SIDE EFFECTS OF STEROID THERAPY IN DERMATOLOGY

Experiences in 215 Cases

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ALL treatment with steroids is relatively recent and new steroids continue to appear. Several papers have been published giving details of side effects and dangers, but it is thought that a further long-term survey of experience, in the skin department of a teaching hospital, may help to increase the fund of knowledge about these drugs. No attempt is made to estimate their value in treatment.

Material

This paper gives the findings in 215 cases treated with adrenocorticotrophic hormone (ACTH), cortisone and other steroids given systemically in the Skin Department of the London Hospital and to Skin Department in-patients. It covers a period of over six years, from the date of the first use of steroid therapy until the end of 1959. The total number is 215, 122 men and 93 women. The diseases for which the drugs were given have been divided into the following groups: (1) eczema; (2) lichen planus; (3) collagen diseases; (4) Besnier's prurigo; (5) alopecia; (6) psoriasis; (7) erythrodermia; (8) seborrhœic dermatitis; (9) bullous dermatoses; (10) miscellaneous.

The period over which the drugs were given varied widely, as would be expected. Some patients had them for only a few days, some for several years continuously, some had repeated courses; often a patient had treatment with more than one steroid.

The doses also varied widely, and it has not been thought necessary to list the exact dosages—their true value would only be shown in relation to body weights, and in any cases they varied repeatedly

with the clinical course. In some patients doses large by generally accepted standards were given, and these are mentioned.

Some general features of routine treatment during this period may here be noted.

At each attendance the patient was weighed, the temperature and pulse were noted, and the urine tested for albumin and sugar. Periodically the blood pressure was recorded. Potassium chloride was given with cortisone. Alkalis were given to those with any history of indigestion and with high steroid doses. Chest X-rays were taken before starting treatment.

In each group of cases noted below the number with side effects is listed; minor variations in weight, the presence of a trace of sugar in the urine or a transient slightly raised temperature have been ignored, attention being paid only to the significance attached by the clinician concerned to these changes, as judged by the clinical notes. Hirsuties, acne, or the development of a moon face have also been ignored.

In those cases where major trouble was associated with the treatment a short case history is appended as a cautionary tale.

Results

It should be noted that many patients had more than one type of steroid drug. In many cases the side effects were mild and treatment was continued; the total duration of treatment is given in these tables, not the period before side effects were present. The ages given are those of the patients when steroid treatment was started.

1. Eczema

Total number of patients, 52: Male, 38; female, 14.

Number of patients receiving courses of steroids: Adrenocorticotrophic hormone (ACTH) (in International Units: I.U.), 1; Cortisone (C), 21; Prednisone (P), 27; Triamcinolone (T), 9; Deltacortisone, 1.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	63	Cardiac failure ..	T	11 wks.
M.	39	Indigestion ..	T	4 "
M.	26	Indigestion ..	C	2 mths.
M.	56	Boils ..	P	9 "
M.	50	Indigestion ..	C	1 mth.
M.	60	Boils ..	C	2 mths.
M.	60	1. Venous thrombosis in leg and pulmonary embolism ..	P	5 "
		2. Purpura, cellulitis, boils ..	T	7 "
M.	50	Indigestion ..	T	1 yr. 2 mths.
M.	54	Indigestion ..	T	2 mths.
F.	52	Indigestion ..	P	11 wks.

Points of Interest:

- M. 56 General anaesthetic—no supplement—uneventfully after steroids (P and C) for ten months.
- M. 71 Herpes zoster while on C—painful.

2. Lichen Planus

Total number of patients, 29: Male, 18; female, 11.

Number of patients receiving courses of steroids: ACTH, 7; C, 13; P, 16; T, 1.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	53	Became aggressive	C	5 wks.
M.	41	Gained 7 lb. ..	P	6 mths. 1 wk.
M.	61	Indigestion ..	P	7 wks.
M.	44	Indigestion ..	P	3 "
F.	49	Indigestion ..	C	6 "
F.	43	1. Gained 8 lb. ...	C	9 "
		2. Indigestion ..	P	13 "
F.	50	Indigestion ..	P	6 "

Points of Interest:

- M. 61 General anaesthetic—no supplement—uneventfully two years after seven weeks of P.
- M. 53 General anaesthetic—no supplement—uneventfully three years after ACTH for three weeks, C for six weeks.
- M. 49 General anaesthetic—no supplement—uneventfully four months after C for two weeks.
- M. 53 X-ray changes suggestive of old pulmonary tuberculosis, not re-activated by five weeks of C.

3. Collagen Diseases

Total number of patients, 9: Male, 2; female, 7. This was made up of 2 dermatomyositis (children), 5 systemic lupus erythematosus (SLE), 1 discoid lupus erythematosus, 1 morphœa.

Number of patients receiving courses of steroids: ACTH, 5; C, 5; P, 5; T, 1.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	3	Consolidation—right mid. lobe	P	9 mths.
F.	3	Infection of hand, cellulitis of buttock ..	P	2 wks.
F.	26	1. Gain in weight	C	1 yr.
		2. Indigestion ..	T	7 mths.
F.	33	1. Indigestion ..	C	2 "
		2. Indigestion ..	P	3 yrs. 1 mth.
F.	25	Indigestion ..	C	2 yrs. 2 mths.
		Death with pyopneumothorax (SLE).		(terminally in large doses and with ACTH)

4. Besnier's Prurigo

Total number of patients, 20: Male, 13; female, 7.

Number of patients receiving courses of steroids: ACTH, 2; C, 4; P, 18; T, 5; Dexamethasone, 2.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	48	Indigestion ..	P	1 yr. 6 mths.
M.	33	Indigestion ..	P	1 yr. 10 mths.
F.	23	Weight gain ..	P	6 mths.
F.	25	Boils ..	P	1 yr. 7 mths.

Points of Interest:

- F. 25 On P—general anaesthetic—extra C. On C—uneventful pregnancy, labour and puerperium.
- M. 38 Patient previously psychotic—no ill effects on P for 16 weeks.
- M. 36 Patient previously psychotic—no ill effects on C for two weeks.
- F. 22 General anaesthetic—no supplements—uneventfully three years after ACTH for one week.
- F. 52 General anaesthetic—? supplements—uneventfully two years after P for four months.

5. Alopecia

Total number of patients, 9: Male, 2; female, 7. This number was made up as follows:

	Total No.	Male	Female
Alopecia areata	7	2	5
Pseudopelade	1	0	1
Male type alopecia ..	1	0	1

Number of patients receiving courses of steroids:
ACTH, 1; C, 4; P, 4; T, 1; Dexamethasone, 2.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	30	Indigestion ..	P	11 mths.
F.	27	Indigestion ..	C	4 "
F.	46	Indigestion ..	C	6 wks.

Points of Interest:

- F. 34 General anaesthetic when on P 10 mgm. daily—uneventful.

6. Psoriasis

Total number of patients, 11: Male, 5; female, 6.
Number of patients receiving courses of steroids:
ACTH, 0; C, 3; P, 3; T, 6; Dexamethasone, 1;
Deltacortril, 1.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	58	Weight gain ..	C	7 mths.
M.	53	Indigestion (known peptic ulcer) ..	T	1 yr. 6 mths.
M.	26	Abdominal pain, laparotomy n.a.d., septicæmia ..	P	1 mth.
F.	26	Indigestion ..	C	10 days

Points of Interest:

- M. 53 General anaesthetic—no supplement—uneventfully after deltacortril for one month, one year and seven months before.
M. 26 General anaesthetic while on P—with supplement—uneventfully after steroids for much of the preceding two years.

9. Bullous Dermatoses

Total number of patients, 40: Male, 17; female 23.

This number was made up as follows:

	Total No.	Male	Female
Pemphigus	11	3	8
Pemphigoid	14	6	8
Erythema multiforme	10	5	5
Herpes gestationis	2	0	2
Dermatitis herpetiformis (D.H.)	3	3	0

Number of patients receiving courses of steroids: ACTH, 23; C, 24; P, 21; T, 8; Hydrocortisone, 1.

7. Erythrodermia

Total number of patients, 15: Male, 10; female, 5.

This was made up of 13 idiopathic cases, 1 Hodgkin's disease, 1 lymphatic leukaemia.

Number of patients receiving courses of steroids:
ACTH, 6; C, 8; P, 11; T, 3; Deltacortril, 1.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	70	Prostatic staphylococcal abscess	C	1 yr. 2 mths.
M.	70	Undue weight gain	C	1 " 6 "
M.	66	(Hodgkin's): indigestion ..	C	1 " 5 "
		Thrombophlebitis; died from femoral thrombosis and pulmonary embolism	P	1 mth.
F.	55	Undue weight gain	C	4 mths.
F.	67	Indigestion ..	P	2 "
M.	64	Abscess of calf ..	P	4 "

Points of Interest:

- F. 64 Herpes zoster—painful—on P.
M. 74 General anaesthetic—? supplements—uneventfully after P for four months.
M. 70 General anaesthetic—? supplements—uneventfully after P for six weeks, C for one year two months.
Herpes zoster—painless—on P.

8. Seborrhœic Dermatitis

Total number of patients, 7: Male, 7; female, 0.

Number of patients receiving courses of steroids:
ACTH, 0; C, 0; P, 6; T, 1; Dexamethasone, 1.

SIDE EFFECTS

Sex	Age	Side Effect	Drug	Length of Course
M.	55	Carbuncle and boils	P	2 years

SIDE EFFECTS

Diagnosis	Sex	Age	Side Effect	Drug	Length of Course
Pemphigus	M.	46	Diabetes, boils	C, P and ACTH	2 yrs.
Pemphigus	M.	53	Mental changes, abscesses, weight gain, cardiac infarction	P	10 mths.
Pemphigus	F.	54	Urticaria (proven sensitivity)	ACTH	2 "
Pemphigus	F.	44	Known bronchiectasis and cor pulmonale: congestive cardiac failure, death	C	9 mths.
Pemphigus	F.	50	Diabetes, wedge collapse of vertebra, death	ACTH and C	1 yr.
Pemphigoid	M.	70	Glycosuria, lag curve	C	3 yrs. 2 mths.
Pemphigoid	M.	71	Diabetes	C	2 yrs.
Pemphigoid	F.	61	Weakness, muscle wasting	P	3 yrs. 5 mths.
Pemphigoid	F.	73	Abscesses, diabetes	ACTH	2 mths.
Pemphigoid	F.	73	Weight gain	C	2 "
Pemphigoid	M.	77	Indigestion	P	1 yr. 2 mths.
E. multiforme	F.	39	Weight gain	ACTH	6 wks.
E. multiforme	M.	32	Indigestion	C	6 mths.
D.H.	M.	64	Indigestion	P	4 days
D.H.	M.	84	Abdominal pain	C	3 mths.
			Weakness	T	4 "

Points of Interest:

- M. 70 Pemphigoid. General anaesthetic—no supplement—when on ACTH for two months.
- F. 44 Erythema multiforme. On steroids 2 years 8 months uneventfully—with past history of nervous breakdown, pleurisy, hæmoptysis and family history of diabetes.
- F. 51 Erythema multiforme. Carcinoma of breast. Death, probably carcinomatosis.
- M. 76 Pemphigoid. Died—retention of urine, prostate enlarged.
- M. 68 Pemphigoid. Known rheumatic heart disease and auricular fibrillation—no ill effects.
- F. 75 Pemphigoid. Died ? cause. Had stroke when on P.
- F. 52 Pemphigus. Died—hydronephrosis, cystitis P.M.—after ACTH for one month before.
- F. 47 Erythema multiforme. General anaesthetic—no supplement—uneventfully after C for one year three months.

Many of these patients, by the nature of their disease, needed large doses of steroids.

10. Miscellaneous Conditions

Total number of patients, 23: Male, 10; female, 13.

This number was made up as follows:

	Total No.	Male	Female
Malignant melanoma	4	3	1
Senile pruritus	2	2	0
Aphthosis (? Behcet's Syndrome)	2	0	2
Urticaria pigmentosa	1	0	1
Cirrhosis of liver, leg ulcer	1	0	1
Acrodermatitis atrophicans	1	0	1
Erythema centrifugum	1	1	0
Sarcoidosis	1	0	1
Purpura cryoglobulinæmia	1	0	1
Hirsuties	1	0	1
Infra-orbital swelling	1	1	0
Lichen simplex	1	0	1
Lymphoedema	1	0	1
Drug eruption (gold)	1	1	0
Acne	1	1	0
Darier's disease	1	0	1
Neurodermatitis	1	0	1
Ulcers of leg	1	1	0

Number of patients receiving courses of steroids: ACTH, 5; C, 10; P, 15; T, 3.

SIDE EFFECTS

Diagnosis	Sex	Age	Side Effect	Drug	Length of Course
Neurodermatitis	F	52	Indigestion	P	4 mths.
Cirrhosis, leg ulcer	F	21	Urticaria (? due to ACTH)	ACTH	3 yrs.
Acrodermatitis	F	52	Vomiting	C	5 mths.
			Weight gain and indigestion	P	2 yrs.
Malignant melanoma	M.	51	Abdominal pain	C (large doses)	1 mth.
Senile pruritus	M.	82	Died with D.U.—melæna	P	11 mths.
Infra-orbital swelling	M.	47	Indigestion	P	4 wks.

Points of Interest:

F. 52 General anæsthetic—no supplements—uneventfully after C for five months, P for one month.

A few case histories are here given as they are of particular interest. Three, as one might expect, concern patients who have been on steroids over long periods and often at a high dosage for serious conditions.

Case No. 1

A woman of 31 developed pemphigus vulgaris in 1956. She has been on steroids ever since, often at a high dosage. Cortisone, ACTH, prednisone and triamcinolone have all been used. She needed for initial control 100 mgm. of prednisone and 100 i.u. ACTH daily. With this and similar episodes of high dosage, she developed a moon face, pigmentation, hirsuties and mild acne. There was also occasional mild indigestion. A little over a year from the onset, when taking prednisone, she complained of a feeling of weakness in the left hip; an X-ray showed no abnormality. Two years later she made the same complaint and an X-ray showed subchondral sclerosis and irregularity of the femoral head. Her right shoulder was painful and an X-ray showed destruction and sclerosis of the articular surface of the humerus, some periosteal reaction at the neck of the humerus and soft tissue calcification. She was discussed by Sweetnam, Mason and Murray (1960). These changes are attributed to her steroid therapy. Subsequently she has been given calcium and anabolic hormones and there has been no progression in the changes.

Case No. 2

A woman of 56 developed pemphigus vulgaris in 1955. She had had a hæmatemesis and melæna from a duodenal ulcer four years before. She was hypertensive (blood pressure 180/110 mm. Hg).

She was given cortisone at first, and after one year ACTH instead. A few months later she had a hæmatemesis. She was found to have pyloric stenosis and had a gastrectomy. A wound abscess (from faecal organisms) later developed. The ACTH was stopped a few weeks afterwards, prednisone was given for a few weeks and then ACTH was given again. She then became hypertensive (blood pressure 195/120 mm. Hg) and went into hypertensive cardiac failure. ACTH was stopped for a month and the skin relapsed.

In September 1958, triamcinolone was given instead; after a period of a few days during which she stopped taking the tablets the skin became worse; on triamcinolone 32 mgm. and ACTH 100 i.u. daily it was controlled. Three weeks later, following an infection of the dorsum of the left hand, she developed gangrene of the left hand and osteomyelitis of the metacarpals with *staphylococcus*

pyogenes. It failed to respond to aureomycin, chloramphenicol, penicillin and streptomycin systemically, but was finally controlled on the administration of sulphadimidine and withdrawal of the steroids.

Three general anæsthetics were given uneventfully, two with steroid supplements, for drainage of the abscess and removal of sequestered bone. The hand recovered useful function and the pemphigus remained in abeyance until 1959 when a relapse was treated with ACTH; while having ACTH she had angina and indigestion.

Case No. 3

A woman of 52, who already had psoriasis, developed pemphigoid in 1954.

Cortisone therapy was begun in September 1954, with ACTH in addition for about four weeks three months later. The blood pressure was then 180/120 to 195/130 mm. Hg. The dose of cortisone often had to be in the region of 150 mg. daily to control the blisters. The blood pressure continued to be high and 17 months from the beginning of the treatment she developed headaches; the blood pressure then ranged from 240/140 to 300/180 mm. Hg. The fundi were normal.

Prednisone (15 mg. daily) was substituted two years after the onset of treatment. A few months later she was found to have hypertensive retinopathy. The hypertension was treated with reserpine and mecamylamine but the diastolic pressure continued to vary between 220/130 and 270/145 mm. Hg and she continued to have headaches.

After two years and four months on prednisone, triamcinolone was given instead. The blood pressure since has been in the range 180/120 to 170/95 mm. Hg.

It is of interest to note that her psoriasis was not improved by prednisone but responded well to triamcinolone.

Case No. 4

A man of 36 with severe Besnier's prurigo was given cortisone for two months in 1955 and prednisolone or prednisone from September 1956 onwards; the dose was never strikingly high.

At the beginning of 1958, he developed metastatic calcification of the fingers and eyes. He was found to be uræmic and to have hypercalcaemia. He had had many specimens of urine tested previously and on review it appeared that the S.G. had always been below 100 and the reaction almost always alkaline or neutral to litmus.

On investigation the serum sodium was found to be low, and the calcium raised; the blood urea was 225 mg./100 ml. and the hæmoglobin 49%. With the administration of sodium chloride the serum calcium fell and

Steroid	Total No. of courses given	Gastro-intestinal Symptoms	Weight Gain	Diabetes or Glycosuria	Skin Infection	Other Side Effects
ACTH	47		1	1	1	2 urticaria *1 hæmatemesis, pyloric stenosis, wound abscess, cardiac failure, angina and indigestion
Cortisone	90	13	7	2	1	1 mental change 1 pyopneumothorax, death (SLE) 1 prostatic staphylococcal abscess 1 thrombophlebitis 1 cardiac failure, death (Known bronchiectasis, cor pulmonale, pemphigus vegetans) *1 hypertension.
Prednisone	125	16	4	1	5	1 thrombosis in leg, pul. embolism 1 femoral thrombosis, pul. embolism, death (Hodgkin's disease) 1 lung infection 1 septicaemia 1 cardiac infarction 1 mental change 1 weakness 1 melæna, death (Senile pruritus) *1 sclerosis of humerus *1 uræmia, calcinosis.
Triamcinolone	37	5			1	1 cardiac failure 1 purpura 1 weakness
C and ACTH†	1			1		1 wedge collapse of vertebra, death (pemphigus)
T & ACTH†	1					*1 gangrene and osteomyelitis of hand
C, P & ACTH†	1			1	1	
Dexamethasone	6					
Hydrocortisone	1					
Deltacortril	3					

N.B. * Patients described in separate case histories.

† Combinations of drugs given at the time of noted side effect: such combinations were employed from time to time in other cases uneventfully and have not been separately noted, but split up and their components included in the totals of the appropriate steroids.

the serum phosphorus rose. The urea fell to 94 mg./100 ml. Subsequently it rose and the hypercalcaemia recurred.

The condition was attributed to chronic renal failure of unknown origin, and the part, if any, played by steroids is obscure.

He continued to have many large boils, one leading to a false aneurysm of the left temporal artery. He had several general anaesthetics uneventfully, some with and some without steroid supplements.

Discussion

Of the many papers written on side effects of steroid therapy that of Nordin (1960) provides a comprehensive survey. Only one, that of Cronin and Wells (1958) was based on dermatological

material. Nordin emphasizes 'an appreciable mortality in association with steroid therapy.' We have been fortunate in this respect in our series.

Olesen and Quaade (1961) think that steroid therapy is possibly a contributory cause of pneumothorax in patients with staphylococcal pneumonia. This is of interest in connection with the post mortem findings in our case of SLE who came to autopsy.

Bayliss (1958) and others have emphasized the importance of inability, in the patient treated with steroids, to react to stress—particularly important

in anaesthesia. There may be a pituitary as well as an adrenal element in this unresponsiveness (Ferriman and Page, 1960), so that ACTH may not be relied upon in its treatment. The same problem is mentioned by Wells (1961) in a symposium on rheumatoid arthritis, and discussed in detail by Lennard-Jones and Wolfe (1960), who suggest the administration of large doses of cortisone at operations in those who have had treatment with steroids during the previous 18 months. It is not suggested here that the good fortune of some of our patients in having survived operations without steroid supplements is an argument for omitting such additions.

At the present time increasing numbers of patients are being given steroids by their own doctors, as well as in hospitals. It may be salutary to record our experiences.

Summary

The complications of systemic therapy with steroids are surveyed in the 215 patients treated in the skin department of a teaching hospital over a period of rather more than six years.

The findings are summarized in the table on page 449.

Conclusions

It is unwise to make dogmatic generalizations on a single series. It is clear, however, that our most frequently encountered complication has been indigestion (a common symptom, and perhaps not always caused by the steroids); the steroids most used—cortisone, prednisone and triamcinolone—have been associated with it in roughly equal proportions. Most of the serious side effects have occurred in patients with high and long continued dosage for serious conditions.

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