TABLE III—*Details on Four Patients with Cell-mediated Immunity to Intrinsic Factor and Hypogammaglobulinaemia*

Case No.	Serum		Lymphocytes		Hb (g/100 ml)	Mean Corpuscular Volume (fl)	Intrinsic-factor Secretion (U/hr)	Serum B_{12} (pg/ml)	% B_{12} Absorption*	
	Parietal-cell Antibodies	Intrinsic-factor Antibodies	Intrinsic Factor on M.I.F. Test	Intrinsic Factor on Trans-formation Test					B_{12} Alone	B_{12} + Intrinsic Factor
1	—	—	—	+	13·8	82	141	—	0·6	16·4
2	—	—	+	—	14·0	82	60	250	0·7	15·5
3	—	—	+	—	15·6	78	0	75	0·8	18·9
4	—	—	—	+	11·1	66	82	130	Normal plasma level	—
Normal Values	—	—	—	—	—	80–90	⩾2000	⩾170	⩾10	⩾10

*% of 1·0 μg oral dose of B_{12} in 24-hour urine in Schilling test.

low, due to either iron deficiency or anaemia of infection (table III).

Discussion

Cell-mediated intrinsic-factor immunity was present in at least 85% of patients with pernicious anaemia and was absent in 105 controls. A few patients with thyrotoxicosis, atrophic gastritis, or hypogammaglobulinaemia also gave positive results.

The association between pernicious anaemia and hypogammaglobulinaemia was reviewed by Chanarin (1969). Twomey *et al.* (1970) found that four out of 10 immunoglobulin-deficient patients had pernicious anaemia, and Hughes *et al.* (1972) found five examples of pernicious anaemia among 12 such patients. Additional patients were described by Douglas *et al.* (1970), Cowling *et al.* (1974), and Ginsberg and Mullinax (1970). Gelfands *et al.* (1972) reported a mother and identical twins all with pernicious anaemia; the twins had immunoglobulin deficiency.

Serum intrinsic factor antibody was present in the case reported by Ginsberg and Mullinax (1970) and in one of the twins reported by Gelfand *et al.* (1972). This child also gave a positive result on M.I.F. and transformation tests using hog intrinsic factor.

Our results show that out of nine patients with hypogammaglobulinaemia four had cell-mediated immunity against intrinsic factor by conventional tests and in this respect resembled patients with pernicious anaemia. None of these patients had serum antibodies against intrinsic factor or parietal cells. These data support the view that the cell-mediated immunity is the prime factor in bringing about atrophic gastritis in this group. But the low serum gastrin levels found in these patients, together with atrophy of the antrum as well as body of the stomach, suggest that the pathological condition in these patients differs from that seen in cases of pernicious anaemia (Hughes *et al.*, 1972).

Atrophic gastritis of varying degree is a very common lesion of the stomach, which increases in frequency with increasing age. Only very few cases progress to pernicious anaemia and the role of intrinsic factor antibody in this transition is not known. It is of particular interest that evidence of cell-mediated immunity was present in some patients in this group. Only long-term follow up, however, can indicate whether these particular patients will progress eventually to pernicious anaemia. The same arguments apply to the positive results in the other groups.

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Double-blind Cross-over Trial of Flurbiprofen and Phenylbutazone in Ankylosing Spondylitis

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Summary

A double-blind cross-over study in 35 patients with ankylosing spondylitis was carried out comparing flurbiprofen (150 mg daily)—a new non-steroidal anti-inflammatory agent—with phenylbutazone (300 mg daily) over a four-week period. Flurbiprofen was well tolerated and shown to have therapeutic efficacy approaching that of phenylbutazone. The results suggest that flurbiprofen may prove a valuable alternative in the treatment of ankylosing spondylitis, and long-term efficacy and tolerance studies are clearly indicated.

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Introduction

Flurbiprofen (B.T.S. 18·322, 2-(fluorobiphenylyl) proponic acid) is a member of the phenylalkanoic acid series. It differs from its predecessors (ibuprofen and ibufenac) in having a biphenyl nucleus but like them possesses antipyretic, anti-inflammatory, and analgesic properties—a triad essential

for antirheumatic efficacy. It is devoid of glucocorticoid activity, its mode of action is not mediated through the adrenal cortex, and its analgesic action is peripheral rather than central (Adams and McCullough, 1970). Flurbiprofen is one of the most potent non-steroidal anti-inflammatory compounds yet reported, having a reported minimal potency in mice of 60-790 times that of acetylsalicylic acid (Masumoto and Takase, 1973).

Preliminary clinicopharmacological studies and clinical evaluation of flurbiprofen in man (Chalmers *et al.*, 1972) have shown it to be well tolerated and non-toxic on a short-term basis. In this same study it was shown to be effective in rheumatoid arthritis. More recently a small study from the Westminster Hospital showed flurbiprofen to be superior to placebo and indomethacin in ankylosing spondylitis (Sturrock and Hart, 1974). Since many would consider phenylbutazone to be the drug of choice in the management of ankylosing spondylitis the possible emergence of a preparation of comparable efficacy which is better tolerated in the short term and safer in the long term could be an important contribution to the management of this and other chronic rheumatic diseases. The Committee on Safety of Medicines' *Register of Adverse Reactions* (January 1964-October 1971) reported 227 deaths from phenylbutazone and 71 from oxyphenbutazone (Girdwood, 1974). These two drugs together are second only to the oral contraceptives as causes of drug deaths. There is a clear need for a safer antipyretic, anti-inflammatory, and analgesic preparation for use in many rheumatological conditions and particularly in ankylosing spondylitis, where long-term therapy is often indicated. This study is aimed at assessing the effect of flurbiprofen and comparing its efficacy with that of phenylbutazone on a short-term, double-blind, cross-over basis. Phenylbutazone was chosen because it is the long-established drug of choice in this condition. Only those patients known to tolerate phenylbutazone were accepted for the trial so that major side effects were not expected from this preparation.

Patients and Methods

Outpatients of either sex who fulfilled the criteria for the diagnosis of ankylosing spondylitis (Bennett and Wood, 1968) were selected from among those attending the Guy's arthritis research unit clinics. Patients were admitted to the trial only if the disease state was such that improvement could be expected with treatment—that is, those cases where the spine was already rigid and changes in spinal movement could not be assessed were excluded. Other exclusions from the study were (*a*) women of child-bearing age, (*b*) patients on anticoagulant therapy, (*c*) patients with a history of hepatic or renal disease, (*d*) those with a history of gastrointestinal haemorrhage, and (*e*) those who gave a history of dyspepsia or intolerance of phenylbutazone. Informed consent was obtained from all patients and permission was received from their general practitioners before the trial began. Altogether 32 men and five women, ranging in age from 18-69 years (mean 42·1 years), were admitted to the trial. Their mean duration of disease was 11 years (range 1-29 years) (tables I and II). A double-blind cross-over technique was used, patients receiving four weeks' treatment of each trial drug in turn with the sequence determined by random allocation. To overcome the problem posed by the fact that flurbiprofen is in capsule form while phenylbutazone is in pill form and to ensure that the bioavailability of phenylbutazone was not altered a double substitution technique was used. Thus patients were given either one capsule (50 mg) of flurbiprofen plus one placebo tablet (identical in appearance to phenylbutazone tablets) three times a day or one tablet of phenylbutazone (100 mg) plus a placebo capsule three times a day for the first period and for the second period the alternative combination was given. The trial was preceded by a "wash-out" period of 48 hours, during which time paracetamol alone was used, all anti-inflammatory preparations being discontinued. Throughout the trial a standard regimen comprising spinal mobilizing exercises was adopted. If further analgesia was required during the period of study paracetamol tablets were taken and the number noted. Assessment on both clinical and laboratory indices was made after the wash-out period and at the end of each four-week period. All assessments throughout the trial were made by the same doctor.

TABLE I—*Age Distribution of Patients in Trial according to Drug Sequence*

Age in years:	<20	20-29	30-39	40-49	50-59	60-69	Total
Flurbiprofen/phenylbutazone	0	4	7	4	2	0	17
Phenylbutazone/flurbiprofen	1	3	6	4	2	2	18
Total	1	7	13	8	4	2	35

TABLE II—*Duration of Disease in Patients in Trial according to Drug Sequence*

Duration (years):	1	1-9	10-19	20-29	Total
Flurbiprofen/phenylbutazone ..	0	7	8	2	17
Phenylbutazone/flurbiprofen ..	1	6	8	3	18
Total	1	13	16	5	35

Clinical investigations included a grading of the functional capacity and severity of disease according to the criteria of Steinbroker *et al.* (1949). Subjective global assessments were based on answers to agreed questions. A five-point scale (1-5) was used for severity of day and night pain, and the duration of morning stiffness was recorded in minutes. The patient's and the physician's assessment of progress were each recorded on a five-point scale after each four-week period.

Objective measurements included the following: chest expansion (circumferential) at the level of the 4th intercostal space (as recommended by the New York Symposium (Bennett and Wood, 1968)), fingertip-to-floor measurements, occiput-to-wall distance, intermalleolar straddle, and a range of spinal measurements (Moll and Wright, 1971). Anterior spinal flexion was measured as the distraction on flexion between points 5 cm below and 10 cm above the lumbosacral junction—that is, levels joining two dimples of Venus. Similarly, lateral spinal flexion was measured by noting the increase in length between two points marked on the lateral trunk (at a level of the xiphisternum and highest point on the iliac crest) on sideways flexion. Spinal extension was measured by noting distance travelled by plumb line pointer hung from fixed mark on lateral chest on leaning backwards.

At the end of the trial the patients were asked to state their preference for the first or second month of therapy. Likewise the physician, basing his opinion on objective criteria, noted which treatment period seemed to produce the more favourable clinical response.

Results

Thirty-seven patients entered the trial. Two men withdrew, one because of an unrelated episode of hypertensive encephalopathy necessitating admission to hospital and the other because of side effects while receiving flurbiprofen Within two weeks of beginning flurbiprofen the patient had developed headaches, vertigo, and hot flushes. These symptoms cleared on temporarily discontinuing therapy but recurred with reintroduction of the drug.

The functional state, according to the criteria of Steinbrocker (1949), and previous drug therapy of the patients are shown in tables III and IV. The results of both sub-

TABLE III—*Functional State (Steinbroker et al., 1949) of Patients in Trial according to Drug Sequence*

Functional capacity	I	II	III	IV	Total
Flurbiprofen/phenylbutazone ..	1	15	1	0	17
Phenylbutazone/flurbiprofen ..	0	16	2	0	18
Total	1	31	3	0	35

TABLE IV—*Previous Drug Therapy of Patients in Trial according to Drug Sequence*

	Aspirin	Phenyl-butazone	Indo-methacin	Others	Radio-therapy
Flurbiprofen/phenylbutazone	1	15	4	2	3
Phenylbutazone/flurbiprofen	1	12	8	2	3

jective (table V) and objective assessments (table VI) were analysed. The overall assessment of patient and doctor are analysed in table VII. In 12 cases the doctor assessed flurbiprofen as producing the best results, and 11 patients preferred it. The doctor preferred phenylbutazone as treatment in nine cases, but 15 patients preferred it. Nine patients had no preference for either drug, and the doctor's assessments indicated no preference in 14 cases.

TABLE V—*Analysis of Subjective Assessments of Pain on Five-point Scale according to Drug Treatment*

		Mean Initial Score	Mean Final Score	Wilcoxon's Test Statistic T	Critical Values of T 5%	Critical Values of T 10%	P
Pain	Flurbiprofen	2·5	2·1	80	65	75	0·2
	Phenylbutazone	2·5	1·8				
Night pain	Flurbiprofen	1·9	1·6	61·5	34	41	0·2
	Phenylbutazone	1·9	1·5				

Only five patients reported taking paracetamol tablets during the trial, two patients during both treatment periods, two during the flurbiprofen treatment only and one during the phenylbutazone treatment only. The subjective assessments of pain during the day and night showed very little difference between the two drugs. Day and night pain was reduced by both, phenylbutazone showing a slightly lower mean score ($P > 0·2$). On the objective assessments only the differences in duration of morning stiffness reached statistical significance, phenylbutazone producing the greater improvement ($P < 0·05$). Both drugs showed an improvement over the initial scores. For all the other objective criteria differences between the drugs were insignificant ($P > 0·2$).

SIDE EFFECTS

Individual side effects occurred nine times among six patients receiving flurbiprofen. Rash was reported once, sore throat once, loose bowels once, constipation once, flatulence once, anorexia twice, epigastric pain once, and abdominal pain once. These were mild and cleared while remaining on the drug. Four patients reported side effects while receiving phenylbutazone. Two had headaches, one fatigue, and one exacerbation of psoriasis.

The laboratory studies showed no changes in haemoglobin, white blood count, platelets, erythrocyte sedimentation rate, alkaline phosphatase, aspartate, aminotransferase, or blood urea. As expected phenylbutazone showed a significant uric-acid lowering effect (mean fall 1·4 mg/100 ml) which was absent in the case of flurbiprofen.

Discussion

This study was designed to assess the value of a new non-steroidal anti-inflammatory agent, flurbiprofen, in the treat-

TABLE VI—*Results of Objective Assessments and Statistical Analysis of Differences between Treatments with Flurbiprofen (FBP) and Phenylbutazone (PBZ)*

	Mean Initial Score (±S.E. of Mean)	Drugs	Mean Final Score (±S.E. of Mean)	Difference (±S.E. of Difference) between Final Scores	Statistical Significance: Paired t	D.F.	P
Duration of morning stiffness (min)	64·9±27·9	FBP	109·8±39·3	76·7±32·7	2·33	34	0·05>P>0·01
		PBZ	33·1±20·6				
Chest expansion (cm)	3·49±0·30	FBP	3·85±0·31	0·10±0·16	0·60	34	>0·20
		PBZ	3·95±0·28				
Fingertips-floor measurement (cm)	19·83±2·84	FBP	19·07±2·79	0·88±0·70	1·26	34	>0·20
		PBZ	18·19±2·70				
Neck-wall measurement (cm)	2·56±0·67	FBP	2·34±0·64	0·28±0·15	1·87	34	0·1>P>0·05
		PBZ	2·06±0·60				
Intermalleolar straddle (cm)	94·76±3·32	FBP	98·75±3·66	0·28±1·31	0·21	34	>0·20
		PBZ	99·03±3·55				
Spinal extension (cm)	4·58±0·52	FBP	4·79±0·48	0·01±0·26	0·04	34	>0·20
		PBZ	4·80±0·46				
Spinal flexion (cm)	3·83±0·41	FBP	4·15±0·42	0·06±0·13	0·45	34	>0·20
		PBZ	4·09±0·41				
Spinal lateral flexion, left (cm)	2·22±0·26	FBP	2·09±0·27	0·10±0·11	0·90	34	>0·20
		PBZ	2·19±0·29				
Spinal lateral flexion, right (cm)	2·30±0·26	FBP	2·12±0·25	0·09±0·12	0·83	34	>0·20
		PBZ	2·03±0·26				
Spinal lateral flexion, sum (cm)	4·53±0·50	FBP	4·21±0·51	0·01±0·20	0·03	34	>0·20
		PBZ	4·22±0·54				

TABLE VII—*Overall Assessments by Doctor and Patients. Results are Numbers of Patients*

		Very Much Worse	Worse	No Change	Better	Very Much Better	Total
			Patients' Assessments				
Flurbiprofen 1st	Flurbiprofen	0	3	7	7	0	17
	Phenylbutazone	0	4	3	9	1	17
Phenylbutazone 1st	Flurbiprofen	2	6	5	4	1	18
	Phenylbutazone	0	1	7	7	3	18
Combined	Flurbiprofen	2	9	12	11	1	35
	Phenylbutazone	0	5	10	16	4	35
			Doctor's Assessment				
Flurbiprofen 1st*	Flurbiprofen	0	1	5	10	0	16
	Phenylbutazone	0	5	9	1	1	16
Phenylbutazone 1st	Flurbiprofen	0	5	8	4	1	18
	Phenylbutazone	0	1	7	10	0	18
Combined	Flurbiprofen	0	6	13	14	1	34
	Phenylbutazone	0	6	16	11	1	34

*Assessment of one patient in this group was not avaliable.

ment of ankylosing spondylitis and to compare it with phenylbutazone. The need for a safe and efficacious alternative to phenylbutazone becomes clear from a study of the *Register of Adverse Reactions* (January 1964-October 1971) made available by the Committee on Safety of Medicines for January 1964-October 1971. During this period there were 864 reports of side effects from phenylbutazone of which 227 were fatal (including aplastic anaemia 101 cases, agranulocytosis 25 cases, and thrombocytopenia 11 cases). There were also 71 deaths among 283 reports of adverse reactions with oxyphenbutazone. Fowler (1974), analysing these deaths, showed that while most of the cases of agranulocytosis occur within the first three months 65% of the more frequent and more serious complication, aplastic anaemia, occur after this time interval. In ankylosing spondylitis long-term therapy for more than three months is almost invariably indicated.

Our results show that there is little difference between flurbiprofen and phenylbutazone according to most subjective and objective criteria. Phenylbutazone was, however, significantly better than flurbiprofen for duration of morning stiffness. This statistical bias may give a false impression; in fact only three of the 35 patients suffered prolonged morning stiffness while receiving flurbiprofen.

Gross alterations in formulation of trial drugs could alter bioavailability (Cromie, 1963). This problem was avoided by the use of a double-blind substitution technique in which both drugs were presented in their usual form, dummy substitutes of the alternative drug being given concurrently.

Only those individuals known to be tolerant to phenylbutazone were admitted to the trial. It is therefore not surprising that there were no serious side effects from this preparation. It is encouraging that only one patient out of the 37 developed side effects with flurbiprofen necessitating withdrawal from the trial. This individual had vertigo, a symptom which cleared within 48 hours of stopping the drug but returned within hours of restarting. He was therefore withdrawn from the trial despite dramatic clinical improvement with the drug.

Paracetamol as a rescue drug was little used, no doubt because patients with ankylosing spondylitis had, on the whole, become accustomed to their chronic pain and in any case found great benefit from the enforced drug therapy dictated by the trial. Furthermore, many patients who claimed to be symptom free at the start of the trial made a great improvement within days of beginning either preparation (two patients played their first round of golf for years). It seems that many individuals with chronic disability fail to take their medication, not realizing how unwell they are. Many patients with ankylosing spondylitis for this reason are lost to follow up and rheumatology clinics should take every opportunity to prevent this happening.

In conclusion, we have shown that flurbiprofen is effective in ankylosing spondylitis, remarkably free from side effects, and likely to have an important part to play in the management of this chronic disorder.

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Abnormal Drug Metabolism after Barbiturate and Paracetamol Overdose

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Summary

Drug-metabolizing capacity has been assessed by serial measurements of the plasma antipyrine half life in 11 patients with severe barbiturate intoxication and in 17 patients with acute hepatic necrosis due to paracetamol overdosage. Drug metabolism was strikingly enhanced after barbiturate overdosage, and this effect was still present six weeks later. In contrast the antipyrine half life was greatly prolonged in patients with paracetamol-induced acute hepatic necrosis but returned to normal or near-normal values within seven to 21 days.

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Introduction

Long-term administration of hypnotics such as barbiturates, glutethimide, and diphenhydramine-methaqualone (Mandrax) can cause stimulation of hepatic microsomal enzyme activity and thereby enhance the rate of metabolism of many drugs (MacDonald *et al.*, 1969; Stevenson *et al.*, 1972; Breckenridge *et al.*, 1973 a). This stimulatory effect develops over three to four weeks and persists for a similar period after the inducing drug is discontinued. The barbiturates produce a dose-related induction of microsomal enzymes in man (Breckenridge *et al.*, 1973 a), and marked acceleration of drug metabolism might be expected after severe overdosage with these drugs since this probably represents the maximum stimulus for induction likely to be encountered in practice. On the other hand, drug metabolism is likely to