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ORAL ADMINISTRATION OF CORTISONE (CORTONE) IN BRONCHIAL ASTHMA

By

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In a paper published by the Journal of Allergy in 1951, E. Schwartz has reported successful results of oral administration of cortisone in three cases of bronchial asthma. All three seem to have been of the severe type of asthma that is intractable to ordinary therapy. Skin tests produced, it is true, fairly strong positive reactions to one or more exogenous allergens, but in spite of specific desensitization little or no improvement occurred. It is not clear from Schwartz' description whether these were "mixed" cases, *i.e.*, cases in which both exogenous and endogenous causal factors play a part, *but in which the latter usually predominate*. No data are given as to any focal investigation, the sedimentation rate, etc., nor is it stated whether or not measures were taken to eliminate any infection. Hence Schwartz' paper, though admittedly demonstrating that treatment with cortisone *per os* may be effective in certain cases of this nature, bring about a complete remission, and that with small daily doses this remission may be made to persist, does not make clear those points on which we must base our evaluation of the reason for the intractability of these cases.

The dosages used by Schwartz differed somewhat in his three cases. To produce a remission he started with a fairly large daily dose, 25 mg every four hours, or a total

of 150 mg; the second day this was reduced to 25 mg $\times$ 4; the next four days to 25 mg $\times$ 2. Thereafter the patient received a daily dose of 25 mg (in another case 25 mg $\times$ 2), administered shortly before retiring to bed. The duration of the follow up is not clear, but the above-mentioned medication apparently resulted in a remission lasting some considerable time. No side-effects appear to have been observed, with the exception of transient retention of fluid in case 3.

In an earlier paper (1) the present writer has considered only in passing the possibility of treatment with cortisone by mouth. Its demonstration by Schwartz is probably the first in the literature, so far as allergic diseases are concerned. On the other hand, more extensive experience would seem to have been gained with this form of treatment in rheumatic diseases, and tends to show that with prolonged oral administration of cortisone it is possible in certain cases to keep the patients virtually symptom free over long periods. An instructive case of this kind is described in a booklet entitled "Principles of Treatment with Corticotropin ACTH 'RMC'," published in May this year by the Roskilde Medical Company (4). Favorable results have been obtained e.g. at the Department of Rheumatology, Södersjukhuset, Stockholm (personal communication to the author by Docent E. Jonsson). The doses, however, had to be kept relatively high, so that side-effects could not be avoided.

It seems evident that Schwartz' results merit the greatest attention, not least from the practical clinical standpoint. One of the most burning and difficult questions associated with the rational management of allergy patients is that of how to evacuate the many cases of chronic asthma that at present constitute such a heavy burden for the allergy clinics of our hospitals for *acute* diseases. These include the majority of asthma cases hypersensitive to aspirin and a substantial proportion of the cases complicated by infections; namely, those in which effective elimination of the infection cannot be accomplished, such as cases with purulent bronchitis, bronchiectases, etc. In many of these it is possible to bring about a

fairly rapid complete remission by using ACTH (or cortisone). But if the treatment is interrupted an exacerbation will often occur within a short time. If it were possible to obtain a lasting remission by more continuous and protracted oral administration of cortisone, then it would perhaps allow of at least a partial evacuation of cases of this type.

Below are described a few experiments recently undertaken by us for the purpose of throwing light on these questions. The treatment here was instituted with ACTH and, after producing a complete remission, was changed to cortone by mouth—this in order to avoid large doses of cortone and to gain time.

Case 1. E. M. S., housewife, born 1893.

No familial history of allergy. The patient was quite healthy until 1928, when she developed a stubborn cough, chest wheezing and incipient dyspnea in connection with a "cold". During the first two or three years these symptoms returned mainly in the autumn and winter. In the thirties, symptoms of vasomotor rhinitis supervened. It was then found that *aspirin preparations too provoked severe attacks*¹. The patient underwent long periods of both inpatient and outpatient treatment at different hospitals, being operated upon for polypus and sinusitis. Since October, 1949 she has been hospitalized for five long periods at the Department of Allergy, Södersjukhuset, undergoing control examinations at the Outpatient Department in the intervals. Skin spectrum negative; 10.7 per cent eosinophils in the blood; S.R. varying between 90 and 7 mm; hypertension; ECG normal. Chest roentgenogram showed an increase of the interstitial tissue. Cholelithiasis was present ("no filling of the gall bladder").

As from the autumn of 1949 there have been permanent somewhat severe asthma symptoms, with prolonged and frequent status asthmaticus. Treatment consisted in the use of various symptomatic agents: adrenalin, iodine, theobromine, theophylline (also in the form of aerosol), sulfa drugs, theophyllamine, eucalyptus tar inhalation, ether antihistaminics, etc., but did not produce a condition that would have justified the discontinuation of adrenalin injections. During bad spells the dose had to be increased to 0.05 ml (1 per mille) 5-6 times daily; during better ones it could be reduced to 0.5 ml 2-3 times daily. Even during the intervals as an outpatient at least 2-3 injections a day were constantly necessary, despite which severe status asthmaticus repeatedly occurred.

¹ As the writer has earlier (1) been able to show, the action of ACTH does not confer any protection against sensitivity to aspirin—a circumstance that is noteworthy from several points of view.

In June, 1951, ACTH (Acton) was resorted to, and later, cortone tablets (per os). The patient was then receiving five adrenalin injections of 0.5 ml each per day, yet still had fairly severe symptoms. Sibilant râles were pronounced diffusely over both lungs. Table I shows the medication and the condition from May 31 to July 26 (the patient was discharged July 5).

This case, which in regard to its course, form, and its refractoriness to all antiallergic medication hitherto tried, can justifiably be labelled intractable, being assignable to the aspirin-sensitive asthma group, illustrates strikingly the exceptional effect that ACTH may exert even in such cases. For years the patient, notwithstanding permanent adrenalin medication (in the form of injections), remained in a condition varying between distressing asthma and status asthmaticus. After a few doses of ACTH there was a dramatic change: After 1-2 days the patient was symptom free and had no distress; the adrenalin could gradually be decreased and after a short time discontinued. Of special interest is that the remission persists unchanged, despite a progressive reduction of the daily dose of ACTH to 5 mg (23-26 June). Considering this, and the salutary results of cortone medication by mouth in asthma which had been reported by Schwartz, as well as the fact that in earlier treatment of this case with ACTH (Feb. 12-15, 1951) the effect proved to be of very short duration, it seemed plausible to find out whether the remission could be made to persist by the oral administration of cortone in small doses. On discontinuing the ACTH treatment we therefore (on June 27) prescribed two cortone tablets daily ($25 \text{ mg} \times 2$); since the patient's condition remained good under this therapy we decreased the daily dose to one tablet (25 mg), and as from July 3 to one tablet every other day. So far (July 26) the good condition has persisted, despite the complete avoidance of adrenalin.

It may be added that the small doses of cortone used here seemed to have little or no influence on the eosinophil cell count.

TABLE I

Date	Adrenalin injection	Actrone	Cortone (Cortisone) by mouth	Subjective symptoms	Sibilant râles
May 3 ¹	0.5 × 5		o	Mod. severe	Numerous
June 1	" "			Moderate	"
2	" "			Appreciable	"
3	" "			"	"
4	" "			"	"
5	" "	10. mg × 4		Moderate	"
6	" "	" "		Inappreciable	Sparse
7	" "	" "		Symptom free	"
8	" "	" "		" "	None
9	0.5 × 3	" "			
10	" "	" "			
11	" "	5 mg × 4			
12	0.5 × 2	" "			
13	" "	" "			
14	0.5 × 1	" "			
15	" "	" "			
16	" "	" "			
17	" "	" "			
18	" "	" "			
19	Discontinued	" "			
20		" "			
21		5 mg × 2			
22		" "			
23		5 mg × 1			
24		" "			
25		" "			
26		" "			
27		Discontinued	25 mg × 2		
28			" "		
29			25 mg × 1		
30			" "		
July 1			" "		
2			" "		
3			o		
4			25 mg		
5			o		
6			25 mg		
7			o		
8			25 mg		
9			o		
10			25 mg		
26					

Symptom free during remainder of follow-up period.

During remainder of hospitalization time, an occasional sibilant râle was detected, the patient otherwise being quite free from rhonchi.

25 mg cortisone by mouth every other day. Continuing

None
None¹ Date of discharge.

At the present time, however, cortone tablets are practically impossible to obtain in Sweden, though cortisone for injection purposes is in fairly good supply. Through the agency of Mr. H. Ekstrand, a pharmacologist, we have been enabled to utilize this latter drug; for by processing cortisone in a certain way he has succeeded in producing pills each containing 25 mg. On being discharged the patient was given twenty-five of them and instructed to take one every other day. The cost of this treatment at present is in the region of 70 Crowns per month. In this connection it should be added that the costs of other medicine could be reduced to a minimum.

The intractability of this case may be due, with some probability, to the organic pulmonary changes and to the affection of the bile duct (the patient herself has declined to undergo operation).

Case 2. R. E., housewife, born 1915. No familial history of allergy.

Severe asthma since 1940. The distress was most pronounced nocturnally, the patient often having to sit up or walk about for hours. In addition there was gradually increasing dyspnea on exertion, walking uphill, climbing stairs, etc. Repeated hospitalization produced no improvement. The patient discovered six or seven years ago that *aspirin preparations provoked severe attacks*.—Of late, persistent status asthmaticus. In addition she had been distressed in recent years by nasal obstruction, sneezing and discharge of mucus.

Findings at examination of March 1-3, 1951: S.R. 9 mm. Six per cent eosinophils. Moderate status asthmaticus. Numerous coarse sibilant râles, which rapidly increased when the patient assumed a recumbent position. Skin spectrum negative. Nose and throat: purulent maxillary sinusitis.—The patient was submitted to radical operation (Docent Frenckner).—S.R. 12-9-4 mm.—Blood pressure 115/80.

In this case too, all the conventional therapeutic measures were tried, though without any really conspicuous result. True, some improvement occurred under medication with iodine, atropine, calcium and theobromine, plus adrenalin (as an injection) 0.5 ml $\times$ 6, as well as theophylline aerosol (Bruneau) and eucalyptus tar inhalation; for instance, the nocturnal distress abated considerably. Measures against the sinusitis were carried out without complications on March 22 under ACTH protection (10 mg $\times$ 4 for two days prior to the operation). About a week later a pronounced exacerbation occurred in conjunction with retention of pus in the maxillary sinus, necessitating further measures (May 21), which were again taken after premedication with ACTH

(10 mg $\times$ 4, May 18-20). The effect this time was very conspicuous and of somewhat longer duration. At the end of May, however, there was a further exacerbation, necessitating adrenalin 0.5 mg $\times$ 3 to 4 (as from June 6). Between 8th and 10th June, 10 mg ACTH 4 times daily was again administered. A marked improvement occurred; on June 18 the adrenalin could be decreased to 0.5 ml $\times$ 1, and on June 20 it was discontinued. However, the asthma symptoms gradually returned with increasing severity. Adrenalin had to be resorted to once more on June 25 (0.5 ml $\times$ 3 to 4). On June 26 and 27, ACTH was again administered (10 mg $\times$ 4). On the 28th the patient was put on two cortone tablets per day, the dose being reduced to one tablet daily on July 2 the patient having remained on this dose since her discharge¹. An attempt may be made later to reduce the dose to one tablet every other day. The patient's condition has hitherto (July 26) been good: uninterrupted sleep, little or no cough, no appreciable dyspnea on exertion; however, she has not been altogether free from ronchi. Blood pressure unchanged.

This case warrants, on the whole, the same conclusions and remarks as those in the preceding one. However, case 2 shows even more clearly that in all probability the maintenance of the remission under cortone-cortisone medication was not due to the ACTH medication, but rather to the administration of cortone.

We have given, in a further five cases, this combined treatment with ACTH followed by cortone. In each case the adrenalin could be discontinued and other medicine reduced to a minimum without any exacerbation occurring. Four of these cases have so far remained quite symptom free on a daily dose of 25 mg cortisone; in the fifth case the ACTH treatment brought about an appreciable improvement, though not a complete remission. Under the subsequent oral administration of cortisone the improvement has persisted more or less unchanged. No deleterious side-effects have so far been observed, and there have been no signs of retention of fluid or disturbances in the carbohydrate metabolism. Nor, in view of the small doses of cortisone used here, does it seem likely that such complications may occur. However, only after a lengthy follow up will a definite answer to this question be

¹ Due to the lack of cortone tablets we had to resort to cortisone pills in this case too.

possible, as well as to that of the long-term value of the oral mode of treatment. If this latter should prove to be as good as it promises to be, then we shall have acquired a method of treating severe chronic asthma cases, refractory to ordinary antiallergic therapy, that should make possible a partial evacuation of such cases from our hospitals for acute diseases, on which they now constitute such a burden.

The intractable category of asthma comprises, as is known, but a small proportion of all asthma cases. Usually it is a question of old "neglected" cases, often assignable to the refractory aspirin-sensitive group (about 8-10 per cent of all asthma cases) and mostly complicated by infections. As the writer has pointed out in an earlier paper (1), *the main significance of the effect of ACTH and cortisone in the allergic diseases, and especially in asthma, is probably that it makes possible and facilitates, respectively, the essential elimination of infection and the specific desensitization.* As a rule, therefore, it will merely be a question of short treatments of two or three days at a time, possibly repeated once or twice until the *causal* treatment has been completed. And as emphasized earlier, ACTH here is probably the most appropriate agent because of its very rapid effect in most cases.

Radical measures against infection, as the writer suggested in the aforementioned paper, very often entail a *lasting* remission that persists even if all medication be discontinued. This is found perhaps most commonly and strikingly among cases of asthma in children. The following is a case in point, relating to an elderly man.

Case 3. F. O., retired shopkeeper, born 1887.

Since 1940, progressively increasing asthma symptoms together with symptoms of vasomotor rhinitis. Of late, persistent severe distress, especially at night and on exertion.—S.R. 20 mm. Twenty per cent eosinophils in the blood. Skin spectrum (Jan. 27, 1950) negative. Lungs: pronounced emphysema; numerous sibilant râles diffusely, which rapidly increased when recumbent. Purulent sputum. Ecg. normal. Nose and throat; pansinusitis (Docent P. Frenckner).—In other respects no appreciable disease.

At his first visit the patient showed severe asthma symptoms, dyspnea and wheezing, etc. He was hospitalized on Jan. 24, 1950, and placed under treatment with iodine, adrenalin 0.5 mg $\times$ 6, and theophylline; later also aminophylline, coffein, aerosol (penicillin), and eucalyptus tar inhalation. Despite this treatment his condition after three weeks hospitalization was practically unchanged, with exceptionally distressing nocturnal symptoms. This, we considered, ruled out any operative treatment of the sinusitis.

On Feb. 16 we therefore instituted ACTH treatment. As early as the first night, after two doses of 10 mg, the nocturnal distress subsided and the following day the patient was virtually symptom free. After premedication with ACTH the sinusitis operation was then performed, without any complications. Three or four days later the symptoms returned. The examination for foci or infection now disclosed four rather large dental granulomas, as well as cholelithiasis. Operative measures were taken, under ACTH premedication, for these conditions.—The patient has since (*i.e.*, for about 1½ years) been quite free from asthma. He now moves about and works without the slightest distress.—We thus have here a complete remission of 1 to 1½ years' duration.

This and other analogous cases illustrate strikingly how, in evaluating the *duration* of the remission due to ACTH, we must necessarily consider and seek to appraise the role played by other circumstances—the elimination of causal factors, etc.—in the maintenance of the remission—a consideration which apparently has not always been observed to a sufficient degree.

In the writer's previous paper it was pointed out that the remission produced by ACTH medication in bronchial asthma is usually of short duration, provided it is not utilized for *causal* therapeutic measures. This view should to some extent be modified. The writer has since been able to observe, in two elderly severe cases of "intractable" asthma, not only how ACTH produced a complete remission, but how in one of them that remission has hitherto persisted for about five months. In the other case an exacerbation occurred after about two months; but further ACTH medication again brought about a complete remission, which still (roughly six weeks later) persists. It is impossible, however, to answer with certainty the question of what shall be ascribed here to the effect of ACTH and what may be due to possible other factors.

In a further respect, too, the writer would take this op-

portunity of implementing certain data given in his earlier paper, (1). With the guidance of the literature referred to therein, and on the basis of personal experience at the time, the view was expressed that the tractability of an allergy case to ACTH might be assessed, as a rule, by the response of the eosinophils to a single injection of ACTH. This view manifestly cannot be accepted as generally valid. In two cases in which ACTH led to a complete remission, the eosinophil response was not obtained until after the third and the fourth injection of ACTH respectively. In both cases complete remissions were produced within 24-36 hours.

SUMMARY

In conformity with the view expressed in a previous paper (1), the writer still considers that the main importance of ACTH and cortisone, when their action is utilized in allergic diseases (especially asthma), lies in the arresting of acute exacerbations and in the elimination of infections and the specific desensitization under ACTH protection in cases where these measures, in view of the condition and mode of reaction, would otherwise be difficult or impossible to carry through.

In severe cases, more or less completely refractory to conventional antiallergic measures, the writer, in common with E. Schwartz, finds that the remission produced by ACTH or cortisone can be made, at all events in certain cases, to persist for a lengthy period by the *oral* administration of cortone or cortisone in small doses. No deleterious side-effects have so far been observed under this treatment.

The writer emphasizes and exemplifies the difficulty of judging in certain cases to what degree the *maintenance* of a remission *produced* by ACTH is the result of the ACTH treatment or is due to the intervention or the elimination of other factors.

Attention should also be given to the possibility, according

to E. Schwartz, of replacing ACTH with cortone medication by mouth for the purpose of producing a remission.

In some cases adequate eosinophil responses, despite complete remissions, are not obtained until after the third or fourth injection of ACTH.

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