is also important in studying such variables as serum-uric-acid and serum-cholesterol levels, and it is because this has been impossible that the results obtained have not been submitted to statistical analysis. This report has aimed at attracting attention to the occurrence of hyperuricæmia among relations of patients with xanthomatosis, and to some of the genetic and clinical similarities between gout and xanthomatosis.

Summary

Serum-uric-acid levels in patients with xanthomatosis and members of their families are reported.

Abnormally high values were found among those with essential hypercholesterolæmia, the highest values being recorded in patients with xanthomatosis.

There are clinical and genetic similarities between gout and xanthomatosis.

There does not appear to be an obvious explanation for the association of these metabolic abnormalities.

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CLINICAL COMPARISON OF DIAMORPHINE AND PHOLCODINE AS COUGH SUPPRESSANTS

BY A NEW METHOD OF SEQUENTIAL ANALYSIS

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IN view of recent controversy over the value of heroin in the relief of symptoms it seemed desirable to test one action of the drug in man by a controlled clinical trial.

Heroin has gained the reputation of being the most powerful drug in the suppression of cough and, since this action seemed to be more susceptible to measurement than the relief of pain, the trial was designed to study this effect. The trial compared the effect on cough of three preparations—linctuses of diamorphine (heroin), pholcodine, and a placebo. The original intention was to use the ranking method described by Rushbrooke et al. (1956). Difficulties arose with the method, and it was decided instead to compare the treatments in pairs by a new method of sequential analysis, the theory of which has been described by Armitage (1957).

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Materials and Methods

The patients all had cough of several months' duration. 2 patients were uncooperative and had to be excluded from the trial, and there remained 45 patients. No attempt was made to assess the degree of cough, but its severity in all cases was such as to lead the patients to ask for relief and, in some, to keep them awake for several hours during the night. There were 14 outpatients who all had chronic bronchitis, and 31 inpatients with the following conditions: chronic bronchitis 17, pulmonary new growth 6, bronchiectasis 3, mitral stenosis 3, and chronic pulmonary tuberculosis 2. Most of the inpatients with chronic bronchitis were convalescing from additional illness—e.g., acute respiratory infection, spontaneous pneumothorax, and congestive cardiac failure—but by the time of study their cough had recovered to its usual state.

The linctus of diamorphine was prepared according to the *British Pharmaceutical Codex 1954* and contained diamorphine gr. $^1/_{20}$ in each 60 minims, with oxymel, glycerin, and syrup. The placebo was an identical mixture except that diamorphine was omitted. The pholcodine linctus ('Lipect,' John Wyeth) contained in each dose:

Antazoline hydrochloride	12·50 mg.
Pholcodine	4·00 mg.
Ext. ipecac. liq.	0·03 ml.
Sucrose	3·20 g.

Each mixture was taken, for two days, in a dose of minims 120 at night before the patient went to sleep, the whole course lasting six days. The use of linctus at night rather than during the day would probably make it easier for the patients to assess the severity of their cough. An expectorant linctus was given to some in the day, but apart from this no drugs were given which might have suppressed cough.

In advance the hospital dispensary had arranged for the patients to receive the three drugs in such a way that the six possible orders were distributed randomly among each succeeding group of six patients. The patients were numbered consecutively, and the mixtures were prepared in three bottles labelled with the patient's number and a number showing the order of administration—i.e., 1st, 2nd, and 3rd. No other means of identification appeared on the bottles, and the patients, nurses, and observer were unaware of their contents. When the mixtures were required the patient's number was shown on the prescription sheet and the appropriate series of bottles was delivered by the dispensary.

The patients were told that they were receiving three types of medicine and that we wished to find out which relieved their cough best. They were asked to note the severity of their cough from the time of taking the medicine until going to sleep, so that later they would be able to rank the three treatments in order of preference. After the six-day trial period their preferences were recorded, as bottle numbers; and, after each batch of six patients had been treated, the bottle numbers were interpreted as names of the corresponding linctus mixtures by reference to the dispensary list.

Early in the trial it became clear that the patients were rarely able to give a clear set of preferences, because they usually gave a tie for first or last place, or even for all three mixtures (table 1). For this reason the statistical treatment for ranking methods used by Rushbrooke et al. (1956) would have had to be modified. We decided at this stage to compare the treatments in pairs, using for any one pair of treatments only those patients who gave a clear preference in favour of one or the other. We decided, in addition, to use a new type of sequential analysis, called a "restricted sequential procedure," the theory of which has been described by Armitage (1957). Since this method has not been used previously in clinical trials, its main features are described here.

TABLE I—FREQUENCIES OF VARIOUS ORDERS OF PREFERENCE

Preference			No. of patients
1st	2nd	3rd	
L, P, H	..	..	12
L	P, H	..	11
L	H	P	4
H, L	P	..	5
H	L, P	..	5
H	P	L	2
H	L	P	2
P	L	H	2
P	H	L	1
P	L, H	..	1

H, heroin. L, lipect. P, placebo.

Sequential Analysis of Results

In sequential methods of statistical analysis observations are examined continuously as they become available, and the decision whether to stop at any stage or to make further observations depends on the results so far obtained. Various sequential methods for use in clinical trials have been described by Armitage (1954). These methods had the useful feature that, for comparisons of two treatments, a trial could be ended relatively quickly if the treatments differed very considerably in efficacy, or if their effects were very similar. They had, however, the disadvantage that in intermediate situations the trial could last a very long time because there was no definite upper limit to the number of observations.

Bross (1952) has given two sequential plans for medical trials, in which the number of observations is restricted to be less than some definite upper limit, and one of his plans has been used in a clinical trial by Newton and Tanner (1956). The " restricted sequential procedures " of Armitage (1957) are similar to those of Bross but provide a wider variety of plans suitable for different circumstances.

The results are plotted on a chart (see figure):

Each of the three comparisons between pairs of treatments gives rise to a zigzag path starting at the origin (the point where the horizontal and vertical axes intersect). For each patient giving a preference in favour of one of the two treatments the path is continued one step in a " north-easterly " direction; for each patient giving the opposite preference the path moves one unit in a " south-easterly " direction. The area in which the paths develop is enclosed by three boundaries, shown by heavy lines in the accompanying figure. These are chosen in such a way that, if two treatments are in fact equivalent (so that, in the long run, 50% of the patients' preferences will be in favour of one and 50% in favour of the other), there is a probability of about 0·95 that the zigzag path will end on the middle (V-shaped) boundary, and only 0·05 that it will reach one of the outer boundaries (the two divergent straight lines). In this sense we may say that a path ending on one of the outer boundaries indicates a difference between the treatments which is significant at the 5% level. The probabilities stated above are only approximately correct, and exact calculations for the boundaries used here give values of 0·960 and 0·040.

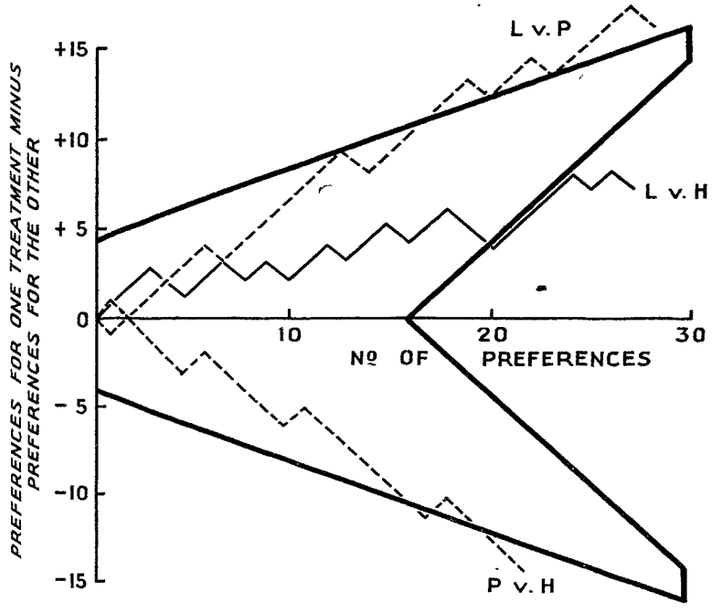

Chart for sequential analysis of results: H, heroin; L, lipect; P, placebo. In each comparison the path is continued one unit " north-east " for a preference for the first-named treatment, and one unit " south-east " for a preference for the second-named treatment.

Apart from the choice of the significance level to which the outer boundaries correspond, one is at liberty to choose the maximum of comparisons needed for any pair of treatments. During the first few weeks of the present trial we were able to assess the rate at which patients became available for treatment and to make a rough estimate of the proportion of patients giving clear preferences. The maximal duration of the trial was determined by other commitments, and we estimated that during this maximal period about 30–35 preferences would be obtained for each pair of treatments. Accordingly a restricted sequential procedure, for which the maximum of preferences was 30, was chosen by reference to table v of Armitage (1957), which gives the equations to the boundaries shown in the accompanying figure. According to this table, if one treatment is such an improvement on another that 85% of preferences are in its favour, in a long run of patients, the zigzag path will hit the appropriate outer boundary about 95 times out of 100. Exact calculations confirm that the exact probability of doing this is 0·953 compared with the nominal figure of 0·95.

TABLE II—FREQUENCIES OF CLEAR PREFERENCES BETWEEN EACH PAIR OF TREATMENTS ACCORDING TO ORDER OF ADMINISTRATION

Order of administration	Preference for	
	Lipect	Placebo
Lipect before placebo	11	4
Placebo before lipect	11	2
Total ..	22	6
	Lipect	Heroin
Lipect before heroin	11	2
Heroin before lipect	6	8
Total ..	17	10

(χ^2 with continuity correction = 3·41; P = 0·07)

	Placebo	Heroin
Placebo before heroin	2	10
Heroin before placebo	2	8
Total ..	4	18

The frequencies with which the treatments were placed in various orders of preference are shown in table I, and the sequential paths for each pair of treatments are drawn in the figure. The two paths obtained by comparing the two drugs with the placebo both crossed the outer boundaries at the 17th preference, which means that both these comparisons are significant at the 5% level. We can attach a rather more precise probability to these results by calculating the probability of reaching, by chance, the observed point on the boundary, or one indicating a more extreme contrast between the two treatments—i.e., one further to the left on either outer boundary—if in the long run the two treatments were preferred equally frequently. This probability is 0·033 for each comparison of a drug with the placebo.

The path obtained by comparing lipect and heroin reached the middle boundary at the 20th preference. Again we can calculate the probability of reaching the observed boundary point, or one indicating a sharper contrast between the drugs. This probability is 0·36, showing that the slight excess of preferences in favour of lipect could easily be due to chance.

If lipect and heroin had both been shown to be better than the placebo at a much earlier stage in the trial, it was intended to omit the placebo so as to concentrate on the comparison of the two drugs. As it happened, all three paths approached the boundaries at about the same time. A few extra cases were treated after the boundaries had been crossed, and it is clear from the figure that the general trend was confirmed by these additional results.

A point of some interest is whether a patient's preference between two treatments depended on the order in which they were given. The clear preferences between each pair of treatments are tabulated in table II according to the order in which the treatments were given. There is clearly no evidence that order of administration had any effect on the comparison of either drug with the placebo, but there is a suggestion that, for the (presumably harder) choice between lipect and heroin, patients tended to prefer the treatment given first.

Discussion

Where it is impossible to make objective measurements of a patient's progress the value of any drug is difficult to assess; but the likely response of patients to drugs will be gauged more reliably by a controlled comparison of the drugs with a placebo than by either experiments on animals or uncontrolled clinical impressions. One objection to this type of trial is that the patients may prefer a drug for reasons other than the pharmacological action under test; diamorphine has hypnotic, analgesic, and euphoric properties in addition to relieving cough. Possibly diamorphine was preferred to the placebo because of its other properties, but this is unlikely because it was, if anything, less popular than the pholcodine linctus.

Another limitation to this, as to any other, type of trial is that the results strictly apply only to the conditions of the trial. Thus, it may be said that a *B.P.C.* linctus of diamorphine given in the largest recommended dose is not evidently superior to a pholcodine compound (lipect) when one dose is given at night to the types of patients tested. We have no evidence on the effect of other dosages and forms of administration or on the response of different types of patients.

The statistical method used in this trial offers certain advantages over previously used methods. The boundaries may be drawn on the chart as soon as a decision has been taken on the maximum of patients to be studied, and the level of significance corresponding to the outer boundaries, for which fewer than the maximum are required. From this stage, and without further statistical treatment, the results plotted on the chart provide a readily intelligible and graphic account of the trend of the results. As soon as a significant difference is observed between one pair of drugs, the trial may be stopped or modified so that attention is concentrated on the remaining comparisons.

Summary

A controlled clinical trial was undertaken to compare the relative effectiveness in relief of cough of heroin linctus *B.P.C.*, a pholcodine preparation (lipect), and a placebo in 45 patients with chronic cough. Each patient received each mixture for two days and placed them in order of preference.

A new method of sequential analysis was applied to the results and was found to have certain advantages over methods used previously.

At the 5% level of significance there was no evidence of difference between the heroin and pholcodine preparations, but both were more effective than the placebo.

We are grateful to Dr. R. D. Green for allowing us to study his patients, and to Dr. Gordon Fryers, of Messrs. John Wyeth & Brother Ltd., for supplies of lipect.

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LOCAL TREATMENT OF BURNS AND SCALDS
USING CHLORHEXIDINE

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ANTISEPTIC methods of treating burns and scalds are unfashionable, but aseptic and antibiotic methods are not free from complications nor are the results always good. In one surgical unit of the Royal Hospital for Sick Children, Glasgow, burns and scalds have been nursed in a small "burns unit" since 1937. Until 1940, the lesions were gently cleansed under sedation or light general anæsthesia and the surface coagulated with tannic-acid solutions, silver nitrate, or a mixture of antiseptic dyes. "Open methods" of treatment were then adopted and bland dressings, pressure dressings, Stannard envelopes, Bunyan bags, local sulphonamides, and local penicillin were all tried, and in the hands of the enthusiast all gave reasonably satisfactory results. During this time there were great advances in the general treatment of the burned patient, and inevitably this led to improved results in the local lesion, irrespective of the local treatment adopted. The "exposure method" of treatment was rediscovered and was used as a routine procedure for two years, at first with penicillin powder but later without any antibiotic or antiseptic. To obviate the need for cleansing the damaged surfaces in the severely burned child dibromopropamidine isethionate cream ('Brulidine') was introduced and was the most popular form of treatment for almost three years. Though it is an ideal first-aid dressing, dibromopropamidine delays healing and is unsuitable for routine use.

During 1955, chlorhexidine (bis-*p*-chlorophenyldiguanidohexane, 'Hibitane') was first used in the local treatment of burns and scalds. The early results were so satisfactory that this antiseptic solution has now supplanted all our previous forms of local treatment.

Method

The patients are nursed in three small wards, each with space for three or four cots, grouped round a central corridor which has glass walls. The nurses can consequently observe the patients without entering the wards. Masks are worn by the nurses and doctors when in the wards. No visitors are allowed. No woollen blankets, woollen clothing, or fluffy toys are allowed and no toys of any kind from the general ward are brought into the burns wards. The furniture, walls, and