

An attempt is made to review some of the basic pharmacologic principles, both systemic and local, of the adrenocortical hormones, their new derivatives, and corticotropin, with particular emphasis on the potential side-effects and uses in diseases of the skin. The use of these hormones has proved to be beneficial and is indicated in certain dermatoses. The criteria for the dermatologic use of these hormones is presented and their limitations stressed.

Prolonged use of these hormones results in an exaggeration of their physiologic effects. These effects are the imposed limitation upon the excessive use of these drugs.

Definite care must be exercised in initiating or terminating therapy with these hormones. The sudden cessation of systemic hormones may result in a rebound to the original dermatologic disorder with varying degrees of severity.

In the topical use of fludrocortisone care must be exercised in the amount, concentration, and duration of application, especially in patients with underlying organic lesions, for this hormone may cause potential systemic effects.

A local rebound relapse may occur from the use of topical steroids. Methods of prevention of the local rebound relapse are presented.

The contraindications and the medical management of patients on these hormones are suggested, and the prevention of complications is stressed.

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