increased progressively with the duration of the colitis. Despite the evidence of other workers from Oxford (Acheson, 1960) they felt that their data favoured the view that sacro-iliac joint changes are a direct complication of ulcerative colitis.

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Controlled Trial of Breathing Exercises

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Most clinicians accept breathing exercises as a useful way of treating certain chronic respiratory disorders, notably emphysema and asthma. Many attempts have been made to demonstrate their effect by the use of lung-function tests (Allan, 1952; W. F. Miller, 1954; Becklake *et al.*, 1954; Campbell and Friend, 1955; McNeill and McKenzie, 1955; Sinclair, 1955; Becker and Denny, 1959; McKinley *et al.*, 1961; Cole *et al.*, 1962). Most of these investigations have not produced convincing evidence of improvement; but they have been reasonably criticized by W. F. Miller (1958) and others on the grounds that a group of patients was studied and the results were pooled, thus disguising the possible benefit to individuals, however few, which would justify the method of treatment.

We have tried to meet this objection by a controlled trial of breathing exercises in which simple lung-function tests were used as objective evidence of improvement and particular note was taken of symptomatic change as stated by the patient. We have examined further those patients who improved either objectively or symptomatically within the treated and control groups.

Methods

The study was limited to patients with chronic bronchitis and/or emphysema. Chronic bronchitis was defined symptomatically as a disease characterized by persistent cough and sputum on most days for at least three months of the year. All patients complained that they were short of breath. The presence of minor old tuberculous lesions on x-ray films did not exclude any patient from the survey. The presence of emphysema was judged by chest x-ray examination; the criteria of Simon and Medvei (1962) were used and the relative profusion of peripheral vascular shadowing (Laws and Heard, 1962) was taken into account.

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One hundred out-patients who satisfied the above criteria were randomly divided into two groups according to their date of birth; 51 (even dates) to the control and 49 (odd dates) to the treated group.

On first attendance the M.R.C. Short Questionnaire on Respiratory Symptoms (1960) was completed. Peak expiratory flow rate (P.E.F.R.) was measured with the Wright flowmeter (Wright and McKerrow, 1959). Five readings were recorded and the mean of the last three was calculated. Forced vital capacity (F.V.C.) and forced expiratory volume in one second (F.E.V.₁) were measured with a McKesson Vitalor dry spirometer (McKerrow and Edwards, 1961). Three readings were made and the mean of the last two was calculated.

The patients attended again six weeks and three months later. On both these occasions a different questionnaire was completed which made detailed inquiry into change of symptoms, especially cough, sputum, and dyspnoea. P.E.F.R., F.E.V.₁, and F.V.C. were recorded on each attendance.

The patients in the treated group were given a course of breathing exercises according to accepted principles (Reed, 1952; M. E. Miller, 1953; Storey, 1958; W. F. Miller, 1958). The same physiotherapist, who was experienced in these methods, instructed all the treated patients. They were required to attend for a minimum of six weekly lessons, and requested to practise at home.

The survey was completed between August 1963 and April 1964. The random method of selection ensured that both groups were exposed to similar climatic conditions.

Student's t-test for testing differences between mean values has been used. Results were regarded as significant only if $P < 0.05$.

Comparison of Control and Treated Groups

During the course of trial three patients developed lung abscess, carcinoma of the bronchus, and active pulmonary tuberculosis respectively. These, together with 10 treated subjects who defaulted from the trial before receiving the full

course of instruction, and 10 subjects (four control, six treated) who failed to attend for the second and/or third interview, were excluded from the trial. There remained a control group of 44 subjects and a treated group of 33.

The mean age, sex distribution, weight, sitting height, initial P.E.F.R., F.E.V.₁, and F.V.C. of these two groups were compared and the differences were not significant. Symptoms of cough and dyspnoea, and smoking habits, were graded, the M.R.C. questionnaire being used. Grades were similarly distributed in the two groups. There was radiological evidence of emphysema in 50% of the control group and in 58% of the treated.

Drug therapy of these patients continued as clinically indicated during the trial. The number of those receiving antibiotics, bronchodilators, or both, was similar in each group. No patient received bronchodilators on the days of interview.

During the course of observation 18 (40%) of the control group had a chest cold (defined as increased cough and phlegm for three weeks or more), compared with 19 (58%) of the treated group.

Seven patients in the control group and three treated patients cut down their smoking by one grade, as defined in the M.R.C. questionnaire.

Results

The mean values of P.E.F.R., F.E.V.₁, and F.V.C. for each attendance are shown in Table I. The t-test showed no significant difference between successive measurements in either group. The mean values for the treated group are consistently lower than the control values, but the difference was not significant at the 5% level.

TABLE I

Attendance	Control		Treated	
	Mean	S.D.	Mean	S.D.
P.E.F.R. { 1 .. 212 133			173 94	
(l./min.) { 2 .. 207 132			167 83	
{ 3 .. 208 131			173 89	
F.E.V. ₁ { 1 .. 1,336 727			1,235 562	
(ml.) { 2 .. 1,371 961			1,245 534	
{ 3 .. 1,339 735			1,181 511	
F.V.C. { 1 .. 2,181 898			2,111 865	
(ml.) { 2 .. 2,241 954			2,158 694	
{ 3 .. 2,203 884			2,112 868	

The symptomatic changes over each six-week period between interviews are recorded in Table II. It can be seen that a higher proportion of treated patients claimed that their shortness of breath had improved, but that the reverse was true for cough and sputum.

TABLE II

Symptom	Period of Observation	Improved (%)		Worse (%)		Same (%)	
		Control	Treated	Control	Treated	Control	Treated
Cough	First	30	27	36	45	34	28
	Second	30	30	30	30	40	40
Sputum	First	36	27	25	39	39	34
	Second	30	21	25	24	45	55
Dyspnoea	First	25	36	32	24	43	40
	Second	18	30	39	30	43	40

The records of those patients who had improved over the course of the three months' observation, either symptomatically or on the basis of lung-function tests, were further examined. An improvement of 20% in two out of the three measured variables (P.E.F.R., F.E.V.₁, F.V.C.) was arbitrarily selected as a significant index of improved function. Ten patients (23%) in the control group and eight (24%) treated subjects showed such improvement over one or both periods of

observation. Nine control subjects (20%) and 14 (42%) of those treated claimed that they were less short of breath at the end of the three months. Comparison of mean F.E.F.R., F.E.V.₁, and F.V.C. of the two groups who improved symptomatically did not show significant change over the period of observation.

Finally, comparison of the groups of "improved" subjects with the entire treated or control groups from which they were selected again showed no significant difference in mean P.E.F.R., F.E.V.₁, or F.V.C.

Discussion

These patients received short courses of breathing exercises (between six and nine lessons in all), and conclusions drawn from this survey apply only to courses of similar scope. We chose a course of this length because it represented common practice at this and probably other hospitals. W. F. Miller (1954) claimed improvement in various lung-function tests after breathing exercises, but his patients were mostly brought into hospital for three months and instructed two to four times a day. It would be impossible to treat in this way every patient with chronic bronchitis and/or emphysema who complained of dyspnoea. Indeed, to prescribe a short course of breathing exercises to every such patient presenting at this hospital would probably overwhelm existing physiotherapeutic facilities.

Neither control nor treated group showed improvement in mean P.E.F.R., F.E.V.₁, or F.V.C.; and there was a similar proportion of individuals who did show such improvement in each group. It has been reasonably argued that P.E.F.R., F.E.V.₁, and F.V.C., measurements involving maximum effort, would not necessarily detect improvement achieved by breathing exercises, which seek to inculcate an even, controlled rhythm of respiration, with emphasis on prolonged rather than forced expiration. However, more sophisticated measurements of gas exchange and work of breathing have not, in general, shown any improvement (Becklake *et al.*, 1954; Campbell and Friend, 1955; Sinclair, 1955; McKinley *et al.*, 1961).

Of the treated group 40% claimed that they were less short of breath at the end of the three months' observation, compared with only 20% of the control group. It is recognized, however, that, even if the placebo effect is discounted, many patients who have been enthusiastically and kindly treated at frequent intervals by any method are reluctant to disappoint their doctor by saying that they are no better or are worse (Livingstone *et al.*, 1958). A more careful examination of symptomatic changes (Table II) showed that the treated group fared less well when cough and sputum are considered. Six patients in the treated group who claimed improved breathing said that at the same time their cough was worse and their sputum had increased in volume. We regard such a combination of symptoms as unlikely: it may well represent the effect of gratitude discussed above. Certainly there was only one patient with such a combination of symptoms in the control group.

The course of breathing exercises prescribed was short; yet it exposed bronchitics on occasion to weather which they would have been wise to avoid, and in a few cases it involved some financial loss to the patient. The inconvenience is perhaps reflected in the high rate of default (20%) in the treated patients. Even if the benefit of breathing exercises were accepted, we strongly feel that it would rarely outweigh the disadvantages of frequent attendance as an out-patient.

Summary

A controlled trial of breathing exercises in 100 patients with chronic bronchitis and/or emphysema is reported.

There was no objective evidence of improvement in the treated or control group as a whole when simple tests of lung function were used. The proportion of individuals showing such improvement was the same in both groups.

Although a higher proportion of patients in the treated group claimed relief from their dyspnoea, a more careful examination of their symptoms suggests that they were moved by gratitude rather than fact.

We think it highly unlikely that the short course of breathing exercises used in this trial is of benefit.

We should like to thank Mrs. K. A. Conyers, M.C.S.P., for her skilled and enthusiastic help. We are indebted to Dr. H. J. Anderson and Dr. D. S. Cadman for permission to study patients under their care; to Professor W. I. Cranston for criticism of the manuscript; and especially to Dr. W. W. Holland for his advice throughout.

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Glycodiazine in Diabetes Mellitus: a Clinical Trial

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Glycodiazine is the first of the sulphonamidopyrimidines, a new group of orally effective hypoglycaemic drugs, to undergo clinical trial for the treatment of diabetes mellitus. This compound, 2-benzenesulphonamido-5(β-methoxy-ethoxy)-pyrimidine, was selected from a large number of related substances synthesized by Gutsche *et al.* (1964) because it showed potent hypoglycaemic activity in animal experiments. Structurally it somewhat resembles tolbutamide (see Formulae), the chief difference being the incorporation of a pyrimidine ring in place of the urea group. Glycodiazine is also similar to the sulphonylureas in that its blood-sugar-lowering effect depends upon the presence of functioning beta-cell pancreatic islet tissue (Kramer *et al.*, 1964).

Structural formulae of glycodiazine and tolbutamide.

Glycodiazine has now been under clinical trial in Germany and Austria for over three years, and the reports of its use (Leubner, 1964; Robbers *et al.*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964) have been sufficiently encouraging to justify more widespread trial. This paper presents the results of

treatment with glycodiazine of a small number of carefully observed diabetic patients for periods of up to 14 months.

Patients

Diabetic clinic patients were admitted to the trial during a period of one year. They were chosen if oral hypoglycaemic therapy was indicated, unless they were already satisfactorily controlled on another preparation. Thirteen were newly diagnosed diabetics, 10 had had diabetes for periods ranging from 8 months to 14 years, but control on diet alone or other oral hypoglycaemic agents was unsatisfactory, and two were satisfactorily controlled on insulin. One of these last two patients was taking only 12 units of insulin zinc suspension daily, and although the other was taking 44 units of insulin she had previously been well controlled on tolbutamide. Of the 25 patients 13 were men and 12 women. Their ages ranged from 34 to 74 years; one was under 40, six were 40 to 49, five were 50 to 59, and 13 were 60 and over. Only two patients were more than 10% above standard weight for height, sex, and age (Australian Institute of Anatomy, 1957).

At least four weeks before entering the trial all patients were prescribed a diabetic diet with specific daily allowance of carbohydrate. Glycodiazine treatment was initiated with a dose of 0.5 g. daily taken before breakfast, or 0.5 g. twice daily taken before breakfast and before the evening meal. When necessary the dose was increased to 0.5 g. thrice daily by adding a tablet before the mid-day meal. After three to six months' treatment with glycodiazine the patients were changed to a placebo preparation for at least four weeks. At a different time they were given tolbutamide for a month, the dosage of the latter being the same as the maintenance dose of glycodiazine for that patient.

The patients attended the clinic weekly for the first month, fortnightly for the second month, and thereafter every four weeks. At each visit to the clinic blood was taken from the fasting patients for determination of glucose (Hagedorn and

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