This method of therapy is particularly valuable for out-patients, and most of the patients in this series were treated as such.

The results obtained in this series (88% initial improvement) were maintained by most of the patients over a nine-months period. In those cases in which relapses did occur they were slight and easily controlled by further local treatment. No deaths occurred in this series. These results compare favourably with the experience of others with local therapy (Truelove, 1956, 1957, 1958; Watkinson, 1958).

Corticosteroid therapy has many disadvantages when given systemically. Among these are the insidious onset of infection (*British Medical Journal*, 1954; Stevens, 1960), acute adrenal insufficiency in response to sudden stress (*Lancet*, 1957), and other multiple possible dangers (corticoid psychosis, osteoporosis, perforation of peptic ulcer, etc.). Local corticosteroid therapy, however, carries none of these risks and, so far, no complications have been reported following its use.

If systemic corticoid therapy is to be used in ulcerative colitis, then the co-employment of local steroids enables a smaller dosage to be given and thus reduces the dangers.

Summary

One hundred cases of ulcerative colitis were treated with prednisolone-21-phosphate enemata. The results on the whole are good, an 88% improvement rate being obtained initially. A follow-up for nine months after therapy is reported.

The patient should have a reserve supply of treatment for immediate use in a relapse.

Very long courses of treatment have been found of value in certain cases.

I thank Dr. J. M. Naish especially for his help and guidance. I also thank all the physicians and surgeons of Bristol who kindly allowed their patients to take part in the trial, and Dr. P. A. Thorn and Dr. J. V. S. A. Davies, of the Royal Hospital, Wolverhampton. Messrs. Glaxo Laboratories kindly made available generous supplies of the stabilized aqueous solution of prednisolone phosphate in plastic disposable enema bags.

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"The National Spastics Society's projects for 1961 include the construction of the first purpose-built secondary school in Britain for spastic children and a centre for spastics who require special education. Work will be started on building our sheltered workshop in Birmingham for 120 spastics regarded as unemployable in open industry, and we hope to finalize the site for a similar project in the south of England. In addition, major extensions and alterations to improve facilities at nine of our schools and centres will be carried out. Early in the New Year we shall be taking the first steps in providing a staff training centre, where expert advice will be given to those who look after and teach spastics. Altogether £800,000 will be spent on building programmes during the coming year." (Dr. C. P. Stevens, director, National Spastics Society.)

DEPRESSION TREATED WITH IMIPRAMINE: A FOLLOW-UP STUDY

BY

L. G. KILOH, M.D., M.R.C.P., D.P.M.

Reader, Department of Psychological Medicine,
University of Durham

AND

J. R. B. BALL, M.B., B.S., D.P.M.

Senior Registrar, Department of Psychological Medicine,
Royal Victoria Infirmary, Newcastle upon Tyne

A controlled trial of imipramine ("tofranil") in the treatment of out-patients suffering from depressive states was reported by Ball and Kiloh (1959). It was found, when assessed after a period of four weeks, that 74% of the cases of endogenous depression showed a good response to imipramine as compared with 22% of the cases receiving placebo. In reactive depression a similar degree of improvement was obtained in 59% of the patients on imipramine as compared with 20% given placebo.

It was stated that many of the patients who failed to respond to their initial treatment were given the alternative tablets. This constituted a cross-over experiment within the main trial. Furthermore, the view was expressed that a follow-up study of the trial cases to provide a longer-term assessment of the effects of treatment might be of value.

An extensive literature now exists concerning imipramine, but controlled studies of its effects are still scanty. Up to May, 1960, only three papers have been traced describing investigations in which some attempt has been made at control. One of these (Sloane *et al.*, 1959) involved only 12 patients and was abandoned after two weeks. A partially controlled trial was reported by Lehmann *et al.* (1958). Eighty-four patients were treated, 51 of whom suffered from endogenous depression. After the first 42 patients had been collected and treatment was in progress, it was decided to subject these to a double-blind procedure. One-half continued to take imipramine and the other half were given placebo tablets. Assessments were made after two weeks. Of the 21 patients on placebo, 10 became worse, whilst of the 21 patients remaining on imipramine 3 relapsed. The difference was accepted as significant statistically. All 10 patients who relapsed on placebo improved within two weeks when imipramine was substituted.

Leyberg and Denmark (1959), as a prelude to a full-scale trial of imipramine, conducted a controlled cross-over study of its effects on 20 long-term hospitalized cases of endogenous depression. For two weeks half the patients were given imipramine and half placebo. In the second two weeks the procedure was reversed. The results were regarded as encouraging.

None of these studies can be accepted as adequately controlled.

Cross-over Study

Endogenous Depression.—Of the original placebo group, 17 cases were subsequently given imipramine, and eight of these showed a satisfactory response within four weeks. 27 cases were treated initially with imipramine, and five of the seven which failed to respond

were later given placebo. None of these showed any response.

Reactive Depression.—15 of the original placebo group were subsequently given imipramine. Of these, six made a good response. Of the 22 cases treated initially with imipramine, five of the failures were given placebo as a second line of treatment. None of these made any response.

The trends shown in these figures are what might be expected from the results of the original trial. The numbers involved are too small to evaluate statistically.

Follow-up Study of Trial Cases at Six Months

Altogether 97 cases were included in the trial. With two exceptions all were followed up. Both defaulters were treated originally with placebo, one improving, the other making no response. A third patient died after being on the trial for three months. Initially he was given placebo without effect, and this was followed by a course of E.C.T. which produced considerable benefit. He remained well during the subsequent four weeks but died suddenly as the result of a myocardial infarct. All these cases are rated as failures at six months.

Endogenous Depression.—After six months most of the patients that had done well with imipramine remained well. Of the 55 cases of endogenous depression included in the trial 44 were given imipramine, either as a first line of treatment or after a period on placebo. 29 (66%) of these showed a good initial response. This figure includes one patient, originally reported as a failure, who made a delayed but sustained response, improvement beginning after six weeks on the drug. After six months 21 (48%) of the 44 cases remained well. Of the eight relapsed cases four had ceased to take the drug after five to six weeks because of side-effects. The other four cases were still taking imipramine (100 mg. daily) at the time of relapse.

Reactive Depression.—Similarly, most of the cases of reactive depression responding to imipramine continued to do well after six months. Of a total of 37 cases given imipramine 20 (54%) showed a good initial response. This includes one case, originally classed as a failure, that began to improve after five weeks. 15 (41%) remained well at six months. Of the five cases which relapsed, two ceased to take the drug at six weeks because of side-effects; in one the drug was stopped at 10 weeks, and the other two relapsed while still taking imipramine.

Although on the whole the results of treatment with imipramine were well maintained, of the 49 cases of reactive and endogenous depression that responded initially to the drug, 13 relapsed during the six months of observation. Of these, seven ceased to take the drug prior to relapse, and it seems likely that this was the cause of failure in these cases. In some of the others it may well be that the maintenance dose was inadequate. The possibility also exists that some of these patients were not taking their tablets. Nevertheless, making allowance for all these possibilities, it does appear that the occasional patient may make a good initial response to the drug, only to relapse while still taking what is apparently an adequate dosage. This fact emphasizes the need for close and continued supervision of all cases, particularly those who have entertained suicidal ideas. The fact that the initial response has been dramatic is no indication for relaxing surveillance of the patient.

No group of patients treated with E.C.T. was included in this trial, but in a parallel investigation of the effects of iproniazid on endogenous depression (Kiloh *et al.*, 1960) it was found that although 49 (94%) of a group of 52 cases showed a good immediate response to E.C.T., after six months, only 25 (48%) remained well. This may be compared with the figures for endogenous depression treated with imipramine. Out of 44 cases, 29 (66%) showed a good initial response and at six months 21 (48%) remained well. Many of the relapses of the cases given E.C.T. occurred within two to three weeks of cessation of treatment, and the period of benefit could not be regarded as commensurate with the efforts involved in giving and receiving the course of treatment. The conclusion seems inescapable that when assessed at six months there is little to choose between the effects of E.C.T. and of imipramine. On the other hand, there is no certainty that the group of patients responding to E.C.T. is identical with that responding to the drug. There is evidence that some cases relapsing after E.C.T. may make a good response to one or other of the antidepressive drugs (Delay and Deniker, 1959), and the converse also appears to be true.

Of the cases of endogenous depression that failed to respond to imipramine in this series, six were given E.C.T. Four showed a good immediate response, though one of these relapsed within two weeks, while the other two were unrelieved. Two cases had modified leucotomies, one doing well and the other badly. Six further cases were subsequently given courses of phenelzine ("nardil") and three of them made good responses.

Duration of Treatment and Maintenance Dosage

Little precise information is available as yet regarding the period of drug administration necessary to avoid relapse. Moore (1960) suggests that once optimal improvement has been obtained the dose should "gradually be reduced for a period of a few weeks" and then stopped. This would seem to imply a duration of administration of three to four months, though some patients, he admits, require imipramine for periods of a year or longer. Ruskin and Goldner (1959), state that many patients are able to discontinue imipramine without relapse within six months, but others may require continuous medication for two years or more. In most of these as little as 25 mg. daily seems to be sufficient.

In this trial some patients recovered after taking the drug for as little as four to eight weeks and have remained well up to the time of writing after periods of 8 to 14 months. On the other hand, several patients have taken the drug for a year or longer and any attempt at cessation is accompanied by a return of symptoms. Of 36 cases assessed as "well" at six months (and still well up to the time of writing), 15 had ceased to take the drug but the remaining 21 were still taking imipramine. In 11 of these imipramine was later discontinued without relapse after periods ranging from 7 to 11 months. The remaining 10 cases were still taking the drug after periods of 8 to 14 months. The fall-out of patients whose treatment had been successfully terminated appeared to be roughly linear with time (see Table I). If all the cases are taken into consideration the average period of administration is about six months. There is no significant difference

in this respect between the endogenous and the reactive groups. It is probable that a number of cases might well have had their medication terminated earlier without ill effects. The linear relationship between improvement and duration of treatment in this series

TABLE I

Period of Administration of Imipramine in Months	No. of Patients Completing Treatment	No. of Patients Still Taking Imipramine
1	1	—
2	3	—
3	3	—
4	3	—
5	2	—
6	3	—
7	1	—
8	3	1
9	2	3
10	2	2
11	3	—
12	0	3
13	0	—
14	0	1

might be cited as evidence to support the suggestion of Post (1959) that imipramine controls the symptoms of the condition until its natural periodicity determines the end of the depressive illness.

The maintenance dose employed varied from 75 to 150 mg. daily, the great majority remaining well on 100 mg. a day. In none of the patients receiving imipramine for prolonged periods was there any evidence of tolerance or addiction being established. The maintenance dose has remained low, though it might require some variation from time to time. This was also the experience of Ruskin and Goldner (1959).

Relationship of Improvement to Gain in Weight

Loss of weight represents an important feature of the clinical picture both of endogenous and of reactive depression, and it is not surprising, therefore, that improvement in the mental state should be reflected in gain of weight.

Cases of endogenous depression remaining well at six months showed an average gain in weight of 3½ lb. (1.6 kg.), the change in weight varying from a loss of 14 lb. (6.4 kg.) to a gain of 14 lb. (6.4 kg.). The patient who lost 14 lb. (6.4 kg.) in weight had in fact gained a similar amount during the course of his depressive illness. Cases that remained depressed at six months, including those that had relapsed, showed an average gain of ¼ lb. (113 g.), which in fact was contributed by a single patient who had put on 10 lb. (4.5 kg.). Among cases of reactive depression the changes were more striking, ranging in those that were well at six months from 0 to 42 lb. (19 kg.), with an average of 8 lb. (3.6 kg.). The gain among the failed cases was 2 lb. (0.9 kg.), this being contributed largely by two patients, each of whom gained 14 lb. (6.4 kg.).

Time of Beginning of Improvement and of Maximal Improvement

There was no significant difference in these respects between the endogenous and the reactive groups.

In endogenous depression clinical improvement began after periods of drug administration ranging from five days to six weeks, with a mean of 18 days. Maximal improvement occurred after the drug had been taken for periods varying from two to 12 weeks, with a mean of six weeks.

In reactive depression, improvement was noted after periods of one to six weeks, with a mean of 18 days.

Maximal improvement occurred after periods ranging from 1½ to 24 weeks, with a mean of eight weeks.

There appeared to be no relation between the time taken for the beginning of improvement and the time of maximal improvement.

In many cases in this trial reported as not responding to imipramine the drug was stopped after four weeks. The results might have been a little better still had the period of administration been increased to six weeks in all cases.

Side-effects

In the original trial, 27 of 49 cases on imipramine reported side-effects of one kind or another, while 13 of 48 cases given placebo also reported side-effects. In all these cases the complaints were made spontaneously and no attempts were made to elicit information, in case this suggested which of the two treatments the patient was receiving. During the follow-up period the question of side-effects was considered in more detail, and of the total of 81 patients who received imipramine at one time or another, 67 (83%) complained of side-effects. These are listed in order of frequency in Table II.

TABLE II.—Side-effects

Dry mouth	44	Unsteadiness	2
Sweating	26	Diarrhoea	2
Constipation	19	Depersonalization	2
Faintness or dizziness	16	Abdominal distension	1
Nausea ± vomiting	11	Grand mal	1
Shakiness or tremor	7	Blackouts	1
Sleepiness	7	Hypomania	1
Malaise	6	Dyspnoea	1
Difficulty in accommodation	6	Oedema of legs	1
Unpleasant taste	5	Pains in muscles	1
Skin rash	5	Pruritus	1
Weakness of legs	4	Headaches	1
Flushing	4	Anorexia	1
Difficulty with micturition	3	Sleep disturbance	1

Many patients had two or more side-effects, the combination of dry mouth and sweating being particularly common. In general there was a direct relationship between the intensity of the more common side-effects and the dose of imipramine. It must be stressed, particularly so far as some of the less-often described effects are concerned, that they may not have been due to the drug at all. Skin rashes, for instance, were urticarial in nature and with one exception disappeared without withdrawal of the drug. On the other hand, although hypomania occurred only once and only one patient developed an attack of grand mal, both these events were felt to have a close relationship to the drug administered. Several cases have been reported (Levene and Lascelles, 1959; Brooke and Weatherly, 1959; Moll, 1959) in which large doses of imipramine of the order of 1,000 to 5,000 mg. taken in suicidal attempts have given rise to attacks of grand mal; and E.E.G. studies of epileptics given intravenous imipramine have shown that the drug potentiates focal and generalized spike or sharp-wave discharges (Kiloh *et al.*, 1961).

The patient who had a "blackout" was a woman of 73. She fell and broke several ribs. It was felt that this was a hypotensive rather than an epileptic attack.

No deaths directly attributable to therapeutic doses of imipramine have been published, and even after massive quantities have been taken in attempts to commit suicide, recovery is the rule. Only one recorded case has proved fatal. This was a girl of 19 years who died three and a half hours after taking 4,250 mg. of imipramine. She became deeply comatose, suffered generalized convulsions, and developed a right bundle-branch block (Michon *et al.*, 1959).

Although the side-effects may be described as unpleasant rather than dangerous they do represent a drawback to treatment with the drug. A number of patients find them intolerable, and considerable persuasion is necessary on occasion to maintain the patient on the drug even though he may have responded well as regards his depressive illness.

Summary and Conclusions

A six-months follow-up study of 97 patients included in a clinical trial of imipramine confirms that this drug is an effective method of treatment of both endogenous and reactive depression.

A strict comparison with the effects of E.C.T. in endogenous depression was not carried out, but from figures obtained in another trial it is clear that the relapse rate among cases showing a good immediate response to E.C.T. is so high that after six months the effects of E.C.T. and of imipramine are of a similar order.

It appears that even though the initial response to imipramine is dramatic and the maintenance dose seemingly adequate, relapse may occur in occasional cases. This seems most likely to occur within two months of the initial improvement. Regular surveillance of all cases under treatment with imipramine is rendered all the more necessary because of this possibility.

The duration of treatment with imipramine necessary to avoid relapse is very variable and is likely to be an individual matter. It may be related to the natural periodicity of depressive illness. The mean duration of treatment was about six months, with a range of one to more than 14 months.

Although an initial daily dosage of 250 mg. was used, experience with patients not included in this trial suggests that 150 to 200 mg. of imipramine a day is sufficient in a substantial number of patients, but the larger amount is necessary in some. Once maximal improvement has been obtained the dose can be reduced to 75 to 100 mg. daily. In a few patients higher maintenance doses are necessary (150 to 200 mg.), and any attempt to reduce the dose below this level leads to a return of symptoms.

In cases responding to imipramine, improvement occurred in five days to six weeks, with a mean of 18 days. Maximal improvement was seen after periods of treatment varying from 1½ to 24 weeks, the mean being seven weeks. There was no indication of why such large variations in the individual responses should exist. It is not possible to declare treatment with imipramine a failure unless it has been given for six weeks, though after three weeks the chances of success show a steady decline with the passage of time. It must be accepted that when the response to the drug is so protracted, unless the symptoms are relatively mild, the advantages of drug treatment over E.C.T. become questionable, for the latter form of treatment can be relied upon to provide speedy, though not necessarily permanent, relief of the patient's symptoms.

Side-effects were produced in 83% of patients treated with imipramine. These are seldom dangerous, but the discomfort engendered often leads to refusal by the patient to continue with treatment, even though the presenting symptoms have been relieved. The most serious side-effect seen in this trial, though the rarest, was an attack of grand mal. From experience with

other patients it appears that some caution is necessary in giving imipramine to epileptics, and it may be necessary to increase the amount of anticonvulsant drugs. In patients known to have suffered from epilepsy in the past but no longer on medication, it would seem to be a wise precaution to cover the period of imipramine administration with anticonvulsants. An occasional patient in whom there is no history of fits may suffer one or more attacks of epilepsy while taking imipramine.

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METHAQUALONE AS A HYPNOTIC

BY

T. W. PARSONS, M.B., Ch.B.

AND

T. J. THOMSON, M.B., F.R.F.P.S., M.R.C.P.

From the Materia Medica Department, Glasgow University, and the Medical Wards, Stobhill General Hospital, Glasgow

Methaqualone ("melsedin"; 2-methyl-3-o-tolyl-4-quinazalone hydrochloride) is a synthetic non-barbiturate hypnotic. Ravina (1959) reported on its value given as an oral dose of 150 mg.: in 54 out of 100 patients the hypnotic effect was superior to that of previously administered hypnotics; placebo tablets were not used in Ravina's series.

The present investigation was designed to assess the relative merits of methaqualone and a standard dose of cyclobarbitone; an inert tablet was used as a control. The design of the trial was similar to that used by Thomson (1958).

Method

The patients were in general medical wards and presented the usual wide range of diseases; there were 79 women and 21 men, and their ages ranged from 32 to 74 years. Only those who required hypnotic drugs were included in the trials. All other sedatives were withheld during the period of observation; when any patient developed a new symptom which in itself might have caused insomnia during a trial, he was excluded from the series. Three clinical trials were carried out using the same plan of investigation. The two drugs to be compared were dispensed as white sugar-coated