40% alcoholic saline without the coloured indicator gave better fixation.

Some pipettes contain a great deal of mucus, which clots when processed, trapping many of the cells. The technical staff in the laboratory also found the pipettes unpleasant to handle, especially in view of the fact that the stem of the pipette may be contaminated after use.

Reading the Smears

A Davis pipette smear, at its best, consists of an evenly spread suspension of superficial squamous cells. The complete spectrum of cells seen in the Ayre smear is not present, and endocervical cells are very seldom seen. Endometrial cells, for which a pipette smear is said to be better, are also seen more rarely than in the Ayre smear. Even when the pipettes are processed promptly, we have found that the quality of the cell-preservation and staining is poor by comparison with the Ayre smear. The Davis smears are so homogeneous that they become monotonous to read, and "saturation point" is reached more rapidly. Each slide takes longer to screen than an Ayre smear, since it is more difficult to spot single atypical cells than such cells occurring in groups. With practice and some changes in criteria the screening-time may be reduced, but in no circumstances would we expect it to be less than the time necessary to screen the Ayre smear.

Sensitivity of the Cytopipette

It will be seen from Table I that the pipette method picks up only half the cases of malignancy found by the Ayre smear. The six Davis pipette smears that were negative when the Ayre smears were positive were re-screened, and in no cases were any abnormal cells found. We believe that the failure to detect malignant cells in these six cases was a sampling error, not a screening error. Macgregor, Fraser, and Mann (1966) have reported a similarly poor detection rate in their recent Aberdeen survey. In those cases where atypical cells indicated the need for close follow-up the pipettes were again only half as accurate as the Ayre smear.

The only advantage of the Davis pipette is that patients can take their own sample without the need to attend a clinic or to see a doctor; it might therefore be possible to reach a larger proportion of the population at risk. However, the low rate of detection would necessitate repeated screenings of each patient at fairly short time-intervals, and although the initial response might be good, it could prove difficult to persuade women to take repeated samples, especially in view of the complaints from the clinics participating in this survey. Like Macgregor and her colleagues, we think that the cytopipette is not an appropriate instrument for urban-community-screening programmes.

Conclusions

Our results leave us in no doubt that when a cervical cytology specimen is taken by a doctor the Ayre smear is a more effective method than the Davis cytopipette in the detection of malignancy. The Davis method has been extensively used in Denmark (Bredahl *et al.*, 1965) and in the United States (Davis, 1962). Its greatest advantage is that it can be used as a "do-it-yourself" method; it may have a place in screening programmes where facilities for expert gynaecological examination are not widely available. The Ayre scrape is a more efficient method, and its use also ensures that the cervix comes under expert scrutiny. We believe that it is the method of choice for population screening for cervical cancer, in this country at least.

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Preliminary Communications

Mefenamic Acid and Flufenamic Acid compared with Aspirin and Phenylbutazone in Rheumatoid Arthritis

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Aspirin and phenylbutazone (Butazolidin) are well established in the treatment of rheumatoid arthritis. Pharmacological studies have shown both to possess anti-inflammatory properties when measured in the laboratory animal. More recently two anthranilic acid derivatives, mefenamic acid (Ponstan) and flufenamic acid (Arlef), were shown to have the same property (Winder *et al.*, 1962, 1963) and subsequently both have been found useful in patients with rheumatoid arthritis (Coodley, 1963; Young, 1963).

As mefenamic acid is now freely available, and as flufenamic acid may become so, it is essential that their relative merits should be compared with existing standard remedies. We report the main findings of a double-blind crossover trial of all four drugs in outpatients with rheumatoid arthritis. The drugs were assessed by a variety of methods, and estimates were made also of the reliability of patients in consuming the prescribed drugs. Details of the trial will be published later in full.

Procedure

Female outpatients with rheumatoid arthritis (as defined by American Rheumatism Association criteria) of more than one year's duration received, during three consecutive periods of four weeks, mefenamic acid, flufenamic acid, and either aspirin or phenylbutazone in one or other of all possible orders according to a balanced Latin-square design. Both aspirin and phenylbutazone are superior to placebo. Confirmation of this fact seemed unnecessary and ethically undesirable, and these drugs were therefore taken as standards for comparison with the two new drugs. Some patients are sensitive to either aspirin or phenylbutazone, so each drug was included in the design, half the subjects being allotted a sequence containing one drug and half containing the other. Ordinarily the choice depended on the statistical design, but if a patient was believed to react

unfavourably to either drug a sequence omitting the drug in question was requested. This request was made on four occasions, but the allotted sequence was in fact inappropriate only once. Otherwise the physician remained completely ignorant of the particular treatment which each patient received. Finally, most subjects continued for a fourth period, during which they received whichever drug they had considered most effective in the first three periods. This was achieved by an appropriate instruction to the pharmacy and did not involve the physician in breaking the code. Eleven of the subjects had been receiving steroids and three antimalarials. The dosage of these drugs was stable and was continued unchanged throughout the trial. The remaining patients received neither steroids nor antimalarials. Free access to paracetamol was allowed throughout, but all other analgesics were stopped and no change was permitted in any ancillary therapy during the trial.

Initially, comparison was between a dose of 720 mg. of aspirin, 100 mg. of phenylbutazone, 500 mg. of mefenamic acid, and 200 mg. of flufenamic acid, each given three times daily. In order to achieve the optimum dose the subjects were seen and their progress was briefly reviewed at the end of the first week of each period. The physician was then allowed to alter the dosage to twice or four times daily if alteration seemed desirable on grounds of therapeutic response and toxic manifestations, or to continue unchanged. If toxic effects were severe the drug was changed to that planned for the next period.

Assessment of the subjects was largely made by means of data which the admitting physician and a physiotherapist independently recorded on admission to the trial, and at the end of the first and fourth weeks of each period. In addition, the subjects themselves completed a daily progress chart, including a record of their main drug and supplementary analgesic (paracetamol) consumption. Patients returned any unused drugs, and the numbers returned served as a check on the quantities consumed. Erythrocyte sedimentation rate, white blood cell counts, and haemoglobin estimations were made initially and at the end of each period of treatment.

Results

Of 68 patients admitted to the trial, eight withdrew before completing three periods. Four withdrew for social or personal reasons—two were receiving aspirin and one each phenylbutazone and flufenamic acid at the time of withdrawal. Four withdrew for medical reasons—one receiving phenylbutazone suffered an exacerbation of her arthritis, one receiving aspirin developed symptoms related to high blood-pressure, one receiving mefenamic acid as well as steroids developed symptoms of an acute gastric ulcer which was radiologically confirmed, and one also receiving mefenamic acid had a haematemesis without radiological evidence of gastric ulceration. The latter two made a good recovery with conservative treatment and withdrawal of mefenamic acid.

During the first period of four weeks a modest reduction in both symptoms and joint pain on active movement occurred in most patients, not significantly more often on any one particular drug. In subsequent periods the average severity changed very little. As all but two of the patients had been receiving some analgesics, usually salicylates or phenylbutazone, before the trial, substantial changes were not expected with the trial treatments, nor did they occur.

With adjustment of dosage as described, the four drugs were equally effective. Improvement or deterioration of symptoms was not significantly commoner or greater on any one treatment, and there were no significant changes in joint pain on movement, or dexterity, walking-speed, angle of maximum shoulder abduction, grip-strength, or proximal interphalangeal joint sizes. Such changes as did occur in these variables were uncorrelated with each other.

The prescribed dose was changed at the end of the first week of a period on 90 of 192 possible occasions, as shown in the Table. The dose was increased more often than decreased. There was no significant difference in dose adjustment between the four drugs, though treatment was prematurely discontinued on a slightly higher proportion of occasions with the two newer drugs ($P=0.24$). Paracetamol consumption varied greatly from patient to patient, but showed no consistent differences related to the principal treatment given. In the fourth period of the trial each patient received a second course of the drug she preferred from among those administered in the three previous periods.

Changes in Prescribed Doses of Drugs

Drug and Initial Dose	No. of Periods	Dose Reduced	Dose Increased	Treatment Prematurely Discontinued	Total
Aspirin, 720 mg. t.d.s.	35	4	13	1	18
Phenylbutazone, 100 mg. t.d.s.	30	0	10	1	11
Mefenamic acid, 500 mg. t.d.s.	65	1	27	6	34
Flufenamic acid, 100 mg. t.d.s.	62	1	21	5	27
Total	192	6	71	13	90

Phenylbutazone was preferred slightly but not significantly more often than any other drug (by 37% of the 30 patients who had received it). Flufenamic acid was least popular (24% of 62 patients), but again not significantly ($\chi^2=2.02$ over all four drugs, $0.5<P<0.6$).

There were no outstanding differences between the unwanted effects of the four drugs. For example, dyspepsia was reported in 13 (37%) patients while taking aspirin, in 8 (27%) while taking phenylbutazone, in 13 (20%) while taking mefenamic acid, and in 21 (34%) while taking flufenamic acid ($\chi^2=1.86$, $0.6<P<0.7$). Diarrhoea occurred in 3 (8%) while on aspirin, 8 (12%) on mefenamic acid, and 6 (9%) on flufenamic acid. Nine patients developed rashes, seven while receiving mefenamic acid and two receiving phenylbutazone. The greater incidence with mefenamic acid is significant by Fisher's exact test ($P=0.02$), but a single "significant" finding at this level might easily arise by chance among so many possible comparisons.

Conclusion

In women with rheumatoid arthritis mefenamic acid and flufenamic acid appear to be satisfactory substitutes for aspirin and phenylbutazone, but have no particular superiority. After adjusting doses to the need of individual patients the mean daily dosage used was aspirin 2.4 g., phenylbutazone 0.33 g., mefenamic acid 1.7 g., and flufenamic acid 0.67 g. These can reasonably be regarded as equipotent doses.

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