We have to thank the Director of Medical Services, Kenya, for permission to publish this paper and for the help and facilities he has given us in this work. We are grateful to Dr. D. M. Blomfield, Acting Provincial Medical Officer, Coast Province, for his help in the survey in his province. We are especially grateful to Dr. D. H. Mackay, Provincial Medical Officer, Nyanza, and to Dr. H. J. S. Coldham for making it possible for us to examine many hundreds of inhabitants of the Kisumu area, including babies in arms. Without their help much of this work would have been impossible. To Mr. S. McDonald, of the Kisumu laboratory, we are indebted for help in examining sickle-cell slides and for his help in the surveys in general.

REFERENCES

- Allison, A. C. (1954a). *British Medical Journal*, 1, 290.
 — (1954b). *Trans. roy. Soc. trop. Med. Hyg.*, 48, 312.
 Atlas of Tanganyika (1948). 2nd ed. Survey Dept., Lands and Mines, Dar-es-Salaam.
 Brain, P. (1952). *S. Afr. med. J.*, 26, 925.
 Foy, H., Brass, W., Moore, R. A., and Timms, G. L. (1955). *British Medical Journal*, 1, 285.
 — Kondi, A., Timms, G. L., Brass, W., and Bushra, F. (1954). *Ibid.*, 1, 294.
 Garnham, P. C. C. (1949). *Trans. roy. Soc. trop. Med. Hyg.*, 43, 649.
 Hiernaux, J. (1952). *Ann. Mus. roy. Congo belge*, 2, 1-42.
 Macdonald, G. (1951). *Brit. med. Bull.*, 8, 33.
 Mackey, J. P., and Vivarelli, F. (1954). *British Medical Journal*, 1, 276.
 Moore, R. A., Brass, W., and Foy, H. (1954). *Ibid.*, 2, 630.
 Raper, A. B. (1949). *E. Afr. med. J.*, 26, 281.
 Shortt, H. E. (1951). *British Medical Journal*, 2, 1103.
 Vandepitte, J. (1954). *Ann. Soc. belge Méd. trop.*, 34, 501.
 Wilson, D. B., Garnham, P. C., and Swellengrebel, H. N. (1950). *Trop. Dis. Bull.*, 47, 677.

CHLORPROMAZINE, RESERPINE, AND ISONIAZID TREATMENT IN MENTAL DISORDER

A PRELIMINARY COMMUNICATION

BY

J. K. HEWAT, M.D., C.M., D.P.M.

P. W. W. LEACH, M.R.C.S., L.R.C.P., D.P.M.

AND

R. W. SIMPSON, M.D., D.P.M.

(From Knowle Hospital, Fareham, Hants)

Chlorpromazine, reserpine, and isoniazid have all been used recently in psychiatry with apparent benefit, but their place in the therapeutic field has not yet been fully established. There is considerable need for carefully controlled investigations to assess their individual and combined effects.

A controlled trial of this type is being undertaken at this hospital, using a factorial design as the method of statistical analysis. This method has not previously been applied in medicine, so far as we are aware, although its use in other scientific fields is well known. It enables an assessment to be made of different substances in various combinations, in addition to the effects of each substance individually. In our particular trial this requires the use of eight separate tablets to cover all possible combinations of the drugs, their single use, and the use of an inert substance alone. These tablets are, of course, of identical appearance.

The toxic effects of each drug, when used alone, are well known, but it was thought essential to investigate the effect of the three drugs in combination, which is the subject of this report.

The side-effects of chlorpromazine have been summarized by Charatan (1954), the main ones being toxic jaundice, pyrexia, tachycardia and dyspnoea, nausea, anorexia and epigastric distress, and variable alterations in the leucocyte count. Tasker (1955) has reported

a case of fatal agranulocytosis. Postural hypotension and pallor have also been reported. A further complication, less widely known and occurring with large doses, is an effect on the extrapyramidal system. Kinross-Wright (1954), de Boucaud and Fournial (1954), and J. F. Donovan (1955, personal communication) have reported cases of temporary Parkinsonism with large doses.

The main side-effects of reserpine noted by Moyer (1954), apart from its hypotensive action, are bradycardia, nasal congestion, fatigue and weakness, dizziness, and increased bowel movements. Winsor (1954) also reported leg pains and dyspnoea. Weber (1954), using large doses, reported temporary Parkinsonism in psychiatric patients.

Isoniazid in normal therapeutic dosage rarely causes toxic symptoms. McConnell and Cheetham (1952) noted one case of pellagra, and Zabad (1953) mentions a case of mental disorder. Both cases probably occurred when the patient's original nicotinamide level was low and were cured when isoniazid was withdrawn and nicotinamide administered.

First Trial

Method.—Sixteen patients (eight males and eight females) with chronic psychoses and of widely varying somatic and physiological types were selected. The treatment lasted three weeks and consisted of the oral administration of a compound tablet containing chlorpromazine, 25 mg., reserpine, 1 mg., and isoniazid, 50 mg. Beginning with one tablet, the dose was increased every day until four tablets daily were being given. Daily clinical records were made in order to note any signs of toxicity at the earliest possible stage. Temperature, pulse, and blood-pressure readings were charted daily and weekly weights recorded. The following haematological and biochemical investigations were carried out before and during treatment: haemoglobin, W.B.C. and polymorph count, blood urea, total protein, albumin, globulin and fibrinogen, serum bilirubin, gold flocculation, thymol turbidity, and serum alkaline phosphatase.

The following side-effects were observed:

Cardiovascular System.—A definite fall in blood pressure (more than 20 mm. systolic or 10 mm. diastolic) occurred in eight patients. The average resting pulse rate fell from 86 to 73.

Autonomic System.—Nasal congestion in 3 patients, dryness of mouth in 2, pallor in 6, flushing in 4.

Central Nervous System.—Parkinsonism (rigidity, mask-like face, salivation, and tremor) in 6, tremor (without other Parkinsonian signs) in 4, drowsiness in 1, insomnia in 1, giddiness in 2, headache in 1.

Metabolism.—Increase in weight (1-11 lb.—450 g.-5 kg.) in 12, loss of weight (1-4 lb.—450 g.-1.8 kg.) in 2.

Other Symptoms.—Pains in trunk and limbs in 4, malaise and weakness in 8, shivering in 9, jaundice in 0.

All these side-effects cleared within a few days of stopping treatment. Six patients did not complete the course of treatment owing to the apparent severity of certain side-effects. No abnormal haematological or unequivocal biochemical changes were observed.

Second Trial

In view of the unexpectedly high incidence of extrapyramidal signs it was decided to carry out a further trial using a smaller dosage. Another series of 16 patients (eight males and eight females) were selected, and were given half the original dosage—namely, chlorpromazine, 50 mg., reserpine, 2 mg., and isoniazid, 100 mg., daily for four weeks.

From experience gained in the first trial laboratory investigations were reduced to blood urea, total proteins, serum

bilirubin, gold flocculation, thymol flocculation, thymol turbidity, and serum alkaline phosphatase.

The following side-effects occurred :

Cardiovascular System.—Hypotensive and bradycardic trends similar to those in the first trial were noted (although one patient showed a slight increase in resting and active pulse rates).

Autonomic System.—Nasal congestion in 2 patients, dryness of mouth in 2, pallor in 0, flushing in 1.

Central Nervous System.—Parkinsonism in 0, tremor in 1, drowsiness in 3, giddiness in 2, headache in 0.

Metabolism.—Increase of weight (2–17 lb.—0.9–7.7 kg.) in 11, weight loss in 1, no change in weight in 1, weight not obtainable in 3.

Other Symptoms.—Malaise and weakness in 2, pains in trunk or limbs in 1, jaundice in 0, shivering in 3.

As in the first trial, all side-effects cleared rapidly when treatment was stopped. No abnormal haematological or biochemical changes were found.

Therapeutic Effects in Both Trials

These effects will be dealt with more fully in the large-scale investigation. Although the duration of treatment is too short and the number of patients too small on which to have a firm opinion, these preliminary observations did suggest that the combination of the drugs had a definite effect on the mental state.

The general clinical impressions in both trials were as follows :

First Trial		Second Trial	
Much worse ..	4	Much worse ..	1
Worse ..	3	Worse ..	2
No change ..	5	No change ..	3
Better ..	4	Better ..	7
Much better ..	0	Much better ..	2
		Uncompleted ..	1

Where the effect was beneficial the trend was towards a quieter, more co-operative, and more relaxed patient.

Discussion

An unexpected finding was the high incidence of extrapyramidal signs when the individual dosage of each drug was considered.

With regard to isoniazid therapy, Rubin *et al.* (1952) reported that prolonged administration to dogs resulted in ataxia and convulsions, but, so far as we know, these effects have not been reported in man. Elmendorf *et al.* (1952) state that instances of toxicity similar to those in dogs might be observed in man when the drug was used in larger dosage and for longer periods. Although Parkinsonism has not been reported as a toxic effect of isoniazid, the drug's possible potentiating action in this respect cannot yet be excluded. Chlorpromazine and reserpine have both been noted to cause temporary Parkinsonism, but in each case with larger doses than those used here. Chlorpromazine does not commonly cause such signs, but Kinross-Wright (1954), using an average daily dose of 400–600 mg., reported a few cases of Parkinsonism. de Boucaud and Fournial (1954) and Donovan (1955, personal communication) observed similar cases during treatment with large doses.

In the treatment of hypertension Moyer (1954) used reserpine in doses up to 6 mg. daily for three months, and Dustan *et al.* (1954) used doses up to 10 mg. daily for two to eight months. In neither series were Parkinsonian signs noted. Weber (1954) gave much higher doses in psychiatric patients (10–20 mg. intramuscularly for several days, followed by 6 mg. by mouth daily), and extrapyramidal signs occurred in most of his cases.

Chlorpromazine and reserpine are thought to exert their therapeutic effects through their depressant action on sub-cortical centres, and the occurrence of extrapyramidal signs might be regarded as an expression of such activity rather than as a toxic phenomenon. In view of the moderate doses used in these trials the emergence of such signs suggests

that the drugs may act synergistically on subcortical centres such as the bulbar reticular formation. It is most likely that chlorpromazine and reserpine are the drugs concerned here.

The extrapyramidal effects cannot be regarded as entirely undesirable, and in fact it is the aim of some Continental workers to produce these in order to obtain the optimum therapeutic result.

Another interesting side-effect was the complaint by four patients of a severe feeling of weakness and loss of energy. This may be an exaggeration of the tranquillizing effect of reserpine potentiated by chlorpromazine.

The cardiovascular and autonomic effects have been noted by other workers and require no further discussion.

Summary and Conclusions

Reference is made to a projected therapeutic trial of chlorpromazine, reserpine, and isoniazid, using a factorial design as the statistical method.

The toxic effects of chlorpromazine, reserpine, and isoniazid are summarized.

The results are given of two preliminary trials using (a) the maximum dosage originally intended for use in the main trial, and (b) half this dosage. Sixteen patients were treated in each of these trials, and the results are tabulated with particular reference to toxic effects.

Although Parkinsonism is known to occur with chlorpromazine and reserpine when used singly in large doses, its occurrence with small doses in combination was unexpected, and it is suggested that they might have a potentiating action. This action may have therapeutic significance.

These preliminary trials with the combination of the drugs did not reveal any contraindication to proceeding with the main investigation as planned, apart from a slight modification in dosage.

We wish to thank Dr. A. J. Galbraith, physician superintendent, under whose direction and advice these trials were carried out, and our medical colleagues at Knowle Hospital, all of whom helped in this trial. We are also grateful to Ciba Ltd. for supplying the drugs and to Dr. C. D. Falconer in particular for his technical advice. Dr. E. M. Darmady and the Central Laboratory, Portsmouth, rendered invaluable assistance by advising on and carrying out the haematological and biochemical investigations.

REFERENCES

- Charatan, F. B. E. (1954). *J. ment. Sci.*, **100**, 882.
 de Boucaud and Fournial, P. (1954). *Presse méd.*, **62**, 1358.
 Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H. (1954). *Ann. N.Y. Acad. Sci.*, **59**, 136.
 Elmendorf, D. F., jun., Cawthon, W. U., Muschenheim, C., and McDermott, W. (1952). *Amer. Rev. Tuberc.*, **65**, 429.
 Kinross-Wright, V. (1954). *Postgrad. Med.*, **16**, 297.
 McConnell, R. B., and Cheetham, H. D. (1952). *Lancet*, **2**, 959.
 Moyer, J. H. (1954). *Ann. N.Y. Acad. Sci.*, **59**, 82.
 Rubin, B., Hassert, G. L., jun., Thomas, B. G. H., and Burke, J. C. (1952). *Amer. Rev. Tuberc.*, **65**, 392.
 Tasker, J. R. (1955). *British Medical Journal*, **1**, 950.
 Weber, von E. (1954). *Schweiz. med. Wschr.*, **84**, 968.
 Winsor, T. (1954). *Ann. N.Y. Acad. Sci.*, **59**, 61.
 Zabad, M. (1953). *Lancet*, **1**, 295.

An exhibition of x-ray photography at the Royal Photographic Society (16, Princes Gate, London, S.W.7) from December 13 to 22 will illustrate how extensively radiography is now used in industry. Although in the decades after its introduction radiography was, mainly confined to medicine, Roentgen's paper in 1895 announcing his discovery of x rays had included an x-ray photograph of a piece of metal "showing want of homogeneity," and within a year the radiographic examination of a welded joint was reported from America. Nowadays it is possible to detect defects in steel welds and castings 10 in. (25 cm.) in thickness. Radiography is increasingly being used for inspection purposes in the aircraft, shipbuilding, oil, and other major industries.