supraorbital nerve area did little or nothing to relieve the pain, indicating that the source of the neuralgia was deeper and would require an inner Gasserian alcohol injection or a fractional section of the inner half of the sensory root to cure it.

Glossopharyngeal tic, though very much rarer than the trigeminal form, perhaps in the order of 1 to 100 cases, is now better known since I first described it (Harris, 1921). It is still often confounded with trigeminal tic or with otic or geniculate neuralgia, but its definite characteristics should be sufficient to distinguish it. The pain is usually felt on swallowing, and often runs into the ear, which may become so sensitive that the patient will leave the ear for years unwashed. Touches on the tonsil will often start the pain, which is referred to the throat and ear and to the back of the cheek in front of the ear. The painful paroxysms recall the trigeminal type, and the only cure is avulsion of the nerve.

The nerve may be irritated by a basal tumour, and trigeminal tic may also be closely simulated by intracranial pressure from an acoustic neuroma or other basal tumour, such as an intracranial aneurysm of the internal carotid artery.

Summary

Five cases of a form of trigeminal neuritis are described in which paroxysmal trigeminal tic follows at varying intervals after a period of total unilateral facial numbness.

The question whether the cases of trigeminal neuritis described are due to latent disseminated sclerosis is considered disproved.

Paroxysmal trigeminal tic occurs in a considerable proportion of cases of disseminated sclerosis, without previous numbness and anaesthesia of the face.

In many cases of disseminated sclerosis temporary numbness of one side of the face may occur, with anaesthesia and loss of taste on that side. These cases do not later develop paroxysmal trigeminal tic.

Loss of taste, either temporary or permanent, on the front of the tongue is commonly found in unilateral fifth-nerve paralysis in addition to the spontaneous cases of numbness in trigeminal neuritis and in disseminated sclerosis.

Analysis of 2,000 cases of trigeminal tic shows that this neuralgia occurs about twice as often in women as in men.

The lesion producing the numbness and anaesthesia of the face in trigeminal neuritis is probably a root neuritis of the fifth nerve close to or just inside the pons.

The frequency of trigeminal tic, unilateral and bilateral, in disseminated sclerosis is almost certainly due to local irritation of the trigeminal spinal root by the diffuse patches of sclerosis in the pons.

Rare forms of trigeminal pain due to medullary or pontine thrombotic lesions are described.

An occasional difficulty—even impossibility—in producing total anaesthesia and cure of third-division neuralgia, either by injection or by surgical root resection, is described.

Reasons are given for ascribing the origin of trigeminal tic to peripheral causes in the end-nerve filaments in the jaws.

Paroxysmal trigeminal tic of the ophthalmic division is compared with post-traumatic supraorbital pain resembling ciliary neuralgia.

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PROLONGED TREATMENT OF RHEUMATOID ARTHRITIS WITH A.C.T.H. ALONE AND WITH GOLD*

BY

J. GOSLINGS, M.D.

W. HIJMAN

P. M. v. LIMPT

Department of Rheumatology

AND

HENRIËTTE A. v. GILSE

Department of Endocrinology and Diseases of Metabolism

(From the Medical Service, University Hospital, Leyden, Holland)

From the first publications of Hench *et al.* (1949) and Thorn *et al.* (1949) the following conclusions can be drawn: (1) adrenocorticotrophic hormone (A.C.T.H.) has a very favourable effect on the symptoms of rheumatoid arthritis, (2) the symptoms reappear when the administration of A.C.T.H. is discontinued, and (3) with the dosage used untoward reactions appear. When, in October, 1949, a certain quantity of A.C.T.H. ("cortrophine," Organon†) was put at our disposal, we set ourselves to search for a maintenance dose which would keep the rheumatic process under control but cause no untoward reactions; and to inactivate the rheumatic process with A.C.T.H., and during its administration to begin with one of the approved medical therapies, in the hope that no relapse would then occur after discontinuation of the A.C.T.H. injections.

Here, therefore, we concern ourselves exclusively with clinical application. The theoretical bases and the pathophysiological and chemical problems of A.C.T.H. therapy have been dealt with in the comprehensive survey with extensive bibliography of Boland (1950).

Plan of Study

Three women and two men with rheumatoid arthritis, and one man with ankylosing spondylitis, were selected for treatment. The diagnosis was based on the results of the clinical data, biopsies, x-ray photographs, serology, and other non-specific data such as sedimentation rate (Westergren); haemoglobin, etc. In view of the fact that we were striving to find an effective treatment for rheumatoid arthritis, complete rest in bed was prescribed for all the patients for a fortnight before and after the beginning of the A.C.T.H. treatment. This was followed by a period of graded re-educative remedial exercises and mobilization. Spectacular exertions, of which some patients were already capable after a few days, were thus intentionally avoided.

During the pre-treatment period a thorough physical examination was carried out, with special documentation of the condition of the joints (ergometry, measuring, photographing, and filming of the swellings and of limitations of function). Special laboratory investigations were made of kidney function (concentration, phenol red, urea clearance), liver function (galactose-tolerance test, van den Bergh reaction, prothrombin index, cholesterol

*This research was aided by a grant from the Institute for Preventive Medicine, Leyden.

†We are much indebted to Organon, Oss (Holland), who kindly supplied us with the pituitary adrenocorticotrophic hormone used in these studies.

esters, alkaline phosphatase, Hanger test, bromsulphalein test), adrenocortical function (insulin tolerance test, Robinson-Power-Kepler test, total neutral urinary 17-ketosteroids), as well as routine blood smears and counts, and electrocardiograms. There was no restriction of food, apart from a low salt content (about 2 g. NaCl a day), but the composition of the diet was noted daily. No balance studies were made, since we wanted to find the best treatment, and it seemed advisable not to interfere with an increased appetite, from which the patient might benefit.

During the treatment period the investigations were repeated at regular intervals, and at first the blood pressure was taken daily and the weight recorded weekly.

The general scheme of treatment was :

1st day: 3×25 mg. A.C.T.H. intramuscularly, with application of Thorn tests after the first injection.

3 days: 6×10 mg. A.C.T.H.

10 days: 6×7 mg. A.C.T.H.

2 weeks: 6×3 mg. A.C.T.H.

2 weeks: 6×2 mg. A.C.T.H.

2 weeks: 6×1 mg. A.C.T.H.

The dose of A.C.T.H. is expressed in mg. of an American standard preparation. The different lots used have been assayed in accordance with the Sayers test. The equivalent of 25 mg. American standard preparation contains: vasopressin and oxytocin: lot 1, 0.33–0.66 E; lot 2a, 0.7–0.9 E; lot 3x, 0.125 E; lot 4, 0.35–0.70; prolactin, none; thyrotropic and gonadotropic hormone, a very small amount or none.

In determining the quantity of A.C.T.H. to be injected, we followed the basic idea that, after an optimal improvement with a relatively high dosage, the condition could be stabilized with a low maintenance dose.

Sayers *et al.* (1949) and Li (1950) found that already a very short time after injection A.C.T.H. could not be detected in the blood. We therefore considered the possibility that frequent injections might give better results. The 14-day limit was chosen, as any possible relapse would almost certainly fall within this period. Diagnosis of a relapse was based on the reappearance of signs and symptoms of arthritis, in addition to a rise in sedimentation rate (E.S.R. expressed throughout as 1 hour/2 hours value).

Case 1

A woman aged 37—height, 5 ft. 4½ in. (1.64 m.); weight, 7 st. 2 lb. (45.4 kg.)—had had rheumatoid arthritis since 1942, beginning 10 days after fifth delivery. During the first few years treatment with various courses of gold therapy was successful, but a relapse occurred about six weeks after each course. A complete remission during pregnancy in 1948 lasted until three days after delivery. She was a thin, tired woman, not looking ill; the rheumatic process was localized chiefly to the shoulders, elbows, and hands; the mammae were atrophic; and there were remains of a "gold" dermatitis to the right of the mouth. E.S.R. 14/32, Hb 12 g.%. During the last few years menses were irregular, with sometimes an interval of a few months.

With the A.C.T.H. dosage the articular symptoms reacted very quickly, the stiffness first, then the pain, and finally, on the third day, the swelling. On the second day the patient could comb her hair for the first time in five months; the next day she could take off her wedding ring for the first time in four years. On the ninth day the dermatitis, which had been visible for four years, had disappeared. The increasing appetite was, no less striking.

From this time improvement in her general condition was less spectacular, but progress continued during the fifth and sixth weeks (6×2 mg. A.C.T.H. per day). The E.S.R. fell to 1/3, her complaints were limited to tenderness on pressure or painfulness on motion of some proximal interphalangeal joints. Fatigue, however, still persisted. On the 39th day the dosage

was decreased to 6×1 mg., and seven days later the E.S.R. was 5/12, while two days later she complained of slight pain in the right forearm, followed after another five days by measurable swelling of the second metacarpo-phalangeal joint of the right index finger. Most of these symptoms disappeared again with one day of 5×7 mg., and then daily 5×3 mg. of A.C.T.H. At the same time (72nd day) gold treatment was begun.

It is known that at the beginning of gold treatment the E.S.R. often rises and the condition of the patient may temporarily deteriorate. The A.C.T.H. was maintained at 5×3 mg. a day for seven weeks. During this period her condition did in fact grow worse, combined with objective signs in the right shoulder, the right elbow, and some proximal interphalangeal joints, but was definitely less serious than on admission. As soon as the optimal condition was reached again the A.C.T.H. dosage was gradually decreased by one injection a day, while the gold treatment was continued. The gradual decrease in the A.C.T.H. dosage seemed desirable to avoid possible symptoms of a temporary shortage of endogenous A.C.T.H.

On the 138th day A.C.T.H. was discontinued; the patient had by then received a total of 1,960 mg. of A.C.T.H. and 1,540 mg. of gold (aurothioglucose). The gold treatment was then continued with a maintenance dose of 50 mg. once every two weeks. Fourteen weeks later the patient's condition showed a slight but clearly visible deterioration: some finger-joints were swollen again. The gain in weight was maintained (see Fig. 1), E.S.R. 10/25, Hb 12.2 g.%, menses regular, mammae containing glandular and fatty tissue, fatigue less evident.

FIG. 1.—Weight records of five patients treated with A.C.T.H. The weight of the sixth was taken only once, at the beginning of the treatment, as the clinical condition did not permit movement of the patient.

Case 2

A man aged 44—height 5 ft. 6 in. (1.68 m.), weight 9 st. 2 lb. (58 kg.)—had had severe rheumatoid arthritis and psoriasis since 1939, with some complete remissions. Varying success with many types of therapy: amidopyrine ("pyramidon"), gold, manganese preparations, x rays, etc. Since January, 1949, in bad condition, with no favourable reaction to any therapy.

He was an emaciated man, suffering severe pains, looking very ill, with temperature continuously subfebrile to febrile (minimum 37.5° C., maximum 40° C.), blood culture repeatedly negative, E.S.R. 145/154, Hb 8.05 g.%. There was very extensive psoriasis, which latterly had a tendency to improve, and extensive abnormalities characteristic of rheumatoid arthritis in practically all the joints, with contracture and subluxation of both knees.

The severity of this case induced us to prolong the initial period of high-dosage A.C.T.H. On the second day with maximum temperature 37.5° C., his appetite was considerably increased, and he slept well and felt much better. On the fourth day swelling of the left hand began to decrease. The affected joints gradually became less painful, and after a week he needed hardly any analgesic, which before he had used in large quantities. The skin symptoms also showed a rapid improvement. In the third week of treatment the temperature

rose once to 38° C., while the E.S.R., which had dropped to 51/78, was up to 75/108, with the psoriasis worse and the rheumatic complaints showing no further improvement. Dosage was still 6×7 mg. at this time. On the 32nd day of treatment dosage was decreased to 6×3 mg. because of our small supply of A.C.T.H., and his temperature rose almost immediately to a maximum of 39° C., the E.S.R. became 138/150, and swelling of the joints and pains increased, especially in the hands.

An attempt was made to check the process with a relatively high dosage (6×15 mg.) and then to maintain the improved condition with a smaller quantity of A.C.T.H. At first there was the usual favourable effect; the temperature returned to normal, and only the psoriasis did not improve. After a few

from the scheme. Experience with Cases 1, 5, and 6 indicates that this last dose is too small. In view of the shortage of A.C.T.H., we did not dare to risk a relapse, which would compel a temporary increase in dose. On the 65th day gold treatment was started; on the 120th day the patient received her last A.C.T.H. after gradual decrease in the number of daily injections. The patient had had by then a total of 1,839 mg. A.C.T.H. and almost 1,500 mg. aurothioglucose. She received a maintenance dose of aurothioglucose of 50 mg. once every two weeks. Sixteen weeks later her condition was still excellent, with only minimal complaints of the knees. E.S.R. 10/24, Hb 11.3 g.%. Her weight remained constant at 64 kg., and she was very satisfied and cheerful (see Fig. 2).

FIG. 2.—Case 3. Rheumatoid arthritis treated with diminishing doses of A.C.T.H. Gold therapy began on the 65th day and continued with a maintenance dose of 50 mg., administered once every two weeks in the out-patient department. (The top chart shows 17-ketosteroid excretion.)

days of 6×10 mg. a relapse occurred. On the 75th day the A.C.T.H. therapy was discontinued and the treatment with gold begun, while amidopyrine had already been given for a few days. The condition of the rheumatic process remained stationary, but the psoriasis had meanwhile assumed very serious proportions and was of an atypical erythrodermic nature with strong livid colouring. On the 99th day the A.C.T.H. therapy was resumed with a dosage of 8×3 mg. This produced only a slight temporary effect. On the 125th day the A.C.T.H. was finally stopped after a gradual decrease of the number of daily injections.

In all, this patient received 3,170 mg. of A.C.T.H. in two periods of 75 and 27 days respectively, with an interval of 23 days. After this the psoriasis got gradually worse and the rheumatic process took a mutilating form. The patient became cachectic and died approximately 16 weeks after the last A.C.T.H. injection. Necropsy showed bronchopneumonia and atrophy of the adrenal cortex, especially of the zona glomerulosa, with local fibrosis and depletion of lipoids. Microscopical examination of the hypophysis is being carried out.

Case 3

A woman aged 33—height 5 ft. 7½ in. (1.72 m.), weight 7 st. 10 lb. (49.2 kg.)—had had rheumatoid arthritis since 1937, with secondary osteoarthritis of both knee-joints, moderately active and slowly progressive. The patient several times received gold therapy, to which she reacted favourably in the beginning, but not at a later stage. Other forms of treatment were unsuccessful. Several days before each menstruation the pain and stiffness of the joints increased and became most severe during the first two days of each cycle. She was a pale, thin, gloomy woman, with the hands, wrists, elbows, knees, and feet affected. E.S.R. 15/36, Hb 11.6 g.%. With this patient the clinical course of the illness corresponded roughly to that of Case 1. After 30 days' treatment she had only slight pain in the knees when walking upstairs. In the seventh week of treatment (dosage 6×2 mg.), she had a common cold. The E.S.R., which had fallen to 4/10, rose to 24/27. There were no joint complaints. In view of the intercurrent infection, we decided not to lower the dosage to 6×1 mg., and thus deviated

During treatment her menses became slightly irregular, the shortest cycle being 18 days. In spite of the satisfactory therapeutic results, premenstrual intensification of joint symptoms sometimes recurred. Repeated endometrial biopsies revealed both ovulatory and anovulatory bleeding. We were unable to find a correlation between the occurrence of premenstrual complaints and the type of bleeding.

Case 4

A man aged 65—height 5 ft. 7 in. (1.70 m.), weight 11 st. (70 kg.)—had had rheumatoid arthritis since 1942 with contracture of the knee-joints. Various reactions to many kinds of treatment—e.g., gold (last series of injections in 1947), amidopyrine, salicylate, "atophan," "menformon," etc. He had a somewhat grey complexion (aurosis?), but otherwise looked healthy. He was sullen and made no effort to co-operate. The rheumatic process had affected practically all the joints, with a rheumatic nodule on the right elbow and secondary osteoarthritis of both knees. On further physical examination no abnormalities were found, except a trace of pretibial oedema. E.S.R. 125/135, Hb 10.9 g.%. Since February, 1948, he had albuminuria, a full analysis of which had been made elsewhere. Blood pressure, blood urea, renal function, and urine sediment were normal during that period: this was confirmed on admission here. The congo-red test was negative. It was difficult to decide whether we had to deal with a late gold nephrosis of long standing or an albuminuria as an accompanying symptom of rheumatoid arthritis (Schneiderbauer, 1938; *New Engl. J. Med.*, 1947).

In this case of rheumatoid arthritis, too, a very striking reaction was observed at the beginning of treatment. On the 16th day the E.S.R. had fallen to 15/33, and there were no complaints of pain; the swelling had gone, and even the contracture of the knee-joints had diminished. The nodule could no longer be felt. The patient had also undergone a change and become friendly and cheerful. After the dosage had been decreased to 6×3 mg. the E.S.R. rose again (54/68). A higher dosage (6×7 mg.) produced only a temporary fall. After 26 days with 6×7 mg. the E.S.R. was again 120/126.

It is possible that the first rise in the E.S.R. was the result of a knee regression, the second of an intercurrent cold. It is noteworthy that both times the patient had no joint complaints, while objective symptoms of relapse were also absent. On the 60th day the A.C.T.H. therapy was stopped owing to lack of material. The following day signs and symptoms of arthritis reappeared. On the 73rd day A.C.T.H. was once more available and the patient received 8×3 mg. The clinical condition now improved considerably, but the E.S.R. remained very high.

Finally we gradually lowered the dosage by decreasing the number of injections. The patient received a total of 2,625 mg. A.C.T.H. in 118 days. A change-over to amidopyrine had to be stopped because of granulocytopenia.

Because of the albuminuria we were very cautious in the administration of gold. The patient received only a few injections containing a very small quantity of gold. These were immediately discontinued when erythrocytes appeared in the urine. According to the few data available, the albuminuria had since February, 1948, gradually risen from 0.5 to 3 g. per litre. During the two treatment periods the variations were so pronounced (2-40%) that it seemed impossible to draw any conclusion on the influence of A.C.T.H. on the albuminuria.

At his own request the patient left the hospital. On the day of departure a blood sample was taken. When the laboratory reported that the blood urea had risen considerably (96 mg. per 100 ml.) he had already gone. Soon afterwards he was admitted elsewhere. Five weeks after the last A.C.T.H. injection the patient died of uraemia. Necropsy was not performed.

Case 5

A woman aged 56—height 5 ft. 7½ in. (1.71 m.), weight 8 st. 12 lb. (56.5 kg.)—had had very active rheumatoid arthritis since 1948, but received no treatment. The process was localized to practically all the joints, with slight contrac-

ture of both knees. E.S.R. 126/153; Hb 10 g.%. She was undernourished, could hardly walk a few yards, and was sullen and unfriendly. A few abnormalities were discovered during the routine examination; the Robinson-Power-Kepler test was positive, the quantity of urine excreted during the night (500 ml.) being more than the largest quantity (320 ml.) excreted during the day (factor A=17.5). With the insulin tolerance test, the lowering of blood-sugar values was insufficient and occurred too late, the initial level not being reached after two hours.

The articular signs and symptoms improved within an extraordinarily short time from the start of treatment, and the E.S.R. dropped linearly to a level of 10/22 on the 12th day. In view of this favourable effect and the rapid rise in excretion of 17-ketosteroids in the urine (maximum 53.5 mg. per 24 hours) and the high blood-sugar level with the abnormal glucose tolerance test, we lowered the dosage more rapidly: four days 6×7 mg., followed by six days 6×3 mg. and 16 days 6×2 mg. On the 15th day of treatment the pain and swelling of the joints had completely disappeared. In the subsequent period during which the dosage was 6×1 mg., a relapse occurred with a rise of the E.S.R.

With one day on 5×7 mg. and then 5×3 mg., the patient again reached an optimal condition. At this point a gold treatment was started. As pronounced diabetes had meanwhile developed (see below), we decided to stop the A.C.T.H. (on the 66th day). Next day there was an acute and violent swelling of several metacarpo-phalangeal joints, with redness and distended veins suggestive of gout. This disappeared after a few days, while a relapse of the rheumatoid arthritis gradually became perceptible in all the previously affected joints, the process being, however, clinically less violent than on admission. The clinical treatment with gold and physiotherapy was continued. Four months after the cessation of A.C.T.H. administration the patient's general condition was tolerable.

FIG. 3.—Case 5. Rheumatoid arthritis treated with A.C.T.H. The total daily dose of A.C.T.H. was divided over six injections, that of insulin over two injections.

†Aurum = First day of gold therapy. E.S.R. = First hour value obtained by Westergren method. G.T.T. = The blood sugar was determined initially before the oral administration of 50 g. of glucose, and ½ hour, 1 hour, 1½ hours, 2 hours, and 2½ hours later.

the rheumatic process much less active, and the E.S.R. 58/79; she could then walk fairly well.

Special Observations

As stated, the patient had an abnormal blood-sugar curve to start with. Her fasting blood-sugar values were constantly at the upper limit of normal or abnormally high (110/136 mg. per 100 ml.). During the first days of treatment they rose to a maximum of 187 mg. per 100 ml., and then gradually returned to the initial level. In the first week the glycosuria was maximally 34 g. daily, which was much more than with the other patients. These signs of disordered carbohydrate metabolism at first diminished, then suddenly progressively increased during the low dosage of 6×1 mg. (fasting blood sugar 250 mg. per 100 ml., glycosuria up to 200 g.). It is possible that an inter-current cold was a provocative agent in this case. When during four weeks the diabetes did not improve we decided to discontinue the A.C.T.H. therapy (66th day). The fasting blood-sugar levels remained high, and the glycosuria diminished slightly (the greatly decreased food intake during the relapse occurring in this period must be taken into account). When, after a few weeks, the condition remained unchanged, though perhaps on a lower level, we gave the patient insulin. With a relatively low dosage (maximum of 36 units daily), administered during one month in gradually diminishing quantities, the starting condition was reached three months after the last A.C.T.H. injection (see Fig. 3).

As a second untoward reaction, we must report a series of symptoms which were a result of vascular occlusion: paraesthesiae in the fingers, with cold finger-tips; at a later period disappearance of the radial pulse and failure to register oscillation on oscillometric examination of the left upper arm; and finally a homonymous hemianopsia on the left side as a result of an occlusion of the right posterior cerebral artery. Whether the A.C.T.H. can be held responsible for the vascular signs in this patient is unknown. An arteriosclerotic retina was diagnosed before the treatment, and the renal threshold for glucose excretion was too high. The already existing pre-diabetic condition also seems to point to general arteriosclerosis. The occlusion of the radial artery was accompanied by relatively slight clinical signs of decreased peripheral arterial blood supply. This points to a good collateral circulation and a vascular obliteration which has developed very slowly, again suggesting a diminished circulation before the administration of A.C.T.H.

It is also worthy of note that a parotid swelling (chronic parotitis?) which the patient had shown for some years disappeared completely after four days of A.C.T.H. injections, to reappear only two months after cessation of this treatment. Biopsy revealed a (sub-)chronic inflammation with lymphocytic infiltration.

Case 6

A man aged 32—height 5 ft. 7½ in. (1.71 m.), weight 9 st. 11 lb. (62.1 kg.), known to us since 1947 as suffering from ankylosing spondylitis with typical x-ray signs in the sacro-iliac joints and vertebral column. He had been treated several times with x rays and amidopyrine, with varying success. The E.S.R. was never lower than 45/80.

He showed severe spinal stiffness, and was unable to attend to his administrative activities; E.S.R. 73/115, Hb 12.2 g.%. The E.C.G. showed a short P-R interval and prolonged QRS time.

A.C.T.H. treatment had a very rapid effect. On the morning of the third day the patient could leave his plaster bed without help, which he had never been able to do before. This as well as the increased 17-ketosteroid excretion (maximum 67.8 mg. in 24 hours) was sufficient reason for us to lower the dosage more rapidly than originally planned. After 15 days the patient received 6×2 mg. A.C.T.H. a day, the E.S.R. being at that moment 4/9. Except for the sudden appearance of an auricular fibrillation (see below), the clinical progress continued uninterrupted, and the mobility of the vertebral column increased regularly. After the patient had received 6×1 mg. daily for a week, there was a slight relapse and the E.S.R. rose to 45/84. With a dosage of 5×7 mg. for a day,

followed by 5×3 mg. for 39 days, the complaints once again rapidly disappeared and the E.S.R. dropped, though more slowly than at the beginning. In this period amidopyrine medication was started, while the A.C.T.H. dosage was gradually and regularly reduced, as in the case of patients 1 and 3. With one dose of 3 mg. a day the complaints began to return (17th week). Amidopyrine, in combination with 2×3 mg. A.C.T.H. a day, created a very satisfactory condition, however. This scheme of treatment was continued for 42 days in the out-patient department; the patient had already resumed his normal activities (16th week). On the 175th day the A.C.T.H. treatment was finally stopped and the patient's condition remained satisfactory. The E.S.R. did not run parallel with the good clinical condition and fluctuated round values of 45/70. The weight remained constant.

The abnormal E.C.G. has already been mentioned. Auricular fibrillation occurred on the 23rd day, and the E.C.G. showed that this fibrillation was a rapid one with aberrant ventricular complexes. The patient reacted promptly to quinidine sulphate, and the A.C.T.H. therapy was continued. No more sudden attacks occurred. The A.C.T.H. was not necessarily directly responsible for the auricular fibrillation, for it can appear spontaneously with the mentioned pre-existing E.C.G. alterations.

Laboratory Data

Thorn Tests.—These were performed on the first day of treatment after administration of 25 mg. A.C.T.H. intramuscularly. Circulating eosinophils were counted in the counting-chamber (diluting solution: eosin 0.1 g., 40% formol 1 ml., distilled water to 100).^{*} In five of our six cases a fall of more than 50% was noticed after four hours. In some this fall still continued after that time. In Case 2 there had been an eosinopenia for more than a year before treatment. The rise of more than 50% in the U/C ratio was seen only in three of the six patients (Cases 1, 3, and 4). There was no correlation between the results of these tests and a good clinical reaction, and no connexion could be shown between the reappearance of eosinophilic cells and the occurrence of a relapse.

Carbohydrate Metabolism.—In all cases there was a rise of the fasting blood sugar, which returned to normal with lower dosage. The glucose-tolerance curves were temporarily of a lag type. The most striking deviations were found in Case 5 with diabetes. The other two women showed only temporary glycosuria. There was no ketonuria, the CO₂-combining power of the blood fluctuated, but remained within normal limits.

Electrolyte Metabolism.—In view of the fact that retention of sodium and chloride was expected, combined with an increased potassium excretion, we prescribed a low-sodium diet (about 2 g. NaCl) and 4–5 g. potassium daily. The blood values remained strikingly constant. With all the patients we noticed an almost complete disappearance of sodium and a great decrease in the amount of chloride in the urine during the first days. Parallel with this there was a slight retention of fluid in the first week. No oedema was seen, and the blood pressure remained constant.

17-Ketosteroids.—The urinary excretion of the neutral 17-ketosteroids increased considerably, reaching its maximum after about a week. This maximum was about 30 mg. per 24 hours, except in Cases 5 and 6, in which it was about 60 mg. During the further course of A.C.T.H. treatment these values diminished, but they

^{*}This method has been used in our department for the last four years and has proved to be satisfactory in all respects. It was described for the first time by Zollikofer (*Zeitschrift für mikroskopische Technik*, 1901).

always remained above the initial levels, which were on the whole subnormal. After discontinuation of A.C.T.H. therapy there was a rapid return to the initial value. Results of a chromatographic analysis of the 17-ketosteroid mixture produced under influence of A.C.T.H. will be discussed elsewhere.

Serology.—The following serological tests were regularly performed: anti-streptolysin-titre, L and O agglutination, and the modified Rose test (van Loghem-Langereis, 1950). The clinical condition and the values of the titres showed a distinct parallelism (see table). We are here at variance with the results obtained by Ragan *et al.* (1949). The explanation may be that our period of observation was longer.

Table Showing Changes in the Serological Reactions in Case 3. A.C.T.H. was Administered During 120 Days

Day of Treatment	A.S.T.	L Aggl.	O Aggl.	Sensitized Sheep Cell Aggl.
1	80	160	160	32
8	80	80	160	16
16	80	160	160	0
24	50	20	160	8
31	32	20	40	0
52	40	0	180	0
66	25	20	0	0
80	45	0	20	0
94	45	0	20	0
115	125	0	40	6
134	70	0	40	0
194	70	0	40	8
	80	0	40	0

X-ray Photographs.—No change occurred in x-ray pictures of the joints.

Temperature.—Apart from the change already recorded in Case 2, we saw an immediate drop of 0.5° to 1° C. in some of the patients, even in cases where the temperature was apparently normal before treatment.

Weight.—With all the patients, appetite increased from the first day. On an average, the need for calories was roughly doubled. In accordance with this, there was a regular increase in weight, which certainly cannot be explained on the basis of fluid retention (see Fig. 1).

Untoward Reactions

Apart from the untoward reactions recorded in the clinical reports of the individual patients, the following details seem worthy of note. After the first injections, two women (Cases 1 and 3) complained of vague spasms in the abdomen (uterus?), which were difficult to locate. These spasms disappeared spontaneously after a few minutes. A few weeks after the beginning of the treatment, all the patients developed acne, chiefly in the face. The female patients showed a slight increase of hair on the cheeks, upper lip, and extremities. The face became fuller, but a real "moonface" was not to be observed. The pigmentation of the skin increased more or less intensely, diffused as well as localized in freckles, in the folds of the skin, and on places of venepuncture, injections, biopsy scars, Pirquet reactions, and, in Case 3, on the elbows and the knuckles of the hands. All the symptoms mentioned disappeared during the protracted lower A.C.T.H. dosage (see Figs. 4 and 5). We were very much struck by the similarity of these pigmentations to those seen in Addison's disease.

General Remarks on Dosage

On the results of experiments, Li suggested the desirability of dividing the daily dose over several injections. We think this suggestion may be of importance to the

FIG. 4.—Case 3. Pigmentation of the hand on the 62nd day of treatment. Dosage 6×2 mg. A.C.T.H. daily; total amount received, 1,359 mg.

clinician. On transition from 4×5 mg. to 6×3 mg. (Case 1), the laboratory data indicated an intensified adrenocortical activity, which was fully comparable to that at the beginning of the administration of A.C.T.H.: retention of water, Na and Cl; K excretion; glycosuria with increased fasting blood-sugar values; and increase of the 17-ketosteroid excretion.

From our studies, we are inclined to draw the conclusion that the dosages originally indicated by Hench *et al.* (1949), Thorn *et al.* (1949), Elkinton *et al.* (1949), Markson (1949), and other authors are too high for moderately severe cases. This view has meanwhile also been expressed by other workers (Mach *et al.*, 1950; Bröchner-Mortensen *et al.*, 1949). We, too, perhaps set the initial dose too high. This dose leads to a rapid decrease of the E.S.R. with remarkable improvement of the clinical condition, but at the same time causes signs and symptoms of hyperfunction of the adrenal cortex. During the protracted low dosage thereafter these untoward reactions mostly disappeared again, while the rheumatic process remained favourably

FIG. 5.—Case 3. Return to normal condition—14 weeks after last A.C.T.H. injection.

(The two photographs were taken under identical conditions.)

affected. It thus seems worth investigating in the future what can be achieved with a lower dosage from the beginning, even though results may be obtained more slowly. It may be possible to avoid untoward reactions in this way. And with clinical application in cases of rheumatoid arthritis it is not always necessary to make the patients reach an optimal condition in a very short time.

In four cases (1, 3, 5, 6) it was possible to maintain the clinical remission with 6×2 mg. In three cases (1, 5, 6) the dose was lowered to 6×1 mg. a day; in all three the result was a relapse. Two patients (2, 4) had a recurrence of signs and symptoms with a higher dosage (6×10 mg. and 6×7 mg. respectively). Both were serious cases complicated by other affections.

Summary

Five patients with rheumatoid arthritis and one with ankylosing spondylitis have been treated with A.C.T.H. in low dosage over a period of two to six months.

In three moderately severe cases of rheumatoid arthritis and in one serious case of ankylosing spondylitis the result was favourable. In two cases of rheumatoid arthritis with a complication (psoriasis, albuminuria) the improvement was temporary and relapse occurred in spite of a repetition of the initial high dosage.

The condition of the four favourable cases was maintained with 6×2 mg. of A.C.T.H. daily. A dosage of only 6×1 mg. daily resulted in a relapse in three of them.

An attempt was made to maintain their improved condition with gold therapy. More experience with this combined treatment is required before conclusions can be drawn.

The commonly known untoward reactions were observed in a varying degree. One patient developed a serious diabetes and also showed symptoms of vascular occlusion. These phenomena gradually disappeared with a low dosage or after discontinuation of the A.C.T.H.

We are much indebted to Professor Dr. S. E. de Jongh for his invaluable advice and the continuous interest he took in our work, to Professor Dr. A. Querido for his encouragement and guidance, to Professor Dr. J. Mulder and Professor Dr. E. Gorter for the facilities granted, to Dr. A. J. Zwart, Voorspuys, Mr. W. A. L. Dekker, Dr. H. P. Jonxis, and Dr. K. D. Wotman for the chemical examinations, to Mr. A. Kassenaar for the hormone analyses, and to Dr. J. J. van Loghem and Dr. E. J. van Loghem-Langereis for the serological investigations. For technical assistance our thanks go to our nursing, laboratory, and secretarial staff.

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BURNS—I. INITIAL TREATMENT, LOCAL AND GENERAL*

BY

R. P. OSBORNE, F.R.C.S.

(From the Plastic Surgery Department, Royal Southern Hospital, Liverpool, and Ministry of Pensions Hospital, Stoke Mandeville, Bucks)

A very considerable number of articles have been written on this subject during the last 10 years. The purpose of this paper is not to present anything new, but to emphasize certain points which, while often neglected, are essential if the objects of treatment are to be achieved. In brief, these objects are to restore the patient to his or her normal mode of living in the shortest possible time and with the minimum loss of function and disfigurement.

Success in these aims will be greater in those hospitals where there exists a plan of treatment from admission to discharge—a plan understood and adopted by all concerned. Experience may be a great teacher, but the registrars and house-surgeons, who so often play a major part in these cases, should from the outset have available the experience of their seniors; otherwise their bitterness will be as nothing compared with that of the patient.

Prevention and First Aid

Between wars, burns continue to occur with depressing frequency (Colebrook, 1950); depressing because so many could be avoided by common-sense methods. Fireguards should be essential, and not luxuries, wherever there are children or known cases of epilepsy in the household. The shining red element of an electric fire is an object of attraction to a child—an object to be grasped by the exploring hand with possible crippling consequences, and yet so easily avoided if the fire is fixed high up on the wall of the room. Tea-pots, tea-cups, and cooking utensils should be placed out of reach of a child's hand.

Immediately after the injury the patient will be suffering from shock of nervous origin—that is, akin to fainting. For this condition the treatment consists in keeping the patient warm (not hot), giving sweet drinks, and imparting calm reassurance. The use of narcotics will depend upon the presence of a doctor and the absence of any other undiagnosed injury.

The burned areas should be covered with the cleanest material available at the site of the accident, varying from sterile gauze in factory dressing stations to the cleanest linen material in the home, kept in position by firm but not tight bandages. Blisters should not be punctured. Clothing should not be removed unless there is a considerable delay before a hospital can be reached.

Burns Units

The Burns Unit of the Birmingham Accident Hospital, designed and planned with such magnificent results by Bourdillon and Colebrook (1946), is something to envy. With the present financial state of the National Health Service it is unlikely that other cities will be so fortunate. A compromise, representing a very definite step in the right direction, was reached by Professor Kilner during the war: it involved the sacrifice of a corner of the ward by converting it into a completely enclosed dressing-room. The expense involved is small and the beds are reduced by only one. Burns should not be dressed in the general ward.

*Read in opening a discussion in the Section of Surgery at the Annual Meeting of the British Medical Association, Liverpool, 1950.