EXPERIENCES WITH A.C.T.H. AND CORTISONE

A NOTE ON LONG-TERM THERAPY

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A.C.T.H. and cortisone have now assumed a most important place in the treatment of a number of diseases for which we could previously do little. The prognosis of the generalized collagen diseases, certain severe skin diseases, particularly pemphigus and acute exfoliative conditions, and several eye disorders has been improved at least from black to grey. To achieve success, however, treatment must usually be continued for indefinite periods, and with the limited supplies so far available this has presented a most difficult problem. Our results in the long-term steroid therapy of these patients at Guy's Hospital are briefly presented.

The first supplies, received in December, 1950, were only sufficient to treat five patients simultaneously. It was therefore essential that a central authority should arbitrate between the requests received from the various members of the hospital staff so that the best use might be made of the amount available. The department of medicine was asked to assume this duty. As soon as a request is received the patient is visited by a member of the department and the dose and method of administration are suggested according to the needs of the case and the current level of supply. While receiving treatment the patient is visited at least once a week, and further therapy is decided in consultation with the member of the staff in charge of the case. Clinical responsibility for the patient remains entirely with the consultant under whose care he had been admitted, and the consultant's wishes regarding dosage are followed as closely as the level of supply allows. If it is impossible to meet a request the circumstances are discussed personally with the consultant concerned.

At first it was decided that patients should receive a set course of approximately three weeks, during which time they were in hospital and under constant observation. Treatment consisted of cortisone, 100 mg. daily by intramuscular injection, or of A.C.T.H., by four intramuscular injections to a total daily dose of about 60 mg. Second courses were given only in exceptional circumstances. It soon became apparent that these drugs were life-saving in certain cases, that bigger initial doses were often necessary, and that maintenance therapy would have to be arranged. Thus a greater proportion of the slowly increasing supplies had to be allotted to long-term cases which required treatment after discharge from hospital.

In mid-1951, following the results of the clinical trial reported by Renold *et al.* (1951), we began to administer A.C.T.H. by the slow intravenous drip method. We found this most satisfactory, an adequate response usually being produced with a daily dose of 20 mg. or less. Thus our supply of A.C.T.H. was enough to treat

three or four times as many patients as when it was given intramuscularly in divided doses. Late in 1951 we received the first supply of oral cortisone tablets, and at the beginning of 1953 A.C.T.H. gel became available. These new preparations were used mainly for maintenance therapy.

Method

Our present practice is to treat patients receiving these drugs for the first time according to one of the following schemes: (1) 20 to 40 mg. of A.C.T.H. daily by intravenous drip for a minimum of eight and occasionally up to sixteen hours (McIntosh and Holmes, 1951); (2) 20 to 40 mg. of A.C.T.H. gel daily, given in a single intramuscular dose; (3) 100 to 200 mg. of oral cortisone daily in four divided doses; (4) 100 to 150 mg. of cortisone intramuscularly in a single daily dose. When it becomes apparent that the disease has been controlled—usually after seven to fourteen days—the daily dose of cortisone is reduced, or the A.C.T.H. is administered on alternate days.

Initially all patients had a chart showing output and intake of fluid, and eosinophil chamber counts were performed thrice weekly. Estimations of the serum sodium and potassium, the urinary 17-ketosteroid excretion, and the erythrocyte sedimentation rate were carried out weekly. We soon found that such detailed laboratory control was unnecessary, and our practice now is to do an initial serum sodium and potassium estimation, which is repeated only if intensive therapy is continued for more than two weeks or if the patient's clinical condition warrants. If the drugs are being given daily we restrict fluid intake to about 50 to 60 oz. (1.4 to 1.7 litres) in apyrexial patients. No added salt is allowed. The patient is weighed every second day and his blood pressure is recorded daily. Drinks with a high potassium content, such as Horlick's or "ovaltine," are given, or capsules of potassium chloride to a total of 4 g. daily may be taken.

The diagnoses of 185 patients treated between December, 1950, and June, 1953, are given in Table I.

TABLE I

Endocrine Disorders		General Medical Disorders	
Addison's disease ..	13	Ankylosing spondylitis ..	2
Adrenalectomy (Cushing's syndrome) ..	8	Asthma ..	8
Congenital adrenal hyperplasia ..	1	Dermatomyositis ..	2
Hypopituitarism ..	4	Disseminated lupus erythematosus ..	5
Dermatological Disorders		Myopathy ..	3
Dermatitis of hands ..	2	Nephritis (inc. nephrotic syndrome) ..	3
Keloid (post-operative) ..	2	Polyarteritis nodosa ..	7
Pemphigus ..	9	Rheumatic fever ..	6
Pruritus ani ..	2	Rheumatoid arthritis ..	50
Psoriasis ..	4	Sarcoidosis ..	4
Haematological Disorders		Scleroderma ..	11
Leukaemia ..	4	Ulcerative colitis ..	3
Thrombocytopenia ..	3	Miscellaneous disorders ..	17
Ophthalmological Disorders			
Choroiditis ..	2		
Iridocyclitis ..	10		
			185

With the exception of those suffering from endocrinological disorders, all received intensive therapy as inpatients in the first instance. The response of these patients accorded well with that to be expected from a study of the literature, which has been well summarized by Thorn *et al.* (1953). We do not propose, therefore, to analyse these results further, but the complications encountered seem worthy of mention. Three patients on A.C.T.H. had gastro-intestinal perforations (one ulcerative colitis, one polyarteritis, and one unsuspected peptic ulcer in a patient receiving treatment for rheumatoid arthritis). Two of these patients died, and we wish to emphasize the way in which A.C.T.H. or cortisone may mask the classical early symptoms of an abdominal emergency. Three patients developed acute psychosis necessitating removal to a psychiatric unit; two of these gave a history of previous mental illness. Two patients (one nephritic, one terminal polyarteritis nodosa) died in uraemia, but death seemed inevitable before steroid treatment. One patient with polyarteritis nodosa developed

steroid diabetes. Further reference is made to this case. Minor complications included abscess at an injection site (four cases), A.C.T.H. sensitivity (one case), hypokalaemia with asthenia (one case), and occasional mild depression. Purulent bronchitis, sinusitis, and minor hand infections seemed to occur much more often than in the rest of the hospital population, and called for immediate antibiotic treatment. Special complications developing during long-term maintenance therapy are discussed under the appropriate sections.

Maintenance Therapy

Table II gives a list of 44 patients whose condition appeared to merit long-term out-patient therapy.

TABLE II

<i>Endocrine Disorders</i>	
Addison's disease	13
Hypopituitarism	4
Congenital adrenal hyperplasia	1
<i>Collagen Diseases</i>	
Polyarteritis nodosa	3
Disseminated lupus erythematosus	2
Subacute collagen disease	1
Scleroderma	5
Rheumatoid arthritis	1
<i>Skin Diseases</i>	
Pemphigus	6
Psoriasis (exfoliative)	2
<i>Eye Diseases</i>	
Choroiditis	2
Iridocyclitis, chronic	4

Note.—Discrepancies between the members in this group and those in Table I are due to numerous factors—death, distance from hospital, continued care under private physician, etc.

Endocrine Disorders

The patients in the endocrinological group have been maintained on oral cortisone under the supervision of Dr. P. M. F. Bishop and have been seen regularly at the endocrinological out-patient department.

Since October, 1952, the patients with Addison's disease have been maintained on 12.5 mg. of cortisone by mouth daily and periodic D.C.A. implants. In addition to the daily dose of cortisone, each patient is supplied with an emergency ration of 100 mg. of cortisone and 3 g. of oxytetracycline ("terramycin") which is for immediate consumption in case of sudden appearance of untoward signs—severe infection of any kind, vomiting, fever. Patients are instructed to report to hospital as soon as possible for further care on these occasions. So far the general health of these patients has been better than when they were maintained on D.C.A. implants alone. Their cases will be reported in full at a later date.

Four patients with hypopituitarism have been given cortisone as daily maintenance treatment, with good response to 12.5 mg. a day in two. A poor result has been obtained in the other two; one of these failed to respond to as much as 50 mg. a day.

The single case of congenital adrenal hyperplasia has responded well to daily doses of 25 mg. of cortisone as reported by Wilkins *et al.* (1951). Her 17-ketosteroid output has decreased and there was commencing breast development.

Non-endocrine Conditions

The remaining cases have been followed at a regularly scheduled out-patient session. This permits regular examination and laboratory follow-up when necessary. Patients who are on treatment are seen weekly or fortnightly; others slightly less often.

Maintenance therapy, in order of frequency of use, has consisted of: (a) 20–35 mg. of A.C.T.H. administered intravenously over an eight-hour period twice or three times weekly. (b) Combinations of one or two intravenous infusions as above and one or two intramuscular injections of 20 mg. of A.C.T.H. gel, so that patients received the equivalent of two or three days' prolonged adrenal cortical stimulation. (c) Combinations of intravenous A.C.T.H.

drips two or three times a week and 50–100 mg. of cortisone, in divided oral doses, on one, two, or three of the off days. (d) Oral cortisone tablets in divided doses.

Our findings are in line with those of Thorn and others in that 20–40 mg. of A.C.T.H. gel is as effective as an eight- to ten-hour drip of 20–40 mg. of lyophilized A.C.T.H. Only small supplies of gel were available during the period of this review.

If intravenous therapy is ordered, the patients arrive about 9 a.m., weigh, urinate, and then sit in comfortable armchairs to receive the drip, which usually finishes between 5 and 6 p.m. This is more convenient for reading, eating, and chatting with fellow "drips," and makes it possible to bring these patients into a busy hospital ward without overcrowding or disrupting the usual order of business. No patient has registered dissatisfaction at the use of armchairs; in fact, most of them have expressed a definite preference for the chair versus the bed.

During this long-term out-patient therapy we have used the clinical laboratory rather sparingly, not attempting any extensive metabolic follow-up. Serum sodium and potassium levels have been carried out weekly or fortnightly. Occasional blood counts, urinalyses, blood sugars, chest films, sedimentation rates, serum protein determinations, etc., have been performed as necessary. Antibiotics (particularly depot penicillin or oxytetracycline tablets) have been prescribed freely whenever there has been evidence of infection. Potassium chloride has been taken by all long-term patients in 3- or 4-g. amounts depending upon their serum levels. The decision to terminate steroid treatment has been reached arbitrarily in discussions with the original consultant. Criteria have varied with the different diseases, but, in general, the key point has been that the patient's condition must have been static for four to eight weeks. Treatment was restarted at the first conclusive evidence of relapse, and has usually produced a response adequate enough to obviate admission to hospital.

Results

Polyarteritis Nodosa

Three patients were referred to the follow-up clinic: reports on them are given below.

Case A.—A woman of 35 was desperately ill when cortisone therapy was begun. She had been asthmatic for some years and was admitted in congestive heart failure with pulmonary infection and intense bronchospasm. There was a scaly rash on forehead and cheeks, her urine contained albumin and red cells, and there was a 25% blood eosinophilia. One month earlier she had had an acute pneumonic episode which had responded to penicillin. Intramuscular cortisone (100 mg. twice on the first day and subsequently once daily) was given together with chloramphenicol. Improvement was rapid, although the oedema persisted in spite of mersalyl injections. Cortisone was stopped after three weeks in order to produce a diuresis. She relapsed almost at once and developed a mononeuritis multiplex. Cortisone was reinstituted, and the daily dose was then gradually reduced to 37 mg. orally; she then again began to go downhill and was given intravenous A.C.T.H. therapy. She has had continuous steroid therapy for 16 months and is at present well and able to perform the normal duties of a housewife. She is subject to occasional asthmatic attacks and still has a mild tachycardia. She continues to receive A.C.T.H., 20 mg. either as gel or by intravenous drip on three days a week and 100 mg. of oral cortisone at week-ends. Any attempt to reduce this dosage is almost immediately followed by a recrudescence of her disease.

Case B.—A man of 52 had a history of a pyrexial illness with marked loss of weight for eight months. He had had a haemoptysis, and serial x-ray films showed patchy transient consolidations in various parts of the lung fields. There were raised purpuric plaques over the hands and legs. He was hypertensive, and the urine contained albumin and casts. Occasional specimens showed glycosuria, but glucose-tolerance tests before and during steroid therapy were normal. Intravenous A.C.T.H. (20–30 mg. daily) was started, and after six weeks this was reduced to 10 mg. three times a week, with 25 mg. of oral cortisone on other days. Within three weeks he developed severe conjunctivitis, and purpura returned on the legs. Increasing the intravenous dose of A.C.T.H. to 25 mg., and then to

40 mg., two or three times a week did not prevent a slow deterioration, and he was readmitted for a month's intensive therapy with daily A.C.T.H. (20-25 mg. by intravenous drip or as gel). He improved greatly and after a further month in hospital, during which he received similar treatment on alternate days, he was discharged in complete remission. He has had out-patient A.C.T.H. treatment three times a week since and also continuous cortisone (100 mg. daily) but his purpura has again returned and the sedimentation rate, normal on discharge, has risen to 74 mm. in one hour (Westergren). He has, however, had little constitutional disturbance. Improved supplies of gel have enabled us to give him A.C.T.H. daily as an out-patient and he is again improving. Ten months after steroid therapy was started it was certain that neither 100 mg. of cortisone daily nor 20 mg. of A.C.T.H. three times a week (by intravenous drip or gel) would keep his disease fully controlled. This case has already been reported in full (Baker, 1953).

No spontaneous remission has therefore been produced in either Case 1 or Case 2 over sixteen and ten months respectively.

Case C.—A man of 45 had had a pyrexial illness for three months with polyarteritis, hypertension, and mild renal involvement. He then developed a patchy peripheral neuritis and his blood showed a mild eosinophilia. He was treated with intravenous A.C.T.H., 20-30 mg. daily, for two weeks and then on alternate days for a similar period. He made a complete recovery apart from slight residual paraesthesia and has been followed for a further five months without any sign of relapse.

Special Complication.—During the four weeks the third patient received A.C.T.H. he developed diabetes. This is said to be rare (Jenkins, 1953). Glycosuria had been found on several occasions before treatment, and two glucose-tolerance tests showed curves of the "lag" type. During treatment he lost 5 lb. (2.3 kg.) in weight in spite of obvious clinical improvement. All specimens of urine showed a brick-red reduction of Benedict's solution at this time. A third glucose-tolerance test, a week after treatment had finished, showed a severe diabetic response, but a further test a week later was almost normal. No glycosuria has been found at out-patient attendances since. At no time did he receive insulin. Results of the glucose-tolerance tests are shown in Table III.

TABLE III.—Results of Glucose-tolerance Tests in Case C

Date	Blood Sugars (mg./100 ml.)					
	Fasting	½ hr.	1 hr.	1½ hr.	2 hr.	2½ hr.
28/1/53	121	225	230	160	128	100
4/2/53	110	207	223	164	113	—
17/3/53	466	530	611	—	500	424
23/3/53	161	194	182	127	127	119

A.C.T.H. therapy was given from February 5 to March 6.

Disseminated Lupus Erythematosus

Two patients in whom the diagnosis has been confirmed by the demonstration of L.E. cells have been followed.

Case D.—A girl of 19 was admitted in May, 1951, severely ill with high pyrexia, polyarthritis, and the typical butterfly rash. She had had two previous acute episodes—the first in 1947, when she was in hospital for eight months with joint involvement and pericardial and pleural effusions, and the second in 1949, polyarthritis being the predominant symptom. She received intramuscular A.C.T.H. (50-80 mg. daily in four divided injections) for three weeks in June, 1951, but this was only partially successful in limiting the disease. Five weeks later a second course was started, the total daily dose being increased to 150 mg. At first she responded well, but in the third week an injection abscess caused her temperature to rise again. A.C.T.H. was stopped after 24 days and treatment by surgical incision and antibiotics was started. She improved steadily after this, and was discharged in September feeling well, although she still had a low-grade pyrexia and a high E.S.R.

A satisfactory remission continued for nine months, when high fever, anaemia, and arthritis returned and she was readmitted again severely ill. A.C.T.H. intravenous drips (45 mg. reduced gradually to 20 mg.) were given daily for three weeks and then oral cortisone, 75 mg. a day, was substituted. Her response to the A.C.T.H. had been excellent, but she lost ground during the

six weeks she received oral cortisone, low-grade pyrexia and joint swelling returning. A.C.T.H. drips twice a week (50 mg.) were started, with cortisone, 25 mg., on the other days. This completely controlled her symptoms and she was discharged on out-patient treatment. The cortisone was omitted after two more months, and she received two intravenous A.C.T.H. drips (25-40 mg.) a week with a third injection of A.C.T.H. gel (20 mg.) on an intermediate day. On this regime she has felt better than at any time since 1947 and is completely apyrexial. The E.S.R., however, remains moderately raised. Steroid therapy was stopped at the beginning of July, 1953, and she remained completely well, although there has been a further increase in the E.S.R. (from 40 to 77 mm. in one hour). It is of interest that in February, 1953, while in remission on maintenance steroid therapy, she developed vertigo. Clinical examination revealed nystagmus on gaze to either side. Without alteration of treatment the vertigo disappeared in three weeks, while the nystagmus has persisted in diminishing intensity since. Electroencephalograms were performed during the vertiginous period and for four months afterwards. The former showed long periods of slow and fast activity, with spikes and waves on overbreathing and photic stimulation which were interpreted by Dr. D. A. Pond as being somewhat similar to those seen in epilepsy. Epileptiform seizures are now well recognized in disseminated lupus erythematosus (Sedgwick and Von Hagen, 1948; Russell *et al.*, 1951). The latter tracing was regarded as approximately normal. This patient noticed some menstrual irregularity during her prolonged course of maintenance therapy.

Case E.—A woman of 35 had had several previous attacks of joint swellings associated with lesions of the fingers originally diagnosed as chilblains. These occurred when she was 13, 21, 23, 27, and 34 years of age. They seemed to respond to gold therapy, and she was well in between the attacks. Six months before her admission to Guy's in May, 1951, she experienced severe generalized joint involvement and the rash appeared on the arms and face for the first time. She rapidly became very ill, with a high pyrexia. Intramuscular A.C.T.H. therapy (50-100 mg. in four divided doses) was given daily for four weeks and then it was changed to a daily dose of 100 mg. of intramuscular cortisone for a further three weeks. A complete remission was produced, although a low-grade pyrexia returned two weeks after stopping treatment. For the next 18 months she remained in partial remission, but her skin never completely cleared and she had bouts of low-grade pyrexia and joint involvement. In the spring of 1953 she began to relapse rapidly and was readmitted. She received A.C.T.H. gel daily for one week, followed by a similar dose on alternate days for a fortnight. Complete remission occurred, and she was discharged on out-patient treatment at the end of May. For two months she received cortisone (75-100 mg. orally) daily for two weeks each month. She lives too far away to make drip therapy practicable. She is moderately well, but relapses during the weeks off treatment.

While the spontaneous remissions and exacerbations in these two patients make it difficult to assess the value of maintenance therapy, it seems that their disease has reached a stage when steady deterioration is to be expected in the absence of steroid therapy, and that they will be able to lead active lives only if this is continued indefinitely. It has certainly proved dramatic in combating the acute stages of the disease.

Subacute Collagen Disease

A woman of 47 was admitted in November, 1952, with pyrexia, polyarthritis, and pericarditis of one week's duration. There was no previous history of rheumatic fever. The E.S.R. was 130 mm. in one hour, the blood showed an eosinopenia and the serum albumin was reduced. She had no rash, however, and marrow study failed to reveal Hargreaves cells. The diagnosis is still uncertain. Salicylates produced no improvement, but she rapidly responded to a daily intramuscular injection of cortisone (100 mg.). This was gradually reduced until after six weeks she was receiving 25 mg. orally when she relapsed. Intravenous A.C.T.H. produced immediate response, and she was discharged to out-patient treatment on three drips a week, which was later changed to cortisone, 75 mg. orally daily. She was so well that after five months all steroid therapy was stopped. Within a week the E.S.R. had risen from 15 to 84 mm. in one hour, and a few days later symptoms of pericarditis returned. These immediately disappeared when drip A.C.T.H. therapy was restarted, and she was then well and about to return to out-patient maintenance treatment. It appears that she will require continuous treatment for an indefinite period.

Scleroderma

We found A.C.T.H. or cortisone of little value in the far-advanced cases with visceral involvement and marked contractures, so that in such patients no attempt at prolonged maintenance therapy was made. Five patients with early to moderate sclerodermatous changes have been followed up for from five to fourteen months. Each has obtained a good response to intensive courses of A.C.T.H. but have relapsed between courses, slipping further downhill with each relapse. Three have now received continuous out-patient treatment with A.C.T.H. for three, two, and two months, with encouraging results. Another has improved on oral cortisone intermittently for six months. The fifth patient, who lived too far away for regular maintenance treatment has benefited from frequent periods in hospital for monthly courses of treatment during the past year.

Scleroderma in its early stages would appear to demand the highest priority for A.C.T.H. or cortisone, and it seems likely that a programme of almost continuous treatment will be necessary. It is now our practice to give each new case an intensive course of A.C.T.H. therapy (20–30 mg. daily by drip or gel) for one month and then decide whether the improvement seen makes long-term treatment worth while.

Rheumatoid Arthritis

The shortage of supplies has enabled us to undertake long-term treatment on only one patient with rheumatoid arthritis, and no conclusions can be drawn from this single case.

Pemphigus

Of the nine patients with pemphigus who received steroid therapy, six were subsequently referred for long-term treatment. Details of these cases are given in Table IV.

(Cases 3 and 4) occurred while the patients were receiving 50 mg. of oral cortisone a day. These patients have at all times responded to A.C.T.H. gel or intravenous drip, a daily dose of 20 mg. usually being adequate, although it has been necessary to give as much as 40 mg. for the first few days. Once the disease has been brought under control no relapse has occurred while the patients have been receiving three injections of 20 mg. of A.C.T.H. a week either as gel or by intravenous drip.

If cortisone is to be used in the treatment of pemphigus, therefore, a daily dose of 300 or 400 mg. may be necessary, and we consider that A.C.T.H., given either as gel or an intravenous drip, is the most economical method of treatment.

The longest remission so far obtained without treatment is nine months (Case 1), while two patients (Cases 2 and 6) are still well six and three months after the cessation of steroid treatment.

Special Complications.—As might be expected when treatment with high doses has to be continued for long periods, two of these patients developed many "Cushingoid" features, but these regressed slowly when treatment was interrupted.

Exfoliative Psoriasis

Two cases which had been treated with most of the widely used remedies were thought severe enough to warrant steroid therapy. Both responded remarkably to daily intravenous A.C.T.H. over periods of three to six weeks. After that, one was just barely maintained for two and a half months with a few skin plaques on three prolonged drips a week: when treatment was stopped he relapsed completely in three weeks, and required another intensive course for two weeks before reaching a point where out-patient main-

TABLE IV

Case No.	Sex	Age	Diagnosis	Condition before Treatment	Months since Initial Therapy	Longest Remission (Months)	Condition on July 31, 1953
1	F	53	<i>P. vulgaris</i>	Generalized pemphigus of mouth and body. Dangerously ill	25	9	On treatment. Very well. Occasional oral blisters
2	F	61	" "	Oral blisters; conjunctivitis. General condition fair	21	6	No treatment. Very well. Occasional oral blisters
3	F	55	" "	Oral blisters. General condition fair	18	3	On treatment. Well and working. Occasional blisters
4	F	52	" <i>ollicaeus</i>	Generalized pemphigus; heart failure. Dangerously ill	12	4	Well but lesions relapsing on face (retreated 10 8/53)
5	F	75	" <i>vegetans</i>	Oral blisters; crops starting on body. Moderately ill	9	0	On treatment. Vegetans lesions still present on face. Constitutionally well
6	F	69	" "	Generalized pemphigus; vegetans lesions on neck. Dangerously ill	8	3*	Very well. Occasional blister. No treatment

* Remission continuing.

Three of these six were critically ill when treatment was started, while the remainder, although having less constitutional disturbance, had extensive oral lesions which seriously affected nutrition. Skin lesions were present in all cases. They have been followed up for periods varying from eight to twenty-five months, and five of the six are leading full active lives with no more disability than an occasional blister. The sixth (Case 5) developed crusted "vegetans" lesions over most of the face which harboured *Staph. aureus* infection. These have so far resisted all attempts at steroid and antibiotic therapy. She is, however, constitutionally well, and new blister formation has been prevented. Since without steroid therapy all these patients would almost certainly be dead, pemphigus is obviously an absolute indication for prolonged treatment with A.C.T.H. or cortisone.

Two cases (1 and 4) were initially controlled by daily intramuscular doses of 200–300 mg. of cortisone for three days followed by 100 mg. Case 2, however, showed no improvement on 100 mg. of intramuscular cortisone daily for ten days, while a relapse of Case 3 failed to respond to 200 mg. of cortisone daily. Furthermore, two relapses

tenance was again feasible. As two more months of high doses of A.C.T.H. three times weekly plus cortisone tablets at the week-end failed to prevent slow deterioration, all steroid therapy was abandoned for a trial period.

The other patient was admitted with widespread psoriasis and pneumonia. Treatment with antibiotics preceded the use of A.C.T.H. by about a week. Response was excellent while in the ward, but out-patient maintenance was hampered by her requirement of large quantities of A.C.T.H. and by irregular attendance due to personal affairs. Eventually her steroid treatment was discontinued.

Complications.—After receiving pig A.C.T.H. for a period of three and a half months, the first patient with psoriasis began to suffer with widespread angioneurotic oedema following and/or during intravenous administration. This was the only drug he was receiving at the time. Skin tests were negative. Treatment was stopped until ox A.C.T.H. could be obtained; during his two months' treatment with this he encountered no difficulty. From our experience with these two patients we do not consider that steroid therapy is indicated in the long-term treatment of exfoliative psoriasis, although it may be of great value in tiding over

the acute exacerbations which occur from time to time. These patients required greater quantities of A.C.T.H. to suppress their disease adequately and continuously than did any other group treated. The maintenance dose of cortisone required was never determined, but it seems certain that it exceeded 100 mg. a day.

• Chronic Non-granulomatous Uveitis

These cases usually are well controlled for long periods on small (25 mg.) daily doses of cortisone by mouth. All four patients have responded to steroids administered in various methods, including cortisone by subconjunctival instillation or drops. Relapses, occurring while patients were receiving local applications, have responded to systematic administration. An occasional seven- to ten-day period of intensive A.C.T.H. therapy has been followed by relatively long symptom-free periods. One patient was maintained completely symptom-free for three and a half months with two A.C.T.H. drips a week. Following cessation of treatment she went two months before misty vision and ocular discomfort returned. She then responded to small doses of oral cortisone.

Choroiditis, Non-specific

Two patients have been given intensive courses of A.C.T.H. and a two-months follow-up on out-patient steroid treatment. Most of the improvement took place during the first three weeks of treatment. There has been no evidence of relapse in five months since treatment was stopped in one; after three months the other patient noted some return of visual symptoms which responded to oral cortisone (25-50 mg. daily).

Discussion

The continued satisfactory response to A.C.T.H. and/or cortisone two or three times a week of these patients with disseminated lupus erythematosus, polyarteritis, scleroderma, choroiditis, and chronic non-granulomatous uveitis deserves emphasis. Similarly, in accordance with Lever's (1953) findings, five of our patients with pemphigus have shown excellent response to prolonged therapy; when relapse has occurred two weeks to nine months after cessation of steroid treatment, reinstitution of treatment has quickly produced regression of lesions. The least satisfactory results have been achieved in the two patients with exfoliative psoriasis who required larger doses of drug more frequently. This was mentioned by Lever (1951). In addition, each of these patients had some associated emotional factors which have been found to be so important in severe psoriasis.

This method of out-patient management offers several worthy features: maintenance of the patient's self-confidence, outside contacts, and home life; continued, rather close, observation by the physician; a tendency to lessen the prolonged stimulatory effects (Ingle, 1950; Gordon *et al.*, 1951) of A.C.T.H. and A.C.T.H. gel (Frazier, 1953) and the adrenal hypoplasia resulting from prolonged cortisone administration (Forsham *et al.*, 1950; Sprague *et al.*, 1950); and it diminishes the cost of the drugs per patient and makes more hospital beds available.

The outstanding lament sounded repeatedly in articles describing the remarkable results obtained with A.C.T.H. and cortisone in diseases of the type mentioned here is their temporary nature, due to the cost of the drug used, the accumulating untoward side-effects, and problems of administration in the case of A.C.T.H. Intermittent dosage as used by Lever and described above seems to be a partial answer to these difficulties and seems worthy of general trial. Russell *et al.* (1951) mentioned intermittent treatment with lyophilized A.C.T.H. intramuscularly on a follow-up basis in some of their patients with disseminated lupus. However, they did not elaborate on the details of treatment or their results. Slow intravenous drip therapy can be offered to out-patients effectively on an intermittent

schedule with little inconvenience to any of the parties concerned—patients, ward nurses, or physicians. A.C.T.H. gel has likewise been used satisfactorily on intermittent-dosage schedule in amounts equivalent to that (lyophilized) used for one intravenous drip. The advantages of a single intramuscular injection which can be given by the patient's own doctor are obvious. Recently the supplies of gel have increased substantially, and it seems that this will be the ideal method for continuous steroid therapy. Patients need attend hospital only for assessment and regulation of dosage at weekly or biweekly intervals, so that many will be enabled to return to work, which was impossible while the necessity for regular intravenous drip therapy continued.

Summary

A brief review of cortisone and A.C.T.H. therapy at Guy's Hospital from December, 1950, to July, 1953, is presented. In the early stages, set courses, generally of three weeks' duration, were given, the various dosage schemes of which are described. The diagnoses of the 185 patients who received treatment are tabulated.

Complications encountered included three cases of gastro-intestinal perforation with two deaths, three psychotic episodes, and one case of steroid diabetes. Four abscesses occurred at an injection site.

It soon became apparent that maintenance therapy was going to be essential in many cases, and the long-term treatment of 44 patients is discussed. Eighteen of these were suffering from Addison's disease or pituitary dysfunction, and these were supervised at the endocrine clinic by Dr. P. M. F. Bishop. The remaining 26 cases were diagnosed as follows: polyarteritis nodosa (3); disseminated lupus erythematosus (2); subacute collagen disease (1); scleroderma (5); rheumatoid arthritis (1); pemphigus (6); exfoliative psoriasis (2); eye conditions (6). The manner in which these patients were treated as out-patients and their subsequent progress are described in detail. The results obtained proved highly satisfactory. Many patients entered a phase of remission enabling treatment to be stopped, at any rate for a time. The two patients with exfoliative psoriasis responded poorly, although the acute phase of the condition was greatly helped temporarily.

The manner in which limited supplies of A.C.T.H. may be conserved by the use of slow intravenous drip therapy is stressed.

We should like to thank the physicians under whose care the patients were admitted for the help and co-operation we received from them. In particular we should like to thank Dr. E. J. Moynahan under whose care four of the pemphigus cases were admitted. He proposes to publish these in greater detail at a later date.

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