of the tumour was made by Dr. D. A. H. Mackenzie. The illustrations were prepared by Miss Jeannette Purkiss.

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Every year fire brigades in the United Kingdom attend about 500 fires in such places as nursing-homes and hospitals of all kinds, clinics and welfare centres, children's and old people's homes, special schools for handicapped children, day nurseries, training centres for ex-Service men, and institutions for the blind. . . . Generally speaking the causes of most of the fires were not peculiar to hospitals but were similar to those of fires in dwellings. Many were the result of carelessness or forgetfulness—for instance, 18 were due to dropped smoking materials, and of these five were started by people who were smoking in bed. An important proportion of fires was concerned with cooking and heating equipment. . . . Six fires originated in hospital boilers or furnaces and seven were caused by chimneys or flues. Two fires arose as a result of a fairly common practice in hospitals—shielding the glare from an electric lamp by draping a cloth or towel round it; and one fire was started by the flame from a lighted sulphur fumigating cone placed on a mattress. Only five of the fires were peculiar to hospitals in that they involved special hospital equipment. There were three fires in sterilizers, two electric and one gas-heated, and the two other fires originated in immersion heaters in *x*-ray developing tanks. One of the most encouraging conclusions of this survey is that the provision of fire-fighting equipment seems to have been adequate, and most of the fires were tackled by the hospital staff, who were able to extinguish 52 of them without fire brigade assistance. . . . (*Fire Protection Association Journal*. July, 1959.)

A CONTROLLED TRIAL OF IMIPRAMINE IN TREATMENT OF DEPRESSIVE STATES

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Imipramine, an iminodibenzyl derivative, is a distant relative of chlorpromazine. Investigation of this substance was carried out by Kuhn, at Munsterlingen, in 1950, but after an initial and limited assessment it was put aside until interest was rekindled in 1954 after the beneficial effects of chlorpromazine had been established (Kuhn, 1957). Like iproniazid, imipramine inhibits the lowering of the serotonin level in the brain caused by reserpine (van Meter *et al.*, 1959). A number of clinical studies published on the effects of imipramine suggest that the drug is of considerable value in the treatment of depression and that its effects are at least comparable to those of electric convulsion therapy (E.C.T.).

In three years Kuhn (1957, 1958) treated 500 patients suffering from various psychiatric disorders with imipramine. The best results were obtained in endogenous depression, and he states that success can be expected in three-quarters to four-fifths of cases. In reactive depression a significant though less marked response was noted.

Kielholz and Battegay (1958) treated 69 cases of severe depression and found that 67% were improved or became symptom-free.

Lehmann *et al.* (1958) reported the effects of imipramine upon 84 patients in whom depression was a prominent feature. Three-fifths of these suffered from endogenous depression. Within eight weeks 60% had recovered or were much improved.

Fazio *et al.* (1958) found that in 50 cases of depression of varied aetiology 32% showed a full clinical remission and 42% were appreciably improved. Imipramine appeared to be most effective in recurrent depression.

Straker (1959) treated with imipramine 26 patients from his private practice mostly suffering from endogenous depression: 80% recovered or were "vastly improved."

Sloane *et al.* (1959) selected 30 patients—the majority suffering from endogenous depression—who would otherwise have been given E.C.T.: 80% recovered, and the authors felt that the results were comparable to or even somewhat better than those of E.C.T. An abortive attempt to carry out a controlled trial on 12 patients was made, but it was terminated after two weeks and no useful conclusions could be drawn.

Mann (1959) gave imipramine to 70 cases of depression of various types and found that 63% recovered or were much improved: 40 cases were described as suffering from "neurotic depression," but this group included many involutional cases.

Azima (1959) used imipramine in 100 patients with depression. Of these, 44 suffered from psychotic depression, and 61.3% of this group showed a marked improvement and 29.5% were moderately improved. Of 38 cases of neurotic depression, 30.3% were greatly improved and 44.6% showed moderate improvement.

Delay *et al.* (1959) treated 137 cases of various forms of depressive disorder. The best results were obtained in cases of recurrent depression, of which 75% recovered or showed great improvement. In involutional melancholia, 67% of the cases responded to the same degree, and in "arteriosclerotic" depression 70% of cases showed a good result. The results were less impressive when the depression occurred as a feature of neurotic illness or in association with psychopathy.

Methods

The purpose of the present trial was simply to decide if imipramine was an effective agent in the treatment, firstly, of endogenous depression, and, secondly, of reactive depression. It is felt that endogenous depression and reactive or neurotic depression are distinct entities, and even though their separation is not always easy to make on clinical grounds this should be attempted in view of the wide differences in the response of the two groups to physical treatments and in their ultimate prognosis (Roth, 1959).

All the cases included in the trial were out-patients, and anyone showing gross retardation or extreme agitation and those in whom the risk of suicide was considerable were automatically excluded, as they were admitted for in-patient treatment. Nevertheless, a number of the patients included were quite severely depressed. One did commit suicide during the trial shortly after starting on the placebo. He was adamant in his refusal to come into hospital.

The clinical trial was organized in conjunction with the hospital dispensary, and cases were allocated at random to the active and placebo groups by the hospital pharmacist. On the first and second days of treatment four 25-mg. tablets were given; the dosage was increased to six, eight, and finally ten tablets daily by the fifth day. Patients were seen weekly, and this dosage was maintained for four weeks. If no improvement had occurred at the end of this period the drug was regarded as ineffective and some other form of treatment was instituted. In most cases the alternative tablets were given for a further period. The results of this crossover trial are not yet available and will be reported at a later date. Patients who responded to the tablets they were receiving were kept on these until maximal improvement was obtained. Without exception this occurred within six weeks of starting treatment. How long it is necessary to continue the administration of imipramine to avoid the risk of relapse has not yet been established.

With regard to preknowledge of what the patient was receiving before the code was broken, we had the usual hints from the side-effects that occurred. However, these proved to be a double-edged weapon—as shown below—and did not invalidate the trial in any degree.

The average age of the patients with endogenous depression was 50.2 years and of those with reactive depression 43.2 years. With regard to sex distribution, of 55 cases of endogenous depression 38 were female and 17 male. Of 42 cases of reactive depressions 26 were female and 16 male.

The results of treatment were assessed as symptom-free, greatly improved, somewhat improved, no change, or worse. For the purpose of assessing the value of the drug as a significant therapeutic agent, the first two of these categories have been combined as a good or worth-while result and the other three as a poor result. Patients showing a good result were able to return to their normal activities without undue effort.

Only the immediate results of treatment are reported in this paper, but the patients are being followed up, and it is felt that the results after three and six months may be of even greater interest.

Results

Of 55 cases of endogenous depression treated, 27 received imipramine and 28 the placebo. On imipramine 20 responded well, while 7 did badly. On the placebo, 6 did well and 22 badly. This is a highly significant difference, and, with Yates's correction applied, $P<0.01$.

Of the 42 cases of reactive depression 22 received imipramine and 20 the placebo. Of those given imipramine 13 were improved and 9 were not; while of the 20 controls 4 improved and 16 showed a poor result. This, too, is a significant result ($P<0.02$). When improvement occurred it was nearly always evident by the end of the third week, sometimes as early as the fourth or fifth day. The mean was 9 to 10 days.

Of the 27 cases of endogenous depression treated with imipramine 20 were females and 7 were males. Of the 20 women 14 did well, and of the 7 men 6 had a good result. Of the 22 cases of reactive depression given imipramine 9 out of 14 women did well, compared with 4 out of 8 men. Freyhan (1959) has suggested that women respond better to imipramine than men. These figures lend no support to this view.

Side-effects

Of the 49 cases on imipramine included in the trial, 27 had side-effects of one kind or another. These included dryness of the mouth, sweating, dizzy feelings, drowsiness, and nausea. Constipation was reported occasionally, as was difficulty in starting micturition. In none of these cases were the effects severe. The side-effects usually became evident during the first week of treatment and tended to improve or even disappear after two or three weeks. One patient, an intractable case of endogenous depression, who in the past had had repeated courses of E.C.T. and a prefrontal leucotomy with only transient benefit, improved rapidly on imipramine, but after three weeks entered a hypomanic phase, which has continued in spite of stopping the imipramine. She gave no history of previous manic swings. An urticarial rash occurred in one patient while taking imipramine, but was regarded as coincidental.

We have had no examples of jaundice resulting from the use of imipramine, though Delay *et al.* (1959) refer to such cases, which appear to have been mild and none fatal. One patient, after two weeks on imipramine, developed a severe diabetes mellitus and was taken off the trial. It is not possible to say with any assurance whether or not there was any causal connexion between the onset of the diabetes and the administration of imipramine. Two cases suffered haematemeses in the second week of treatment with imipramine. One, a man aged 61, died a few days later and was found to have a gastric carcinoma; the other patient is still under investigation. A third patient, noticed to be pale, was

admitted to hospital for investigation, and her stools gave a positive result for occult blood. No cause for this could be found. In these cases the imipramine was discontinued and they were not included in the trial.

Six further patients ceased to take their tablets after a few days because of intolerable side-effects and were therefore excluded. They complained variously of intense malaise and lethargy, weakness and dizziness, and of unsteadiness and palpitations. Of the six patients, four were taking imipramine and two the placebo. Two cases also excluded from the trial failed to keep their out-patient appointments, so that no further assessments were possible.

Of the 48 patients on the placebo tablets 13 showed side-effects, including dryness of the mouth, lethargy and drowsiness, dizziness, constipation, and diarrhoea. One of these also had an urticarial rash. These are what one might term negative placebo effects, and clearly form a safeguard in some degree against breakdown of the double-blind system.

Conclusions

This clinical trial of imipramine set out to decide whether or not the drug had a worth-while effect upon depressive illnesses. So far as endogenous depression is concerned, the trial shows that imipramine is an effective agent, 74% of cases showing a good response.

In a controlled trial involving 81 patients carried out in this department and at St. Nicholas' Hospital to evaluate the effect of iproniazid, 54% of cases of endogenous depression showed a good response. Although the groups of depressives included in the two trials are not strictly comparable—those treated with iproniazid were on the whole more severe—the suggestion emerges that imipramine is the more effective agent. Delay *et al.* (1959) obtained a similar impression. In a group of 137 cases of depression of various causes treated with imipramine, 60% recovered or were greatly improved. A similar comparable trial of iproniazid gave a figure of 47%.

As no group of patients treated with E.C.T. was included in the trial of imipramine, a direct comparison with this form of treatment cannot be made. In the iproniazid trial, E.C.T. gave a good response in 89% of cases, and it is likely that a similar figure would have been obtained had such a group been included in the imipramine trial. If so, it would suggest that, so far as the immediate effects are concerned, imipramine is somewhat inferior therapeutically to E.C.T. However, in view of the high relapse rate among patients treated with E.C.T., it does not follow that this superiority will be maintained after three or six months. Several cases included in the trial had previously had courses of E.C.T., and many of these appeared to respond equally well to imipramine. Only one case was included which might be described as resistant to E.C.T., and this, too, responded well. It has certainly been obvious in this department that since the introduction of iproniazid and imipramine the amount of in-patient and out-patient E.C.T. given has fallen sharply.

The drug treatment of depressive illness has many obvious advantages over E.C.T. However safe the latter has become, there can be no denial that as a method of treatment it is far more unpleasant than taking a few tablets. The drugs produce no confusion or disturbance of memory, which is a particular advantage for those whose work is primarily intellectual. It is possible for some patients to avoid losing work—an inevitable occurrence when out-patient E.C.T. is given—and where facilities for out-patient E.C.T. are not provided or are impracticable admission to hospital may be avoided. Nevertheless, adequate observation and supervision is necessary because of the toxic effects of these drugs as well as the continuing risk of suicide in some cases and the possibility that other forms of treatment may be required.

The side-effects in general are less disturbing than those associated with E.C.T. and on the whole are not serious. A possible danger is liver necrosis, but the frequency and severity of this appear to be less than in the case of iproniazid.

It seems to be well worth trying either iproniazid or imipramine in most cases of endogenous depression before deciding to give E.C.T. It is probably advisable to make exceptions of those cases in which there is a real danger of suicide, cases presenting in stupor or showing marked inanition, and those in which there is any suspicion of liver disease. It must be accepted that if depressive illness is treated with these drugs E.C.T. may still be necessary in a number of cases.

Imipramine appears to be of value also in reactive depression, and 59% of cases treated did well. Many of these cases, though relieved of their depression, continued to experience tension symptoms and other neurotic manifestations, which, however, usually proved much easier to bear than before. In view of the poor response of this group generally to E.C.T., this finding was somewhat unexpected and correspondingly more gratifying.

The real importance of these new antidepressive drugs appears to be twofold. Firstly, they provide an effective, easily administered, and readily acceptable form of treatment in most cases of depressive illness, which is one of the most important categories of mental disturbance with which the physician has to deal. Secondly, the modes of response to these drugs indicate lines of research which may well lead to the elucidation of the aetiological factors which play an immediate part in determining the onset of depressive illness. One feels hopeful that a study of the metabolism of these drugs and of their effect on the brain enzyme systems may well have far-reaching results, for it appears likely that they act upon what one might term the basic mechanisms in depression, and they are certainly more than euphorizing agents like the amphetamines.

Summary

A controlled trial was carried out to evaluate the effects of imipramine on endogenous and reactive depression.

In endogenous depression 74% of cases showed a good response to the drug, while 22% responded to the placebo ($P<0.01$).

In reactive depression 59% responded satisfactorily on imipramine, as compared with 20% on the placebo ($P<0.02$).

On comparing these results with those of a previous trial of iproniazid the impression was obtained that imipramine was the more effective agent in treating endogenous depression.

We thank our colleagues at the Royal Victoria Infirmary and at the Newcastle General Hospital for allowing us to include their patients in this clinical trial, and we are

pleased to acknowledge our indebtedness to Professor Martin Roth for his advice and encouragement. We are grateful to Geigy Pharmaceutical Company Ltd., who supplied the imipramine (" tofranil ") and placebo tablets, and particularly to Dr. Alan Broadhurst for his valuable co-operation.

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CYCLOSERINE IN TREATMENT OF INFECTION OF URINARY TRACT

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Cycloserine, first isolated in 1954 as a fermentation product of *Streptomyces orchidaceus* (Harned *et al.*, 1955), has been extensively investigated in the treatment of tuberculosis. Toxicity in patients given large doses for prolonged periods is the major disadvantage of such therapy (Walker and Murdoch, 1957). Nevertheless, lower oral dosage for short periods is virtually non-toxic provided renal function is good. Under these circumstances much higher urine than plasma concentrations are achieved (Welch *et al.*, 1955). Cycloserine has therefore been used to a limited extent, with encouraging results, in patients suffering from infections of the urinary tract caused by a variety of organisms (Herrold *et al.*, 1955; Hughes *et al.*, 1958). *In vitro* studies have also suggested that concentrations of cycloserine sufficient to inhibit the growth of some strains of coliform organisms are attainable in human urine (Welch *et al.*, 1955; Garrod, 1959). We report here the results of a detailed study of the use of cycloserine in a small number of patients with severe infection of the urinary tract by coliform organisms who have been observed for periods of two to seven months.

Materials and Methods

Clinical

Five female patients have so far been selected for study. Three were diabetic subjects who had suffered severe and repeated attacks of urinary infection characterized by malaise, frequency of micturition, nocturia, and dull loin pain for many months. Treatment with courses of sulphonamides, chloramphenicol, tetracyclines, and streptomycin had failed to relieve the symptoms or to render the urine sterile for an appreciable length of time. Renal biopsy was successfully performed in two of these three patients and histological evidence of pyelonephritis was demonstrated in both. Kidney tissue was not obtained from the third patient. The two remaining patients, who were not diabetic, had acute infections causing severe illness with high fever, rigors, dysuria, and oliguria of short duration. Renal biopsy was therefore not performed because of the delay involved in preparing for this procedure. Similarly, pre-treatment laboratory studies were also curtailed. Individual details of the patients are shown in Table I.

Treatment consisted of the daily oral administration of cycloserine in doses of 250 mg. eight-hourly for 14 days. Each patient was instructed not to drink excessively during this time. Daily observations of the temperature, pulse, and respiration rates and of the urinary volume were made. The patients were questioned and examined daily in respect of the subsidence or otherwise of their disease. Subjective and objective signs of drug toxicity, such as drowsiness, personality change, myoclonus, and epileptiform phenomena, were especially sought.

Bacteriological

As repeated catheterization carried with it the risk of introducing further infection, the following method of obtaining " clean " mid-stream specimens was devised. Patients were instructed to bathe in the early morning, washing the ano-genital region thoroughly with hexachlorophane soap. Urine was voided at 9 a.m. and discarded. Chlorhexidine cream was applied to the labia at 10.45 a.m. At 11 a.m. the patient, in the erect posture, with the labia separated by a sterile gloved hand, voided urine. The mid-urinary flow was collected in a wide-mouthed sterile jar and delivered immediately to the bacteriologist. Three such specimens were obtained on successive mornings before treatment was begun in Cases 1, 2, and 3. Only one such specimen was taken in Cases 4 and 5.

The pretreatment specimens from all patients were examined by standard laboratory procedures—namely,

TABLE I.—*Pretreatment Clinical Observations*

Case No.	Age and Sex	Duration	Temp. Rise	W.B.C. Cells/ c.mm.	E.S.R. Westergren	I.V.P.	Renal Biopsy
1	27 F	12 months	97–100° F. (36·1–37·8° C.)	6,000	50 mm.	Normal	Failed
2	55 F	3 ,,	97–98·6° F. (36·1–37° C.)	7,000	42 ,,	,,	Acute pyelonephritis
3	38 F	12 ,,	97–99° F. (36·1–37·2° C.)	7,500	93 ,,	,,	Chronic pyelonephritis
4	24 F	1 month	99–105° F. (Rigors) (37·2–40·6° C.)	17,200	45 ,,	—	—
5	20 F	3 weeks	99–102·4° F. (37·2–39·1° C.)	10,600	45 ,,	—	—