affective disorders. We have found, for instance, that those patients with anxiety states or depressions most likely to respond to M.A.O.I., or to M.A.O.I. combined with chlordiazepoxide, do generally have certain characteristics in common. Early-morning waking may be present, but more often there is an inability to get to sleep, or there may even be an increased depth of sleep. Many patients also tend to get worse as the day goes on rather than better, which is very different from the constant early-morning waking and diurnal mood-swing of the true endogenous depression. Severe fatigue is a common complaint, and there is a great variation in the patient's symptoms and in his emotionality from day to day. Patients also tend to blame others rather than themselves, and premenstrual tension and irritability are very commonly found in the symptomatology of women who are going to make a good response to the M.A.O.I. drugs.

After four years' experience of a wide range of antidepressant drugs, we have found M.A.O.I. to act best in these anxiety and atypical depressive states, rather than in the more typical endogenous depressive illnesses, which generally do better with imipramine combined with electric convulsion treatment. In fact, it seems that if an anxiety state or an "atypical" depression, particularly of recent origin and occurring in a patient of good previous personality, does not respond within 10 days to one or other of the M.A.O.I. drugs and chlordiazepoxide, correctly given, both the diagnosis and the treatment should be reconsidered. Then, especially in the middle-aged, it will often be found that anxiety symptoms are masking a deep underlying depression needing additional or other treatment.

Summary

Two years ago iproniazid was reported as being valuable in the treatment of "atypical" depressions. Subsequent experience with iproniazid and the newer monoamine oxidase inhibitors (M.A.O.I.) has shown that there is no clear treatment demarcation between some atypical depressions and anxiety states; and many anxiety states have now, in fact, been found to respond equally well to treatment with the M.A.O.I., preferably combined with chlordiazepoxide hydrochloride.

To illustrate these points, the effect of these drugs on 60 out-patients with a diagnosis of atypical depression, anxiety hysteria, or anxiety neurosis is reported. They fall into three groups: 15 patients responded to M.A.O.I. alone, 28 did best with M.A.O.I. combined with chlordiazepoxide, and 17 did not respond to M.A.O.I. Chlordiazepoxide given alone to these patients was much less effective, except in the last group.

These findings are discussed, and stress is laid on the proper use of M.A.O.I. drugs to avoid undesirable side-effects and relapse. The essential factor for success with M.A.O.I. and chlordiazepoxide in the treatment of anxiety states is a good previous personality.

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PHENELZINE AND DEXAMPHETAMINE IN DEPRESSIVE ILLNESS

A COMPARATIVE TRIAL

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The basic cost to the National Health Service of a week's treatment with three common antidepressive drugs is as follows: imipramine, 50 mg. t.i.d., about 11s. 6d.; phenelzine, 15 mg. t.i.d., about 5s.; dexamphetamine sulphate, 5 mg. b.d., 1d.* Yet, so far as we can determine, there appears to be only one report in which the efficacy of one of the more expensive of these drugs has been compared with that of the cheapest by a controlled trial. Doust *et al.* (1959) compared imipramine and dexamphetamine in 24 depressed patients and found neither drug to be significantly better than a placebo.

In the present paper we report a controlled comparative trial of phenelzine, dexamphetamine sulphate, and lactose (as placebo) in the treatment of depressive illness of moderate severity. Apart from the paper by Doust *et al.* (1959), we have not found any report of a controlled trial of dexamphetamine sulphate in depression. There have been a number of controlled trials of phenelzine, but the results are conflicting: thus Rees and Davies (1961) found it of value, but Harris and Robin (1960) and Keith (1959) did not.

There is at present no means of measuring the clinical state of a depressed patient except by the subjective judgment of the clinician. This circumstance does not, of course, impugn the validity of an adequately controlled trial, but the results of such a trial might nevertheless be more convincing if it were shown that the clinical assessments were reasonably reliable—that is, that there was a consistency between the assessments of different clinicians at any one time. In the present trial we have attempted to measure the reliability of our assessments.

Method

Selection for the Trial.—The trial was restricted to patients who were diagnosed as having a primary depressive illness, who did not have symptoms associated with schizophrenia or organic brain disorder, who had not received electric convulsion therapy during the previous three months, and who had had no antidepressive drug treatment during the previous two weeks. No distinction between endogenous and reactive types of depression was attempted.

Subjects.—Forty-six patients entered the trial but three failed to complete it (one left hospital against advice,

*Basic N.H.S. prices in May, 1961, were: "tofranil" (imipramine), 25-mg. tablets, 1,000 for 275s.; "nardil" (phenelzine), 15-mg. tablets, 500 for 97s. 10d. plus 24s. 5d. purchase tax; dexamphetamine sulphate, 5-mg. tablets, 1,000 for 6s.

two became so depressed that electric convulsion therapy was given). Of the 43 subjects completing the trial, 12 were male and 31 female. The median age was 42 years (12 were under 35 years, 11 were aged 35–44, 8 were aged 45–54, and 12 were 55 or over). Thirty-nine of the subjects were attending a psychiatric day hospital, the other four being in-patients.

Drugs.—The drugs given were: phenelzine (30 mg.), dexamphetamine sulphate (5 mg.), and lactose. These were made up in identical-looking tablets and given twice a day, at 10 a.m. and 3 p.m., for five days each week (Monday to Friday); this was done so that all subjects were given the drugs while at the hospital, and it was thus reasonably certain that they actually took the tablets. Subjects received each drug for a fortnight, the trial period lasting for three consecutive fortnights. The drug order was randomized, and until each subject completed the trial his drug order was known only to the pharmacist. In the event, phenelzine was given in the first fortnight to 14 subjects, in the second to 16, and in the third to 13. The corresponding figures for lactose were 17, 15, and 11; and for dexamphetamine sulphate 12, 12, and 16 (for the last three subjects dexamphetamine was omitted, as conclusions about its efficacy had by then been reached).

Assessment and Analysis

The clinical state of a subject was assessed on entry to the trial and at the end of each of the three fortnightly periods. The intensity of seven clinical manifestations was rated, each on a five-point scale (absent, mild, moderate, marked, severe). These manifestations were: depression, retardation, agitation, anxiety, hypochondria, anorexia, and insomnia. Depression was assessed in terms of a depressed appearance of the subject, of the depressive content of his talk, and of his complaint of feeling low-spirited, lacking interest, and having difficulty in concentrating. Agitation was assessed in terms of motor overactivity and of the subject's complaint of restlessness. Anxiety was assessed in terms of the appearance of muscular tension and anxiety and of the subject's complaint of feeling tense or "on edge."

The results were analysed by the sequential method. This implies the use of comparisons between scores. Hence for each clinical manifestation the ratings made at the end of the three fortnightly periods were compared. If, for example, depression was rated as "mild" in the third fortnight where it had been "severe" in the first, then the depressed state of the patient in the third fortnight was ranked as "better than" that in the first; and the assumption was made that the clinical effect of the drug given in the third fortnight was also "better than" that given in the first. In this way the clinical effects of the drugs were compared with one another in terms of "better than," "equal to," or "worse than." The trial was continued until definite results were obtained for the comparative effect of the drugs on the clinical manifestation of depression.

One of us (E.H.H.) made ratings for all 43 subjects. For 34 subjects a second set of ratings was made simultaneously and independently by other observers. In general, the first observer saw the subjects only at the interview assessments (at which the subjects were questioned only by him), but the seven observers who in turn made the second assessments were in constant clinical contact with the subjects.

Results

Comparative Effect of Drugs

The principal results are shown in Figs. 1 to 3. The sequential charts (Armitage, 1960) are constructed so that the outer boundaries correspond with the 5% level of significance—that is, if the two treatments being compared are equally good the outer boundaries would be reached by chance only in 5% of trials; and if one treatment is better than the other to the extent that 80% of comparisons are in favour of the first and only 20% in favour of the second, then the upper boundary has a 95% chance of being reached. Only positive comparisons between two drugs—that is, "better than" or "worse than"—are scored on the charts.

Fig. 1 shows that, in their effect on the clinical manifestation of depression, neither phenelzine nor dexamphetamine was significantly better than lactose. Figs. 2 and 3 show that for agitation and anxiety phenelzine was significantly better than lactose and also significantly better than dexamphetamine. There were relatively few positive comparisons between dexamphetamine and lactose, but there was no trend towards dexamphetamine being better than lactose.

In none of the other clinical manifestations had a conclusive comparison between drugs been reached by the time the trial was ended. But, with the exception of the effect of phenelzine on anorexia, there was no

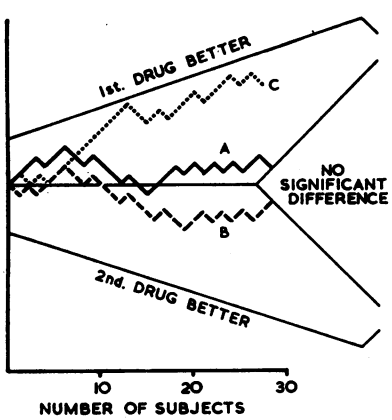

FIG. 1

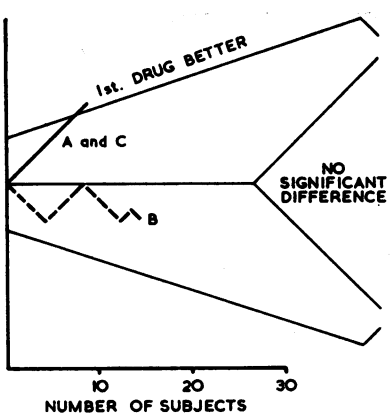

FIG. 2

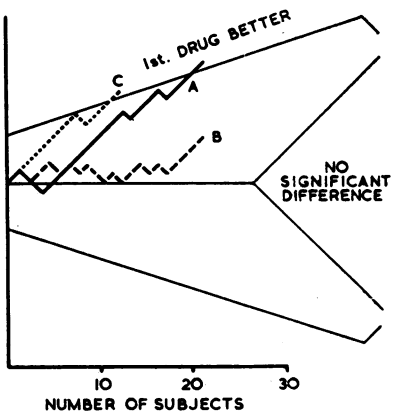

FIG. 3

FIG. 1.—Depression. A, Phenelzine against lactose. B, Dexamphetamine against lactose. C, Phenelzine against dexamphetamine.
FIG. 2.—Agitation. A, Phenelzine against lactose. B, Dexamphetamine against lactose. C, Phenelzine against dexamphetamine.
FIG. 3.—Anxiety. A, Phenelzine against lactose. B, Dexamphetamine against lactose. C, Phenelzine against dexamphetamine.

trend for either phenelzine or dexamphetamine to be better than lactose.

Reliability of the Clinical Assessments

The comparisons used for the sequential analysis were all based on the ratings of one observer. The degree of concordance between these comparisons and those noted by a second observer gives some indication of the reliability of the clinical assessments. Table I shows the concordance between the comparisons based on the ratings for depression and for anxiety. It is clear that there is satisfactory concordance for depression (there being no major disagreements) but a much less satisfactory concordance for anxiety.

Table II shows, in a shorter way, the concordance for all the clinical manifestations. The difference between the proportion of agreements observed (column f) and that expected by chance (column g) is greatest for depression, least for anxiety. Columns a and b also give some measure of the concordance

TABLE I.—*Concordance Between Comparative Assessments of Two Observers (34 Subjects)*

		Second Observer					
		Depression			Anxiety		
		+	0	−	+	0	−
First observer	+	22	10	0	8	10	4
	0	5	17	5	10	16	10
	−	0	13	20	3	12	9

+, 0, and − stand for assessments of "better than," "equal to," and "worse than" (see text).

TABLE II.—*Concordance Between Comparative Assessments of Two Observers (34 Subjects)*

Clinical Manifestation	a	b	c	d	e	f	g
	When One Observer Notes a Change, the Other Observer Notes			Both Observers Note No Change	Total Comparisons	Agreement (%)	
	Same Change	Opposite Change	No Change			Observed i.e. $\frac{a+d}{e}$	Expected
Depression	42	0	33	17	92	64·1	32·7
Retardation	14	1	29	45	89	66·3	49·8
Agitation	16	0	18	36	70	74·3	17·6
Anxiety ..	17	7	42	16	82	40·2	35·5
Hypochondria	11	3	33	45	92	60·9	50·1
Anorexia ..	11	1	38	38	88	55·8	47·9
Insomnia	21	0	23	41	85	73·0	45·2

Note: The total comparisons in column e are not the same for all manifestations because, for various reasons, the full complement of ratings was not always made by both observers.

between observers. If chance were the only factor and the observers' choices were independent of each other, then the numbers in columns a and b would be approximately equal. But in fact, except for the assessment of anxiety, there were many more agreements ("same change") than disagreements.

Subjective Effects of the Drugs

Of eight subjects who said they felt better, steadier, or more relaxed after taking the tablets during a particular fortnight, six had been on phenelzine and one each on dexamphetamine and lactose. Of seven subjects who said they felt "fuzzy," "dopy," dizzy, or otherwise distressed by the tablets during a particular fortnight, five had been on phenelzine and one each on dexamphetamine and lactose. The relation between these subjective effects and the nature of the drug was not studied until the end of the whole trial, and we do not think that the clinical assessments were appreciably influenced by any opinion that effects might have been associated with a particular drug.

No subject claimed that any of the tablets made him feel "pepped up," more energetic, or less depressed.

Effects of Time

Comparison of the fortnightly periods, irrespective of the drugs given, showed the expected improvement in clinical manifestations with time. There was a steady increase in the numbers of subjects noted as "better" when the ratings on entry to the trial were compared with those made at the end of the first, second, and third fortnights. Thus, for depression, these numbers were 15, 21, and 25 out of a total of 36 subjects (in seven subjects no initial rating had been made). As neither phenelzine nor dexamphetamine proved more effective than lactose on the manifestation of depression, the increasing proportions of subjects whose depression was better at the end of successive fortnights than at the start—42%, 58%, and 70%—may be considered to represent the "spontaneous" improvement rate under the conditions of the trial. It is, of course, the high natural rate of improvement in depressive illness that makes the assessment of therapy so difficult unless controlled trials are done.

Discussion

The results indicate that, under the conditions of the trial, neither phenelzine nor dexamphetamine was significantly better than lactose in its effect on the clinical manifestation of depression. On the other hand, phenelzine was significantly better than both dexamphetamine and lactose in its effect on agitation and anxiety. If it is permissible to generalize from the conditions of the trial (where the drugs were given only for a fortnight and where the dose of phenelzine was 30 mg. b.d.), then the results suggest that the beneficial effect of phenelzine in depressive illness may be due more to a sedative than to an antidepressive action. This suggestion is perhaps supported by the fact that one of the most commonly reported side-effects of phenelzine is drowsiness, which implies some sedative action. It may be noted, too, that a combination of dexamphetamine with some sedative drug is nowadays more generally favoured in the treatment of depressive illness than is dexamphetamine alone. The present results suggest that the value of such a combination may depend more on the sedative than on the supposed antidepressive component. Most cases of mild or moderately severe depressive illness are associated with some degree of anxiety, and relief of this anxiety by sedation might be expected to bring about some clinical improvement. Whether a simple sedative such as amylobarbitone sodium would be as effective as phenelzine (or as a combination of dexamphetamine with a sedative) in the treatment of depressive illness has not yet been tested by a controlled trial.

Some measure of the reliability of the clinical assessments is afforded by the degree of concordance between the observers. There was fairly good agreement on the assessment of depression and agitation—that is, on the change of intensity of these manifestations from one fortnight to another. The assessment of anxiety was much less reliable, but it is perhaps pertinent to add that the first observer, who assessed every case and upon whose rating the sequential analysis was based, had greater clinical experience than the other observers. The agreement between comparative assessments—that

is, in terms of better, equal, or worse—was much higher than agreement between actual rating scores. This suggests that, for the purposes of a clinical trial, it may be more reliable for a clinician to assess a patient's state in relative terms (as being better or worse than before) than to rate his condition in absolute terms on different occasions.

Summary

A self-controlled comparative trial of phenelzine (30 mg. b.d.), dexamphetamine sulphate (5 mg. b.d.), and lactose in the treatment of depressive illness is reported. The drugs were given consecutively, each for a fortnight, in randomized order. The results are based on the study of 43 patients.

In their effect on the clinical manifestation of depression neither phenelzine nor dexamphetamine was significantly better than lactose. On the clinical manifestation of agitation and anxiety, however, phenelzine was significantly better than both dexamphetamine and lactose; dexamphetamine was again no better than lactose.

Independent ratings were made by two observers of the changes in intensity of the clinical manifestations. For depression and agitation there was fairly good agreement between the observers; for anxiety the agreement was poor.

The findings suggest that the beneficial effect of phenelzine in depressive illness is due more to a sedative action in relieving anxiety than to a specific antidepressive action.

We thank Professor P. Armitage, of the Medical Research Council's Statistical Research Unit, and Dr. R. Cawley, of the Institute of Psychiatry, for advice on the statistics; Mrs. Vejs, pharmacist at the Bethlem Royal Hospital, for the dispensing; and William Warner and Company for the supply of "nardil" tablets and identical-looking tablets of dexamphetamine sulphate and of lactose.

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Leprosy, a disease which has existed in Fiji for many years, may well be on the way out. The Governor of the territory, Sir Kenneth Maddocks, said recently when he attended the golden jubilee of Makogai Leprosy centre: "We can at last begin to look forward to the day when the centre will no longer be needed. This is a real occasion for rejoicing and thankfulness after 50 years of devoted work." In 1948 the number of patients in the centre was 664. To-day the number there is fewer than 280, and in 1958 and 1959 alone 121 and 131 cases respectively were discharged as cured. The Governor paid a tribute to those who had helped with the centre's work, and, in particular, to the Missionary Sisters of the Society of Mary and the Fijian Sisters of the Little Sisters of Nazareth. He also praised the generosity of the people of New Zealand who had subscribed hundreds of thousands of pounds to a fund for the relief of leprosy.

E.C.H.O. TYPE 9 INFECTION IN 1960

A STUDY IN GENERAL PRACTICE

BY

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The E.C.H.O. viruses as well as other enteroviruses, such as the Coxsackie A and B groups, are now recognized as causative agents in many cases of "non-paralytic poliomyelitis," and this form of enterovirus infection has already been experienced in several areas in Scotland (*Brit. med. J.*, 1961). Although a variety of E.C.H.O. and Coxsackie virus types have been identified in the Western Region in recent years, 1960 was the first year in which there occurred a large-scale epidemic due to a single enterovirus type—in this instance E.C.H.O. 9. Many cases of aseptic meningitis were admitted to the infectious-disease units in the region during the summer and cases of febrile illness with rash, mainly in children, were common. The present paper describes a number of cases of the latter type.

In June two practitioners drew attention to an epidemic of a rubella-like syndrome in children from unrelated families in the northern area of Glasgow. The possibility was recognized that this might be a manifestation of E.C.H.O. 9 infection, and it was arranged that the practitioners would notify such cases to us and thus enable an epidemiological study to be made. Many of these patients were visited by one of us (J. B. L.) and a preliminary account of some of the features noted in them has been recorded (Landsman, MacAnespie, Weetch, and Bell, 1960). More detailed information is provided here.

Material and Methods

Twenty-three families were studied between June and October, 1960. All but one of the cases were seen in their own homes, usually within 24 hours of their notification to us. Most families were visited more than once; at these visits details of history and clinical appearances were recorded and inquiry was made about illness of any kind in the family before the date of sickening of the notified case and during the period of surveillance. Whenever possible, specimens for virological examination were taken from patients and contacts. Throat swabs, rectal swabs, specimens of faeces, or swabs of freshly passed faeces were submitted for virus isolation and serum samples for the presence of antibodies. Only faecal specimens were obtained from the first cases seen, but in later cases throat swabs were mainly used. Many of the patients were children, so that paired samples of serum were not always obtained.

A member of a family who reported some departure from normal health immediately before our first visit or during the 10–14 days when the household remained under our observation was regarded as having had an "incident." As would be expected, some examples occurred where the incident could quite clearly be ascribed to some other cause. There were six such incidents, and these are shown in Table I.