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PRESENT STATUS OF THE THERAPY
OF BRONCHIAL ASTHMA WITH ACTH,
HYDROCORTISONE, AND PREDNISONE

*Experimental and Clinical Observations*¹

By

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The interest in the use of ACTH and the adrenal steroids in the treatment of allergic syndromes in general and of bronchial asthma in particular is by no means spent, inspite of the large number of observations published in recent years. In fact it has taken a fresh lease of life with the introduction into therapy of the new synthetic steroids prednisone and prednisolone.

We consider it appropriate to refrain from going into details of the problems of the treatment of bronchial asthma, with the above mentioned hormones, particularly as their biological and clinical aspects have been extensively dealt with by many authors. Let us only remember that the matter was treated at the II European Congress of Allergology in Copenhagen in 1953, at the II Italian National Congress of Allergology in 1954 and at a recent International Conference on Prednisone in New York in 1955.

We shall thus limit ourselves to reporting our own research carried out during the years 1951-1955 in man, with

¹ Report at the Second International Congress of Allergology. Rio de Janeiro 6-13 November 1955.

a view to clarifying certain particular problems in connection with therapeutic action of these hormones.

In this paper we shall report first our experimental studies and then our clinical observations.

First of all we studied the adrenocortical stimulation of man when ACTH is given intravenously.

MINIMUM BIOLOGICALLY ACTIVE INTRAVENOUS DOSE

We established the minimum intravenous dose of ACTH which was able to produce a cortical stimulation measurable with the laboratory methods at our disposal. From among these, consisting basically of the behaviour of the blood eosinophils and the assay of the urinary oxisteroids and the 17-ketosteroids, we chose the former as according to many authors (*Deltour et al.*, *Best et al.*, *Thorn et al.*, *Wolfson & Fajans* etc.) and in our own experience it furnishes reliable data of adrenocortical stimulation as having taken place. Moreover as it was necessary to study the adrenal response to a single administration of ACTH, the study of the peripheral eosinophils undoubtedly was the method of choice.

In a group of 13 persons we studied the lowering of the eosinophil percentage four hours after the intravenous injection (in 30") of 1, 2 & 4 mg ACTH¹ in various tests, spaced at least 48 hours apart.

The eosinophil count was done according to the method of *Randolph*, as modified by *Henneman et al.* which, also according to our studies (*Argenti & Di Nardo*), may be considered the most reliable.

The results are shown in Fig. 1.

The minimum dose which is certainly active in the great majority of cases, we found to be 4 mg of hormone. This is in agreement with the findings of some authors (*Griffith et al.*; *Linquette et al.*) who obtained a 50 or more percent drop by the intravenous administration of 2.5-5 mg ACTH.

¹ The ACTH was kindly furnished by Messrs. Organon.

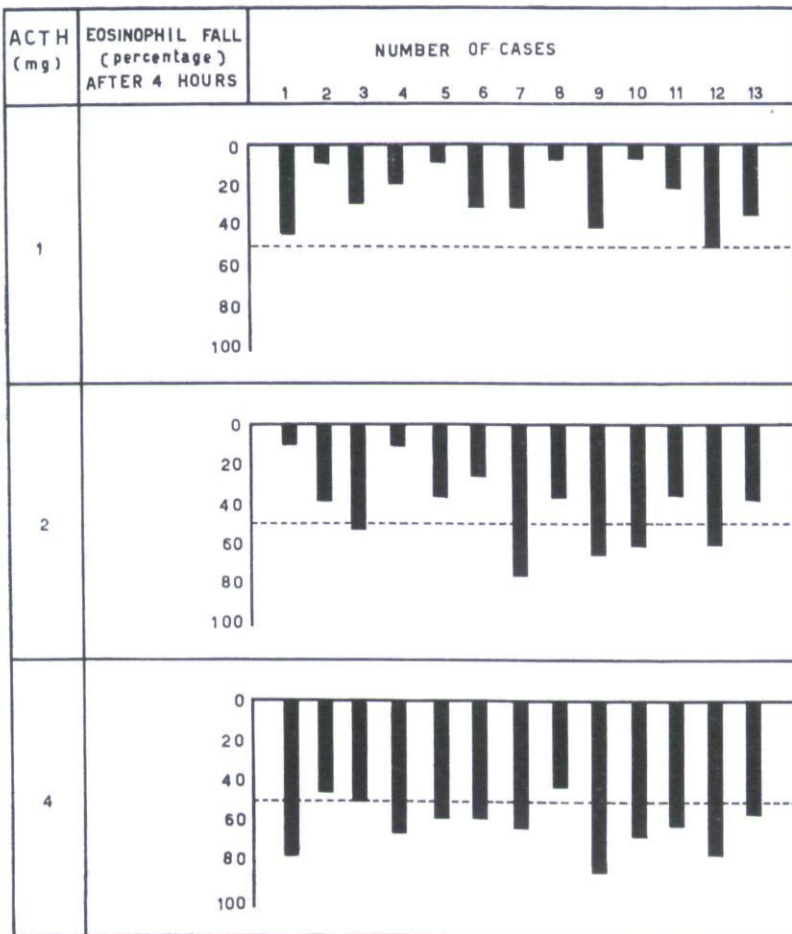


Fig. 1.

ADRENOCORTICAL STIMULATION AFTER THE INTRAVENOUS INFUSION OF ACTH

It has now been definitely established that intravenous ACTH disappears rapidly from the circulating blood owing to its rapid diffusion in the tissues and the body fluids, where after a short period it is no longer detectable, and particularly

due to its destruction in the blood itself, probably by enzymatic mechanisms. This accounts for the necessity of continued intravenous administration of ACTH in order to achieve a prolonged cortical stimulation, a method now extensively used in clinical practice. (*Gordon et al.*, *McIntosh & Holmes*, *Reynold et al.*, *Cohen & Ehrenfeld*, *Linquette et al.*, *Hampton*, *Harvier et al.*, *Segal & Herschfus*, *Di Nardo*, *Mandel et al.*, *Arbesman et al.*, *Jelliffe et al.*, *Lockey et al.*).

In this section we have made a detailed study in normal persons on the duration and the intensity of the adrenal response to the corticotropic stimulus. Here again the functional response was studied by means of the behaviour of the eosinophils. Two to four days interval was maintained between two infusions in the same person. The eosinophil count was taken every 2 hours for a period of 24–48 hours. All the infusions (about 200) were perfectly tolerated. The results of those rare infusions in which fever occurred, have not been included in the figure as it is known that fever as such may bring about a reduction in the circulating eosinophils (*Serafini et al.* 1946, etc.).

Controls made with even very prolonged intravenous infusions of the glucose solution only, did not give rise to a significant variation in the eosinophils (the decrease was always less than 50 % of the initial reading) as already seen by *Cape et al.* Repeated intravenous infusions in the same person, given in the same way and with the same dose of ACTH yielded the same variations of the eosinophils.

Duration of the adrenocortical response.—This study was undertaken in two series. In the first the duration of the infusion was varied while the dose of ACTH remained fixed, while in the second the time remained the same and the dosage of the hormone was varied.

The results of the first series involving 8 persons with *variable duration of the infusion and fixed doses of ACTH* are shown in Fig. 2. The duration of the eosinophil drop of over 50 % is shown in hours for each of the 4 types of infusions (lasting 2, 4, 6, 8 hours). The graph of each type of

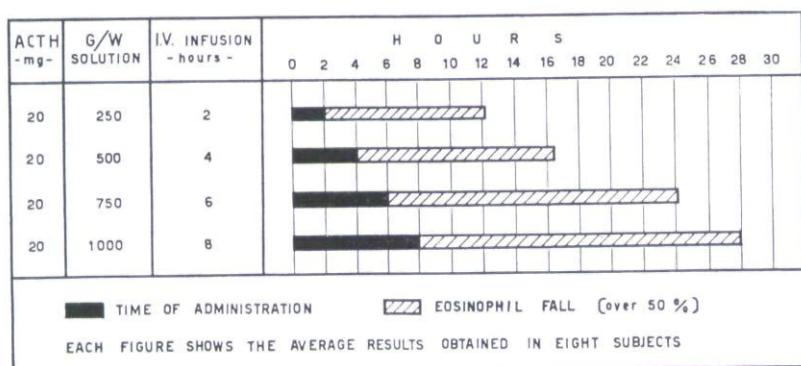


Fig. 2.

infusion represents the average of the results obtained in the 8 persons.

The results show that 20 mg ACTH given intravenously in the course of 2 hours provoke an eosinophil drop of more than 50 % of the initial value continuing for an average of 12 hours (min. 10, max. 16 hours) from the beginning of the infusion. The same dose given in 4 hours produced a similar eosinophilopenia for an average of 16 hours (min. 10, max. 20 hours). When the infusion lasted 6 hours the eosinophilopenia lasted 24 hours on the average (min. 19, max. 28 hours). Finally an infusion of 8 hours duration provoked an eosinophilopenia averaging 28 hours (min. 20, max. 35 hours).

The results of the second series, in which the *duration of the infusion remained constant and the dose of ACTH was varied* (5, 10, 15, 20 mg) are shown in Fig. 3. Here the duration of the eosinophil drop above 50 % is expressed in hours. For each type of infusion the graph shows the average of the results obtained in 10 persons.

These studies show that when the duration of the infusion is kept fixed at 8 hours, 5 mg ACTH produce a significant eosinophil drop for an average of 18 hours (min. 15, max. 21 hours); 10 mg evoked significant eosinophilopenia for an average of 22 hours (min. 18, max. 28 hours); with 15 mg it

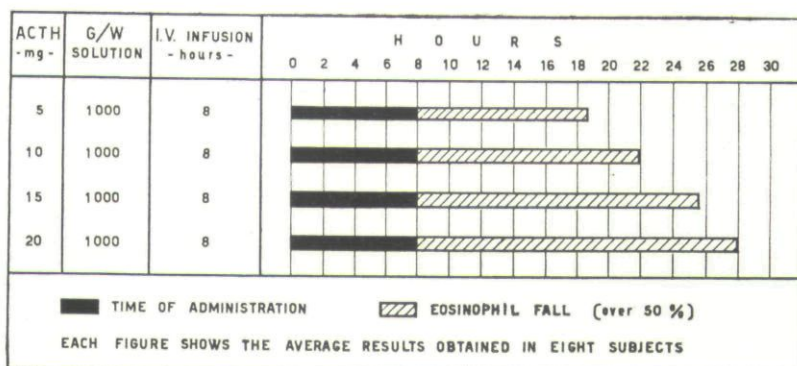


Fig. 3.

was 25 hours (min. 18, max. 34 hours); with 20 mg it lasted for 28 hours (min. 20, max. 36 hours).

The adrenocortical stimulation as indicated by an eosinophil drop of 50 % of the initial value occurs 3 hours after the beginning of the infusion. This is in conformity with the findings of *Cape et al.*

Under the experimental conditions we used, this period remained remarkably constant whatever the duration of the infusion or the dose of the hormone.

Intensity of the adrenocortical response.—Several authors have pointed out that the eosinophil drop after the administration of ACTH can be regarded not only as a qualitative sign of an adrenocortical response having taken place, but also as a quantitative method for establishing the intensity of the response (*Thorn, Brown & Greenblatt, Best et al., Speirs*).

We therefore studied the degree of stimulation by means of the intensity of the eosinophilopenia produced.

We used 2 experimental procedures in which we again in the one case kept the time constant and varied the dose and in the other varied the duration of the infusion and kept the dose constant. Figs. 4 & 5, show the results obtained in the two groups of persons. For each of the 4 types of infusion the average results in the 6 persons studied are shown.

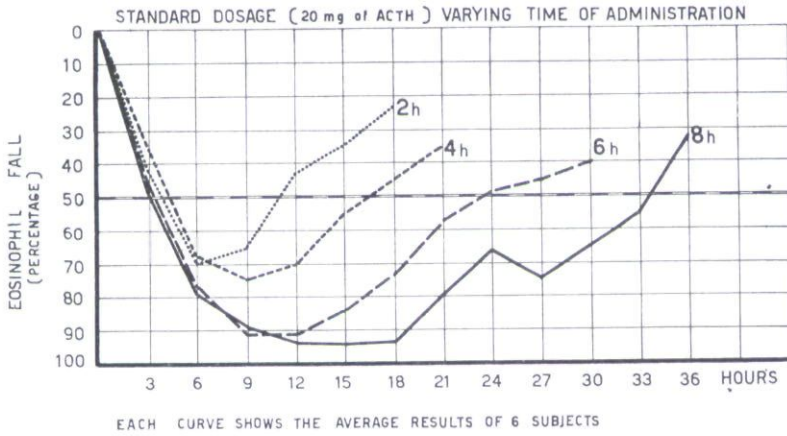


Fig. 4.

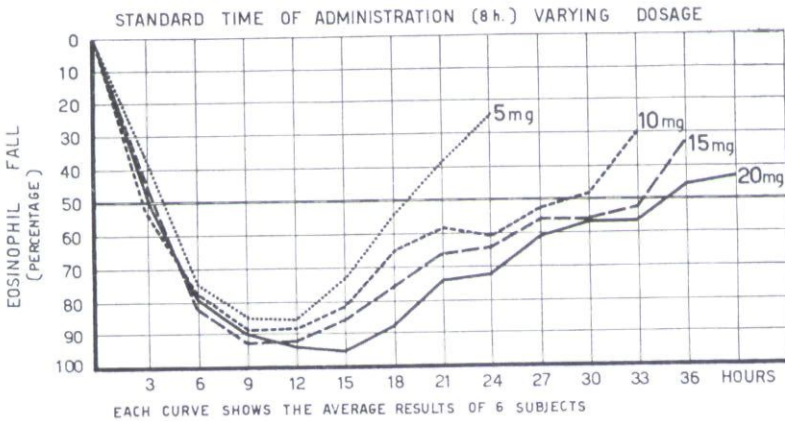


Fig. 5.

When the dose was kept fixed at 20 mg ACTH and the duration of the infusion was varied (fig. 4), the eosinophil drop was 70 % of the initial count when the infusion lasted 2 hours; 74 % when it lasted 4 hours; 92 % for 6 hours and 95 % for 8 hours.

When the duration of the infusion was kept fixed at 8 hours (fig. 5), the maximal eosinophil decrease reached 87 % of

the initial value when 5 mg of ACTH were given; 90 % for 10 mg; 93 % for 15 mg and 95 % for 20 mg.

The maximum eosinophilopenia was generally found between the 8th and the 12th hour after the begin of the infusion.

It can easily be seen that the degree of eosinophilopenia is different in the two series.

When the quantity of ACTH was fixed and the duration varied, there was a noticeable difference in the eosinophilopenia according to the time ranging from 70-74 when the infusion lasted 2-4 hours and reaching 92-95 % when it lasted 6-8 hours.

When the duration of the infusion was kept constant at 8 hours no appreciable variations in eosinophilopenia were found inspite of the differences in the dose (5-20 mg). These was however a slight increase as the dose was enlarged reaching 95 % when 20 mg were given.

ADRENAL RESPONSE OF ASTHMATIC PATIENTS TO CORTICAL STIMULATION

Hitherto the problem of adrenocortical function in asthmatic patients has not been satisfactorily solved. The results obtained by the various authors are not in ageement with each other. One group of students believes that in asthma there is an adrenocortical hypofunction which they have investigated with various methods (*Eriksson-Lihr, Harvier et al., Israels et al., Morgano & Fazio, Andersson* etc.).

A second group considers the adrenal function normal in asthmatic patients (*Hioco & Samter, Quarles van Ufford, Capuani & Clerici* etc.). According to *Rose & Venning* adrenocortical function differs with age, the type and the intensity of the symptomatology. These authors assume that at various ages there may be a certain amount of hypofunction when severe and prolonged asthmatic symptoms are present.

Differences of method may be among the reasons for these

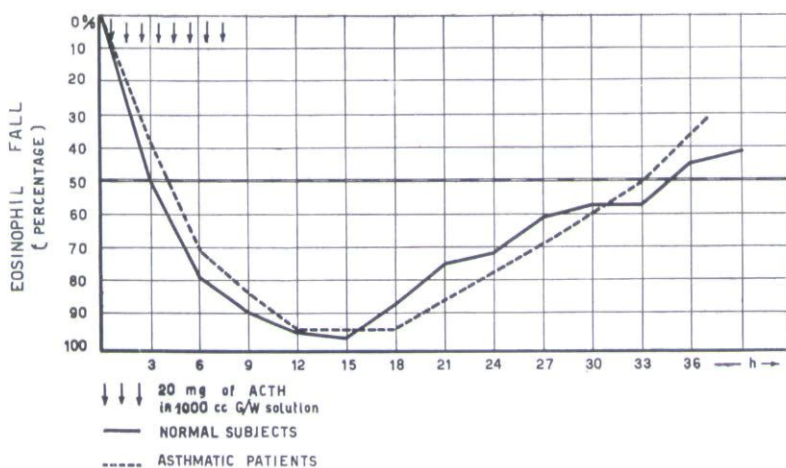


Fig. 6.

divergent opinions. In this connection we must remember that the adrenalin test is not satisfactory as regards adrenal function because the eosinophilopenia which it produces does not depend on a specific stimulation of the pituitary-adrenocortical axis (*De Fossey & Deltour; Almy et al.; De Gennes et al.; Kelley et al.; Kark & Muehrcke; Thorn; Maderna; Speirs & Sullivan* etc.). Even in *Thorn's* test of administering ACTH intramuscularly one can see that its negative result is not always an indication of a lacking adrenocortical response as in cases of so called ACTH resistance."

This report is studies on the adrenal responses capacity to corticotropic stimulation in asthmatic patients.

The 8hour test.—In a group of 15 asthmatic patients we studied the eosinophilic behaviour during and after the intravenous infusion of 20 mg. ACTH in 1000 cc 5 % glucose solution given over 8 hours (*Renold's* test). The technique was the same as that already reported in normal persons. Fig. 6 shows that the course of the eosinophil drop in asthmatic patients is practically identical with that of normal persons.

Repeated daily infusions.—In order to find out whether the adrenals of asthmatic patients have sufficient functional

TABLE 1¹

Case no.	Days of cortisone treatment	Daily dose mg	Total dose mg	Thorn's test % drop Eos.	Renold's tests
1	9	150	1350	95 %	normal
2	10	200	2000	65 %	normal
3	14	100	1400	75 %	normal
4	18	100	1800	75 %	normal
5 ²	60	40	2400	80 %	not done
6 ²	120	60	7200	70 %	not done

¹ The reaction in normal persons is shown on page 247 (fig. 4).

² Patients treated with hydrocortisone.

reserve, we gave 4 patients daily infusions of 20 mg ACTH in 1000 cc glucose solution during 8 hours for a period of 8-12 days. A normal eosinophilopenic response is maintained throughout the whole period of corticotropic stimulation, showing that there is a normal functional reserve after prolonged stimulation.

Thorn's test after prolonged treatment with cortisone.—A group of studies was concerned with the capacity of the adrenals to respond adequately to the corticotropic stimulus after prolonged treatment with cortisone in order to find out whether asthmatic patients might have a more marked tendency to adrenal exhaustion after prolonged treatment with cortisone than normal persons. It is known that this therapy can cause a weakening of the adrenal capacity to respond to ACTH, varying in duration and intensity. (*Engleman et al., Fraser et al., Salassa et al.*). This was already shown experimentally to be the case in 1937 (*Ingle & Mason*) and repeatedly confirmed (*Turiaf et al., Camus et al.*). In the clinical field there have been histological findings of hypotrophy of the adrenals (*O'Donnel et al., Bennet*).

We treated 6 asthmatic patients with cortisone¹ for varying periods and then performed Thorn's test with intramuscular ACTH. In 4 of these cases we also did Renold's 8 hour test.

¹ The cortisone was kindly furnished by Messrs. Merck.

In each case the tests were performed on the day following the suspension of the cortisone treatment. The following table (1) shows the results obtained.

We cannot say what degree of adrenal hypofunction we have produced in our asthmatic patients with the dosage and the duration we have used as the adrenal capacity to respond to the pituitary-adrenocortical stimulus was normal.

ACTH AND ASCORBIC ACID

The potentiating action of ascorbic acid on certain biological actions of ACTH, particularly glycoactivation is well known. Moreover it increases the resistance to cold in animals with intact adrenocortical pituitary system (*Bacchus*). A similar potentiating action is exerted by cortisone. *Bacchus* is of the opinion that the ascorbic acid intervenes by making the metabolic destruction of the cortical hormones slower. This author found that the treatment of guinea pigs with large doses of ascorbic acid prolonged the action of exogenic and endogenic corticoids as measured by the eosinopenic response.

In order to study the relationship between the administration of ACTH and the metabolism of ascorbic acid we carried out two groups of experiments (*Di Nardo & Malizia*).

1)—On the behaviour of ascorbinemia and ascorbinuria during repeated adrenal stimulations with daily intravenous infusions of ACTH.

It was shown that in six persons the daily infusion of ACTH for 4–8 days led to an increase in the urinary excretion of ascorbic acid in the first 3–4 days. This was followed by a reduction below the level which preceded the beginning of the treatment. The ascorbinemia was slightly increased in the first days in which ACTH was given and then returned to the original levels.

2)—On the intensity and the duration of the adrenocortical stimulation by ACTH, as measured by the peripheral eosinophilia, in persons saturated or lacking of vitamin C.

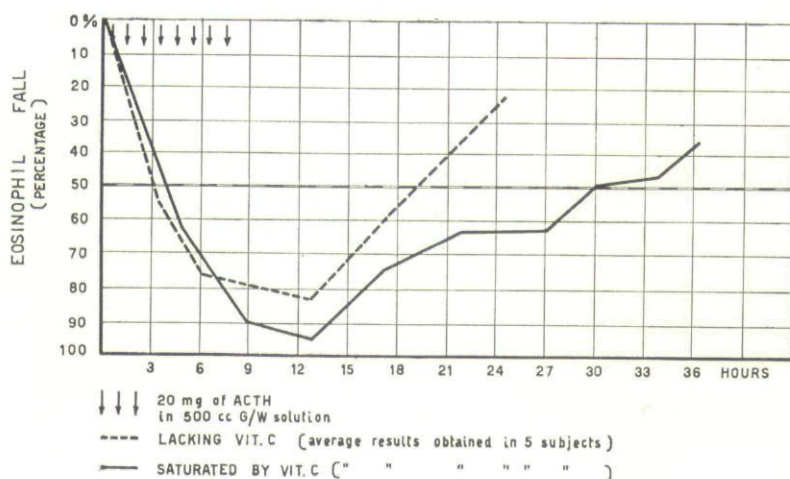


Fig. 7.

The ACTH induced eosinophilopenia in persons depleted of vitamin C was in every case of shorter duration and in 3 out of 5 less intense than in persons saturated with vitamin C (Fig. 7).

Clinical results.

We have had occasion to treat a very considerable number of patients suffering from various allergic condition and particularly bronchial asthma with ACTH (intramuscular; intravenous, continuous or intermittent); with oral hydrocortisone and recently with prednisone orally.

Here we shall report only a few illustrative groups of patients whom we were able to follow very closely. The patients treated had suffered from bronchial asthma for a long time and were severely ill in the period preceding the onset of treatment. In most cases, the asthma was of bronchitic origin. In other cases, however the skin reactions were positive to various inhaled allergens. During hormone treatment no other drug was given except the usual symptomatic preparations.

In hardly any case the treatment with most of the usual

methods brought an appreciable improvement of the symptomatology.

Most of the patients were hospitalized and studied before, during and after treatment.

We have distinguished our therapeutic results as excellent (++++) when there was a complete remission of symptoms; good (++) when there was a marked improvement; medium (+) when the improvement was partial; no result (—) when there was no appreciable improvement.

INTRAMUSCULAR ACTH

The patients were treated for a minimum of 5 and a maximum of 17 days. In 3 cases further courses were given at varying intervals.

The usual dose was 50–100 mg ACTH daily divided in four 6-hourly injections. In many cases the dose was reduced towards the end of the treatment in order to avoid a sudden interruption of treatment. During the treatment the patients were kept on a low sodium diet and were given 1 g potassium chloride daily.

The total dosage of ACTH varied from 175 to 800 mg.

TABLE 2
Intramuscular ACTH.

	Clinical results				Total
	+++	++	+	0	
No. of cases	17	7	4	3	31
%	55	22.5	13	9.5	100

The results of our clinical observations and of the most important studies carried out are shown in the tables 2 and 3. We shall discuss these separately.

In the great majority of cases a rapid remission of the

TABLE 3
Intramuscular

No.	Age	Sex	Diagnosis	Duration years	Skin tests	Duration and severity of symptoms	Duration treatment days	Max. single dose mg	Max. daily dose mg	Total dose mg
1	38	♂	Bronchial asthma	14	neg.	1 month medium	7	12.5	50	300
2	51	♂	B.A.	2	neg.	1 month severe	6	12.5	50	300
3	45	♂	B.A.	6 mths.	neg.	3 days severe	5	12.5	50	250
4	45	♀	B.A.	20	neg.	20 days medium	6	12.5	50	300
5	35	♀	B.A.	15	neg.	15 months medium	6	12.5	50	300
6	62	♂	B.A.	30	neg.	8 months medium	16	12.5	50	710
7 ¹	64	♂	B.A. pul- mon. emph.	10	neg.	several months mild	14	12.5	50	430
8	29	♀	B.A.	1	neg.	10 days mild	5	50	100	300
9 ¹	72	♂	B.A. pul- mon. emph.	9	neg.	2 weeks severe	17	12.5	50	500
10 ¹	10	♂	B.A.	6	neg.	1 month mild	12	5	50	200
11	64	♂	B.A.	2	neg.	some days medium	10	20	80	800
12	35	♂	B.A.	8	wool + house dust +	1 month medium	10	12.5	50	320
13	31	♀	B.A.	2	neg.	several months mild	4	12.5	50	175

¹ The pt. has been treated with several courses of ACTH. The results refer to the first course of treatment.

TABLE 3 (cont.)
ACTH

Clinical results	Duration of remission	Fosinophil fall 4 hours after 25 mg ACTH i. m.	Glycosuria	Vital capacity cc		Blood pressure		Body weight	
				Before	After	Before	After	Before	After
+++	Discharg. after treatment	87%	gr. 10 ⁶ / ₀₀	2300	2900	105/60	155/80		
+	1 day	68%	Nil	1200	2100	170/110	190/130		
+++	Discharg. after treatment	43%	Nil	3000	3500	155/105	140/85	65	67
+++	7 days then discharg.	57%	Trace	1900	2500	120/80	125/85		
+++	1 month then discharg.	35%	Nil	1400	2500	125/85	110/70	54	54
++	1 month no follow up	77%	Nil	1400	2350	115/70	135/90		
++	3 months	75%	Nil			135/80	140/85		
+++	Discharg. after treatment	68%	Nil	2000	2600	135/85	135/80		
+++	2 months	86%	Nil			135/80	105/65		
++	15 days	70%	Nil	1650	2150	115/85	115/80	30.4	33.4
+++	1 day	70%	Nil			130/80	140/80		
+++	2 months no follow up	58%	Nil	2000	3000	130/80	120/75	68	70.5
o	o	52%	Nil			115/70	140/65	60.5	60.5

TABLE 3 (cont.)
Intramuscular

No.	Age	Sex	Diagnosis	Duration years	Skin tests	Duration and severity of symptoms	Duration treatment days	Max. single dose mg	Max. daily dose mg	Total dose mg
14	57	♀	B.A.	40	wool+ house dust+	several months medium	9	12.5	50	300
15	65	♀	B.A.	5	neg.	some days mild	8	12.5	50	375
16	15	♀	B.A.	1	neg.	1 month medium	10	12.5	50	400
17 ¹	46	♀	B.A.	2	neg.	10 days severe	7	25	100	400
18	61	♀	B.A.	3	wool+	1 month medium	8	12.5	50	325
19	21	♀	B.A.	2	neg.	10 days medium	10	12.5	50	400
20	41	♀	B.A.	12	neg.	1 year medium	9	25	100	400
21	45	♀	B.A.	6	neg.	10 days severe	8	12.5	50	300
22	19	♀	B.A. eczema	5	neg.	10 years medium	16	25	100	800
23	40	♂	B.A.	10	neg.	3 months medium	10	12.5	50	450
24	30	♀	B.A.	3	neg.	2 weeks medium	11	12.5	50	500
25	46	♀	B.A.	10	neg.	2 months medium	9	20	80	520
26	31	♀	B.A.	10	neg.	1 month	9	12.5	50	400
27	46	♀	B.A.	2	neg.	1 week	8	25	100	400
28	21	♀	B.A.	3	neg.	1 month	7	25	100	400
29	15	♂	B.A.	5	neg.	1 month	6	12.5	50	250
30 ¹	30	♂	B.A.	5	neg.	1 month	8	12.5	50	300
31 ¹	39	♀	B.A.	9	Weat flour+	1 week	9	12.5	75	375

¹ The pt. has been treated with several courses of ACTH. The results refer to the first course of treatment.

TABLE 3 (cont.)
ACTH

Clinical results	Duration of remission	Eosinophil fall 4 hours after 25 mg ACTH i. m.	Glycosuria	Vital capacity cc		Blood pressure		Body weight	
				Before	After	Before	After	Before	After
++	10 days	88%	Trace	2000	2400	130/80	165/100		
o	o	31%	Nil			125/80	140/75		
+++	2 months no follow up	53%	Trace	1700	3250	125/85	140/75	39.4	44.5
+++	1 month	—	Trace	300	1000	165/90	185/95		
+	3 weeks	53%	Nil	1000	1000	135/80	120/75	48	48
++	1 month	83%	Nil	2500	3000	105/70	125/85		
+++	1 week	81%	Nil	800	1650	140/90	155/95	68.7	72.7
++	1 day	—	Trace	400	1600	150/100	125/75		
+++	2 months	35%	Nil	2400	3400	125/70	140/85	58.5	62.5
++	no follow up	50%	16.66 ⁹ / ₁₀₀	2000	2800	145/90	160/100	67.5	68.6
+++	no follow up	80%	Nil	800	2700	150/100	115/75	46	46.5
+	Few days	50%	Trace	2100	2450	160/100	130/90	80	80
o	o	52%	Trace	2250	2600	135/80	125/80	55	56
+++	Few days	80%	Nil	800	1600	140/90	165/95	68.5	72.5
+++	Few days	30%	Nil	1000	1700	145/90	150/100	50.5	51
+	Few days	70%	Trace	2000	2200	120/75	125/85	32	35
+++	Few days	58%	Nil	2000	2650	150/90	150/100	69	69
+++	Few days	75%	Trace	1500	2000	140/90	150/100	57.5	60

symptomatology was achieved though this had persisted for a long time previously in a severe form. The results can be classified as follows:—17 excellent; 7 good; 4 medium and 3 negative.

The onset of improvement was within the first 24–48 hours and a complete or partial remission was reached on the 4th day of therapy.

The duration of the remission after treatment was suspended was variable, ranging from a few days to several months.

Subjectively the beneficial effect was felt as a decrease in respiratory oppression, disappearance of cough and dyspnoea, a general feeling of well-being, an increase in appetite, ability to sleep. Objectively there was in some cases a complete cessation of auscultatory signs, a marked increase in vital capacity and in the length of voluntary apnoea; in other cases the remission, though very evident, was not complete; still other cases showed a slight yet clearly appreciable improvement.

In the group of the bronchitic asthmatic cases, there were two patients who had severe emphysematous respiratory insufficiency. They had suffered from dyspnoea on exertion for many years and had occasionally had asthmatic crises. Both these cases showed a slight temporary improvement.

Special mention must be made of one of the cases classified as negative. This was a female aged 31 who for one and a half year had been in a sub-asthmatic state during which she had very severe asthmatic attacks. Various forms of treatment had no appreciable result. In this connection it is important that she had a large number of injections of pituitary extract. Treatment was started with 50 mg. ACTH daily distributed in 4 doses. Treatment had to be stopped on the 4th day because her asthma became worse. A particularly severe asthmatic attack occurred regularly a few minutes after the intramuscular injection of ACTH. Assuming that there might be a hypersensitiveness to the hormone, 1 mg. ACTH was injected intradermally. This produced a strongly positive reaction and thus confirmed what had been suspected clinically.

Six patients received several courses of treatment always using the same dose. In 5 cases the relief was each time about the same as achieved with the first course. The other patient showed no improvement whatsoever.

The studies made on our patients treated with ACTH intramuscularly showed the following results:—*Eosinophilia*. In the cases studied we first did Thorn's test, giving 25 mg ACTH intramuscularly. In 23 out of 28 cases the eosinophilic drop below 50 % occurred at the 4th hour. During treatment the eosinophils dropped below 50 % of their initial count in every case. In 8 cases an absence of eosinophils from the circulation occurred. Within certain limits these drops were not in proportion to the dosage used nor to the degree of clinical improvement. In fact in one case in which the clinical results were negative there was a complete absence of peripheral eosinophils.

Miscellaneous studies. In many cases (18 out of 30) there was an increase in blood pressure from a minimum of 15 to a maximum of 50 mm. Hg. In practically all cases the body weight increased. In 5 cases there were signs of generalized edema. Glycosuria occurred in 11 cases ranging from traces to 16.66 $\frac{0}{100}$. There were no significant changes in the glycaemia, the azotemia and the sedimentation rate. The electrocardiograms showed no pathological changes after treatment. The majority of the phenomena encountered were due to the known action of ACTH on various metabolic processes and were in no case of a serious character. This is probably due to the short period of treatment and the small doses used.

TABLE 4
Intravenous ACTH (Intermittent administration).

	Clinical results				Total
	+++	++	+	0	
No. of cases	5	11	4	1	21
%	23.5	52.5	19	5	100

TABLE 5
Intravenous ACTH

No.	Age	Sex	Diagnosis	Duration years	Skin tests	Duration and severity of symptoms	Duration treatment days	Max. single dose mg	Max. daily dose mg	Total dose mg
1	53	♀	Bronchial asthma	20	neg.	9 months mild	15	2	8	120
2	35	♂ ¹	B.A.	1	neg.	15 days medium	14	2	8	110
3	31	♂ ¹	B.A.	11	Horse dandruff	2 months mild	15	2	8	120
4 ¹	43	♀	B.A.	4	neg.	6 months medium	7	2	8	56
5	36	♂ ¹	B.A.	8	wool+ house dust+	16 days medium	7	2	8	56
6 ¹	52	♂ ¹	B.A.	1	neg.	1 month severe	10	2	8	80
7	60	♂ ¹	B.A. pul- mon. emph.	4	neg.	1 year medium	14	2	8	90
8 ¹	40	♂ ¹	B.A.	6	neg.	1 month mild	7	2	8	56
9	30	♀	B.A.	5	neg.	1 month mild	11	2	8	82
10	40	♂ ¹	B.A.	15	neg.	1 year medium	13	2	8	92
11	14	♀	B.A.	1	Dusts+	15 days medium	10	2	8	80
12	50	♂ ¹	B.A.	6 mths.	neg.	6 months medium	8	2	8	50
13	35	♀	B.A.	6 mths.	neg.	3 months severe	13	2	8	100
14	40	♀	B.A.	3	neg.	3 months medium	14	2	8	102

¹ The pt. has been treated by several courses of ACTH. The results concern the first course of treatment.² No further follow up.

TABLE 5 (cont.)
(intermittent administration).

Clinical results	Duration of remission	Eosinophil fall 4 hours after 2 mg ACTH i. v.	Glycosuria	Vital capacity cc		Blood pressure		Body weight	
				Before	After	Before	After	Before	After
++	12 days ²	31%	Nil	1200	2300	120/80	130/90	50.7	52.7
++	3 weeks	67%	Nil	2400	3200			71.1	72.4
+++	2 days ²	71%	Nil	2700	2900			70.6	73.6
++	1 week	79%	Nil	2050	2350	120/80	120/80	41.8	45.9
++	2 days ²	72%	Nil	1850	2300			79.8	80.9
++	2 months	25%	Nil						
+	Few days	46%	Trace	1500	1800	140/85	140/85	61.1	64.4
+++	1 month	44%	Nil	2200	2900	105/75	115/80	55.8	59.8
+	Few days	38%	Nil	1900	2000	110/50	140/80	37.5	38.1
+	1 day	55%	Trace	1900	2200	145/90	150/110	68.5	69.5
++	2 months	50%	Nil	2700	2900	110/70	120/75	37.5	40.5
++	1 week ²	25%	Nil	2200	2500	150/100	140/90	78.6	80.4
++	1 month ²	45%	Nil	1300	2200	120/80	130/90	48.6	52.5
++	6 days ²	65%	Trace	1500	2800	135/90	135/90	38.5	40.6

TABLE 5 (cont.)
Intravenous ACTH

No.	Age	Sex	Diagnosis	Duration years	Skin tests	Duration and severity of symptoms	Duration treatment days	Max. single dose mg	Max. daily dose mg	Total dose mg
15	42	♀	B.A.	17	neg.	2 months severe	12	4	12	120
16 ¹	38	♀	B.A.	9	Wheat meal+	2 weeks severe	13	2	8	100
17	51	♂	B.A.	18	neg.	2 months severe	8	2	8	56
18 ¹	35	♂	B.A.	7	neg.	1 month medium	8	2	8	62
19 ¹	55	♂	B.A. pul- mon. emph.	30	neg.	1 year medium	14	2	8	120
20 ¹	40	♂	B.A.	20	neg.	1 year medium	13	2	8	102
21	38	♂	B.A.	4	neg.	2 months medium	12	2	8	92

¹ The pt. has been treated by several courses of ACTH. The results concern the first course of treatment.

² No further follow up.

INTRAVENOUS ACTH

Intermittent administration.—We experimented with the intravenous route in order to verify the important observation of the clinical and metabolic effects of very small doses of ACTH as compared with those used in the intramuscular route.

The tables show the study of 21 patients suffering from bronchial asthma of various origins (Tables 4 and 5).

The patients were treated from a minimum of 7 to a maximum of 20 days. The usual dose was 8 mg daily (2 mg 6 hourly). In many cases the dose was gradually reduced towards the end of the treatment in order to avoid a sudden interruption. The total dose ranged from 50 to 120 mg.

TABLE 5 (cont.)
(intermittent administration).

Clinical results	Duration of remission	Eosinophil fall 4 hours after 2 mg ACTH i. v.	Glycosuria	Vital capacity cc		Blood pressure		Body weight	
				Before	After	Before	After	Before	After
o	o	85%	Nil	2000	2000				
+++	Few days	75%	Nil	1500	1800	160/100	125/90	57.2	57.8
++	Few days ²	40%	Nil	2300	3400	130/90	140/100	70.5	68.5
+	Few days	58%	Trace	2000	2500	160/100	145/95	70.9	70
++	Discontinued	70%	Nil	1800	2200	125/80	150/95	66.2	65.8
+++	Few days ²	70%	2.85 ^{0/100}	2200	3200	160/90	165/95	58	59.7
+++	Few days ²	50%	Nil	2700	3400	155/80	185/100	84.7	85.3

The clinical results were as follows: 5 excellent; 11 good; 4 medium; 1 negative. The onset of improvement occurred within the first 24 hours and the complete or partial remission was achieved on the 3rd. or the 4th day. The duration of the remission after treatment was stopped ranged from a few days to several weeks as was seen in cases treated by the intra-muscular route.

Seven patients had several courses. The results of subsequent courses were similar to those obtained with the first course but less marked. In one particularly severe case in which the first course had produced a fair result, a second course proved to be practically ineffective.

In most of the cases studied the eosinophils dropped below 50 %. Again there was no relationship between the drop and

the clinical improvement as in some cases there was a marked drop without clinical improvement. The blood pressure was not significantly altered except in 4 cases in which there was a rise of 30–40 mm. during the treatment. Almost all patients increased in weight.

TABLE 6
Intravenous ACTH (Continuous infusion).

	Clinical results				Total
	+++	++	+	0	
No. of cases	10	4	5	1	20
%	50	20	25	5	100

Two cases showed manifest edema. Sugar appeared in the urine of 5 cases ranging from traces to 2.85 ‰. There were no significant changes in glycemia, azotemia and the sedimentation rate. There were no pathological changes in the ECG.

In all cases the dose of 2 mg intravenously was well tolerated.

INTRAVENOUS ACTH

Continuous infusion for 8 hours.—The continuous infusion of small doses of ACTH has ever since it has been used clinically proved to be well tolerated. It has not produced major incidents or collateral phenomena other than those to which the intramuscular route is subject. (*Gordon et al.*; *McIntosh & Holmes*; *Renold et al.* etc.).

The tables show the clinical results obtained in a group of 20 asthmatic patients treated with continuous intravenous infusion. (Tables n. 6 and 7). In each case an intradermal test with 1 mg. ACTH was undertaken before treatment was started in order to discover possible hypersensitiveness. In all cases the test was negative.

The dose per infusion ranged from 5 to 20 mg in 5 % glucose solution; 400–1000 cc at the rate of 30–40 drops per

minute were given over a period of from 2 to 8 hours. The majority of cases received 20 mg ACTH during 8 hours. The eosinophils were counted periodically during and after the infusion with a view to finding the begin and the duration of the adrenocortical stimulation. Thereby each subsequent infusion could be given only after the effect of the previous one had worn off as shown by the return of the eosinophils after their maximum drop back to the initial level. In practice the infusions were given every second or third day.

The results were in 10 cases excellent; good in 4; medium in 5 and negative in 1. The duration of the total or partial remission after stopping therapy ranged from a few days to 6 weeks.

The behaviour of the eosinophils was interesting. A drop of 50 % occurred in each of the 131 infusions made, at the 3rd hour. The maximum eosinophilopenia was reached 8–12 hours after the begin of the infusion and its duration varied according to the dose and the duration of the infusion. When, as in most cases, 20 mg were given over 8 hours the eosinophilopenia lasted from 20–36 hours averaging 28 hours.

Other investigations yielded nothing in particular. 7 patients had secondary symptoms due to the hormone. Three complained of gastrointestinal symptoms; one of headache; one retrosternal pain and a feeling of constriction. One patient had a thrombophlebitis of the cubital vein used for the infusion. None of these symptoms was sufficiently severe to call for an interruption of the treatment.

ORAL HYDROCORTISONE¹

We have made extensive use of hydrocortisone for the treatment of bronchial asthma. In the table we limit ourselves to a group of 16 cases. In these hydrocortisone was given orally in doses of 60–80 mg. daily for the first day and then gradually reduced so as to find the smallest active dose for each

¹ The hydrocortisone was kindly furnished by Messr. Merck.

TABLE 7
Intravenous ACTH

No.	Age	Sex	Diagnosis	Duration years	Skin tests	Duration severity of symptoms	Duration of treatment	Dose of each infusion mg	Duration of each in- fusion hours	Total dose mg	No. of infusions	Clinical result
1	52	♀	Bronch. asthma	7	neg.	Several months medium	13	5-20	8	80	6	+++
2	23	♂	B.A.	4	neg.	mild	13	20	2-8	120	6	+++
3	45	♀	B.A.	1	neg.	medium	16	20	2-8	120	6	+
4	22	♂	B.A.	3	neg.	mild	15	5-20	8	70	5	+++
5	21	♀	B.A.	13	house dust+	8 days medium	18	5-20	8	75	6	++
6 ²	12	♂	B.A.	8	neg.	2 months medium	8	15	2-8	60	4	+++
7	44	♂	B.A. pulm. emphys.	3	neg.	1 month severe	22	5-20	8	110	8	++
8	65	♀	B.A.	2	pollens+	2 months severe	17	5-20	8	100	7	+++
9	41	♀	B.A.	2	wool+ house dust+	1 month severe	14	20	2-8	120	6	++
10	30	♀	B.A.	4	neg.	15 days mild	13	5-20	2-8	75	6	+++
11 ³	12	♀	B.A.	11	house dust+ wool+ beans+	1 month severe	22	10	2-8	80	8	+
12 ²	55	♂	B. pulm. emphys.	10	neg.	several months medium	9	20	8	100	5	0
13	36	♀	B.A.	20	neg.	several months medium	15	5-20	8	85	6	++
14 ³	26	♂	B.A.	1	neg.	few days severe	16	20	2-8	160	8	+++
15	60	♂	B.A.	3	neg.	1 month severe	12	10-20	8	90	5	+++

¹ No follow up.² The pt. had previous treatments with ACTH i.m.³ The pt. had previous treatments with ACTH i.v.

TABLE 7
(*continuous infusion*).

Duration of remission	Side effects	Eosinophil fall 8 hours after start of infusion	Glycosuria	Vital capacity cc		Blood pressure		Body weight	
				Before	After	Before	After	Before	After
1 week ¹	diarrhoea, abdominal, pain, pyrosis	78 %	nil	1800	3000			51	53
10 days ¹	pyrosis	80 %	nil	3000	4200			66	69
1 month ¹		72 %	nil	1600	1800	190/90	160/95	66	66
1 month	retrosternal pain	90 %	nil	3000	3400			56	56
1 month	headache	75 %	nil	2300	3200	180/100	175/100	44	47
1 month		85 %	nil	2300	2700	120/80	115/80		
10 days ¹	mild diffuse abdominal pain	70 %	nil	1500	2300	130/90	130/90	47	49.5
1 month		80 %	nil	1700	2700	150/90	150/85		
few days	elbow vein phlebitis	82 %	nil	1200	1800			79	79
few days ¹		92 %	nil	2700	3500			66	68
1 month		55 %	nil	1500	2000	110/70	135/95	31.5	33
0		77 %	nil	1200	1200	135/85	140/90		
1 month		68 %	nil	2000	2800	115/80	115/80	61	63
6 weeks		91 %	nil	1800	3500	130/95	125/80		
few days ¹		86 %	nil	1600	2800	130/80	140/100	47	48

TABLE 7 (cont.)
Intravenous ACTH

No.	Age	Sex	Diagnosis	Duration years	Skin tests	Duration severity of symptoms	Duration of treatment	Dose of each infusion mg	Duration of each in- fusion hours	Total dose mg	No. of infu- sions	Clinical result
16	29	♀	B.A.	2	neg.	1 month severe	23	5-20	8	100	8	+++
17 ²	40	♂	B.A.	1	neg.	several months severe	14	5-20	8	100	7	+
18	51	♂	B.A. spont. pntx.	14	neg.	9 days spont. right pntx.	33	10	4	80	8	+
19 ²	36	♀	B.A.	5	neg.	1 month severe	6	20	8	120	6	+
20	50	♀	B.A.	15	neg.	several months medium	10	20	8	200	10	+++

¹ No follow up.² The pt. had previous treatments with ACTH i.m.³ The pt. had previous treatments with ACTH i.v.

patient. This was found to lie around 20-40 mg daily. The duration of treatment varied from a few days to 3 months (Tables 8 and 9).

Our results were 10 excellent, 4 good and 2 poor. In general the time required for the onset of clinical improvement was shorter than with ACTH. On an average it took about 24 hours.

TABLE 8
Oral hydrocortisone.

	Clinical results				Total
	+++	++	+	0	
No. of cases	10	4	2	-	16
%	62	25	13	-	100

TABLE 7 (cont.)
continuous infusion).

Duration of remission	Side effects	Eosinophil fall 8 hours after start of infusion	Glycosuria	Vital capacity cc		Blood pressure		Body weight	
				Before	After	Before	After	Before	After
1 month		98 %	nil	3000	3900	140/95	135/85	53	56
10 days		76 %	nil	900	1400	135/80	115/85		
1 month	restlessness	69 %	nil	700	1200	120/90	115/95		
few days		90 %	nil	1000	1500	120/80	120/90		
1 month		88 %	nil	1500	2800	140/100	150/90		

The duration of the remission varied from a few days to 2 months. In no case did we see serious secondary effects. Only three patients showed slight signs of water retention and one a transitory glycosuria.

ORAL PREDNISONE¹

In January 1955 *Bunim et al.* reported the first therapeutic results achieved in rheumatoid arthritis with the two new synthetic steroids prednisone and prednisolone.

The three things that arouse particular interest in these steroids were 1) That their anti-rheumatic and anti-inflam-

¹ Prednisone is the designation given to delta 1-4 pregnandiene 17 alpha 21 diol 3, 11, 20 trione by the Council on Pharmacy and Chemistry of the A.M.A. which was previously known as metacortandracin.

Prednisolone is delta —1-4 pregnandiene 11 beta 17 alpha 21 triol 3,20 dione, formerly known as metacortandralone.

The prednisone was kindly furnished by Messrs. Lepetit.

TABLE 9
Oral hydrocortisone.

No.	Age	Sex	Diagnosis	Dura- tion years	Skin tests	Duration and severity symptoms	Dura- tion treat- ment days	Clinic results	Single dose mg	Daily dose mg	Total dose mg	Duration remission
1	59	♀	Bronch. asthma	1	neg.	2 weeks	15	+++	20	60	900	1 week
2	54	♀	B.A.	10	neg.	1 month	21	+++	20	20-60	480	10 days
3	47	♀	B.A.	4	neg.	1 week	8	++	20	80	600	few days ¹
4	28	♀	B.A.	4	neg.	1 month	10	+	20	80	800	few days
5	58	♀	B.A.	15	neg.	some months	120	+++	20	60-80	7600	1 month
6	75	♂	B.A.	9	neg.	1 month	15	++	20	20-60	700	1 month
7	51	♂	B.A.	2	neg.	2 months	20	+++	20	20-60	700	3 weeks
8	56	♂	B.A.	6	neg.	1 month	20	+++	20	20-60	1000	10 days ¹
9	46	♀	B.A.	8	neg.	1 month	20	+++	20	30-80	1140	8 days ¹
10	24	♀	B.A.	2	neg.	3 weeks	18	+++	20	20-60	720	2 months
11	60	♀	B.A.	7	neg.	some months	10	++	20	80	800	few days ¹
12	53	♀	B.A.	6	neg.	1 week	10	+	20	60-80	760	few days
13	20	♀	B.A.	15	neg.	1 month	11	+++	20	60	660	few days
14	62	♂	B.A.	20	neg.	1 week	15	+++	20	60	900	10 days ¹
15	41	♀	B.A.	5	neg.	10 days	10	++	20	20-60	500	1 month
16	33	♀	B.A.	3	neg.	2 weeks	15	+++	20	60	900	few days ¹

¹ No follow up.

matory efficacy was 3-4 times greater than that of cortisone and 2-3 times greater than that of hydrocortisone. 2) That a satisfactory therapeutic effect can be obtained with minimal doses 2.5-5 mg daily). 3) That side effects are rare, particularly the retention of sodium and the loss of potassium.

The clinical investigation of these products was primarily done with prednisone in rheumatic conditions (*Bunim et al.*, *Ballabio et al.*; *Boland*; *Gray & Merrick*; *Robecchi et al.* etc.). The use of prednisone in bronchial asthma was first reported by us at Utrecht in May 1955. Contemporaneously there appeared articles on cases of bronchial asthma with this preparation by *Arbesman & Ehrenreich*; *Skaggs et al.*; *Schwartz*. Recently other authors (*Barach*; *Lenti*; *Rose*; *De Fossey*; *Teichholtz* etc.) have studied its action in bronchial asthma.

Before describing our clinical results we report our experiments on the biological activity of prednisone in man, consisting of a comparative study of the eosinopenia produced by oral administration of cortisone and prednisone. From the figure 8 it can be seen that an oral dose of 10-15 mg. prednisone has the same effect on the eosinophilopenia as 50 mg cortisone in the same person.

Also *Arbesmann & Ehrenreich* found in 16 cases of asthma that the maintenance dose of prednisone was 10 mg while in order to achieve the same result 53.1 mg cortisone and 41.6 mg hydrocortisone was necessary.

Our study was conducted on 27 cases with a long history and presenting a severe clinical picture at the time treatment was started. The steroid was administered over a period ranging from 6-30 days. Three cases were given repeated courses. We generally used doses ranging from 30-10 mg daily and a total dosage of from 130 to 540 mg.

Our results can be stated as follows:—18 excellent; 3 good; 4 medium; 2 negative (Tables 10 and 11). In one of the cases that showed no improvement there was a marked respiratory insufficiency due to a very severe emphysema. For many years the patient had suffered from breathlessness on exertion and

TABLE 10
Oral prednisone.

No.	Age	Sex	Severity of symptoms	Duration years	Skin tests	Duration treatment days	Daily dose (max.) mg	Total dose mg	Clinical results
1	56	♀	severe	12	neg.	15	30	300	++
2	25	♀	severe	1	horse dand. +	14 ¹	30	270	+++
3	64	♀	severe	6	neg.	7	30	150	+++
4	31	♀	medium	25	dusts +	18	30	315	+++
5	45	♀	severe	30	neg.	20	30	340	+++
6	56	♂	medium	5	neg.	9	30	205	o
7	15	♂	medium	5	wool	10	40	260	+++
8	28	♀	severe	3	neg.	11	40	370	++
9	58	♀	severe	10	neg.	6	60	270	+
10	41	♀	severe	15	neg.	10	20	130	+++
11	68	♂	severe	15	neg.	10	30	140	+
12	65	♀	severe	1	neg.	20	20	180	+++
13	60	♀	medium	7	neg.	20	30	450	+++
14	41	♂	severe	1	neg.	20	30	500	+++
15	50	♂	severe	5	neg.	20	30	500	+++
16	35	♀	severe	10	neg.	15	20	400	++
17	27	♀	medium	1	neg.	18	30	460	+++
18	33	♂	severe	3	neg.	18	30	540	+
19	35	♀	severe	3	neg.	15	30	400	+++
20	49	♂	severe	1	neg.	15	30	400	+++
21	45	♂	severe	2	neg.	15	20	300	+++
22	60	♀	severe	20	pollens +	5	30	150	o
23	60	♂	severe	15	neg.	15 ¹	30	200	+
24	77	♂	severe	1	neg.	15	20	200	+++
25	32	♀	medium	2	neg.	15	20	200	+++
26	68	♂	severe	15	neg.	15 ¹	30	350	+++
27	30	♀	medium	4	neg.	30	20	500	+++

¹ The pt. has been treated by several courses of ACTH. The results concern the first course of treatment.

TABLE 10 (cont.)
oral prednisone.

Side effects	Glycosuria	Voluntary apnoea		Blood pressure		Body weight (kg)	
		Before	After	Before	After	Before	After
—	absent	14"	20"	150/90	140/95	53	55
—	absent	9"	20"	120/80	120/75	49.5	49.5
—	absent	12"	21"	125/85	120/80	54	54
acne	absent	13"	33"	130/80	140/85	44	46
albuminuria	absent	7"	20"	155/100	140/80	72	71
—	absent	16"	14"	145/90	125/80	71	71
—	absent	15"	39"	110/55	110/60	48	48
—	absent	7"	25"	130/95	130/95	58	56
—	absent	7"	18"	145/100	150/90	78	79
—	absent	7"	48"	190/95	170/90	70	70
—	absent	10"	15"	130/90	130/90	—	—
—	absent	7"	35"	230/130	150/90	84	84
—	absent	18"	27"	160/90	155/90	—	—
—	absent	7"	35"	130/90	130/85	72	71
—	absent	10"	28"	160/95	165/90	82	81.5
—	absent	12"	24"	115/75	120/80	—	—
—	absent	15"	40"	110/80	120/80	—	—
—	absent	10"	15"	140/95	140/95	53	53.6
—	absent	8"	32"	—	—	81	81
—	absent	7"	28"	—	—	65	66
—	absent	12"	40"	130/90	130/85	48	49
malaise	absent	—	—	—	—	—	—
—	absent	10"	15"	150/90	155/90	60	60
—	absent	20"	38"	—	—	39	38
—	absent	11"	35"	160/95	150/80	—	—
—	absent	9"	28"	—	—	58	57.5
—	absent	13"	36"	125/75	130/80	66	66.5

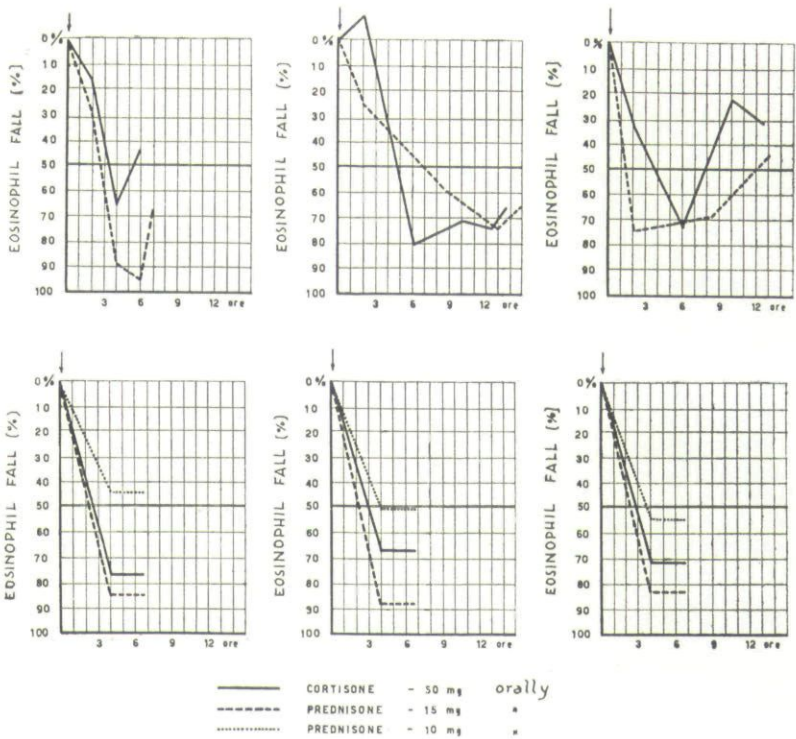


Fig. 8.

had occasionally had attacks of asthma. The second case without result had to suspend the treatment on account of the appearance of generalized symptoms (general malaise, restlessness etc.).

TABLE II
Oral prednisone.

	Clinical results				Total
	+++	++	+	0	
No. of cases	18	3	4	2	27
%	66.5	11	14.5	8	100

In most cases the start of the improvement was observed during the first 24 hours and the maximum obtainable relief was achieved during the first 2-3 days of treatment except in one case in which 6 days were required. The remission of symptoms after the end of the treatment lasted from a few days to several weeks in those cases in which a follow-up was possible. These results are comparable with those achieved with ACTH and cortisone.

Those patients that were given repeated courses had an equally favourable result in subsequent courses as in the first.

There were no signs of generalized edema, however we had one female patient, not included in this study, when there was a secondary rheumatic affection which we treated for one month with prednisone (total dose 500 mg). In this case a water retention with a slight moon face and a slight hypertrichosis of the upper lip appeared in the third week of treatment.

We observed in three cases a decrease of the arterial tension (slight in two cases and marked in the last one). On this particular effect of oral prednisone we are carrying out some researches.

There was no evident change in the quantity of the urinary output. Urine examination never revealed supar.

Taken in general the side-effects after the administration of prednisone in the above indicated doses were less than those usually encountered during treatment with the hitherto known steroids.

As already mentioned only a few patients showed a slight moon face with a development of acne. It must, however, be remembered that in our cases the prednisone was given for a short time only and in small doses.

Concerning the efficacy of prednisone as compared with the other adrenal steroids our cases show some features worth mentioning. For instance in a female patient who had not been helped by medium doses of hydrocortisone, prednisone produced an excellent result. Another patient who was helped considerably by hydrocortisone when this was initially given,

returned in a severe asthmatic condition, inspite of the fact that he was taking hydrocortisone in a dose 40 mg. daily. As soon as treatment with prednisone was initiated there was a rapid remission of symptoms. Also in another case prednisone was proved to be more effective than hydrocortisone. This was a patient in whom hydrocortisone had to be suspended, inspite of a satisfactory therapeutic response, owing to marked signs of water retention. When prednisone was given, the therapeutic effect was just as good, without any sign of retention, in fact the diuresis was increased. Similar cases have been reported by *Skaggs et al.* On the other hand in two cases in which the result of treatment with hydrocortisone was poor, the effect of prednisone was no better, even though in one of them it was given in doses up to 60 mg daily without improving the result.

ACTH ALLERGY

Ever since ACTH has been used therapeutically cases of allergic manifestations attributed to this hormone have been reported (*De Seze et al.*, *Sussmann*, *Swift*). Except for the exceptional cases of sudden death (*Hill & Swinburn*, *Jarvinen* etc.), most of the manifestations were either localized cutaneous reactions at the site of the injection (*Combs et al.*) or generalized urticaria (*Vallery-Radot et al.*, *Schlossmann*, *West*) or Quincke's oedema (*West*), or contact dermatitis (*Zeligmann*). Respiratory symptoms such as bronchial asthma, severe anaphylactic shock (*Wilson*, *Segall et al.*) and serum sickness (*Roskam et al.*) have also been described.

We have had 6 cases of ACTH allergy. The table shows the most important data (Table 12).

In all except one case a history of previous treatment with ACTH or anterior pituitary preparations was given. In three cases the manifestation of hypersensitiveness followed intramuscular, and in the remainder intravenous administration.

In one of our cases treated with intramuscular ACTH, which had violent asthmatic attacks immediately after each

TABLE 12

No	Age	Sex	Previous ACTH or pituitary therapy	Clinical manifestations	Route	Skin reaction to 1 U ACTH i. d.
1	40	♀	Unknown	Asthma	i.v.	++
2	45	♂	ACTH i.d. 2 months before	Asthma	i.v.	++
3	50	♀	Pituitary ther. some months before	Asthma	i.m.	+++
4	35	♂	ACTH 4 months before	Shock, malaise Asthma	i.v. & i.d.	+++
5	51	♀	ACTH i.m. 3 months before	Shock	i.v.	++
6	48	♂	ACTH i.v. 2 weeks before	Asthma	i.m.	+

injection of ACTH the eosinophilic drop that was being studied in the course of the treatment was below 50 % inspite of the clinical manifestations which the ACTH produced.

THE INACTIVITY OF INTRAMUSCULAR ACTH

In the course of studies on the use of ACTH, one case in which 50 mg ACTH daily given intramuscularly evoked no eosinophilic drop whatsoever was seen, nor was there any clinical response (*Serafini, Borghi & Pieri*). Yet when as little as 2.5 mg were infused intravenously during 8 hours there was a drop of over 80 % associated with a markedly beneficial effect on the clinical symptomatology.

In order further to clarify this phenomenon, the patient received up to 50 mg. ACTH in a single dose and 100 mg

in doses in 24 hours intramuscularly. In neither case was either an appreciable effect on the eosinophils nor on the urinary steroids seen. A trial with other makes of ACTH yielded the same results, i.e. no response to the intramuscular injection of 100 mg but a prompt response to 5 mg infused intravenously.

CONCLUSIONS

1)—The nature of the adrenocortical response to intravenous ACTH in man was studied in 3 series.

a)—We found the *minimum active dose* when given intravenously in 30 secs. to be 4 mg.

Gordon assessed the action of ACTH given intravenously to be about 20 times as strong as when given intramuscularly. Our results on the other hand show that when 4 mg are injected rapidly into the vein, this dose corresponds to one sixth, the quantity required when given intramuscularly.

b)—Two kinds of investigations were carried out on the *duration of the adrenocortical response*. The first in which a fixed dose (20 mg.—) was given and the time varied (2–4–6–8 hours), showed that the longer the infusion lasted the greater was the duration of the response. The second in which the infusion lasted 8 hours and the dose of ACTH was varied (5–10–15–20 mg) showed that the higher the dose the longer the duration of the response.

c)—*The intensity of the response* was studied in a similar manner. When the duration of the infusion was the variable factor it was found that the longer it lasted the greater was the intensity of the response while, when the dose was varied this did not appear to influence the intensity of the response provided the duration of the infusion remained unaltered.

2)—In order to establish the adrenocortical response of asthmatic patients, 15 cases were submitted to Renold's 8 hour test. It was found that they responded in exactly the same way as normal persons.

It may be added that in these cases the eosinophilic drop

after 12 daily infusions of ACTH or immediately after prolonged treatment with cortisone shows no difference from that obtained in normal persons.

Our studies and many other clinical considerations lead to the conclusion that asthmatic patients react normally to adrenocortical stimulation by ACTH. Provided the technical points discussed above are taken into consideration, the studies on adrenocortical stimulation by various means undertaken by many authors in asthma confirm this view. On the other hand the asthmatic syndrome may be accompanied by a change in some of the indicators of adrenal function such as the excretion of the urinary steroids. In any case these can be attributed, rather than to a primary adrenocortical deficiency, to a changed peripheral demand for steroids (relative adrenal insufficiency in *Dougherty's* sense).

3)—Regarding the interaction of ACTH and ascorbic acid we were able to show that intravenous ACTH induces a considerable loss of urinary ascorbic acid. On the other hand adrenocortical stimulation with ACTH in the 8 hour test is distinctly stronger in persons saturated with ascorbic acid than in those deprived of it.

As the quantity of ascorbic acid excreted after intravenous ACTH can exceed in the beginning the amount given, a negative balance may be established. This confirms the reports of some authors regarding the appearance of manifestations of vitamin C deficiency, even of real scurvy, in the course of prolonged treatment of particularly sensitive patients with ACTH (*Rosenthal*).

The second group of experiments shows that adrenocortical stimulation with ACTH can occur in persons suffering from vitamin C deficiency, confirming the observations made on scorbutic guinea pigs, but that it is both stronger and of longer duration in persons that are saturated.

Thus the administration of ascorbic acid during treatment with ACTH is useful both for the replacement of that which is lost due to the ACTH and in order to prolong and intensify the adrenocortical response.

4)—Our therapeutic results in bronchial asthma treated with ACTH by various routes, hydrocortisone and prednisone are essentially in agreement with those of most other authors.

These preparations yield a higher percentage of favourable results than can be achieved with any other treatment. Our percentage of favourable results out of more than 200 cases, lie around 85–90 % which is in accordance with the results of *Melli and Zanussi*; *P. Vallery-Radot et al.*

It must, however, be made clear that we are dealing with a temporary remission of symptoms and not a cure. It is therefore still necessary to investigate the etiology in each case of asthma and to adopt such methods of desensitization as may, in suitable cases, bring about satisfactory and lasting results.

It is our intention to underline that the remissions may be total or partial according to the greater or lesser reversability of the morbid condition responsible for the asthmatic syndrome.

Before we can conclude that hormonal treatment is ineffective we must be sure that the preparation used is reliable and that the dose has not been insufficient. We noticed several times with the compounds E or F that the dosage used was insufficient.

Moreover it is our impression that, at least in some cases we have seen, an active bronchial infection makes it necessary to employ doses that are higher than those already known to be effective in the same individual. In such cases the simultaneous administration of antibiotics has proved very effective.

Or we may be dealing with a case of so-called ACTH resistance when the hormone has been given intramuscularly.

When ACTH was given intravenously, either intermittently or continuously, it was found that the percentage of positive cases about equalled that obtained by the intramuscular route but that the improvement was less marked.

In any case the intravenous infusion has the advantage over the intramuscular route that the doses used are considerably smaller, that the remission sets in earlier and that dosage

is more exact. Moreover it is indicated in the rare cases of so-called ACTH resistance.

5)—In most cases that we used hydrocortisone, the dosage is particularly low, relevant side effects are generally less marked and treatment can be continued for many weeks. Our experience agrees with *Bickermann & Barach* who found that phenomena of intolerance were produced in 29 % by cortisone, 15 % by ACTH and in 8 % by hydrocortisone.

Hydrocortisone is particularly indicated in cases of hypersensitivity to ACTH.

Regarding prednisone we are of opinion that its introduction into therapy constitutes an important advance over the hitherto known steroids. It is our impression that it is certainly more active than cortisone even in smaller doses and that undesirable side effects are particularly few.

When we compared the eosinophilic drop produced by oral cortisone and prednisone we found that the latter produces an effect equal to that of cortisone with one third of the dose.

6)—As complete or partial remission depends on the greater or lesser reversability of the morbid condition, we use ACTH and the adrenal steroids to establish the reversability of asthmatic emphysema. A continuous status asthmaticus can look like a pulmonary emphysema. (such conditions have been described by several authors among whom are *Besancon & Coll.* 1945 and *Hamburger* 1948). In these cases we use hormonal therapy to find out whether the symptoms are reversible or definitely irreversible. We consider this test of great diagnostic, prognostic and therapeutic importance.

7)—We have successfully combined the following drugs with hormonal treatment:—*Antibiotics* which yields good and lasting results where there is an underlying bronchitis; *ascorbic acid* which prevents a negative balance and enhances the action of the hormone; *aminophyllin* which is much more effective after treatment with ACTH and increases the vital capacity by 20 % whereas this was only increased by 5 % before hormone treatment. (*Piersanti*).

8)—Though we paid particular attention to this question,

we were unable to establish a strict relationship between the eosinophilic drop and clinical improvement. However, the eosinophilic drop is, within certain limits, a good criterion of dosage of ACTH.

The control of the peripheral eosinophil count we found particularly useful in cases treated with the continuous infusion. Infact we came to the conclusion that it enabled us to ascertain exactly the onset, the duration and, though less reliably, the intensity of the adrenocortical stimulation and we believe that this simple trial added to the clinical observation of the patient is a useful adjunct during treatment with continuous infusion of ACTH intravenously.

9)—The side effects of ACTH therapy are well known and are in general due to overstimulation of the adrenal cortex. Among our cases glycosuria and oedema were particularly frequent.

10)—In our large casistic of recent years we came across 6 cases of ACTH allergy (asthma and anaphylactic shock).

We consider it of practical importance to ascertain, as a general rule, the sensitivity to ACTH in cases in which treatment is to be repeated, apart from the theoretical consideration that, as noted by *Feinberg & Coll.*, inspite of a high level of adrenocortical hormones already in existence, the body can produce new antibodies which can be demonstrated by skin tests and by passive transfer.

11)—The case in which 50–100 mg ACTH given intramuscularly produced neither clinical response nor an eosinophilic drop while these did occur when even as small a dose as 2.5–5 mg were given intravenously, reminds us that ACTH may be inactive when given intramuscularly, not because the adrenocortical response is inadequate but because certain conditions of the tissues prevent the ACTH from passing into the circulation. This may be the explanation of the decreasing activity of ACTH often seen in successive treatments and suggests that the hormone can be inactivated in the tissues in those cases in which there is no clinical response as well as in those in which Thorn's test is negative when done intramuscularly.

SUMMARY

The authors report their experience with ACTH, hydrocortisone and prednisone in the treatment of bronchial asthma, a series of experimental investigations having preceded the clinical studies.

They establish in man the minimum dose of ACTH injected rapidly (30") intravenously which is able to evoke an adrenocortical response, as shown by a significant eosinophilic drop. They also study the intensity and the duration of the adrenocortical stimulation after infusion.

They conclude that the degree and the duration of the response in asthmatic patients, as shown by the 8 hour test, the daily repetition of the infusion of ACTH and by Thorn's test after prolonged treatment with cortisone, are identical with those seen in normal persons.

They report on studies undertaken to define the interrelationship between ACTH and the ascorbic acid metabolism.

Clinical results are reported on the administration of ACTH (intramuscularly or by the intermittent and continuous intravenous route), of hydrocortisone and prednisone, all of which produced a complete or partial remission of symptoms in a high percentage of cases.

The authors recommend the use of these hormones in adequate doses as a means of establishing the reversability of an asthmatic emphysema, and stress their diagnostic, prognostic and therapeutic usefulness.

They also emphasize the advantage of associating hormone therapy with antibiotics, ascorbic acid and aminophylin.

Finally they report 6 cases of ACTH allergy (asthma and anaphylactic shock with favourable outcome) with a positive skin reaction and one case in which the intramuscular injection of ACTH was inactive (so-called ACTH resistance).

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THE AUTHORS' PREVIOUS PUBLICATIONS ON THE SUBJECT OF THIS PAPER

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