PAPERS AND SHORT REPORTS

Ventricular extrasystoles during thiazide treatment: substudy of MRC mild hypertension trial

MEDICAL RESEARCH COUNCIL WORKING PARTY ON MILD TO MODERATE HYPERTENSION

Abstract

One short term and one long term study of the relation between ventricular extrasystoles and thiazide treatment were carried out during the Medical Research Council's mild hypertension trial. In the short term study 110 patients were randomly assigned to one of three treatment groups, bendrofluazide with or without potassium supplements, or placebo. They were studied before starting treatment and nine to 10 weeks later while still taking their randomly assigned drugs. No significant increase in the number of ventricular extrasystoles was associated with short term thiazide treatment, although serum potassium concentrations changed as expected. In the long term study 214 patients who had completed an average of two years' treatment with randomly assigned bendrofluazide or a placebo were studied while continuing to take their trial tablets; the 214 included 20 people who had been randomised at entry to the bendrofluazide group and who had a subsequent history of hypokalaemia. These 20 patients were studied before and after being further randomised to two groups, one continuing treatment without change and one continuing with bendrofluazide and also taking potassium supplements. Counts of ventricular extrasystoles were significantly higher ($p=0.025$) in those receiving long term thiazide treatment than in their controls; however, there was no significant association between the number of ventricular extrasystoles and serum potassium concentrations in this group, although the correlation between number of extrasystoles and serum urate concentrations was significant ($p=0.035$).

Pooled data for both studies showed a highly significant correlation between number of ventricular extrasystoles, and serum potassium concentrations ($r=-0.185$; $p=0.003$), but the correlation with serum urate concentrations was of similar strength ($r=0.178$; $p=0.004$). These biochemical changes may be acting merely as markers of thiazide intake, and the explanation of the association between thiazide treatment and ventricular extrasystolic activity therefore remains uncertain.

Introduction

The use of thiazide diuretics in hypertension has steadily increased during the past 20 years, and the effect of recent publications[1-5] may be to accelerate this trend. The treatment of hypertension is often protracted, and since there are inevitably some risks associated with the use of drugs the adverse effects of antihypertensive treatment are of considerable importance.[6-8]

There have been several publications linking thiazide treatment and cardiac arrhythmias and suggesting that the thiazide induced potassium depletion is the causative factor[9,10]; most of these reports were based on resting electrocardiograms in severely hypokalaemic subjects or in those receiving concurrent digitalis. Two recent studies using exercise and ambulatory electrocardiographic monitoring[11,12] suggested that ventricular extrasystoles occur commonly in hypertensive patients taking thiazides; both investigations, however, were based on small selected groups of patients, and neither included data for a placebo treated group.

The framework of the Medical Research Council's treatment trial for mild hypertension[13] provided an opportunity to use ambulatory electrocardiographic monitoring in a study of ventricular extrasystoles in people with mild hypertension managed in general practice and randomly assigned to thiazide or to placebo; it also permitted assessment of the relation between the prevalence of these abnormal beats and thiazide related changes in the serum potassium and urate concentrations.

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Patients and methods

TRIAL PARTICIPANTS

The organisation of the MRC treatment trial for mild hypertension has been fully described[13] and only the relevant points are given here. The study includes men and women aged 35-64 years with sustained diastolic (phase V) pressures of 90-109 mm Hg. Subjects were identified by screening, and most have been managed and followed up in general practices widely distributed throughout England, Scotland, and Wales. The practices participating in the present study were selected for their proximity to London. At entry to the trial patients are randomly assigned to treatment with bendrofluazide, propranolol, or placebo tablets. Between November 1980 and July 1981, 324 people in the trial were recruited for the two studies reported here.

TWENTY FOUR HOUR AMBULATORY ELECTROCARDIOGRAMS

A frequency modulated cassette recorder (Medilog 2, Oxford Medical Systems) was used. This instrument weighs only 390 g, is small (15·2 × 9·1 × 2·8 cm), and interfered little with activity during the limited period of the study. The electrodes and the proximal portion of the leads were anchored to the skin with adhesive tape, and an elastic vest further helped to reduce electrode movement.

The tapes were analysed electronically by Hertford Medical Ltd using Reynold's Medical Pathfinder System.[14] Validity checks were performed by two observers (WEM and GG), each of whom read independently a randomly selected one hour section of a 10% random sample of all tapes. Recognising ventricular extrasystoles on printouts of this kind is easy, and agreement between the two observers and between the observers and the electronic system was therefore very close.

In a further study of the tapes one observer (PKW) read one hour printouts of a morning's and an evening's recordings of each patient (5-6 am, and 5-6 pm), classifying ventricular extrasystoles as unifocal or multiform and noting the presence of bigeminy, coupling, and R on T forms. The validity of these readings was tested against results obtained by a second reader (GG); again agreement was close.

SERUM BIOCHEMISTRY

On each occasion blood samples were taken immediately before applying the electrodes, centrifuged at the individual clinics, and the serum posted to the Wolfson Research Laboratories in Birmingham, where all analyses were done. It was not possible to ensure that the samples were always taken at the same time in relation to meals or to the intake of potassium supplements.

SHORT TERM STUDY

Recruits for the short term study were new entrants to the mild hypertension trial who had not begun to take trial tablets. All eligible people attending appropriate clinics chosen for their proximity to London were invited to take part; people aged 35-44 were excluded because experience in the trial had shown the prevalence of ventricular extrasystoles to be considerably lower in this age group than in older subjects. Of the 121 possible participants, 110 (91%) consented. In 91 (83%) of these (43 randomised to bendrofluazide, 48 to placebo) a technically satisfactory pretreatment 24 hour electrocardiogram was obtained. The bendrofluazide group was then further randomised: 22 were given either 5 mg of the drug daily together with 16·8 mmol (mEq) potassium chloride, or 10 mg daily with 33·6 mmol potassium chloride; 21 took either the 5 mg or 10 mg dose without supplementary potassium.

Nine to 10 weeks later a second 24 hour electrocardiogram was attempted; satisfactory readings were obtained in 35 (81%) of the bendrofluazide group and in 38 (79%) of those taking placebo tablets.

Serum potassium and urate concentrations were measured before and after the nine to 10 week interval.

LONG TERM STUDY

Recruits for the long term study were people who had completed an average of two years' treatment (range three to 50 months) with placebo or with 10 mg bendrofluazide daily.

Unselected—All eligible people aged 45-64 attending the appropriate clinics were invited to participate. Of 216 invited, 194 (90%) consented; 95 were taking bendrofluazide and 99 placebo. These people were examined only once for the present study: 24 hour ambulatory electrocardiographic monitoring was successfully conducted in 74 (78%) of the thiazide group and 81 (82%) of the placebo group.

Selected, hypokalaemic—Twenty people aged 35-64 years attending the clinics were selected because they had been found to be hypokalaemic (serum potassium concentration $\leq$2·7 mmol(mEq)/l) at least once since entering the mild hypertension trial. All were taking bendrofluazide 10 mg daily. Twenty four hour electrocardiograms were obtained successfully in 18 cases (90%), and these 18 people were then randomly assigned to two equal groups, one to be given oral potassium chloride tablets (48 mmol/day given as Slow-K) in addition to their diuretic treatment and the other to continue taking the unsupplemented diuretic. Twenty four hour tracings and blood tests were repeated five weeks later and were successful in eight subjects in each group.

STATISTICAL ANALYSIS

Distributions of ventricular extrasystolic counts were compared by the Mann-Whitney U test. Correlations including these counts used the expression log (ventricular extrasystolic count + 1000).

Results

SHORT TERM STUDY

Of the 91 patients, 45 (49%) were men. The mean age of all 91 subjects was 54·9 years (SE 5·6). There was no significant correlation between ventricular extrasystolic counts at the beginning of the study and either serum potassium or serum urate concentrations.

During the first nine to 10 weeks of treatment, when the mean serum potassium concentration fell from 4·1 to 4·0 mmol/l in the placebo group and from 4·2 to 3·6 mmol/l in the unsupplemented bendrofluazide group (table I), there was no significant change in the distributions of ventricular extrasystolic counts in either the 38 subjects taking placebo or the 16 taking unsupplemented bendrofluazide; nor was there any within group relation between changes in ventricular extrasystolic counts and changes in serum potassium values.

TABLE I—*Short term study. Changes in serum potassium and urate concentrations and in numbers of ventricular extrasystoles in patients with satisfactory 24 hour electrocardiograms both before and after nine to 10 weeks' treatment*

	Placebo group (n = 38)		Bendrofluazide group			
			Without potassium supplementation (n = 16)		With potassium supplementation (n = 19)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Mean (SD) serum potassium (mmol/l)	4·1 (0·3)	4·0 (0·3)	4·2 (0·4)	3·6 (0·3)	4·2 (0·6)	3·9 (0·5)
Mean (SD) serum urate (mmol/l)	0·357 (0·069)	0·351 (0·065)	0·351 (0·059)	0·426 (0·082)	0·360 (0·068)	0·403 (0·090)
Ventricular extrasystoles/100 000 beats:						
No (%) of patients with < 10	24 (63)	27 (71)	11 (69)	10 (63)	10 (53)	14 (74)
No (%) of patients with 10	8 (21)	7 (18)	2 (13)	3 (19)	3 (16)	4 (21)
No (%) of patients with 100	5 (13)	3 (8)	2 (13)	2 (13)	4 (21)	1 (5)
No (%) of patients with 1000	1 (3)	1 (3)	1 (6)	1 (6)	2 (10)	
No (%) of patients with ≥ 10 000						

Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l. Urate: 1 mmol/l ≈ 17 mg/100 ml.

In the supplemented bendrofluazide group there was a significant ($p < 0.05$) drop in ventricular extrasystolic counts during the nine to 10 week interval. In all those with pretreatment counts of 10 or more ventricular extrasystoles/100 000 beats the count fell, despite a concurrent decrease in the group mean serum potassium value from 4·2 to 3·9 mmol/l (table I). Again no significant within group relation between changes in ventricular extrasystolic counts and changes in serum potassium concentrations was found.

There was no significant correlation between changes in ventricular extrasystolic counts and changes in serum urate concentrations. Figure 1 shows the individual changes in counts.

TABLE II—*Long term study. Unselected participants*

	Bendrofluazide group (n = 74)	Placebo group (n = 81)
Mean (SD) serum potassium (mmol/l)	3·6 (0·4)	4·1 (0·3)
Mean (SD) serum urate (mmol/l)	0·414 (0·089)	0·323 (0·065)
Ventricular extrasystoles (24 h electrocardiogram)/100 000 beats:		
No (%) of patients with < 10	29 (39)	47 (58)
No (%) of patients with 10	20 (27)	17 (21)
No (%) of patients with 100	14 (19)	12 (15)
No (%) of patients with 1000	10 (14)	3 (4)
No (%) of patients with ≥ 10 000	1 (1)	2 (2)

Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l. Urate: 1 mmol/l ≈ 17 mg/100 ml.

LONG TERM STUDY

Unselected—Of the 155 patients, 67 (43%) were men. The mean age of all 155 subjects was 56·4 years (SE 5·5). Table II shows the characteristics of the 74 patients taking bendrofluazide as compared with the 81 given placebo. As expected, there were differences in the mean serum potassium concentrations between the two groups (4·1 mmol/l in controls, 3·6 mmol/l in the thiazide group). There was no significant within group relation between ventricular extrasystolic counts and serum potassium values, nor between ventricular extrasystolic counts and serum urate concentrations in the placebo takers. In the bendrofluazide group there was a significant positive correlation between ventricular extrasystolic counts and serum urate concentrations ($p = 0.035$). The distribution of ventricular extrasystolic counts in the unselected long term bendrofluazide group was significantly ($p = 0.025$) shifted towards higher values when compared with that of the long term placebo takers (fig 2).

Selected, hypokalaemic—Only four of the 16 patients were men; the mean age of all 16 was 54·4 (SE 7·6) years. At the beginning of the five week study period ventricular extrasystolic counts were higher in this hypokalaemic group than in the unselected bendrofluazide takers in the long term study, and higher than those in placebo takers in the short term study and in the unselected placebo group in the long term study; perhaps because of small numbers these differences were not statistically significant. Again there was no relation between ventricular extrasystolic counts and either serum potassium or serum urate concentrations within the group at the beginning of the study. Table III shows the changes which occurred during the five week study period. No significant change in ventricular extrasystolic counts occurred either in the small group randomised to a continuation of unsupplemented bendrofluazide or in that receiving supplementary potassium during the five to six week interval. Serum potassium concentrations rose from a mean of 3·0 mmol/l to 3·2 mmol/l in the unsupplemented group, and from 2·8 mmol/l to 3·5 mmol/l in those receiving supplementary potassium; there was no association, however, between changes in ventricular extrasystolic counts and changes in serum potassium values. Figure 3 shows the individual changes in ventricular extrasystolic counts in these small groups.

TABLE III—*Long term study: selected hypokalaemic participants. Changes in serum potassium and urate concentrations and in numbers of ventricular extrasystoles in patients with satisfactory 24 hour electrocardiograms both before and after 5 weeks' treatment*

	Bendrofluazide without potassium supplement (n = 8)		Bendrofluazide with potassium supplement (n = 8)	
	Before treatment	After treatment	Before treatment	After treatment
Mean (SD) serum potassium (mmol/l)	3·0 (0·3)	3·2 (0·3)	2·8 (0·1)	3·5 (0·4)
Mean (SD) serum urate (mmol/l)	0·401 (0·093)	0·408 (0·111)	0·365 (0·098)	0·333 (0·092)
Ventricular extrasystoles/100 000 beats:				
No of patients with < 10	3	3	4	3
No of patients with 10	1	1	1	3
No of patients with 100	2	2	2	1
No of patients with 1000	2	1	1	1
No of patients with ≥ 10 000		1		

Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l. Urate: 1 mmol/l ≈ 17 mg/100 ml.

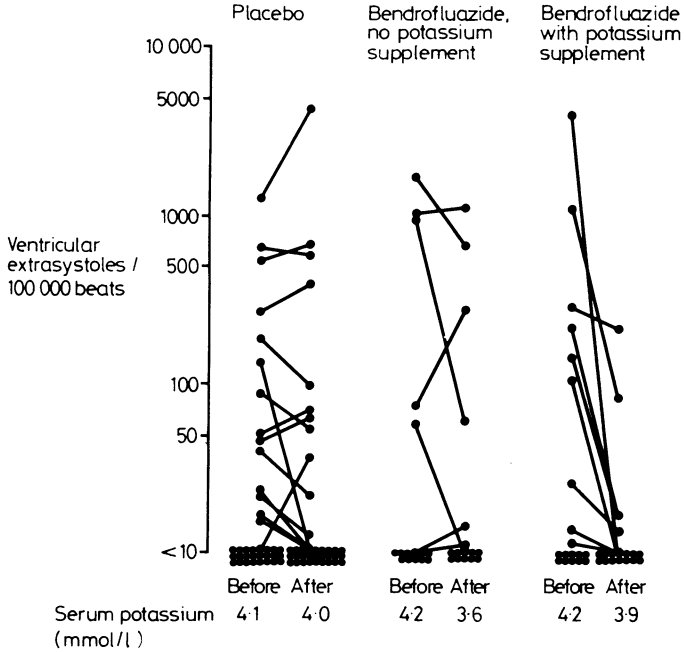

FIG 1—Ventricular extrasystoles/100 000 beats in new trial entrants before and after nine to 10 weeks' treatment with placebo, bendrofluazide alone, or bendrofluazide with potassium supplementation.

Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l.

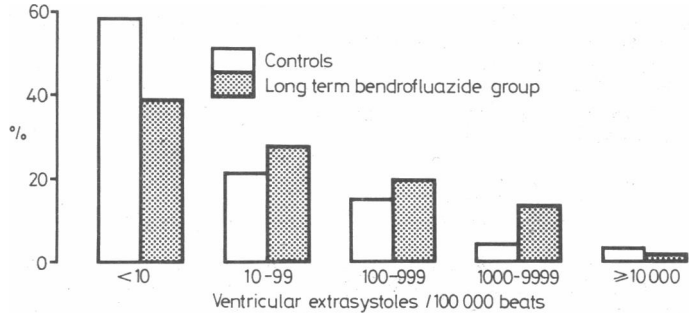

FIG 2—Distributions of ventricular extrasystoles/100 000 beats in long term trial participants taking placebo or bendrofluazide tablets.

TABLE IV—*MRC treatment trial for mild hypertension. Percentage prevalence of special forms of ventricular extrasystoles at entry to short term and long term studies*

Special form of ventricular extrasystoles	Short term study: before treatment	Long term study		
		Unselected		Selected, hypokalaemic
		Placebo	Bendrofluazide	Bendrofluazide
Multiform	10	10	17	35
Couplets	4	2	5	15
R on T beats	1	1	9	10
Bigeminy		1	7	5

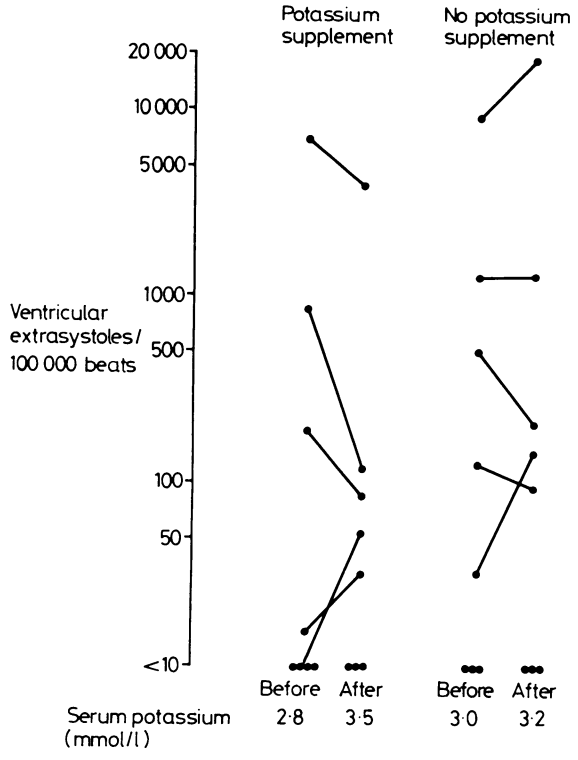

FIG 3—Ventricular extrasystoles/100 000 beats in hypokalaemic subjects taking bendrofluazide before and after five to six weeks' continued treatment with and without potassium supplementation.

Conversion: SI to traditional units—Potassium: 1 mmol/l= 1 mEq/l.

NUMBERS OF VENTRICULAR EXTRASYSTOLES

The actual numbers of ventricular extrasystoles seen in the present study, even in the groups with the highest counts, were small. Some 30% of patients in the long term bendrofluazide group had fewer than 10/100 000 beats (roughly the number of beats occurring in 24 hours at a rate of 70/min), and only 15% had 1000 or more ventricular extrasystoles/100 000 beats.

QUALITATIVE DIFFERENCES IN VENTRICULAR EXTRASYSTOLES

The prevalence of multiform ventricular extrasystoles, couplets, R on T forms, and bigeminy was higher in the long term bendrofluazide takers than in the long term placebo group ($p=0{\cdot}006$ for the presence of one or more of these special forms) and higher in the hypokalaemic than in the unselected long term bendrofluazide group (table IV).

INFLUENCE OF DURATION OF TREATMENT

In the unselected long term bendrofluazide group duration of treatment was negatively correlated ($r=-0{\cdot}40$; $p=0{\cdot}0004$) with serum potassium concentrations. Duration of treatment was not significantly associated with ventricular extrasystolic counts in this group. Even when the data for bendrofluazide takers at the end of the short term study were pooled with those of the long term bendrofluazide takers, no significant relation was found between ventricular extrasystolic counts and duration of bendrofluazide treatment.

SERUM POTASSIUM VALUES AND EXTRASYSTOLIC COUNTS

Despite the absence of evidence of an association between these factors in the separate parts of the study, pooled data relating the serum potassium concentrations and ventricular extrasystolic counts for all patients at entry to the investigations showed a highly significant ($p=0{\cdot}003$) but low value negative correlation ($r=-0{\cdot}185$); the lower the serum potassium concentration the higher the ventricular extrasystolic count. There was also a positive correlation between serum urate concentrations and ventricular extrasystolic counts, closely similar in size and significance ($r=0{\cdot}178$; $p=0{\cdot}004$). In a multiple regression analysis the partial correlation coefficients of serum potassium values and ventricular extrasystolic counts, and of urate values and ventricular extrasystolic counts, were $-0{\cdot}158$ and $0{\cdot}154$ respectively.

Discussion

Reduction in the plasma potassium concentration occurs commonly in patients taking diuretics, and hypokalaemia may develop within a few weeks of beginning treatment.[15] An association between severe hypokalaemia, whatever the cause, and arrhythmias has long been recognised.[10] Arrhythmias are also common in digitalised patients with mild hypokalaemia,[16] and an association between hypokalaemia and arrhythmias after acute myocardial infarction has been observed.[17-20] Holland *et al*[11] and Hollifield and Slaton[12] have reported an association between thiazide induced changes in serum potassium concentrations and premature ventricular contractions during treatment for essential hypertension. Holland *et al*[11] have also reported a striking decrease in the frequency of ventricular extrasystoles after the administration of a potassium sparing agent.

The finding of higher ventricular extrasystolic counts in those receiving long term thiazide treatment, whose mean serum potassium concentration was 3·6 mmol/l, in comparison with counts in placebo takers with a mean serum potassium concentration of 4·1 mmol/l was consistent with the published work, as was the correlation between ventricular extrasystolic counts and serum potassium concentrations in the pooled entry data.

There is, however, no convincing evidence of a simple causative relation between ventricular extrasystoles and low concentrations of serum potassium; the correlations between ventricular extrasystolic count and serum potassium and urate values in the pooled data were almost exactly equal in size and significance; both serum potassium and serum urate concentrations may be acting merely as markers of thiazide intake. Short term patients taking unsupplemented thiazide showed the expected fall in serum potassium concentration but no increase in ventricular extrasystolic counts; those taking supplemented thiazide showed, despite a small drop in serum potassium values, significantly decreased counts. Giving potassium supplements to the selected hypokalaemic patients increased their serum potassium concentrations but did not influence their ventricular extrasystolic counts. No relation between changes in counts and in serum potassium concentrations was found in any part of the study. Perhaps these studies were too small, and too short: the effects of changing serum potassium concentrations may take more than a few weeks to be manifested by changing ventricular extrasystolic counts. Furthermore, day to day variability of ventricular extrasystolic counts and of serum potassium concentrations was not measured. Certainly these results provide no conclusive evidence that either hypokalaemia itself or changes in serum potassium values have a causative role in determining ventricular extrasystolic counts.

The metabolic changes in thiazide takers are complex. There is only a weak relation between serum potassium and muscle

potassium.[21] Furthermore, restoration of serum potassium concentration cannot return intracellular values to normal unless mechanisms maintaining the gradient of potassium across the cell membrane are functioning normally; magnesium depletion occurs in patients taking thiazides[22 23] and impairs the activity of sodium-potassium adenosine triphosphatase.[8]

It is important to note, in any case, that the clinical significance of thiazide induced ventricular extrasystoles is not clear, although the association noted between thiazide administration and special forms of extrasystoles such as multifocal beats, couplets, R on T beats, and bigeminy may be important. Insurance statistics and epidemiological data suggest that otherwise healthy people with ventricular extrasystoles found in resting electrocardiograms have a definitely increased risk of sudden death,[24 25] and ventricular extrasystoles found during ambulatory monitoring appear to identify a group with an increased prevalence of coronary heart disease and risk of sudden death.[26]

It seems certain that if the metabolic effects of thiazide diuretics do in fact increase the risks of coronary heart disease mortality or of sudden death the increase would be detectable only in a large placebo controlled trial. The only relevant study whose results are still awaited is the Medical Research Council's mild hypertension trial; possibly even the results of this large and long term study might not be definitive on this point, but none the less these data are likely to be the most useful available for estimating the importance of findings of the kind given in the present paper.

We are indebted to the general practitioners at the MRC trial centres where the studies were performed, and particularly acknowledge the contribution made to this study by the trial nurses at those centres. Slow-K tablets were provided by CIBA (UK). Electronic analysis of the 24 hour tracings was funded by Merck Sharp and Dohme Ltd. The study was performed while Dr P K Whelton was on leave of absence from the Johns Hopkins University School of Medicine, supported by awards from the Milbank Memorial Fund and the Jane Hilder Harris Fund. Computing was performed, in part, on the Johns Hopkins Clinical Research Center CLINFO computer system.

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(*Accepted 1 August 1983*)

FOR THE EYES, AND THEIR IMPEDIMENTS—*For Eyes that are blasted*—Only wear a piece of black Sarcenet before thy eyes, and meddle with no medicine; only forbear wine and strong drink. *An excellent water to clear the Sight*—Take of Fennel, Eyebright, Roses, white, Celandine, Vervain and Rue, of each a handful, the liver of a Goat chopt small, infuse them well in Eyebright-water, then distil them in an alembic, and you shall have a water will clear the sight beyond comparison. *For a hurt in the Eye with a stroke*—Take Agrimony, and bruise it very well, and temper it with white Wine, and the white of an egg: spread it pretty thick upon a cloth, like a plaster, and apply it to the outside of the eye-lid, and, although it be almost out, it will cure it. *To draw rheum back from the Eyes*—Take an egg and roast it hard, then pull off the shell, and slit it in two, and apply it hot to the nape of the neck, and thou shalt find ease presently. *For the web in the Eye*—Take the gall of a hare, and clarified honey, of each equal proportions: mix them together, and lay it to the web. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)

Correction

Effect of terbutaline sulphate in chronic "allergic" cough

We regret that an error occurred in this paper by Dr R Ellul-Micallef (1 October, p 940). The horizontal axis in figure 2 was labelled incorrectly, and the correct figure is given below.

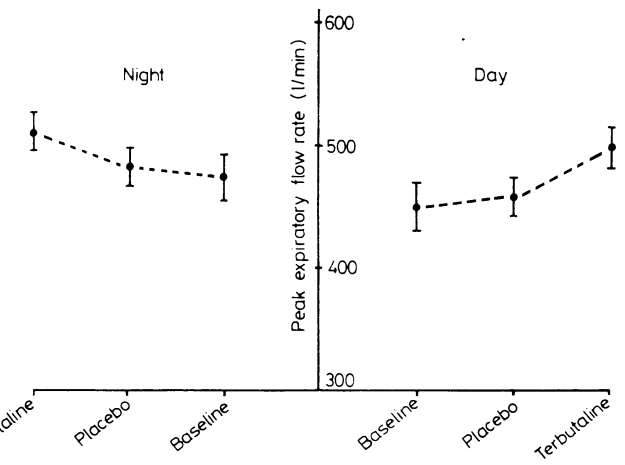

FIG 2—Day and night peak expiratory flow rates. Values represent mean (SEM) rates in each three week period of study.