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

BY

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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

TABLE I.—General Classification

Duration of Treatment	Total	Continued		Stopped	
		No Reaction	With Reaction	No Reaction	With Reaction
3 months ..	210	109	24	23	54
6 " ..	89	72	3	6	8

N.B.—All patients treated for six months are also included among those treated for three months.

various other forms of treatment as required, including gold in 37 cases. Five patients with considerable activity of the rheumatoid process were treated initially in hospital; in assessing the result the effect of rest in bed was discounted. Any patient with dyspepsia or a history of congestive heart failure was not given the drug.

The dosage used varied from 200 to 1,200 mg. daily, averaging 600 mg. Occasionally the dose was gradually reduced, but this often resulted in a lessening of the effect. Some patients were given 800 mg. daily for five days out of every seven to investigate the effect of interrupted dosage on the incidence of reactions.

At the beginning of treatment each patient received a printed sheet, warning against the principal side-effects, with instructions to report to the hospital or family doctor any untoward event. Routine blood counts were not performed.

Patients were examined before treatment, after three months' treatment, and after six months' treatment. Subjectively, improvement was measured by the patient's capacity for and comfort during normal activity at these times, compared with his or her condition before treatment; objectively, the patient was assessed by the method of Janus (1950), including erythrocyte sedimentation rate (Westergren) and joint chart. Based on subjective evidence, the results were graded as follows: ++, indicating considerable remission of symptoms, with complete absence of pain; +, moderate improvement; and 0, absence of response or even deterioration.

Results

A total of 156 patients were reviewed at three months (see Table II); 36 found the drug to be of little or no value; 104 found it to be of moderate value; and 16 had considerable benefit, often amounting to complete remission. Many

TABLE II.—Degree of Improvement After Three Months' Treatment with Phenylbutazone

Disease	Rheumatoid						Degenerative Arthritis		
	Inactive			Active					
Grade ..	++	+	0	++	+	0	++	+	0
Number (156) ..	6	47	14	10	43	20	—	14	2

patients thought there was less stiffness, and there seems to be no doubt that the drug has a more powerful analgesic action than aspirin in full dosage, an effect which is not objectively demonstrable.

This decreased stiffness was never convincingly demonstrated, and its method of production is obscure; it is a definite entity, and occurs in about 70% of cases.

The E.S.R. was unaltered in 60% of the cases; in the remainder there was a rise or fall of more than 10 mm. in approximately equal numbers. In a few cases an improvement in the mobility of the joints occurred, but in each case this could be ascribed to natural remission of the disease; this is felt to have occurred in many of the patients showing a ++ response. It was noteworthy that the best effects were seen in patients with a relatively small number of involved joints, though the length of history did not appear to affect the response.

Reactions

A reaction of one form or another occurred in 81 cases; a further eight had two separate reactions; and three had reactions but had not completed the first three months' treatment. The total number of reactions listed is thus 100. The total assessed (89 patients) is 42.4% of the whole series. This figure is higher than that obtained by Leonard (1953), who found an average incidence of 22% in figures obtained from the literature; it agrees with figures obtained by Hart (1953) and by Freeland *et al.* (1953); 25% of my cases have been forced to stop taking the drug owing to side-effects. The strikingly low figure of 4.7% (Currie *et al.*, 1953) may be the result of the very low dosage they recommend, which in my experience is of doubtful therapeutic value. Table III

TABLE III.—Relation of Reaction-incidence to Dosage

	Daily Dose (mg.)						Stopped Within 2/12 (No Value)
	200	400	600	800	800*	1,200	
Total (221) Reactions (100) ..	7	52	56	30	47	16	13
% reactions ..		19	31	20	18	12	
		36.54	55.36	66.6	38.3	75	

* Interrupted dosage, the drug being given for five days out of every seven.

N.B.—These figures include three reactions not included in Table I, and each reaction in patients having two reactions.

shows that there is a definite increase in the incidence of reactions as the dosage is increased, and that, as has been generally agreed, 1,200 mg. daily is a dangerous dosage; at this level 75% of patients have a reaction.

The relationship between dosage and the incidence of reactions is statistically significant; using the χ^2 test, P is much less than 0.01 ($n=5$, $\chi^2=21.56$). Further, a definite reduction in the incidence occurs when using 800 mg. for five days of every seven compared with continuous administration of 800 mg. daily; in this case P is less than 0.02 ($n=1$, $\chi^2=5.68$). The difference between the former dose and 600 mg. daily is not significant, P being 0.09 approximately.

It has been suggested recently that tolerance to phenylbutazone is greatly reduced in the older patient: this is shown in Table IV; while statistically the significance is not proved, P being less than 0.07 ($n=5$, $\chi^2=10.25$), the

TABLE IV.—Relation of Reaction Incidence to Age

	Age in Years					
	21-30	31-40	41-50	51-60	61-70	71+
Total (210) Reactions (89) ..	13	26	46	79	40	6
% reactions ..	3	8	19	31	24	4
	23.08	30.77	41.3	39.24	60.0	66.6

difference in incidence between the age group 61-70 and that of the decade earlier is significant, the value of P for these two groups being approximately 0.03.

For no obvious reason males appear to be less liable to side-effects than females, the incidences being 28.3% and 47.13% respectively; this difference again is significant, P being less than 0.01 ($n=1$, $\chi^2=7.32$). That this difference is not due to unequal age distribution between the two sexes is shown by the average ages of the two groups, these being 53.57 years for males and 51.19 years for females.

It is striking that 89% of all reactions occur in the first three months of treatment; 75% occur before the end of the first month. In the second three-months period of therapy only 8.99% of patients had to stop the drug because of a side-effect.

Table V shows the relative frequency of reactions occurring during the first and the second three months. Under

TABLE V.—Type and Onset of All Reactions

	General		Dyspepsia		Rash		Oedema		Sore Mouth		Miscell.		Total	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C
In first 3 months	5	1	24	8	5	15	6	5	9	6	5	—	54	35
In second 3 months	—	—	2	1	—	—	—	1	6	1	—	—	8	3

S=Stopped. C=Continued.

the heading "general" are included patients having two or more reactions at the same time; this usually means the combination of a rash with oedema, with or without dyspepsia, and often with fever and considerable malaise. In these cases, and in patients having a rash alone, no significant alteration in the white-cell count, apart from an occasional eosinophilia, has been found. The rash is usually urticarial or morbilliform in type, and is often intensely pruritic, though this may be relieved by the use of antihistamines. Many of these patients have been able to return to the drug later, with no ill-effect.

Under the heading "dyspepsia" is included any gastrointestinal upset, ranging from flatulence to frank haemorrhage in one patient, who was thought to have had an acute gastric ulcer, a barium-meal examination at a later date being negative. Several patients were found to have previously unsuspected peptic ulcers, proved on x-ray examination after typical exacerbations had occurred within a few days of beginning treatment.

There is no doubt that phenylbutazone is extremely dangerous to any patient with proved or suspected peptic ulceration; several of the deaths already reported have been due to haemorrhage from such ulceration. In a few cases the "dyspepsia" merely consists of flatulence, and the patient is able to continue taking the drug in safety. Occasionally the pain is a typical colic, and has been known to mimic appendicitis; the reverse mistake could be tragic, but it almost occurred in one case in which the characteristic signs were late in appearing.

Sodium retention occurs in most patients, as has been demonstrated by regular weighing (Kidd *et al.*, 1953), but in few cases was it troublesome as overt oedema, and then was often controlled by dietary salt restriction.

The most common reaction during the second three months of treatment is soreness of the mouth, frequently accompanied by excessive salivation. Of patients who had to stop treatment at this period 75% did so because of this reaction, which recurs if the drug is given again at a later date. Usually little is to be found on examination, and the trouble is slow to pass away. No treatment has yet been found to produce any benefit.

The cases with miscellaneous reactions were as follows: (1) One patient who suddenly developed auricular fibrillation; she was hypertensive, but showed no evidence of sodium retention, and it is doubtful if this was a true toxic effect. (2) One patient who developed palpitation, and another who suffered from malaise; several patients had these symptoms in very mild form, and only as transitory effects. (3) In one patient a headache of migrainous type recurred each time after phenylbutazone had been given for three or four days; it was not relieved by salt restriction. (4) One patient who developed a febrile illness of uncertain aetiology. On the tenth day of treatment (800 mg. daily) she became febrile, but had no specific complaint or any abnormal physical signs apart from splenomegaly. Her white-cell count was 1,950 per c.mm. (polymorphs 62%, lymphocytes 33%, monocytes 5%). Three days later her total count was 4,800 per c.mm., the differential being unchanged. Her temperature settled spontaneously, and it was felt that she had a virus infection, the normal differential count making the possibility of drug-induced agranulocytosis unlikely. This is undoubtedly a reaction to be feared, but its incidence seems to be extremely low, and much less common with phenylbutazone than with amido-

pyrine. I would like to stress the futility of repeated blood counts as a precautionary measure: the alteration in the blood picture usually occurs with dramatic suddenness.

It will be seen that dyspepsia is by far the most troublesome reaction; its incidence does not appear to have been reduced by the use of thick enteric-coated tablets recently introduced. The mode of production of gastric irritation is obscure, as phenylbutazone is insoluble in an acid medium, and only slight benefit follows administration after meals.

Serum Concentration of Phenylbutazone

The drug, when given by mouth in the thinly coated tablets originally available, is rapidly absorbed, and levels of 6 to 8 mg. per 100 ml. are obtainable six hours after 800 mg. has been given. Pulver's (1950) method of estimation has been modified in the laboratories of the hospital (Moss, to be published) (see Appendix). By the new method it is claimed that 86 to 95% of the drug can be recovered, as compared with 60% by the original process. A good standard of accuracy is obtained, the mean difference of the mean of each pair of duplicate results being ± 0.3 mg. per 100 ml.

A series of readings have been obtained from blood samples taken six hours after the last dose of phenylbutazone had been given in patients who had received the drug

TABLE VI.—Serum Phenylbutazone Levels

Daily Dose	Average Level (mg./100 ml.)	No. of Readings	Range (mg./100 ml.)
200 mg.	7.4	10	3.5-12
400 "	13.7	33	6.1-19.5
600 "	14.76	17	8.5-23.5
800 "	16.3	11	4.5-20.5
800 " *	15.22	17	6.6-21.8
1,200 "	19.55	9	18.8-24.3

* Interrupted dosage, the drug being given for five days out of every seven.

for at least two weeks (Table VI). It will be seen that there is no linear relationship between the concentration and the dosage. The effect of interrupted dosage is also seen. These levels are higher than those obtained by Currie *et al.* (1953) owing to the different method of estimation; in Pulver's original method whole blood is analysed, while Moss uses serum. I consider the therapeutic range to be 12 to 16 mg. per 100 ml., and to maintain this level the dose must remain steady; I was not able to confirm Currie's findings that such levels could be maintained with a dose as low as 200 mg. daily.

The blood level drops slowly after administration of the drug is stopped; appreciable levels remain after two weeks, and it appears that about 15% of the circulating level is metabolized daily. This agrees with the figures of Burns *et al.* (1952). There has, as yet, been no evidence of cumulation, and if concentrations are measured at long intervals a level at, say, three months is often lower than one obtained early in the administration. There is thus nothing to confirm the unexpected finding of a lower reaction incidence obtained with interrupted dosage: the incidence for a comparable blood level—that is, 600 mg. daily—is still much higher than for 800 mg. given for five days out of every seven. No correlation was observed between the blood level and the incidence of reactions.

In patients whose response to therapy is doubtful it is useful to obtain a blood concentration; this is at times found to be unusually low, and if raised to the "therapeutic range" the desired effect may be obtained.

Discussion

It would seem that an average incidence of reactions of 30 to 40% is to be expected from the use of phenylbutazone. In view of this high level of toxicity, should the drug be used? It is undoubtedly of benefit as an analgesic: it

seems to be the most powerful (after the corticosteroid hormones) in arthritis; and, in fact, Mason (1953), comparing the effect of phenylbutazone with that of A.C.T.H., found little difference in analgesic properties. Currie's original view that the drug has an anti-inflammatory effect was supported by the early experimental work on animals but has not been substantiated clinically (Hart, 1953; Cudkowicz and Jacobs, 1953). Is its value as an analgesic outweighed by its dangers? I consider that, given adequate medical supervision, the toxic effects should be sufficiently minimized. Agranulocytosis is the most dangerous reaction, but it is a remote chance in any given patient, who is often willing to take some risk to obtain relief from a painful and crippling disability.

To minimize reactions the following conditions must be observed.

Selection of Cases.—There must be a reasonably sure diagnosis of arthritis, either degenerative or of the rheumatoid type, including ankylosing spondylitis. It is not the treatment for rheumatic fever, in view of its lack of anti-inflammatory effect. Any patient with a history of dyspepsia, and especially in the presence of peptic ulceration, or having congestive heart failure, should not be given the drug, and older patients should be given small doses only. The most suitable type of case seems to be the patient in a "chronic" phase who has to undergo a fair amount of effort, either bread-winning or housework, often with a considerable amount of pain. It must be emphasized that this treatment has no curative value, and that accepted forms of treatment, including gold, must be used also as indicated.

Management.—The patient must be warned of possible dangers before beginning treatment, and instructed both to stop the drug and to report to the doctor immediately should any untoward effect occur.

Dosage.—The optimum safe dose is still a matter for debate; Lawrence (1953) advocates using single doses of 400 mg. at prolonged intervals, of up to ten days, while Currie uses 200 mg. daily or on alternate days. These doses seem to be too low to be of therapeutic value. Hart (1953) uses 400 mg. daily, and Freeland *et al.* (1953) 600 mg. daily. This latter appears to be a commonly accepted level. My figures (Table III) show a lower incidence rate using 800 mg. daily for five days out of every seven, and this is now the dose that I use most commonly.

If these conditions are observed there seems to be no reason why the drug should not be used by the family practitioner, who must, however, be on the alert for possible cases of agranulocytosis. The patient's symptoms are of far greater value in early diagnosis than repeated leucocyte counts, which overtax pathological departments and may engender a false sense of security.

Summary

A series of 210 patients who have been treated with phenylbutazone is reviewed. The incidence of reactions is analysed. The use of the drug is discussed.

My thanks are due to Dr. H. Stuart Barber for encouragement and advice in the preparation of this paper; to Dr. R. Ellis for permission to include several of his patients in this investigation; to Mr. Moss for estimation of serum phenylbutazone levels; and to Miss Abberley for secretarial assistance.

APPENDIX

Estimation of phenylbutazone in blood has been carried out by Pulver (1950), who hydrolysed the substance, with formation of hydrazobenzene, which then rearranged to benzidine. This latter substance was estimated colorimetrically by a diazo reaction. The method used in the present investigation was based on the same series of reactions, but differs in the method of hydrolysis and the reagent used for the final colour reaction.

Reagents

(1) A.R. acetone. (2) N sulphuric acid. (3) 0.5% sodium nitrite: store at 0° C. (4) 1.8% N-sulphatoethyl-*m*-toluidine in water. Stored at 0° C, this solution keeps for several weeks, but should be discarded if a brown tint appears. (5) Standard phenylbutazone solution. 3 mg. per 100 ml. in A.R. acetone. Store in a tightly stoppered bottle.

Procedure

One ml. of serum is added to 4 ml. of acetone in a glass-stoppered centrifuge tube of 8-ml. capacity. After shaking well the mixture is stood for 30 minutes, and is then centrifuged, the stopper being retained in the tube during this procedure. Duplicate portions of 1 ml. of supernatant solution are removed and transferred to conical "pyrex" centrifuge tubes of 15-ml. capacity, graduated to tenths of a millilitre. A duplicate standard is set up simultaneously by taking two portions of 1 ml. of the standard phenylbutazone solution, in similar graduated centrifuge tubes.

The bulk of the acetone is now cautiously evaporated off in a hot-water bath, the tubes being agitated gently to prevent loss by spurting or bumping.

One ml. of N sulphuric acid is added to each tube, and the tubes are placed in a boiling-water bath for four hours. At half-hourly intervals the volumes in the tubes are restored to 1 ml. by addition of distilled water. The final volume is 1 ml. After hydrolysis the tubes are chilled in ice-water, and 0.5 ml. of ice-cold sodium nitrite solution is added, followed by 2 ml. of ice-cold N-sulphatoethyl-*m*-toluidine, the solution being mixed well after each addition. The purple colours are allowed to develop for 30 minutes at room temperature.

The serum tubes have a slight turbidity at this stage, owing to the presence of unsaponified lipid material. This turbidity is removed by the addition of 0.25 ml. of 40 to 60° light petroleum, shaking briefly, and centrifuging. Three ml. of the aqueous phase is then removed. The standards are similarly treated with light petroleum.

The coloured solutions are read in a spectrophotometer at 525 mμ or in a colorimeter with appropriate filter. The standards correspond to a serum level of 15 ml. per 100 ml.

A linear relationship was found between colour intensity and concentration of phenylbutazone. Normal serum gives a negligible colour by this method. Recoveries of phenylbutazone added to normal sera were 86 to 95%. In a series of 50 estimations the duplicate serum phenylbutazone levels differed from their mean by amounts varying from ± 0.0 to ± 0.8 mg. per 100 ml. The mean difference from the mean was ± 0.3 mg. per 100 ml.

The N-sulphatoethyl-*m*-toluidine was supplied by Imperial Chemicals (Pharmaceuticals) Ltd., Manchester. I am grateful to Geigy Ltd. for a gift of purified butazolidin.

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The *British Journal of Anaesthesia* enters its second quarter-century of publication with a modernized format and an increase in size. In future it will appear six times a year instead of quarterly. The January issue, which includes a historical note on gas cylinders, a short biography of Dr. Z. Mennell, and papers on current techniques and modern anaesthetic agents, reflects the important part which British workers have played and continue to play in the development of anaesthesia.