# ACUTE DISSEMINATED ENCEPHALOMYELITIS TREATED WITH A.C.T.H.

BY

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In 1951 I drew some analogies between the neurological syndromes of serum sickness, polyarteritis nodosa, and acute disseminated and post-exanthematous encephalomyelitis (Miller, 1951). All these conditions show a tendency to gross and often evanescent focal symptoms arising at every level of the nervous system, occasional apoplectic syndromes suggestive of lesions involving major cerebral blood vessels, and pathological changes concentrated in close relation to the cerebral vasculature. It was suggested that some such cases of acute disseminated encephalomyelitis may have their foundation in an allergic vasculitis—an "urticaria of the nervous system"—and trial of cortisone or A.C.T.H. in the treatment of these conditions was suggested.

Although these drugs are known to be without beneficial effect in experimental acute infections of the nervous system of virus origin, such as equine encephalomyelitis and Lansing poliomyelitis (Milzer, 1951), Moyer and his co-workers showed in 1950 that adequate dosage with A.C.T.H. protects effectively against the clinical manifestations of experimental "allergic" encephalomyelitis produced in guinea-pigs by repeated injection of heterologous (rabbit) brain emulsion. Pathological changes in the brains of the protected animals were minimal. Whether such protection is due to inhibition of antibody formation or to a more purely vascular reaction at the site of the lesion (as in inhibition of the Shwartzman phenomenon) is undecided.

Kabat *et al.* (1952) have produced pathological evidence suggesting that the inhibitory effect of cortisone (Kabat *et al.*, 1951) on the development of the similar experimental encephalomyelitis produced in the rhesus monkey by injections of heterologous and homologous brain tissue emulsified with Freund adjuvants (Kabat *et al.*, 1947; Morgan, 1947) is due to suppression of the granulomatous response to the antigenic brain emulsion at the site of injection. It is possible that this local granulomatous reaction is responsible for antibody production; at any rate it appears to be an invariable accompaniment of the development of encephalomyelitis under these experimental conditions (Kabat *et al.*, 1948). Kabat's assumption that the local response plays a causal part in the pathogenesis of the encephalomyelitis is, however, not beyond question: suppression of the neurological illness could be interpreted as a parallel effect of cortisone on hypersensitivity reactions rather than as a secondary result of suppression of the granuloma.

Evidence of the mode of action of cortisone and A.C.T.H. in anaphylactic hypersensitivity in general is somewhat conflicting, and Kabat *et al.* (1952) believe that the balance of such evidence is in favour of inhibition of antibody production as the effective mechanism. In support of this is the observation that whereas these drugs completely or almost completely inhibit the active Shwartzman phenomenon, which depends on the active production of antibody, they are much less effective (if indeed they have any action at all) in inhibiting the passive Shwartzman phenomenon caused by reaction of antigen with antibody already present. In their view the undoubted inhibition of experimental acute disseminated encephalomyelitis by cortisone and A.C.T.H. is probably due "to an alteration in the experimental conditions shown to be necessary for the production of the disease, rather than to any fundamental effect on the disease itself." The pathogenesis of human acute disseminated encephalomyelitis is unknown, and Kabat's view, if correct, provides a further reason for hesitancy in anticipating an effect of cortisone on the human disease analogous to that seen under experimental conditions. Furthermore, should the action of the drug be in fact due to inhibition of antibody production, it is understandable that, even granting the existence of some pathogenetic relationship between experimental allergic and human—for example, post-infective—encephalomyelitis, prophylaxis of the disease in man might be possible but therapy ineffective if the established condition represents a response to antibody already formed at the onset of the illness.

It had previously been shown that some protection against the development of experimental allergic encephalomyelitis was offered by the administration of nitrogen mustard (Koprowski *et al.*, quoted by Moyer *et al.*, 1950) or of salicylates (Good *et al.*, 1949), both of which block antigen-antibody reactions. Antihistamine drugs (Lumsden, 1949) have also been shown to offer some protection against allergic encephalomyelitis in the guinea-pig, though they were without therapeutic effect in the established condition. In this last instance, however, pharmacological evidence would suggest a suppressive action on the "peripheral" pathological expression of an antigen-antibody reaction rather than an inhibition of the reaction itself.

In 1949 Pickar and Kramer reported prompt improvement of a single case of encephalomyelitis following antirabic vaccination (showing a strongly positive skin reaction to the vaccine) after the administration of diphenhydramine hydrochloride.

Glaser and Smith (1951), in reviewing encephalomyelitic syndromes following antirabic therapy, described a fatal case in which 100 mg. of cortisone was given to the patient before he expired. Garrison (1952) reported "dramatic improvement" in a single case of encephalomyelitis complicating antirabies vaccine (phenolized rabbit-brain virus) treated with large doses of cortisone (375 mg. daily for two days, and 100 mg. daily during the subsequent four days). This patient showed great improvement within 24 hours, by which time his high fever subsided. He remained drowsy, however, for four days and retention of urine persisted for six days: five weeks later a single extensor plantar response was the only residual evidence of his illness.

The present paper reports results obtained in a preliminary series of seven cases of acute disseminated encephalomyelitis treated with A.C.T.H. The difficulty of assessing the value of therapy in this disease is evident, as the condition often recovers spontaneously with dramatic suddenness. The results obtained cannot be claimed to be conclusive, but they suggest that the drug may have some value in the therapy of human encephalomyelitis in keeping with its known effectiveness in protecting animals against experimental "allergic" encephalomyelitis.

### Selection of Material and Method of Treatment

The material used comprises seven cases clinically diagnosed as acute disseminated encephalomyelitis. All these showed evidence of an acute non-suppurative inflammatory disease of the neuraxis arising in the absence of any relevant neurological past history—except for Case 5, which was regarded as a probable instance of relapsing encephalomyelitis. Tests for syphilitic tuberculous infection of the nervous system were negative in every case, no patient showed recognizable clinical features of infection with the familiar neurotropic viruses, and serological tests for toxoplasmosis were negative in Cases 5 and 7, in which this appeared to be a possible diagnosis. The diagnostic criteria formulated by McAlpine (1931) were found to be of considerable value in assessment. Cases in which there was real doubt about the diagnosis were excluded from the series, as were several patients in whom the diagnosis was clearly correct but who were already showing evidence of spontaneous improvement when they were first seen.

All the patients reported were deteriorating clinically at the time treatment with A.C.T.H. was instituted. The first three cases were treated with A.C.T.H., given by subcutaneous hyalase drip as a measure of economy, but as increasing supplies of the drug became available six-hourly intramuscular injections of 25 mg. were given routinely, augmented by occasional additional injections if a rise in the eosinophil count suggested that 100 mg. daily was physiologically ineffective. Laboratory control was not maintained, however, in the two cases that followed chicken-pox (Cases 2 and 4), which were treated in other hospitals.

The Table summarizes the main features of these cases, which are amplified below.

*Summary of Main Features*

| Case No. | Age in Years | Preceding Infection, etc. | Neurological Syndrome | C.S.F. | Duration of Symptoms at Start of Treatment | Duration of Treatment in Days | Total Dosage of A.C.T.H. (mg.) | Control by Eosinophil Counts | Progress after Institution of Treatment with A.C.T.H. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | Respiratory illness | Transverse myelitis | Normal | 42 hours | 5 | 200 | + | Apparently dramatic response. Rapid and complete recovery |
| 2 | 6 | Varicella | Stupor, flaccid quadriparesis, ataxia | ,, | 5 days | 4 | 125 | 0 | No dramatic response. Good recovery within four days |
| 3 | 31 | Chilling only | Transverse myelitis, with some drowsiness | ,, | 12 ,, | 7 | 700 | + | Improvement within 12 hours. Fair recovery |
| 4 | 6 | Varicella | Coma, meningism | Mixed pleocytosis (16 cells) | 48 hours | 3 | 300 | 0 | Deterioration during first 15 hours. Improvement began after 36 hours. Complete recovery in seven days |
| 5 | 14 | Fifth post-coryzal episode of apparent recurrent encephalomyelitis | Stupor, cerebellar syndrome, diplopia | Normal | 12 ,, | 1 | 100 | + | Improvement within six hours. Complete recovery in seven days |
| 6 | 30 | Nil | Severe ascending myelitis, with meningism | 1. Normal<br>2. Mixed pleocytosis (36 cells) | 19 days<br>28 ,, | 8<br>5 | 560<br>575 | 0<br>+ | Great deterioration<br>Slight deterioration |
| 7 | 12 | (Brother of Case 5) Coryza | Stupor, cerebellar syndrome | Normal | 15 hours | 3 | 325 | + | Improvement within 12 hours. Complete recovery in three days |

### Case 1

*Transverse myelitis developing after acute respiratory illness. Treatment with A.C.T.H. began within 42 hours of onset. Apparent improvement within one and a half hours of first injection. Transient increase of disability 36 hours after beginning treatment was associated with a rise in the eosinophil count, and continued improvement rapidly followed an increase in dosage. 200 mg. of A.C.T.H. was given in a hyalase drip over five days, and complete recovery occurred in seven days.*

On October 24, 1951, a 22-year-old medical student developed an acute respiratory illness of a type which was common in his neighbourhood at the time. This began with 24 hours of laryngitis followed by fever and cough. He became short of breath and developed moist sounds at both lung bases and in the right axilla. He was given penicillin and sulphonamides by his doctor, and although his evening temperature remained between 99 and 100° F. (37.2 and 37.8° C.), his condition was improved on the fourth day. On the night of the fifth day, however, he was awakened from sleep by severe pain in the small of the back. The pain was chiefly in the muscles, more severe on the right than the left, and it was so intense in every position that it prevented sleep after the onset. Next morning the pain was still intense, and by the afternoon of the following day (sixth day of illness) he found some difficulty in raising himself from the bed.

Examination on the evening of the same day revealed a temperature of 101.5° F. (38.6° C.), tenderness of the quadratus muscles, and weak flexion of the back and hips. There were no reflex or sensory changes, but the story was highly suggestive of a developing myelitis, and he was admitted to hospital. Later that night the plantar responses became equivocal and pronounced dysuria developed. The next morning (seventh day of the illness) he had developed severe weakness of both legs and bilateral partial foot-drop, with extensor plantar responses; micturition had become so difficult that manual pressure on the bladder was required. By the afternoon of the same day the back pain was less intense but weakness of the legs and back more profound, and micturition more difficult. Arrangements were made for catheterization and tidal drainage, but again the bladder was emptied successfully by manual compression. There was no headache or meningism, and the spinal fluid was normal in pressure and composition.

At 6 p.m. on the seventh day, 42 hours after the onset of neurological symptoms, he was given 10 mg. of A.C.T.H. intramuscularly, and a subcutaneous drip containing 20 mg. of A.C.T.H., 1,000 units of hyalase, and 250,000 units of penicillin was given via the soft tissues of the thigh. At this stage the eosinophil count was 309 per c.mm. The patient described great subjective improvement within 90 minutes of the initial intramuscular injection. For the first time in 21 hours he passed urine without difficulty; he also claimed some improvement of power in the legs, which could not be objectively confirmed.

During the next 24 hours the patient was given the 20 mg. of A.C.T.H. in the initial hyalase drip, and he again claimed improvement in his general condition and in the power of his legs. His eosinophil count, however, had dropped only to 206 per c.mm., and next morning (ninth day of illness), when a second similar drip had been running for 12 hours, he once more found difficulty in micturition. The eosinophil count at this time was 211 per c.mm., and in view of the failure to obtain a better reduction it was felt that dosage was physiologically inadequate. The drip was therefore continued, but a further boosting dose of 10 mg. of A.C.T.H.

was given. Within four hours he was again passing urine normally and the eosinophil count had fallen to 92 per c.mm. The strength of the subcutaneous drip was therefore doubled. It now contained 40 mg. of A.C.T.H. in the pint (570 ml.), and this amount, given every 24 hours during the next three days, succeeded in bringing the eosinophil count down to between nil and 6 per c.mm.

From the time of the second boosting dose there was no further difficulty with the bladder, and improvement was progressive and remarkably rapid. By the morning of the tenth day there was a striking objective improvement in the motor power of the legs and the patient could easily sit up unaided. The plantar responses, which the previous day had been clearly extensor, became equivocal, and on the morning of the eleventh day they were flexor, and remained so. When the drip was dismantled, 72 hours after the second boosting dose was given, there was no muscular weakness or abnormal physical signs. The temperature had become normal within 12 hours of the starting of treatment, and by the time treatment was discontinued the E.S.R. had fallen from 42 to 34 mm.

On the thirteenth day of the illness the patient was allowed out of bed and walked the length of the ward without difficulty. However, he had some pain in the back during the following night, and he was therefore kept in bed for a further three days, during which time his sole complaint was of some nocturnal discomfort in the back. By the seventeenth day these symptoms had entirely disappeared, and his E.S.R. had fallen to 20 mm. in the hour. He was able to walk without difficulty and was discharged to his home.

Convalescence was uneventful, the only residual symptoms being occasional backache and some stiffness and pain in the muscles of the left calf and thigh. These symptoms disappeared completely within three weeks, and there has been no subsequent disability of any kind.

### Case 2

*Encephalitic illness with flaccid quadriparesis beginning in a child of 6 five days after the appearance of chicken-pox. Treatment was started five days after the onset of symptoms and 25 mg. of A.C.T.H. was given daily by hyalase drip during the subsequent three days. During this time there was only slight improvement. On the last day of treatment the strength of the drip was doubled, and during this period of 24 hours, in which she was given 50 mg. of A.C.T.H., rapid and complete recovery occurred.*

Ten days before admission to hospital this 6-year-old girl developed a typical chicken-pox rash and was well in herself within 48 hours of its onset. Five days before admission, however, she stopped eating, complained of feeling generally unwell, went spontaneously to bed, and slept a great deal during the day as well as at night. Two days before admission she became unsteady on her feet and with her hands, weak in all her limbs, drowsy, and apathetic. She complained of severe headache and had much difficulty in micturition.

Examination on admission revealed no fever, neck stiffness, or abnormal signs in the cranial nerves. The pupils and optic fundi were normal and there was no nystagmus. The child was stuporous, answered questions with great difficulty, and was grossly ataxic. She could not sit up, though she could place her two forefingers together with fair accuracy. The limbs were completely flaccid and the deep reflexes profoundly depressed symmetrically. The plantar responses were extensor. There was no family history of tuberculosis, or any preceding history of relevant disease, the Mantoux reaction was negative, and the spinal fluid entirely normal in pressure and composition. The initial eosinophil count was only 12.5 per c.mm,, and in view of this initial low level it was not possible to assess the physiological adequacy of A.C.T.H. dosage by serial counts.

At 7 p.m. on the day of admission to hospital (ten days after the appearance of the chicken-pox rash and five days after the onset of symptoms), a hyalase drip was given by way of the soft tissues of the thigh, and during each of the next three periods of 24 hours she received a pint (570 ml.) of saline containing 25 mg. of A.C.T.H., 1,000 units of hyalase, and 250,000 units of penicillin. There was no dramatic improvement. On re-examination after three days' treatment she was more easily roused and more willing to talk, the hypotonia was less profound, and there was some improvement in muscular power, but the deep reflexes and plantar responses were unchanged.

In view of the absence of any clear response and of the impossibility of assessing whether a physiologically effective dose was being given, it was decided to discontinue treatment. During the next 24 hours, however, the remaining allotment of A.C.T.H. for this patient (50 mg.) was given in the form of a hyalase drip twice the strength of those previously administered.

During this 24 hours she showed much improvement, and at the end of this period she could sit up, take food, and talk freely. The deep reflexes were still sluggish, but the plantar responses had become flexor. Improvement was maintained, and on the next day she was reading comics and was able to get out of bed and play in the room. Ten days later she was discharged without symptoms or residual physical signs, and her health has since been excellent.

### Case 3

*Transverse myelitis of gradual onset, with some impairment of consciousness, after chilling in a man aged 31. Treatment was begun 12 days after the onset of symptoms, and during the subsequent seven days 700 mg. of A.C.T.H. was given. There was appreciable improvement within 12 hours, and this was continued. On conclusion of treatment spastic paraplegia remained, and slow improvement has occurred during subsequent months.*

Thirteen days before admission to hospital this 31-year-old man was working as an erector on a high building in very cold weather. The next morning he awoke feeling miserable and had a weary sensation in his legs. These symptoms persisted during three days at work, and on the fourth day of the illness severe pain occurred in both legs and he found it difficult to cycle home. He stayed in bed and was seen by his doctor two days later. On this, the sixth day of the illness, he became very drowsy, and the pain in the legs spread up to the lumbar region. Two days later, however, he felt better and got out of bed to see the doctor; he found, however, that his legs were so weak that he could not walk for more than 20 yards, so he returned to bed. During the next five days his condition deteriorated. Severe back pain continued and there was progressive weakness of the legs, which twitched a good deal during the night. From the tenth day of the illness he noticed increasing difficulty in passing urine.

On admission to hospital on the twelfth day of his symptoms he was drowsy, but gave an excellent history when roused. There was no neck stiffness or fever. The abnormal findings in the nervous system were spastic weakness of the right arm with increased reflexes, symmetrical absence of the abdominal responses, spastic weakness of both legs, more pronounced on the left, with exaggerated knee-jerks and ankle clonus. The plantar responses were bilaterally extensor and a crossed extensor reflex was obtained on both sides. There was profound impairment of superficial sensation below and including the eighth thoracic dermatome. Vibration sense was intact, but muscle-joint sense was greatly impaired peripherally, and the patient stated that while he was quietly lying in bed the legs felt as though they were dangling over the side. He could hardly move the left leg at all, and could raise the right knee only a few inches from the bed. He could not dorsiflex the left foot, and this movement was weak on the right. Spinal fluid was entirely normal, and the blood eosinophil count was 180 per c.mm.

A subcutaneous drip containing 40 mg. of A.C.T.H., 1,000 units of hyalase, and 250,000 units of penicillin was given

through the soft tissues of the thigh. Twelve hours later the eosinophil count had dropped to 50 per c.mm. and there was a striking improvement in the patient's clinical condition. Consciousness was clear, and, although reflex changes were as before and there was no alteration in sensory level, all movements of the right leg were greatly improved and power in the left leg was as good as that in the right leg had been the previous evening.

On the second day of treatment the patient stated that the lower part of his body felt less numb, but there was no objective sensory improvement. Dysuria was no longer present and spontaneous twitching of the legs had ceased. He was now able to perform isolated movements of the toes of the right foot, and the crossed extensor response was no longer obtainable on either side. However, his eosinophil count had risen to 200 per c.mm., although two intramuscular boosting doses each of 20 mg. of A.C.T.H. had been given during the course of each day, raising the actual total daily dosage to 80 mg. during the first 48 hours. In view of the doubtful physiological response the hyalase drip was abandoned at the end of this period, and during the subsequent five days the patient was given 100 mg. of A.C.T.H. daily in six-hourly doses of 25 mg. each, and his eosinophil count remained in the region of 20.

During these five days improvement was rapid. On the fourth day of treatment (second day of full dosage) deep reflexes in the right arm were normal and all movements of the legs had improved. On the sixth day of treatment there was shrinkage of the area of sensory loss from above and below.

Improvement continued after completion of the course of A.C.T.H. There was one brief setback on the fourth day after treatment was abandoned, during which the patient complained of drowsiness, some increased difficulty in using the legs, and an increase of numbness on the front of both thighs. However, the next day improvement continued spontaneously.

Seven days after the completion of treatment leg movements were full but weak, and the patient could hoist himself into a sitting position with his legs over the side of the bed, though they were not yet strong enough to support the weight of the body unaided. Muscle-joint sense had returned completely, and superficial sensory loss was limited to symmetrical areas over the second lumbar dermatome. Abdominal responses remained absent, knee- and ankle-jerks were overbrisk, and the plantar responses were extensor.

Three months after the illness the findings were those of a featureless spastic paraplegia of mild degree without sensory change, and the patient could walk well with the aid of sticks.

### Case 4

*Severe encephalitic illness with coma, meningism, involuntary movements, disappearance of deep reflexes, extensor plantar responses, and spinal-fluid changes beginning in a 6-year-old child five days after appearance of chicken-pox. Treatment with A.C.T.H. was begun within 48 hours of the onset of symptoms, and 300 mg. of A.C.T.H. was given during the subsequent 72 hours. Deterioration occurred during the first 15 hours of treatment, but improvement was noticeable 24 hours later and was progressive from this time, with perfect recovery except for emotional lability nine days after the onset.*

Seven days before admission to hospital this 6-year-old boy had a typical chicken-pox rash. Five days later, when the rash was fading, he developed frontal headache and drowsiness; and during the subsequent 48 hours headache persisted, drowsiness increased, and he became restless, confused, and quite oblivious of his surroundings.

On admission two days after the appearance of nervous symptoms he was mute and restless, and there were violent non-purposive movements of all limbs. He had severe neck stiffness and almost continuous irregular involuntary movements of the eyes, with periods of several seconds during which they remained fixed upwards and convergent. He was doubly incontinent, and the temperature was 99° F. (37.2° C.). Judging from his violent responses to gentle stimulation there appeared to be general skin hyperaesthesia. The knee- and ankle-jerks were sluggish, the abdominal reflexes and cremasterics brisk, and the plantar responses clearly extensor. There was no true nystagmus, and the optic fundi were normal. The spinal fluid showed a normal protein content but contained 16 cells per c.mm., 10 of which were polymorphonuclear leucocytes. He was given an immediate injection of 25 mg. of A.C.T.H., and during the next 72 hours received 300 mg. in all by similar six-hourly intramuscular injections. The dosage was not controlled by eosinophil counts.

On re-examination 15 hours after the first injection (after the administration of 75 mg. of A.C.T.H.) the child's condition had deteriorated. Stupor had deepened to coma, and he was quite unresponsive. The abdominal reflexes had disappeared, though the cremasterics were retained, and neither knee- nor ankle-jerks could be obtained. There was involuntary and continuous twitching of the eyelids and of the right angle of the mouth. Otherwise the signs were unchanged, except that the involuntary ocular movements previously described were more persistent and more violent.

On examination 24 hours later there was some improvement. Coma alternated with episodes of extreme restlessness and the child screamed on lumbar puncture, which now yielded 20 cells per c.mm. Polymorphonuclear leucocytes still predominated and the protein content remained normal. Neck stiffness was less severe, and the ocular movements and facial twitching were less continuous. Within the next 24 hours pronounced improvement occurred. stupor giving place to the picture of cerebral irritation, and at the end of this time (63 hours after the beginning of treatment) neck stiffness had disappeared, the child looked round when his name was called, and he followed the nurse round the room with his eyes. He was still mute and doubly incontinent, but now responded violently to subcutaneous injection. He was very restless and was moving his legs, which had previously been quite still, though reflex signs remained unchanged.

This improvement was maintained. Twenty-four hours after completion of treatment (seventh day of illness) he spoke a little and was intermittently rational. The reflex signs of an upper motor neurone lesion faded, the gross general ataxia which became evident during recovery gradually disappeared, and sphincter control returned. Four days after completion of treatment there was no residual disability. The child was somewhat labile emotionally, the knee- and ankle-jerks remained absent, but all other signs had disappeared and he was perfectly well. He had little memory for the illness of the preceding ten days. Improvement after this time was continuous, and within three weeks the child was apparently normal.

### Case 5

*A.C.T.H. treatment of the fifth encephalitic illness occurring in a boy of 14 during the course of five months. Each episode followed an upper respiratory infection, and the usual clinical features were drowsiness, meningism, nystagmus, hypotonia, and disappearance of deep reflexes with extensor plantar responses. Treatment began 12 hours after the onset of the fifth attack. Improvement was evident within six hours of the starting of treatment, and in 18 hours the patient was well except for nystagmus, which disappeared within seven days.*

In July, 1951, a 14-year-old boy had a minor head injury. He received a blow on the left parietal region and was dazed for two hours. There was a haematoma at the site of injury, but there were no abnormal neurological signs, the *x*-ray film of the skull was negative, headache disappeared within three days, and the patient returned to school two weeks later without symptoms.

In November, 1951, he had a severe head cold with fever, cough, and sore throat. Ten days after the onset, when his respiratory symptoms had almost disappeared, he became drowsy, with meningism, retention of urine, disappearance

of deep reflexes, nystagmus, hypotonia, and ataxia. The superficial reflexes disappeared, and the plantar responses became extensor. He was stuporous for ten days before recovery began. Diplopia and nystagmus subsided in two weeks, and on discharge from hospital a month after the onset of the illness his symptoms and signs had completely disappeared.

Two months later, in January, 1952, a similar illness with identical symptoms and signs followed a further head cold. On this occasion recovery was more rapid; consciousness was clear within five days of the onset and the patient asymptomatic five days later without residual physical signs.

A month later sore throat without coryzal symptoms was followed by a similar illness. On this occasion diplopia was localized to a paresis of the right internal rectus. All ancillary investigations were negative except that an electroencephalogram showed gross abnormality (generalized asynchronous theta and delta activity with a focus of delta waves in the right posterior temporal region). Consciousness was clear within five days, double vision and nystagmus again cleared a week later, and at this time the patient was well once more.

The fourth episode occurred in March, 1952, after a severe head cold. Abnormal signs were as before. On this occasion the neurological illness was more prolonged and the patient was unrousable for eight days. Four specimens of spinal fluid were normal, and the fifth showed nine lymphocytes per c.mm. as the only change. The electroencephalogram again showed evidence of diffuse disturbance of cerebral function, but the focus in the right temporal region was less clearly defined. Complete recovery occurred within 16 days of the onset, and a week later the electroencephalogram was much more normal, showing merely a well-sustained alpha rhythm interspersed with diffuse theta activity.

He was readmitted in May, 1952 (two months after the fourth episode), having had a heavy coryza for four days. He retired to bed the day before admission quite well except for his cold, but awoke at midnight mentally confused, restless, ataxic, and with marked difficulty in micturition. In the morning he was stuporous, with double vision, gross nystagmus in all directions, hypotonia, ataxia of limbs and trunk, disappearance of all deep reflexes, and flexor plantar responses. The spinal fluid was normal.

Twelve hours after the onset of this episode 25 mg. of A.C.T.H. was given by intramuscular injection, and this was repeated three times in the next 24 hours. Within six hours the patient was less drowsy and nystagmus in all directions less gross. Improvement was progressive, and 18 hours after the beginning of treatment consciousness was normal and all signs had disappeared except for fine nystagmus in all directions and sluggishness of the deep reflexes. No further A.C.T.H. was given: improvement was progressive, and nystagmus finally disappeared on the seventh day. As in the previous episode, electroencephalographic changes indicating a severe disturbance of cortical metabolism (generalized asynchronous delta activity) gave place to a more normal record as the symptoms subsided.

Ancillary investigations in this case included culture of the spinal fluid and its injection into the brains of mice and guinea-pigs without pathological result. Serological tests for toxoplasmosis, cold agglutinins, and heterophil antibodies, and biopsy of one of a group of enlarged cervical glands all failed to reveal any evidence of specific disease. All ancillary general medical investigations, including serological tests for general infections, Mantoux tests, extensive radiological examinations, including air-encephalograms, were negative. Arrangements were made for cerebral angiography, but these were abandoned when the patient's brother (Case 7) developed a similar illness after an upper respiratory infection.

### Case 6

*Severe subacute ascending myelitis in a 30-year-old woman with an episode of meningism one month after the onset. Deterioration occurred during an initial (uncontrolled) course of A.C.T.H., and there was further slight deterioration during a second course of treatment in the meningitic phase.*

A 30-year-old housewife was well until April 11, 1952, when she developed unpleasant tingling under the left breast which lasted for a week, and was followed by progressive numbness of the left leg and left side of the trunk. Within a few days the right foot became numb and cold, numbness spread upward to the right leg and trunk, and stiffness of the legs developed with increasing dysuria.

When she was admitted to another hospital on May 1, examination revealed a flaccid paraplegia with paralysis of the left leg, absent abdominal responses, increased knee- and ankle-jerks, flexor plantars, and marked impairment of all forms of sensation below the fifth thoracic dermatome. The spinal fluid dynamics and composition were normal, and there were no signs above the upper level of sensory loss. From May 1 to 6 she was given 80 mg. of A.C.T.H. daily in four intramuscular injections, and during the next two days 40 mg. daily in two doses. Dosage was uncontrolled by eosinophil counts. During this course her condition became much worse. On the third day of treatment weakness of the right leg became absolute, with complete loss of sensation below T 5 and retention of urine. Ancillary tests were entirely negative.

The patient was admitted to the Royal Victoria Infirmary on May 9. Her signs at this time were of an apparently complete cord lesion, the upper level of which had ascended to T 3, with a zone of hyperaesthesia at T 2. Below this level there was complete sensory loss and disappearance of all reflex activity. For 24 hours before admission she had complained of shooting pain down both arms and of severe headache which was associated with meningism. Re-examination of the spinal fluid showed normal dynamics and protein content, with 36 cells per c.mm., 11 of which were polymorphonuclear leucocytes. It was felt that this was a case of ascending and possibly necrotic myelitis which had clearly not shown any response to A.C.T.H. in dosage probably physiologically adequate though uncontrolled. The chances of the cord lesion responding to treatment appeared remote, but, in view of the onset of meningism and the clinical evidence of upward extension of the spinal lesion, a further course of A.C.T.H. was given in the hope of averting respiratory failure or an encephalitic illness.

During the subsequent five days she was given 100 mg. of A.C.T.H. daily and the eosinophil count was maintained below 10 cells per c.mm., with the addition of occasional boosting doses. She received 575 mg. of A.C.T.H. in all.

During the first four days of treatment her condition showed slight deterioration. Grip in both hands became weak and the deep reflexes in the arm, previously brisk, were elicited with difficulty and finally disappeared. Neck stiffness and headache remained as before. On the fifth day she developed a high fever with pyuria and basal pneumonic signs. In view of this, treatment with A.C.T.H. was abandoned. The fever and these infective signs responded to antibiotics, and meningism disappeared 40 hours after A.C.T.H. was discontinued.

During the next two months there was no change in the neurological signs. Retention of urine remained complete, and there was no recovery of sensation, motor power, or reflex activity, or any evidence of extension of the lesion.

### Case 7

*Acute encephalitic illness with cerebellar symptoms following an upper respiratory infection in a boy of 12. Treatment with A.C.T.H. began within 15 hours of the onset and improvement was evident 12 hours later. 325 mg. of A.C.T.H. was given during the course of 72 hours, with complete recovery except for minor residual signs.*

This patient, a 12-year-old boy, is the younger brother of Case 5. On May 19, 1952, seven months after the onset of his brother's illness, and six days after the elder boy's fifth encephalitic episode, described above, he developed a syndrome closely similar in type.

Two years previously this boy had sustained a fractured skull, with transient loss of consciousness, but he made an excellent recovery and had no subsequent symptoms except for occasional headaches and rather unruly difficult behaviour of doubtful significance.

On the morning of May 19, at which time he was recovering from a severe head cold contracted one week previously, he awoke complaining of dizziness, headache, and double vision on looking to either side. He fainted on endeavouring to leave his bed, and within six hours of the onset became drowsy, though he could be roused.

On examination 15 hours after the onset he was stuporous but talked sensibly on being wakened. He complained of occipital headache, double vision, and giddiness on raising his head from the pillow. The positive signs on examination were meningism, gross nystagmus which was present in all positions of the eyes and maximal on lateral deviation, gross generalized hypotonia, sluggish deep reflexes in the arms, and almost extinct knee- and ankle-jerks. The plantar responses were flexor and the abdominal reflexes tired easily. The spinal fluid was entirely normal and the electroencephalogram showed diffuse theta activity with paroxysmal bursts of higher amplitude but no evidence of a focal lesion.

The boy was given 50 mg. of A.C.T.H. intramuscularly on admission and 25 mg. six-hourly during the subsequent 72 hours. Twelve hours after treatment started he was more alert, nystagmus was less sustained, and the right ankle-jerk was easily obtained. Re-examination 36 hours after the onset of treatment showed complete disappearance of meningism and nystagmus. Diplopia had disappeared, headache was the sole subjective complaint, and reflex changes were as before.

On completion of treatment there were no symptoms, and the only abnormal signs were sluggish knee- and ankle-jerks. Hypotonia had completely disappeared. Ancillary investigations were entirely negative.

## Discussion

The hypothesis on which this therapeutic experiment is based is that the clinical syndrome of acute disseminated encephalomyelitis in man may arise on the basis of vascular and perivascular changes in the nervous system which are interpreted as pathological expressions of a non-specific hypersensitivity reaction of anaphylactic type, probably primarily vascular but involving, either simultaneously or secondarily, the extravascular mesenchymal tissues of the neuraxis. Some hope that the disease in man might be influenced by cortisone or A.C.T.H. is offered by the observations that these drugs exercise a powerful prophylactic effect on experimental "allergic" encephalomyelitis, which is in some ways strikingly similar to the human disease; and that they suppress the established general manifestations of serum sickness—a frank expression of hypersensitivity which may rarely be complicated by an encephalomyelitic syndrome.

Even if theoretical and practical objections to this hypothesis prove invalid, and it is ultimately shown to be an approximation to the truth, the limitations of its therapeutic application are at once apparent. The most that could be hoped for on theoretical grounds is that physiologically effective dosage of cortisone or A.C.T.H. might diminish the inflammatory response by decreasing or abolishing exudation from damaged blood vessels, and might possibly accelerate the absorption of exudate and the resolution of inflammatory change which presumably occur during spontaneous recovery. This implies two practical limitations: first, that the drug would be likely to influence the condition only during the phase of exudation and acute inflammation; and, secondly, according to this hypothesis the focal and general neurological symptoms of encephalomyelitis arise from damage to neurones and their processes by oedema, haemorrhage, or toxic substances essentially secondary to vascular-mesenchymal inflammation: any detectable clinical response to therapy could at best be anticipated only in relation to symptoms arising from neural lesions not already irreversible by reason of their duration or their initial severity. Even on theoretical grounds no response would be expected, for example, in the rapidly fatal encephalomyelitic illness of which the pathological basis is a diffuse cerebral purpura, or in those cases of severe myelitis which are characterized by actual necrosis of the spinal cord.

Critical consideration of the present small series of cases does nothing to invalidate these theoretical views, and offers a small amount of admittedly fragmentary clinical evidence in their support.

The mortality of encephalomyelitic cases admitted to the Royal Victoria Infirmary is in the region of 27% (8 of 30 cases occurring between 1930 and 1940), and somewhat similar figures are reported by most other observers. Certainly in "spontaneous" cases and in those following Jennerian vaccination, and probably in post-exanthematous instances, fatalities occur almost entirely among patients in whom coma is a clinical feature. Only one of the present patients, however (Case 4, following chicken-pox), was ever more than stuporous, and although this was an unusually severe illness, encephalomyelitis following varicella is widely regarded as having a rather better prognosis than similar illnesses following some other exanthemata such as measles. The absence of fatalities in the present series is therefore valueless in the assessment of treatment.

In one case (Case 6, subacute ascending and probably necrotic myelitis) treatment with A.C.T.H. clearly exerted no beneficial effect: unequivocal clinical deterioration occurred during both an initial uncontrolled and later a controlled course of treatment.

In neither of the instances of encephalomyelitis following chicken-pox (Cases 2 and 4) was the course or duration of the illness materially different from that which is often seen in untreated cases, though the improvement which coincided with increased dosage in Case 2, and that which followed an initial phase of deterioration in the much more severe Case 4, are compatible with the view that the drug exercised a favourable effect on the condition.

In Cases 5 and 7, clinical improvement was evident within six and twelve hours of the initial injection of A.C.T.H. respectively, and a similar response has since been observed in a sixth encephalitic episode in the former case that is not detailed here. Unfortunately the previous history of cerebral trauma in both these cases, as well as the remarkable familial incidence, renders diagnosis ultimately problematical. Cases of relapse and recurrence of encephalomyelitis are not rare, and several have been personally observed, though never with so many attacks as have been seen in Case 5. However, the encephalitic nature of the syndrome with a maximal though not exclusive incidence on the cerebellum or its connexions, its relation to preceding banal infection, its rapid and complete resolution clinically and electroencephalographically, and the absence of spinal-fluid changes, would appear to render any diagnosis other than acute disseminated encephalomyelitis difficult to sustain.

In Case 3 the improvement in mental acuity and in the clinical manifestations of the transverse cord lesion which was observed within 12 hours of the first injection is surprising, even on theoretical grounds, in view of the 12-day history of the condition. It should be noted, however, that this patient was still deteriorating clinically when treatment began, which presumably argues a continuing inflammatory reaction in the nervous system, and that he was left with appreciable disability, in keeping with the duration of his cord lesion. The slight relapse which occurred four days after completion of treatment is perhaps also a point in favour of the view that A.C.T.H. may have exercised a suppressive effect on the symptoms in this case.

These cases are numbered in the order in which they were treated, and it is ironical that the evidence in favour of a therapeutic response is more suggestive in Case 1 than in any subsequent patient. In this instance a combination of

circumstances—in particular an intelligent patient and a very alert practitioner—led to reference of the case at a much earlier stage in the development of the disease than is usual. Although clinical deterioration until treatment was instituted was rapidly progressive, it is clearly impossible to claim with any certainty that the apparent response was more than coincidental. Nevertheless the relapse associated with objective evidence of physiologically inadequate dosage, and the resumption of improvement when dosage was increased, as well as the remarkably complete recovery which was evident within a matter of days, render coincidence a not entirely satisfying explanation: that resolution of the condition was related to the administration of A.C.T.H. would appear to be a distinct possibility.

Acute disseminated encephalomyelitis is a rare disease, and, although it is fully appreciated that no firm conclusions can be drawn from the present small series of treated cases, they are reported in the belief that the results are suggestive enough to merit similar trial on a larger scale. In the absence of any other effective or rational therapy such a trial would appear justifiable, though a word of caution is advisable. Diagnosis of acute encephalomyelitis following exanthemata is usually simple, but the "spontaneous" examples, and those following non-specific infections, may present difficult diagnostic problems. Administration of A.C.T.H. to cases of virus disease such as poliomyelitis is at best useless, and recent evidence suggests that it may be actively harmful. In bacterial infections such as cerebral abscess or tuberculous meningitis its use might well be disastrous. For these reasons, and also in order not to confuse assessment of the value of the drug in the disease under consideration, the employment of this experimental therapy should be limited to cases of acute neurological illness in which an unequivocal diagnosis of encephalomyelitis can be competently sustained. The present paper shows that in such cases the drug is harmless if nothing more.


### Summary

Seven cases clinically diagnosed as acute disseminated encephalomyelitis have been treated with A.C.T.H. They comprise two cases of encephalomyelitis following varicella, two cases of transverse and one case of subacute ascending myelitis, and two (familial) cases of encephalitic illness following non-specific infection, in one of which there have been recurrent encephalitic illnesses. Acute disseminated encephalomyelitis has a pronounced tendency to rapid, spontaneous, and often complete recovery, and no final conclusions regarding the efficacy or otherwise of A.C.T.H. can be reached without extended observations on a scale which would permit of statistical evaluation. It is believed that the results reported here are suggestive enough to justify further trial.


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# ANURIA TREATED BY CORTISONE*


BY

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The present trend in the treatment of anuria is in favour of a conservative policy using a balanced fluid and electrolyte intake with a low-protein diet in the hope of a spontaneous remission (Bull *et al.*, 1949). In cases in which gross oedema or some electrolyte imbalance has already occurred active measures to substitute for the kidney must be used.

Methods of treatment based on the primary aetiology, such as decortication, nerve block (surgical or pharmacological), alkalization of the urine, etc., are not often successful. This relative failure may be due to the presence of other unsuspected aetiological mechanisms. The possibility that an acute allergic reaction in the kidneys is a causal factor in some cases is considered in this communication. To test this hypothesis we have tried the effect of cortisone in a miscellaneous group of four cases of anuria. The cortisone used was cortisone acetate ("cortone"), and was given by intramuscular injection, except where oral administration was specified.

### Case 1

A man aged 33 was admitted to the Mater Misericordiae Hospital on October 27, 1950, suffering from rheumatoid arthritis, grade II, of ten years' standing. The previous history was irrelevant. There were four areas of alopecia areata on the scalp. His general physical examination was otherwise normal, but the urine contained a very faint trace of albumin, a few squamous cells, and a very rare leucocyte. The electrocardiogram was normal; the blood pressure was 140/80; and the E.S.R. 45 mm. (1 hour). Seven days after admission he was started on cortisone treatment. By November 30 the arthritis had improved by 80%, and cortisone was discontinued on November 26.

By December 1 a relapse of the arthritis was evident and cortisone treatment was resumed: 100 mg. a day orally, in three doses, was given, and because of a favourable response it was reduced to 50 mg. on December 5. As, however, a considerable amount of fluid had developed in the left knee, the dose was increased to 100 mg. a day by mouth on December 13. On December 15 the patient returned home on this dosage, and on the 24th he developed acute pharyngitis with pyrexia of 101° F. (38.3° C.), and was treated with penicillin. Some hours later there was a transient erythematous rash on the trunk. On December 25, contrary to instructions, he ceased taking cortisone; next

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