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THE ADRENAL RESPONSE TO CORTICOTROPHIN

EFFECT OF A.C.T.H. ON PLASMA ADRENAL STEROID LEVELS

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In certain diseases corticotrophin (A.C.T.H.) is used as a therapeutic agent with the object of reversing or modifying the underlying pathological process by increasing the secretion of adrenocortical steroids. The hormone is injected intramuscularly or intravenously, the amount given being increased or reduced according to the clinical response, which varies widely in different patients. For example, Kellgren *et al.* (1952) observed that, whereas in one patient intramuscular A.C.T.H. might relieve the symptoms and signs of rheumatoid arthritis and induce metabolic changes indicating hypercorticism, in another patient presenting a somewhat similar clinical picture the same treatment failed to produce any clinical improvement or metabolic changes. They noted that some patients showed excellent clinical improvement when given cortisone by mouth but derived little benefit from intramuscular A.C.T.H. All the cases which responded to either A.C.T.H. or cortisone showed an eosinopenia, which suggests that in these a significant increase in circulating adrenocortical hormones had been achieved.

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In the present investigation the effectiveness of A.C.T.H. as an adrenal stimulus has been assessed by estimating the concentration of adrenocortical steroids in peripheral blood.

Materials and Methods

Adrenocortical hormones were estimated by a method which is relatively specific for 17:21-dihydroxy-20-keto-steroids such as hydrocortisone, cortisone, and their metabolic reduction products (Nelson and Samuels, 1952; Bayliss and Steinbeck, 1953). The volume of plasma required for each estimation has limited the number of determinations made in each patient. The mean value for isolated determinations in normal subjects by our method is 9.5 μ g. of 17-hydroxycorticosteroids per 100 ml. plasma with 95% fiducial limits of 3 to 16 μ g. The accuracy of the method is such that a difference of 3.3 μ g. per 100 ml. between samples is significant.

Ordinary A.C.T.H. (Armour) and a long-acting preparation of A.C.T.H. in gelatin and propylene glycol ("acthar gel") were used in this investigation.

Results with Intravenous A.C.T.H. (Table I)

A.C.T.H. dissolved in saline was infused intravenously at as constant a rate as possible, the concentration being arranged so that the amount given per hour was contained in 100 ml. of saline. When the response to different doses or different batches of A.C.T.H. was determined in the same patient, an interval of at least three days was allowed to elapse between each infusion to avoid producing adrenal hypertrophy. When the response to repeated stimulation with A.C.T.H. was investigated the infusions were given daily.

Of the twelve patients only two were not clinically ill at the time of study, Case 7 being a normal control and Case 8 being referred as a case of Addison's disease, a diagnosis which was not confirmed. Of the ill patients, No. 6 had been in status asthmaticus for five days when given his first infusion, but was asymptomatic when given the second a week later.

A slight increase in the plasma level of 17-hydroxycorticosteroids was detected within 15 to 30 minutes of starting the infusion, and a definite increase had occurred within an hour (Cases 1 to 5). The levels after two hours were not very different from those at one hour, and thereafter remained constant for six hours in Case 1, but rose still higher in Case 4. When the infusion was continued for six or eight hours there was no consistent rise after the fourth hour (Cases 7 to 9). On stopping the infusion the steroid level remained high for an hour and then fell, returning towards the control value within three hours (Case 4).

The effect of different doses of A.C.T.H. given at intervals of at least three days was studied in Cases 8 to 11. In Case 8 there was little difference in the degree of steroid elevation induced by 0.25 and 2.5 units per hour for eight hours, and in Case 9 after eight hours the effect of 2.5 and 5 units per hour was the same, but 0.25 unit produced a smaller rise. Cases 10 and 11 were given repeated six-hour infusions of A.C.T.H. in doses ranging from 0 to 3.3 units per hour. The results for Case 10 (Fig. 1) suggest that a dose of about 1 unit per hour caused maximum adrenal stimulation. (The poor response when 1.8 units was infused was probably related to difficulties in maintaining the drip at a constant rate during this particular infusion.) In Case 11 maximum stimulation was obtained with a dose of about 0.7 unit per hour.

Infusions of A.C.T.H., repeated daily, produced after six or eight hours a progressive rise in the steroid level, suggesting that repeated daily stimulation increased the hormonal output from the adrenal glands (Cases 3B, 3C, 12A, and 12B).

No significant difference was observed in the response to different batches of A.C.T.H. in Cases 6 and 7. The dosage

TABLE I.—*Response to Intravenous Infusion of A.C.T.H.*

Case No.	Age	Sex	Diagnosis	Batch No.	Dose (Units per Hour)	Duration of Infusion (Hours)	No. of Infusion*	17-Hydroxycorticosteroids (μg./100 ml.) Hours after Start of Infusion													
								0	1	2	4	6	7	8	9	10	24				
1	75	M	Bronchitis	K. 56109	1.7	6	1	15	16	20	29	34	27	27							
2	39		Asthma		2.0	2	1	12	17		25	25									
3A	73	F	Temporal arteritis	K. 56009	1.0	2	1	25	27	29	37	32									
4	67	M	Carcinoma lung	J. 10402	2.5	6	1	9			23		36	39	19	12					
5	73		Asthma	K. 56009	2.5	8	1	7			17					20					
6A	32	"	"		2.5	8	1	13													
6B	"	"	"	K. 55608	2.5	8	1	7				26									
7A	29	"	Normal	K. 56109	3.3	6	1	4			28	26									
7B	"	"	"	K. 80709	3.3	6	1	10			33	25									
8A	46	"	Malnutrition	K. 54006	0.25	8	1	7			34				28						
8B	"	"	"	"	2.5	8	1	11			34				34						
9A	40	"	Asthma	"	0.25	8	1	8			19				20				12		
9B	"	"	"	"	2.5	8	1	12			30				34				7		
9C	"	"	"	"	5.0	8	1	17			38				35				4		
10A	49	"	"	Saline	0	6	1	11				12									
10B	"	"	"	K. 56109	0.3	6	1	1				19									
10C	"	"	"	"	0.9	6	1	6				27									
10D	"	"	"	"	1.3	6	1	5				30									
10E	"	"	"	"	1.8	6	1	4				21									
10F	"	"	"	"	3.3	6	1	4				31									
11A	32	"	"	Saline	0	6	1	12				9									
11B	"	"	"	K. 56009	0.45	6	1	8				16									
11C	"	"	"	"	0.7	6	1	10				27									
11D	"	"	"	"	1.5	6	1	7				24									
11E	"	"	"	"	2.5	6	1	12				25									
12A	73	F	Temporal arteritis	K. 56109	2.0	10	1	16							67						
12B	67	M	Asthma	K. 56009	2.0	10	1	12							76						
12C	"	"	"	"	2.0	10	3	6													
12D	"	"	"	"	2.0	10	1	13													

* The figure 1 indicates the first infusion of A.C.T.H. or an interval of at least three days since the previous infusion. Other figures indicate the number of the infusion during which blood samples were taken when the infusions were repeated daily.

TABLE II.—*Response to Single and Repeated Injections of Acthar Gel*

Case No.	Age	Sex	Diagnosis	Batch No.	Dose (Units)	No. of Injection*	17-Hydroxycorticosteroids (μ g./100 ml.) Hours after Injection										
							0	1	2	4	5	6	8	12	14	24	
13	39	F	Pneumothorax ..	K. 46710†	80	1	13						21		14		12
14	23	M	Adenitis	"	80	1	10								9		11
15	54	"	Gastric ulcer ..	"	80	1	17	21		24						13	
16	45	"	Headaches	"	80	1	7				28		23	5			12
17	30	F	Anxiety state ..	"	80	1	8					38	15		12		8
18	49	M	Hydrarthrosis ..	"	80	1	5									20	
19	54	F	Asthma	"	80	1	6						43	43			10
20	60	M	Temporal arteritis	"	80	1	13			31							14
21	18	"	Rheumatic fever	"	80	1	16			39							8
22	60	"	Bronchitis	"	80	1	14										13
23	49	"	"	"	80	1	13						24				6
24	56	"	Leukaemia	"	80	1	17						37				
25	38	F	Barbiturate poisoning	"	80	1	8								40		
26	47	"	Asthma	"	80	1	10			36							23
27	41	"	"	"	80	1	12			21							28
28	70	"	"	"	80	1	18						55				50
29	69	M	Coronary thrombosis	"	80	1	9							40			21
30	30	"	Pleural effusion ..	4 ml. Gel	0	1	8				8			8	2		11
31	40	F	Duodenal ulcer ..	" " "	0	1	6				6			3	9		9
32A	51	"	Asthma	K. 46710	40 daily	1	10				27						
32B						4	5				33						
32C						8	19				78						
32D						10	4				—						
33A	40	M	Idiopathic granulocytopenia	"	40 daily	1	2				18						
33B						3	4				34						
33C						5	6				30						
34A	73	"	Asthma	K. 47311	40 12-hourly	1	9										
34B						2	12										
34C						3	15										
34D						4	10										
34E	73					5	11										
34F						6	5										
34G						7	2										
35A	49	F	Normal	K. 46710	25 daily	1	11				40						
35B						2	12				47						
35C						3	24				56						
36A	66	M	Asthma	"	20 12-hourly	1	—				12						
36B						3	5				20						
36C						5	8				11						
36D						11	6				27						
36E	26	M	Normal	"	20	13	1				8						
36F						15	4				21						
37																	
38	72	F	Mitral stenosis ..	"	20	1	12			32	23			5			
39	33	M	Varicose eczema ..	"	20	1	7			13	12			29			
40	54	F	Malnutrition	"	20	1	6			12	5			4			
41	50	"	Dyspepsia	"	20	1	12			33	22			14			
42	72	M	Anxiety state	"	20	1	13			34	52			13			
							19			27	37			21			

* The figure 1 indicates the first injection of A.C.T.H. Other figures indicate the number of the injection following which blood samples were taken.

† Batch K. 46710 contained 20 units A.C.T.H. per ml. Batch K. 47311 contained 40 units A.C.T.H. per ml.

used, however, was probably greater than the maximum stimulating dose and too large to indicate minor differences in the potency of the various batches given.

There was no apparent correlation between either the clinical state of the patient or the control level of plasma 17-hydroxycorticosteroids on the one hand and the height to which the steroid concentration rose during the infusion on the other. With two exceptions, a dose of A.C.T.H. ex-

FIG. 1.—Case 10. The response to repeated six-hour infusions of A.C.T.H. given at intervals of at least three days in doses ranging from 0 to 3.3 units an hour. The results are plotted as the rise in plasma 17-hydroxycorticosteroids at the end of the infusion above the control value obtained just before each infusion was started.

ceeding 1 unit per hour raised the steroid level to a range varying from 24 to 36 µg. per 100 ml. in all patients receiving their first infusion. The two exceptions were Case 10E, in which there was difficulty in maintaining a constant drip rate, and Case 3B, in which the steroid level rose to the unusually high value of 67 µg. per 100 ml.

Results with Acthar Gel (Table II)

A single intramuscular injection of 4 ml. of acthar gel containing 80 units of A.C.T.H. was given to 17 patients (Cases 13 to 29), all of whom were comfortable at the time of study, except three with asthma (Cases 26 to 28). Injections into the gluteal muscles did not hurt, but a few into the lateral aspect of the thigh caused some pain. A significant increase in the plasma steroid level was found after two hours, and the maximum concentration was reached in four to eight hours. Thereafter the steroid level usually fell. In Cases 13 to 16 the concentration had returned to or below the control value in 12 to 14 hours; in Cases 17 to 19 it was still elevated at 12 to 14 hours, but was at or near the control value in 24 hours; in Cases 20 to 23 it was at or near the control value in 24 hours, but few intermediate estimations were made; and in only Cases 26 to 29 was the level still raised significantly 24 hours after the injection. As a control the same volume of gelatin menstruum containing no A.C.T.H. was injected in Cases 30 and 31 and caused no significant rise in the plasma steroid level.

A single injection of 20 units of acthar gel was given to Cases 37 to 42. In five the steroid level reached a maximum within two to four hours and had returned to or below the control value by eight hours. In Case 38 absorption was apparently delayed and the maximum level observed was at eight hours.

No correlation was detected between the clinical state of the patient and the height to which the plasma steroid level rose. In several the maximum level after 80 units of acthar gel was not significantly higher than after 20 units in other patients.

Repeated Injections.—Five patients were given repeated injections of acthar gel every 12 or 24 hours (Cases 32 to 36). The steroid concentration four hours after the injections rose progressively to high levels in Cases 32 and 35 (Fig. 2), but in Cases 33 and 36 the results were variable and inconsistent. The differences in individual response were considerable (compare Cases 33 and 35). No consistent elevation of the plasma steroid level was found 24 hours after the daily injections, neither did an injection every 12 hours produce a consistent elevation up to the time of the next injection.

FIG. 2.—Case 35. The progressive increase in plasma 17-hydroxycorticosteroids following repeated daily injections of 25 units of acthar gel.

Results with Ordinary A.C.T.H. (Table III)

Single Injection.—A single intramuscular injection of 20 to 50 units dissolved in 4 ml. of saline was given to 16 subjects, of whom eight were clinically ill at the time of study (Cases 45, 46, 49, 50, 51, 52, 54, and 56). The maximum increase in circulating adrenocortical steroids occurred after one to two hours. Thereafter the concentration fell, returning towards the control value in four to six hours. The height to which the steroid level rose varied widely in different patients. Cases 49 and 56A showed the greatest response of the ill patients, but the levels induced in the others were not consistently different from those found in the normal and convalescent subjects. Cases 44A and 50 showed no apparent response. The variability of the response in different individuals was so great that no significant difference in the effect of 20, 30, 40, or 50 units of A.C.T.H. could be detected.

Repeated injections of 20 to 25 units of A.C.T.H. in 4 ml. of saline were given six-hourly to Cases 45, 46, 52, and 56. The height to which the steroid level rose after two hours did not increase with successive injections, nor was the elevation of steroid concentration persistently prolonged into the sixth hour.

Discussion

At any given time the plasma concentration of adrenocortical steroids depends upon the amount being secreted by the adrenal glands and the amount being excreted in the urine and faeces, utilized in the tissues, and metabolized to compounds not estimated by the analytical method used. When the plasma level is changing rapidly too much emphasis cannot be placed on the exact concentration at a particular time. Although some degree of individual variation in responsiveness to hormones is to be expected, the differences after A.C.T.H. are marked, and may be related to differences in the responsiveness of the patient's adrenals, and also in the rate of absorption and destruction of the administered A.C.T.H., in the potency of different batches of A.C.T.H., and in the rate of utilization and elimination of the adrenocortical steroids secreted. It has been suggested

TABLE III.—Response to Single and Repeated Intramuscular Injections of A.C.T.H. in Saline

Case No.	Age	Sex	Diagnosis	Batch No.	Dose (Units)	No. of Injection*	17-Hydroxycorticosteroids (μ g. 100 ml.) Hours after Injection					
							0	1	2	3	4	6
43A	45	M	Dyspepsia	K. 56109	20	1	7	29	26	23	14	
43B	"	"	"	K. 80709	20	1	12		20		10	
44A	50	"	Bronchitis	"	20	1	8		10		7	5
44B	"	"	"	"	40	1	11		15		16	6
45A	65	F	Asthma	"	20	1	11		27		16	7
45B	"	"	"	"	20	2	7		32		7	7
45C	"	"	"	"	20	13	4		26		17	5
46A	49	M	Psoriatic arthritis	K. 56009	20	1	7		22			8
46B	"	"	"	"	20	9	14		22			10
46C	"	"	"	"	20	19	9		16			9
47	27	F	Normal	K. 54006	25	1	6	23	32	23	19	
48	54	"	Asthma	"	25	1	—	6	18		8	
49	67	M	"	"	25	1	14	65	48	32	34	
50	47	F	Rheumatic fever	"	25	1	8		4		9	8
51	62	M	Asthma	"	25	1	5	22	19		24	20
52A	50	"	Anaphylactoid purpura	"	25	1	8					7
52B	"	"	"	"	25	5	10					18
52C	"	"	"	"	25	9	6					4
52D	"	"	"	"	25	12	5					4
53	55	"	Dyspepsia	K. 56109	30	1	10	21	25		17	
54	54	"	Asthma	"	30	1	13	28	22	18	13	
55	32	"	Normal	"	30	1	7	29	29	19	12	
56A	46	"	Anaphylactoid purpura	"	30	1	27		54	26		
56B	"	"	"	"	20	11	27		32	30		
57	52	"	Bronchitis	K. 80709	40	1	6		29		7	
58	49	"	"	K. 54006	50	1	16	26	32	33	29	

* The figure 1 indicates the first injection of A.C.T.H. or an interval of at least three days since the previous injection. Other figures indicate the number of the injection following which blood samples were taken. All injections were given six-hourly.

that the differing response of individual patients may be partly a reflection of the level of endogenous hormone production. "If the administered dose of hormone greatly exceeds endogenous production it causes some degree of hypercorticism . . . but if the administered dose is less than the amount produced endogenously the pituitary-adrenocortical system merely adjusts itself to a lower level of production and the net result is no change" (Kellgren *et al.*, 1952).

Duration of Response

There are striking differences in the duration of the adrenal response when A.C.T.H. is given by intravenous infusion, and when it is injected intramuscularly in saline or in gelatin. The duration of the response depends upon the length of time that the stimulating action of A.C.T.H. is applied. By intravenous infusion A.C.T.H. causes a rapid rise in the plasma steroid level, and thereafter the concentration remains constant during the remainder of a six- or eight-hour infusion. When the infusion is stopped the steroid level quickly falls, in keeping with the evidence that A.C.T.H. is rapidly destroyed in the blood stream (Sayers *et al.*, 1949; Greenspan *et al.*, 1950; Reiss *et al.*, 1951; Pincus *et al.*, 1952). Intramuscular injections of A.C.T.H. in saline usually cause a rapid rise in the plasma steroid level, reaching a maximum in one or two hours. Thereafter the concentration falls, returning in most instances to the control value in four to six hours. Two patients showed no apparent response to 20 to 25 units, and one little response to 40 units, although A.C.T.H. of the same batch given by the same route was effective in other patients.

This lack of response to intramuscular A.C.T.H. in saline has been observed by other workers, and Thorn and his associates (Renold *et al.*, 1952) ascribe it to destruction of the hormone at the site of injection because patients unresponsive to intramuscular A.C.T.H. respond when the hormone is infused intravenously. When A.C.T.H. is incorporated in a gelatin menstruum its effect is prolonged. After large doses of 80 units the plasma steroid concentration rises within one to two hours, but does not reach a maximum until four to eight hours. Thereafter the level usually falls, returning to the control value in 12 to 24 hours. After 20 units of acthar gel the maximum level is usually reached in two to four hours and returns to the control value within eight hours. The action of gelatin is to retard absorption and perhaps also to prevent local destruction of A.C.T.H., so that the maximum plasma steroid concentration is delayed and the adrenal response more prolonged.

Degree of Plasma Steroid Increase

The degree of steroid elevation produced by A.C.T.H. infused intravenously over a constant time depends upon the rate of hormone infusion up to an optimum beyond which no further increase occurs. Our data suggest that over a six- or eight-hour period as little as 1 unit an hour will cause maximum adrenal stimulation. This dosage is similar to that suggested by Thorn and his colleagues (Renold *et al.*, 1952), who found that, whereas the urinary excretion of 17-ketosteroids increased with 0.12, 0.3, and 0.75 unit an hour for eight hours, no further increase occurred with 1.2, 2.5, or 5 units an hour. In all but two of our patients receiving their first infusion, a dose of A.C.T.H. exceeding 1 unit an hour raised the steroid level into the range of 24 to 36 μ g. per 100 ml. This comparatively narrow range suggests that in these patients the degree of steroidogenesis achieved in response to maximum stimulation over six or eight hours was not greatly different from one patient to another, or, alternatively, the rate of elimination of the steroids secreted was similar. Too much significance cannot be attached to the height of the steroid levels obtained after a single intramuscular injection of A.C.T.H. in saline or gelatin because of the rapidly changing plasma concentration, but in many instances the values were comparable to those obtained after maximum stimulating doses of A.C.T.H. given intravenously. In the dosage used clinically A.C.T.H. by intramuscular injection in saline or gelatin may cause maximum adrenal stimulation, but because of variations in the rate of absorption and destruction of the A.C.T.H. the duration of the response may be so brief and short-lived that it appears submaximal.

The different responses to 20 units of A.C.T.H. infused intravenously over eight hours or injected intramuscularly in saline or gelatin are compared diagrammatically in Fig. 3.

Increasing the duration of the infusion or repeating the infusion at frequent intervals would be expected to produce a greater secretory response, and this has been achieved by the second method. In some patients repeated injections of acthar gel have induced progressively higher steroid levels, but in others this effect was not apparent, nor was it found in patients given repeated intramuscular injections of A.C.T.H. in saline, although other workers studying the urinary excretion of 17-ketosteroids have shown that this may increase adrenal secretion progressively (Sprague *et al.*, 1950). In a few instances intravenous and intramuscular A.C.T.H. produced a greater response than the level of 24 to 36 μ g. usually encountered. It is not possible to relate these unusually marked responses to the control level of

circulating adrenocortical steroids, nor is it possible from our data to tell whether they are the response of adrenal glands previously hypertrophied by increased secretion of endogenous A.C.T.H. or are due to decreased excretion, utilization, or metabolism of the adrenal hormones secreted.

No striking differences in the potency of various batches of A.C.T.H. have been observed in the few observations made in this study, and further investigation of this by

FIG. 3.—The responses to 20 units of A.C.T.H. given by intravenous infusion over eight hours and by intramuscular injection dissolved in saline and suspended in a gelatin menstruum.

biological assay in human subjects would not be practicable by our method. The clinical variations in the response to intramuscular A.C.T.H. in saline observed by Kellgren *et al.* (1952) are probably related to differences in the rate of absorption and destruction of the administered hormone, although in some instances, such as the case reported by Kersley *et al.* (1952), the disease process may not be influenced by increased levels of circulating adrenocortical steroids. The clinical dosage of A.C.T.H. appears so much larger than the amount secreted endogenously that it is unlikely that the pituitary-adrenal system can adjust itself so that there is no change in the steroid output from the adrenal glands.

If therapeutic effect depends upon the duration of the elevation of adrenocortical steroids in the blood stream, A.C.T.H. in gelatin or by intravenous infusion—or cortisone or hydrocortisone—is the agent of choice. Despite the theoretical objections to infusing a foreign protein intravenously no untoward effects have been observed by us, using Armour's A.C.T.H., nor by Thorn (Renold *et al.*, 1951), whose experience is much greater than ours. It must be determined for how long and at what intervals the infusions should be given to obtain the best therapeutic benefit, but there is ample clinical evidence of the greater efficiency of this method over intramuscular injections of A.C.T.H. in saline (Gordon *et al.*, 1951; Mandel *et al.*, 1951; Renold *et al.*, 1951). Not only is this method more effective and more reliable in raising the steroid level, it is much more economical in material.

Summary

The adrenocortical response, as reflected by changes in the plasma level of 17-hydroxycorticosteroids, has been determined after intravenous infusions of A.C.T.H. and after single and repeated intramuscular injections of A.C.T.H. in saline and in gelatin.

Infused intravenously A.C.T.H. causes a rapid rise in the plasma steroid level, which remains elevated during the rest of the infusion. Over a period of six to eight hours 1 unit an hour seems to cause a maximum response.

By intramuscular injection A.C.T.H. in saline usually causes a rapid rise in the plasma steroid level, which reaches its maximum in one to two hours. Thereafter the concentration falls, returning to the control value in four to six hours. Considerable individual variations in response were observed, and are largely attributable to differences in the rate of absorption and destruction of the administered hormone.

The incorporation of A.C.T.H. in a gelatin menstruum delays its absorption and prolongs its effects to a variable extent depending upon the rate of destruction of the injected hormone.

Factors influencing the adrenal response to A.C.T.H. are discussed.

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USE OF PHENYLBUTAZONE IN RHEUMATOID ARTHRITIS

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When phenylbutazone ("butazolidin") was first introduced to this country the report on its effects by Currie (1952) caused it to be hailed as a new "wonder drug" and likened to the corticosteroid hormones. Then the high incidence of toxic effects began to be discovered, and the pendulum of opinion has swung to the other extreme; at present many practitioners refuse to give the drug even to patients who have had it for long periods with no ill effects.

I hope to demonstrate that this view is pessimistic: given adequate management the drug has a definite place in the treatment of some forms of arthritis.

Present Series

Phenylbutazone was given to 210 patients (53 male, 157 female) (Table 1). In 186 the condition was a polyarthritis of the rheumatoid type. The remaining 24 had a degenerative arthritis of one or both hip-joints. In most patients with rheumatoid arthritis the disease was in a chronic phase (either static or of low-grade activity), and they were attending the out-patient department. They continued to have