It is suggested that atherosclerosis may be the primary cause of change in the subclavian artery previously ascribed to external pressure.

The importance of aortography to demonstrate the branches of the aortic arch in the thoracic outlet syndrome is emphasized.

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SEQUENTIAL METHODS APPLIED TO THE STUDY OF PROCHLORPERAZINE

BY

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The ability of the pharmaceutical chemists to synthesize compounds of potential therapeutic value in psychiatry is not matched by a corresponding ingenuity in the methods for their clinical evaluation. Consequently the psychiatrist is often baffled by an array of drugs of uncertain therapeutic value and is inclined to criticize the chemist rather than himself for this state of affairs. A need has therefore arisen to develop methods of clinical trial which are rapid and which use simple but reliable criteria of therapeutic effect. Once an overall effect has been established more detailed inquiries can follow. These observations apply particularly to the so-called "tranquillizers"—that is to say, drugs which allay states of over-excitement, such as anxiety and its somatic manifestations, without decreasing alertness and awareness.

Purposes and Design of the Trial

We therefore had two complementary purposes in undertaking a clinical trial of a new tranquillizer. The first was to see if the statistical method of sequential analysis (Armitage, 1954) could be successfully used in a psychiatric drug trial of this kind; if so, the advantages of simplicity in design and of economy in time and numbers of patients treated might be considerable. Our second aim was an attempt to find out whether a new

phenothiazine derivative, prochlorperazine ("stemetil"), was as effective in reducing tension and anxiety in psychoneurotic out-patients as some published studies have claimed.

Prochlorperazine is 1-[3-(2-chloro-10-phenothiazinyl)-propyl]-4-methylpiperazine. It is a member of the phenothiazine series of drugs and its effects are similar to those of chlorpromazine. It is prepared for clinical use in two forms, the dimaleate and the dimethane sulphonate. In dosage of less than 40 mg. of the maleate a day side-effects are not troublesome. Jaundice and blood dyscrasias have not so far been reported.

The drug is probably of most use in the management of schizophrenia, but striking claims have been reported for it in the neuroses. Wennersten (1956) quotes unpublished data on 1,429 patients with various neurotic illnesses in whom the response to prochlorperazine was excellent or good in 73%. Vischer (1957) gave the drug to 38 patients with various organic and psychiatric illnesses and claimed that 21 became completely free of psychoneurotic symptoms. Lesse (1957) claims effective relief of 20 out of 37 patients with moderate anxiety, but observed the drug to be less effective with marked anxiety. McAfoos (1957) found all his 37 patients with anxiety reactions helped by prochlorperazine and psychotherapy. Stevenson (1957), in a study of 100 patients of widely different diagnostic categories, claims good relief of anxiety in 83%. Most authors recommend a dose of 15–20 mg. a day and claim that the response is prompt, either within days or one or two weeks. These trials can be criticized on the grounds that they were uncontrolled, the diagnostic categories were ill-defined or ill-assorted, and the criteria of improvement were unclear.

The statistical method, sequential analysis, determined the design of the present trial. A control treatment (placebo) and the new treatment (prochlorperazine) were both given to each suitable patient as he became available. The patient had to decide which of the two treatments he preferred. The sequential plan used had to meet the following requirements. The proportion of response to the placebo was expected to be at least 35% (Beecher, 1956); but if we were able to detect, with a probability of 0.95, a favourable response to prochlorperazine in 70% of patients, this would be considered a sufficient advantage to justify recommending it. The proportion of preferences in favour of prochlorperazine would depend to some extent on the distribution of assessments on the five-point score described below and on the correlation between the two responses from the same subject, but rough calculations suggest that it would be in the region of 0.8. This is the value of θ (the proportion of untied pairs favouring prochlorperazine) which would be obtained if preferences were based purely on favourable responses (rather than the five-point score) and if there were no correlation between the two responses from a subject (cf. Fig. 2 of Armitage, 1954; Snell and Armitage, 1957).

The trial was to be decided on the outcome of this test. As a further exploration of the application of sequential analysis we attempted to use a measurement of anxiety (the clinical symptom which prochlorperazine was most likely to benefit) as the criterion of the effectiveness of the treatments. The appropriate method in such a case is a sequential t-test. The plan chosen to test the null hypothesis that there is no change in the patients' anxiety scores with prochlorperazine at a significance level of 0.05 is described below.

Selection of Patients.—All new psychoneurotic out-patients whose principal complaints were in the opinion of the psychiatrists due to anxiety or tension were considered for the trial. These patients were then given an anxiety questionnaire on which they had to score 10 or more points in order to enter the trial. The questionnaire contained 30 items, each of which could score one point. The items were selected from previous investigations of the incidence of subjective and somatic symptoms in anxious psychoneurotics (Cameron, 1944; Eysenck, 1953; Sainsbury and Gibson, 1954). Each item was worded so that it clearly referred to the patient's state during the previous few days.

Administration of Tablets.—Two 5-mg. tablets of prochlorperazine were taken thrice daily for one week and two identical placebo tablets were taken thrice daily during the other week. The order in which the treatments were taken was randomized and was unknown to the doctor prescribing them. As each patient qualified for admission to the trial he was given the next two serially numbered envelopes marked "1st week" and "2nd week," one containing 42 5-mg. tablets of prochlorperazine and the other 42 placebo tablets. The following explanation was given by the doctor: "I want your help in finding which of these two medicines is best for you during the next two weeks, so please follow the instructions exactly so that you can come and tell me whether you prefer those which you took during the first or during the second week when you keep your appointment on . . ." Printed instructions and two questionnaires were also stapled to the envelopes issued to the patient.

Assessment of Clinical Effect

The criterion of the tablets' effectiveness was simply whether the patient felt better while taking the first or the second week's treatment. His preference was decided by the answer he gave to the following printed question at the end of each week: "Since you began taking the pills, have you been feeling 'much better,' 'better,' 'no change,' 'worse,' 'much worse'?"

A requirement of the sequential method is that the decision on the success or failure of the treatments must be made on a single criterion, which in this trial was the preference recorded after one week's treatment on each kind of tablet. This limitation was not unfitting, as a simple design was one of our aims, and the patient's preference is an appropriate criterion for a tranquillizer intended for out-patients in whom a subjective impression of improvement is the effect most sought.

A more objective measure of clinical effect was attempted, however. As previously stated, in order to enter the trial the patient had to score 10 or more on an anxiety questionnaire. The patient was asked to complete the same questionnaire at the end of the first and again at the end of the second week, and the difference between his anxiety score with prochlorperazine and placebo was recorded (see Table) as it became known.

Statistical Assessment

A feature of the sequential method is that the results are plotted on a graph as they become known (Fig. 1). If, for example, prochlorperazine is preferred by the patient, this is marked as one step in a north-east direction, but if the placebo is preferred it is marked one step in a south-east direction; should the result be a "tie"—that is, they are equally preferred or neither

Anxiety Scores With Prochlorperazine and Placebo, and Data for Plotting Path of Sequential *t*-Test

(1) Patients (n)	(3) Anxiety Scores of Patients		(4) Difference (d) Prochlor- perazine Minus Placebo	(5) Sd	(6) Sd ²	(7) $z = \frac{(Sd)^2}{Sd^2}$
	Prochlor- perazine	Placebo				
1	19	22	-3	-3	9	1.00
2	11	18	-7	-10	58	1.72
3	14	17	-3	-13	67	2.52
4	17	19	-2	-15	71	3.17
5	23	22	+1	-14	72	2.72
6	11	12	-1	-15	73	3.08
7	15	14	+1	-14	74	2.65
8	19	11	+8	-6	138	0.26
9	11	19	-8	-14	202	0.97
10	8	7	+1	-13	203	0.83
11	21	22	-1	-14	204	0.96
12	18	16	+2	-12	208	0.69
13	19	16	+3	-9	217	0.37
14	18	20	-2	-11	221	0.55
15	19	19	0	-11	221	0.55

is preferred—the graph is not marked. The results are plotted in this manner until the path on the graph reaches one of its boundaries; the upper one indicating a decision in favour of the new treatment, the lower in favour of the placebo; while the middle boundaries indicate that there is no important difference between the two. How these boundaries are drawn will depend upon three specifications. The investigator must first decide on the chance he is prepared to take of recommending the new treatment when, in fact, it is no better than the old (or placebo in this case). We specified the customary 5% level. Similarly he should also state the risk he will take of failing to recommend the new treatment when it really is an advantage. The other specification is the value of θ , the proportion of preferences in favour of prochlorperazine which would be considered a definite medical gain and which, therefore, should not be missed. As explained above, we set this at 0.8. Having chosen these critical values, a table was consulted which gives figures for the equations of the lines A, B, C, and D in Fig. 1 (Armitage, 1954, p. 263).

FIG. 1.—Path of the results and the boundaries (A, B, C, D) for a sequential test to detect the difference between two proportions at the 5% level if the preference for placebo is 35% and prochlorperazine 70%.

The significance of the differences between the anxiety scores of the patients on the two treatments was examined by a sequential t-test. This test "... can be regarded as one in which the value of Student's 't' is calculated at each stage and plotted against n, the number of pairs. . . . The trial is continued until the sample path formed by joining the successive values of t crosses one of the three boundaries indicating either a significant difference in favour of one or other of the treatments or a non-significant difference" (Armitage, 1954). Instead of t, z is calculated at each stage ($z = (Sd)/Sd^2$, where d, in this trial, is the difference between a patient's anxiety score with prochlorperazine and with placebo; Sd is the sum of these differences for all patients so far observed; and Sd^2 is the sum of the square of the differences). With this method the first rule is to make an estimate of δ , the difference between the effects of the two treatments which one would wish to detect ($\delta = \text{mean difference/s.d. of differences}$). As we had not the data to do this we referred to Table III in Armitage's paper (1954, p. 267), which gives the critical value of δ that can be detected, with a P of 0.95, if a fixed-sample-size t-test on the mean of 20 differences were used.

This value of δ determined the boundaries of the plan shown in Fig. 2.

FIG. 2.—Path of the results and the boundaries for the sequential t-test (z is derived from t).

Findings

The patients were all initially diagnosed as suffering from psychoneurotic reactions, with anxiety as the principal symptom. In most of them the somatic manifestations of anxiety were also prominent. There were no notable differences in clinical symptoms between those who preferred prochlorperazine and those who preferred placebo. Their mean ages were 33.0 years and 37.6 years respectively, and their mean duration of illness was 36.4 months and 33.5 months. There was no association between the patient's preferences and the order in which the two treatments were given.

Each patient's preference for prochlorperazine or placebo was made known to us as soon as it was obtained by the doctor. The preferences were then plotted on the diagram shown in Fig. 1. The horizontal axis (x) records the number of patients who expressed a preference, and the vertical axis (y) the number of patients who preferred prochlorperazine minus the number who preferred the placebo.

The middle boundary of the graph was crossed after 14 patients had expressed a preference. At this point the trial was finished. The decision reached, therefore, was that there was no important difference between the two treatments; in fact, the two treatments were equally effective (each was preferred seven times). We have therefore no evidence that out-patients whose predominant complaint is anxiety fare any better when treated with 30 mg. of prochlorperazine daily than with dummy tablets.

The trial was decided by the 14 patients who were able to say which treatment they preferred; six were unable to make a choice between the drugs because neither had any effect. A total of 20 patients therefore entered the trial.

The details and results of the sequential t-test are given in the Table and Fig. 2. The columns in the table are: (1) the patients in serial order; (2) and (3) their anxiety scores with prochlorperazine and with placebo; (4) the differences, d, between these scores; (5) the cumulative total of the differences, Sd; (6) the squares of the previous column; and (7) the z scores. In Fig. 2 the z scores are plotted against the number of patients.

It was found that the lower boundary, which indicated no significant difference between the effects of the treatments on anxiety scores, was crossed when n was 13. Two further patients were added to confirm that the path was continued. This finding is consistent with that obtained when the patient's preference was the criterion of therapeutic effectiveness.

Discussion

Before considering whether the methods used in this trial fulfil our purpose, which is to describe a rapid and reliable method of clinical assay of new tranquillizers, the conclusions reached on the therapeutic value of prochlorperazine is examined.

The finding that prochlorperazine had no appreciably better therapeutic effect than a placebo is valid only for patients in whom anxiety is the predominant symptom; nevertheless it is with this group of out-patients that a tranquillizer is most likely to be successful. The patients received seven daily doses of 30 mg. Though this dose is higher than in most investigations it is still possible that a larger dose might have been more effective. Troublesome side-effects were not encountered. It might also be objected that the optimal effect would not be obtained in one week. A short period of treatment was chosen because previous studies had claimed an effect within a week, but also because the patient had to express a preference. To enable him to do this the duration of treatment had to be brief enough to allow him to make a comparison. Lastly, it is possible, had we stipulated a lower proportion of preferences for prochlorperazine as representing a real advance in therapy, we would then have detected an advantage for it. The previous studies claimed 70% or higher successes with prochlorperazine. As we expected a similar proportion of successes it was economic to choose this figure to represent a real gain in therapy.

More relevant to the question of the value of sequential analysis is the confidence with which the conclusion can be accepted. The probability of reaching the middle boundary when the two treatments are equally effective is 0.95. So the risk of concluding that there is no important difference when, in fact, one of the treatments is superior (by the specified proportion)

is 5%. An advantage of this method is that the risk of making errors of this kind is stated (Bross, 1952).

In both of the methods described the number of patients needed to decide the outcome was less than would be needed, on the average, with the equivalent fixed-sample-size test. This economy in cases is a valuable feature of sequential methods. The small numbers were also determined by the comparatively high proportion of preferences required for the new drug before we were willing to recommend it.

Because the procedure is so simple both methods are well suited to the trial of new drugs in a busy out-patient clinic or admission ward. Suitable patients are observed as they occur in the course of the daily work; the data are analysed without any computation or only one computation with the sequential t-test; and the psychiatrist is only required to assess carefully one crucial clinical characteristic of each patient. The last consideration, however, also imposes a restriction which may limit their application: improvement in the mental state of psychiatric patients must often be assessed on a number of aspects of behaviour. It should be possible to overcome this difficulty by setting up sequential tests for two or three essential clinical features to run concurrently. In our trial, for example, we might have begun by proposing that it would be decided in favour of prochlorperazine only if and when the path in both the sequential test of the patients' preferences and the sequential t-test of the measure of their anxiety crossed the upper boundary, and the decision "no important difference" be made only when the middle and lower boundaries are crossed. Should the upper boundary be crossed on one characteristic and another boundary on the other the result would be inconclusive concerning which treatment is therapeutically superior; but the information obtained would presumably still be a valuable guide to that aspect of behaviour on which the drug's activity is effective.

Conclusions and Summary

In psychiatry there is a need for rapid and reliable methods for the clinical assay of the many new compounds of potential therapeutic value now being manufactured. The method of sequential analysis was considered for this purpose. A trial was therefore undertaken to compare the effectiveness of a new tranquillizer, prochlorperazine, and a placebo in the treatment of anxious psychoneurotics.

After each patient had received each treatment for a week he stated which was preferred. No important difference at the 5% level of significance was found between the treatments when 20 patients had entered the trial.

Each patient also completed an anxiety questionnaire at the end of each week. A sequential t-test was undertaken and no significant difference was found between the decrease in anxiety scores with each treatment after 13 patients had entered.

It is concluded that in certain circumstances sequential methods are well suited to the early evaluation of new psychiatric drugs. They are easier to administer, more economical, and give a more precise decision than conventional tests.

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AN APPRAISAL OF PHENYLBUTAZONE SUPPOSITORIES

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The patient with both rheumatoid arthritis and a peptic ulcer presents a difficult therapeutic problem. Drug therapy for the joint condition, whether with salicylates, phenylbutazone ("butazolidin") and its analogues, or adrenocorticosteroids, may have harmful effects upon the upper gastro-intestinal tract. Aspirin in high or low dosage can cause gastric irritation and probably bleeding (Douthwaite and Lintott, 1938; Muir and Cossar, 1955). Corticosteroids may produce peptic ulcers (Sandweiss, 1954). Similarly, a risk of phenylbutazone is peptic ulceration (Raffensperger, 1953), which can be fatal from perforation (Shield *et al.*, 1953; Beutler and Bergenstal, 1954) or from haemorrhage (Stephens *et al.*, 1952; Benstead, 1953). Phenylbutazone has other complications, such as depression of the bone-marrow and agranulocytosis (Dilling, 1953; Leonard, 1953), skin rashes (Cudkowicz and Jacobs, 1953), stomatitis (Freeland *et al.*, 1953); visceral lesions (MacCarthy and Jackson, 1955), and water retention (Wilkinson and Brown, 1953), which may precipitate cardiac failure in the elderly. However, the toxicity of any drug must be weighed against the benefits conferred by it, and we believe that its use is justified in carefully selected cases of the painful and crippling rheumatic disorders. The avoidance of gastric irritation has been a particular interest, and we report a small clinical trial where phenylbutazone has been given as a suppository rather than as a tablet or by injection.

Material and Methods

There were 26 patients. Nineteen suffered from rheumatoid arthritis; 11 of these also had a duodenal ulcer, two a gastric ulcer, two a hiatus hernia, two had a dyspepsia of unknown origin which made oral therapy impossible, and two developed a dyspepsia on phenylbutazone tablets. Two patients had ankylosing