THE TREATMENT OF ASTHMA WITH CORTICOTROPHIN

BY

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Stimulation of the adrenal cortex by adrenocorticotrophic hormone (corticotrophin, A.C.T.H.) has been used with success in various hypersensitivity conditions, and was the subject of a review by Rackemann (1951). Naturally, asthma has featured among the disorders so treated, and further assessment of its use and possible abuse seems desirable in this condition, which has been increasingly recognized as liable to cause a fatal outcome in severe cases. While cortisone has also been used in trials by mouth, by injection, or by inhalation, its use is not here considered.

Present Cases

When the present series of 10 asthmatic cases was treated, A.C.T.H. was still scarce, and certain strict criteria were imposed before giving such treatment: (1) all were admitted to hospital suffering either from severe status asthmaticus or from prolonged and incapacitating asthma; (2) they showed little or no response to other routine forms of therapy, including intravenous aminophylline; and (3) so far as possible, they were unaware that A.C.T.H. was being given lest the idea of some new magic treatment should play a largely psychological part in any improvement. Most of the cases were so severe that it was felt scarcely justifiable or necessary to risk fatalities by a control series such as that usefully described by Ball (1954).

Case 1

A farmer aged 40 had for seven years had repeated infections of the accessory nasal sinuses, requiring operation more than once. Eighteen months before admission he had asthmatic symptoms which were thought to be mainly of infective origin. He entered hospital in a mild status asthmaticus, and treatment, including antispasmodics, penicillin, physiotherapy, and intravenous aminophylline, produced only slight improvement. X-ray examination of his sinuses showed widespread infection; he was producing on an average 1 fl. oz. (28 ml.) of purulent sputum daily.

A.C.T.H. was started in a dosage of 30 mg. eight-hourly intramuscularly, and within 36 hours he was much less distressed than he had been for many weeks. The dosage was gradually diminished until a total of 510 mg. had been given in seven days. Two days later he was able to return home in quite a comfortable state.

He started to relapse after a few weeks, and four months after discharge he had to be readmitted urgently. During bronchoscopy under thiopentone anaesthesia he suddenly collapsed and died, and at necropsy his whole bronchial tree was full of sticky mucopurulent secretion.

Case 2

An intelligent and sensible housewife aged 53 was seen at home as an emergency in status asthmaticus so severe that two hours previously her own practitioner had thought her to be on the point of death. In spite of intravenous aminophylline she was still extremely shocked and distressed in her breathing.

She was at once admitted to hospital and given A.C.T.H., 30 mg. intramuscularly six-hourly. Within 12 hours she was comfortable, and within 48 hours she was completely free from wheezing. The total dosage was 730 mg. in nine days.

It was possible to discharge her from hospital on the ninth day, and, although two further admissions were necessary in the next 12 months, she did not require further A.C.T.H. until two years later, when she was readmitted to hospital in a similar, almost moribund, condition. With 100 mg. of A.C.T.H. in the first 24 hours, followed by 200 mg. of A.C.T.H. gel in the next four days, she again made a remarkable recovery.

Case 3

A bill-poster aged 19 gave a six-year history of asthmatic attacks at intervals of some months for no known cause. He was admitted to hospital in severe status asthmaticus, which showed poor and transient response to injections of adrenaline and intravenous aminophylline. Although of fine physique, he was becoming very exhausted, and on the fifth day A.C.T.H. was started. Some improvement was achieved with a total dosage of 425 mg. in five and a half days, but 48 hours after stopping treatment his asthmatic state gradually became worse than ever. No infective element was apparent. After an interval of 12 days, a further course of A.C.T.H. was begun with a higher initial dosage, 150 mg. in the first 24 hours, and on this occasion he showed great improvement within 48 hours. The total dosage for the second course was 500 mg. in seven days, and the patient has remained remarkably well since that time, for a period of over one year.

Case 4

An unemployed man aged 47 dated his asthmatic symptoms from 1940, when he was subjected to blast and exposure followed by evacuation from Dunkirk. From 1950 to 1952 he was under constant out-patient supervision and was twice admitted to hospital for treatment, which had included left hilar denervation; to none of these attempts did he make any satisfactory response and he was never found to be free from some degree of wheezing, although his vital capacity was always well above 4,000 ml. For a few years he had also complained of Raynaud's phenomenon in both hands, and during the two-year period of observation he was unable to resume his work in a tobacco factory.

On his third admission a course of A.C.T.H., 1 g. in 12 days, was given; this produced considerable temporary improvement in his Raynaud's phenomenon, but the relief to his chest was negligible.

Case 5

A housewife aged 36, who had always had a mild asthmatic tendency, had been very much worse since the birth of her child six months previously. She was admitted in status asthmaticus and A.C.T.H. was started; after receiving 120 mg. in 48 hours her chest symptoms were greatly relieved, but mental confusion with euphoria caused the A.C.T.H. to be discontinued.

Within three months she again had to be admitted to hospital in a relapse, which responded to routine measures sufficiently well for her to take her own discharge on the third day.

Case 6

A professional man aged 41, of the keenest intelligence, was one of the series who knew he was receiving A.C.T.H. and appreciated the significance of it. In infancy he had had eczema and in childhood some asthma, which moderated during adolescence. During the preceding five years he had had several attacks of infective bronchitis during the winter, and for three months he suffered numerous bad asthmatic attacks. In view of the possible infective factor of recent years, he was admitted for investigation, including bronchography, which did show dilatation of a few scattered bronchi in either lung.

Possibly, he thought, because of the bronchogram or possibly for psychogenic reasons, he shortly had another severe asthmatic attack, which was unabated after three weeks, by which time his response to intravenous aminophylline was very poor.

He was readmitted, therefore, and A.C.T.H. therapy was started with 30 mg. six-hourly. After the second injection he described a cessation of spasm with a great feeling of relief, and a total dosage of 540 mg. was given in four and a half days. Relapse occurred on two occasions at approximately three-monthly intervals after this, demanding further A.C.T.H. therapy for nine days on each occasion. The results were good, though not quite so remarkable as during the first course.

Case 7

A housewife and schoolteacher, aged 49, with a previous history of "hay-fever" from the age of 18 up to 40, had 10 months previously started getting violent spasms of cough with tenacious sputum, soon accompanied by asthmatic symptoms. She stated that she had not had a single undisturbed night for nine months on this account, and severe exacerbations had occurred on three occasions. She was a nervous woman, severely distressed physically and mentally by constant dyspnoea, and repeatedly in mild status asthmaticus, which was only slightly, if at all, relieved by intensive routine measures, including bronchoscopic aspiration under general anaesthesia. A.C.T.H. gel was given intramuscularly in daily doses of 100, 60, and 60 mg.; and then 40 mg. for seven days.

Great improvement was felt within 24 hours, and within three days she was much clearer than she had been for many months. Although a relapse occurred three months later, it was ultimately controlled by routine measures without A.C.T.H.

Case 8

A housewife aged 54 was the most chronic asthmatic of the whole series. During the 34 years of her trouble she had seen a vast number of doctors, undergone numerous investigations, and received the widest variety of treatments. For eighteen months she had been getting worse than ever, and she stated that for six months she had never been free from wheezing unless she used an atomizer, from which she was inseparable. Every night for five years she had woken in an attack, and it was clear, as she herself admitted, that the psychogenic factor was by far the most important in the aetiology of her asthma.

Worn out mentally and physically as she was by her almost constant mild status asthmaticus, she was given 100 mg. of A.C.T.H. gel intramuscularly one evening at 6 o'clock. At 9 p.m. a kind but unwitting night nurse gave her two codeine compound tablets unaware that she was sensitive to aspirin. Within three hours the patient was in the most severe status asthmaticus, shocked, and almost pulseless, recovery taking place shortly after an intravenous injection of aminophylline, 0.48 g.

Further treatment with A.C.T.H. gel was interrupted for 10 days; she then received a total of 400 mg. in 10 days. By the third day of this course improvement was evident, and by the sixth day she stated that she felt clearer on the chest and better than she had done for many years. At this time her lungs were completely free from adventitious sounds.

She continued fairly well at home for many months after this treatment, requiring many fewer "remedies" than before, although adrenaline injections and her atomizer were still in use. For eighteen months she did not approach a state severe enough to warrant further A.C.T.H. therapy; her husband then started to obtain supplies of A.C.T.H. gel from America, and for many months she had been receiving a maintenance dose of about 20-40 mg. twice weekly. She has not attended for follow-up during this time, but reports from her own practitioner and from her husband seem to indicate clearly that the previous efficacy of the substance is much reduced and may soon be negligible.

Case 9

A woman aged 57 had suffered from asthmatic attacks for many years and had needed admission to hospital on several occasions. Complicating factors were gross sinus in-

fection and scattered fibrosis with bronchiectasis in both lungs. A well-marked psychological element also played a part in perpetuating her symptoms, and when the time came for her to undergo the most necessary sinus operations she admitted that the fear of operation and anaesthesia added very much to her chest troubles. She entered hospital in severe asthma, which was showing scarcely any improvement on routine measures, including intravenous aminophylline. She was despondent and exhausted from lack of sleep. As penicillin was having no effect on her infection chloramphenicol was substituted. After two days, although her sputum was somewhat cleaner, she was still very breathless. A.C.T.H. was started next day, and after 48 hours she showed great improvement physically and mentally. A total dosage of 300 I.U. in six days rendered her well enough to undergo operation in the following week.

Case 10

A retired man aged 72 who had suffered from a cardiac infarct two years previously, had complained of asthmatic symptoms for only about five months before admission, though he had probably experienced mild bronchitic trouble for some years. Since the onset of his bronchospasm, he had had treatment in various parts of the country with numerous medicaments and had on several occasions received a course of A.C.T.H., with the result that he had become very reliant on it and very introspective about his condition.

He was admitted, together with a vast number of drugs and remedies, in severe status asthmaticus, occasioned very largely by the misguided administration of two injections of morphine $\frac{1}{4}$ gr. (16 mg.), with atropine, 1/100 gr. (0.65 mg.), based on the idea that his asthma might have been of cardiac origin. He had already placed himself again on A.C.T.H., but clearly, after 24 hours, it was making little or no impression on his asthmatic state. Intravenous aminophylline, an iodide mixture, and physiotherapy were much more successful in producing steady improvement, with expectoration of increased amounts of slightly infected sputum.

After two weeks' relative freedom from symptoms his wheezing again flared up acutely, resulting in great

Summary of Cases

Case No.	Sex	Age	A.C.T.H. in mg.	Duration (Days)	Remarks	Response
1	M	40	510	7	Chronic asthma—infected	Good
			730	9	Severe status asthmaticus. Comfortable in 12 hours	Excellent
2	F	53	100 + 200 gel	5	" "	"
			425	5½	Status asthmaticus	Moderate
3	M	19	500 (12 days later)	7	"	Very good
4	M	47	1,000	12	Chronic asthma	Very poor, but Raynaud's phenomenon relieved
5	F	36	120	2	Status asthmaticus	Good, but treatment stopped on account of mental confusion
6	M	41	540	4½	Status asthmaticus	Excellent—relief within 36 hours.
			820	9	"	Slower improvement
7	F	49	670	9	Chronic asthma in mild status	Excellent
8	F	54	500 gel	10	Chronic asthma in status	"
9	F	57	400 gel	10	Chronic asthma with infected bronchiectasis and perisinusitis	Good
			300	6	"	"
10	M	72	415 Several previous courses	8	Recurrent status asthmaticus	Fair

despondency; for two days he struggled on with the previous regime, finding his physiotherapy more and more exhausting, and then he felt he must demand further A.C.T.H. Starting with 30 mg. four-hourly, he experienced relief within eight hours, and was able to be transferred home within 10 days. It was clear that, in this case, the possible psychological effect of having A.C.T.H. could not be excluded; he admitted that it did not have such a dramatic effect in relieving his symptoms as on some previous occasions.

A summary of the salient features of the cases is set out in the Table at the foot of the previous page.

Discussion

In 10 cases of severe and intractable asthma treated with A.C.T.H. the initial response was considered to be very poor in one, fair in one, good in four, and excellent in four; in one of the latter it was probably life-saving on two occasions.

All patients showed relapse of symptoms sooner or later after cessation of treatment, but only three required more than one course of treatment (excepting one who had an immediate relapse). Two of these patients knew they were receiving A.C.T.H., felt the need of it during a severe exacerbation of symptoms, and were agreed that its action was slightly slower and less dramatic on each subsequent occasion.

An initial dosage of 25–30 mg. (I.U.) intramuscularly six-hourly, or even eight-hourly, appeared satisfactory, usually producing great relief within 12–36 hours; it was possible to reduce the dosage after 48–72 hours to 20 mg. eight-hourly for the next two to three days, and then to 10 mg. eight-hourly for a further two days. An average course of seven days' treatment with this diminishing dosage therefore totalled about 450 mg. However, in any statement of dosage used and compared with other authors, it must be remembered that the potency of different extracts may have shown considerable variation. The longer-acting A.C.T.H. gel, used in two cases, seemed just as efficacious as the more standard product, in a daily dosage of about half the amount, and with the added advantage of necessitating only one injection in 24 hours. It is noteworthy, perhaps, that in one of these cases an injection of 100 mg. of A.C.T.H. gel did not prevent a violent asthmatic reaction to aspirin given some three hours later.

In only one patient (Case 3) did the amount of the initial dosage seem important; a higher dose of 150 mg. in 24 hours for an immediate relapse after his first course produced a remarkably good effect, whereas 100 mg. in 24 hours had been somewhat disappointing.

An ill effect was noticed in only one patient: this woman was of rather an unstable temperament, and marked euphoria necessitated stopping treatment after 48 hours. Other reactions are unlikely to be troublesome with the dosage and duration of treatment described, while a mild degree of euphoria may be considered helpful, although not of primary therapeutic importance.

The good effects obtained are not evidently counteracted by some degree of bronchial infection, but in this series measures were being taken simultaneously to treat any such infection with antibiotics and physiotherapy when necessary. In the most heavily infected case (No. 9) it is doubtful if the patient would ever have been rendered fit for her much-needed radical sinus operation without the use of A.C.T.H.

The findings are in agreement with most other authors, that in A.C.T.H. we have a potent substance in the treatment of asthma. Friedlaender and Friedlaender (1951b) gave it to 10 severe chronic asthmatics in a dosage of 52 mg. six-hourly, intramuscularly, with total dosage of 600–870 mg. in 6–13 days. They found dramatic improvement in six patients within 24–36 hours, fair response in two, and no real improvement in two. They pointed out that the relief was of brief duration before recurrence, and that seasonal hypersensitive cases should therefore give the most satisfactory results. Possibly, symptoms recurring after

such treatment might more easily be controlled by "conventional" therapy, but the reverse could also occur.

Segal *et al.* (1951) treated 20 severe asthmatics with courses of A.C.T.H. in total dosage of 240–900 mg. over periods of 2½–19 days. As five patients needed more than one course, 27 courses in all were given, and, of these, 24 produced partial or complete remission of symptoms, as follows: eight for one to two weeks, 10 for two to four weeks, and six for four weeks to seven months. They concluded it was better to give short intensive courses of A.C.T.H. therapy rather than try a prolonged maintenance dose.

Rather less impressive results occurred in 18 patients similarly treated by Arbesman (1951), as six of these showed no improvement whatsoever; the average length of remission of symptoms achieved in the rest was three to six weeks. Brown *et al.* (1951) treated 30 chronic asthmatics ambulant over 10 months, the patients giving their own injections and deciding their own requirements, which ranged from 10 mg. twice daily to 12 mg. on alternate days. Relapse of symptoms occurred in all patients soon after cessation of treatment.

Levin (1953) pointed out the benefits of using A.C.T.H. gel; he achieved good or excellent results in 10 adults and six children, some of whom were treated ambulant. One injection of 40–60 mg. was given daily for two to five days; the injections were remarkably painless and there were no undesirable reactions. He considered that with such treatment available the asthmatic should never need A.C.T.H. by intravenous drip.

The exact mode of action of A.C.T.H. in asthma remains somewhat obscure. Elkinton *et al.* (1949) made careful studies in a 12-year-old boy to assess whether adrenal cortical stimulation was proportional to the clinical improvement. With eosinophil blood counts, balances of chloride, sodium, sugar, potassium, and nitrogen, and study of 17-ketosteroids they could find no such correlation, and it has been suggested from the findings that in asthma the beneficial effect may depend upon some special function of the hormone. The lack of any definite correlation between clinical response and the eosinophil count has been confirmed by Friedlaender and Friedlaender (1951a) and by Feinberg *et al.* (1951).

It cannot be over-emphasized that the treatment described should in no way replace attempts at full assessment of the asthmatic case, so that more rational and radical therapy can be given whenever possible. If used, it is thought preferable that the patient should not know what he is receiving, as, if its dramatic effect is evident to him, he may demand it for ever afterwards when distressed, and morally it may prove very difficult for the practitioner to withhold it. In fact, one can visualize the asthmatic almost as addicted to A.C.T.H. as, say, to his inhaler, and, worse still, if used too often this substance might gradually lose its beneficial effect, a point strongly suggested by two cases in the present series. I am also of the opinion that, at present, it is wiser to restrict the use of A.C.T.H. to the relief of a severe exacerbation of symptoms by a short course, to be repeated if necessary.

Conclusions

A.C.T.H. is most efficacious in the treatment of severe status asthmaticus, and can be life-saving when all else fails.

As it should not be necessary in such a case for treatment to last for more than five to nine days, very few ill effects are to be expected.

An average initial dosage of 25–30 mg. six-hourly is satisfactory, and must be reduced gradually after improvement has occurred, usually within 48 hours.

It is suggested that the use of A.C.T.H. should at present be restricted to very severe cases that are resistant to other forms of treatment, and, if possible, the patient should not know what he is receiving.

Heavily infected cases respond as well as others do, but should be treated with extra caution.

There is no convincing evidence in the present series or in published cases to suggest that a longer remission of symptoms occurs after A.C.T.H. therapy than after any other treatment which succeeds.

A.C.T.H. in no way avoids the expediency of all the other established methods in the assessment, treatment, and management of the asthmatic case.

Summary

The use of adrenocorticotrophic hormone is described in 10 asthmatics. In eight of these there was a remarkable relief of severe acute respiratory distress, resistant to other forms of therapy.

It is suggested that this substance should at present be used in asthma only as an emergency measure.

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EXCHANGE TRANSFUSION AS A MEANS OF REMOVING BILIRUBIN IN HAEMOLYTIC DISEASE OF THE NEWBORN

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Damage to the brain occurs with varying frequency in haemolytic disease of the newborn. Exchange transfusion, as ordinarily carried out, is not entirely effective in preventing it.

It is now known that brain damage is found in association with a great excess of plasma bilirubin in the following conditions: (1) haemolytic disease of the newborn from iso-immunization relative to blood-group antigens D, E, A, and S; (2) prematurity without haemolytic disease; and (3) some types of "familial" hyperbilirubinaemia. Claireaux *et al.* (1953) have shown that in the first two conditions the yellow pigment in affected brains is the indirect-reacting plasma bile pigment, bilirubin. They have reviewed the evidence that this pigment is damaging to brain tissue, and that the direct-reacting bile pigments are innocuous. Some further indications of the toxic character of bilirubin have been published by Lathe (1954).

A more detailed study of the pigment changes in haemolytic disease of the newborn was undertaken with a view to developing methods of avoiding its accumulation. It seemed possible that the role of bilirubin would be made clear from the clinical results of preventing high plasma bilirubin concentrations in infants with haemolytic disease. An encouraging report by Hsia, Allen, Gellis, and Diamond (1952) and Hsia (1953) has now come to our attention. The work described here confirms their observations regarding the pattern of bile pigment changes in the plasma in haemolytic disease,

and shows that it is possible to control the plasma bilirubin concentration by exchange transfusion.

Methods and Materials

Clinical Material.—Observations have been made on a series of infants affected with haemolytic disease at this hospital. The brief clinical descriptions of six of these have been drawn from the case records. Serological data have not been included individually, since there was a common basis for serological diagnosis of haemolytic disease in all six cases: (1) mother's group was Rh-negative, (2) maternal antibodies were present, (3) infant's group was Rh-positive, (4) infant cells gave a positive test with rabbit anti-human globulin serum (Coombs +). The blood specimens removed at exchange transfusion of three infants at the Hammett Hospital have also been available for study. **Blood specimens** were taken from heel pricks when not otherwise stated. **Haemoglobin** estimations were made with a visual colorimeter (M.R.C. grey wedge) which was suitably calibrated—100% haemoglobin being taken as 14.8 g. per 100 ml. **Bile pigment** estimations were made on serum and plasma by the method of King (1951). In Cases 1 and 2 the relative proportions of direct- and indirect-reacting pigments were estimated semi-quantitatively by the appearance of pigment bands on chromatography columns (Cole and Lathe, 1953). In Cases 4, 5, and 6 the proportions of the two types of pigment were determined quantitatively by the method of Malloy and Evelyn (1937).

Plasma Bilirubin in Haemolytic Disease

No detailed study of bile pigment metabolism in a series of untreated cases of haemolytic disease of the newborn has yet been published. That such a study would have shown a wide variation from case to case is suggested by the data of Hsia, Allen, Diamond, and Gellis (1953), and of Mollison and Cutbush (1954). In this hospital there has been an opportunity of studying a number of affected infants who were not given an exchange transfusion because the cord blood contained more than 105% haemoglobin. Some of these infants later gave evidence of a considerable haemolytic process as shown by the changes in haemoglobin and plasma bile pigments. Two contrasting cases are described. Case 1 is an instance of haemolytic disease in which no exchange transfusion was given. In Case 2 only a simple transfusion was possible.

FIG. 1.—Changes in concentration of blood haemoglobin and of plasma bile pigments in Case 1.

FIG. 2.—Changes in concentration of blood haemoglobin and of plasma bile pigments in Case 2.