sentative sections. The study was financed in part by a grant from the Punjab University.

REFERENCES

- Arnott, W. M. (1954). *Brit. med. J.*, **2**, 887.
 Enos, W. F., Holmes, R. H., and Beyer, J. (1953). *J. Amer. med. Ass.*, **152**, 1090.
 Hannah, J. B. (1958). *Cent. Afr. J. Med.*, **4**, 1.
 Higginson, J., and Pepler, W. J. (1954). *J. clin. Invest.*, **33**, 1366.
 Keys, A., Kimura, N., Kusunawa, A., Bronte-Stewart, B., Larsen, N., and Keys, M. H. (1958). *Ann. intern. Med.*, **48**, 83.
Lancet, 1955, **2**, 1123.
 Lober, P. H. (1953). *Arch. Path. (Chicago)*, **55**, 357.
 Malhotra, R. P., and Pathania, N. S. (1958). *Brit. med. J.*, **2**, 528.
 Muir, C. S. (1960). *Brit. Heart J.*, **22**, 45.
 Steiner, P. E. (1946). *Arch. Path. (Chicago)*, **42**, 359.
 White, N. K., Edwards, J. E., and Dry, T. J. (1950). *Circulation*, **1**, 645.
 Wilens, S. L. (1951). *Amer. J. Path.*, **27**, 825.
 World Health Organization (1958). *Wld Hlth Org. techn. Rep. Ser.*, No. 143.
 — (1959). *Ibid.*, No. 168.

SEQUENTIAL TRIAL OF ISOCARBOXAZID IN ANGINA PECTORIS

BY

ALAN P. GRANT, M.D., F.R.C.P.I., M.R.C.P.

Belfast City Hospital

The evaluation of a new type of compound in the treatment of angina pectoris is well recognized as being difficult. Since the introduction of monoamine oxidase (M.A.O.) inhibitors the first successes claimed have not been confirmed and subsequent reports have been conflicting. The problems involved have been surveyed in a leading article in the *British Medical Journal* (1960). The initial reports on many of these compounds have not been concerned with a control series, and later studies with a double-blind technique have been less enthusiastic. Some effect upon the symptom of angina seems probable, however, and a search is being made for further compounds of this series with fewer side-effects and greater efficacy. Controlled trials are still necessary, therefore, to reach a conclusion on the value and place of these drugs in the routine treatment of angina.

The results of a controlled assessment of isocarboxazid ("marplan"; 3-benzylhydrazinocarbonyl-5-methylisoxazole) is reported below, and a brief attempt is made to assess clinical factors that might have influenced response.

Material and Method

Selected out-patients with a convincing history of angina pectoris were considered for the trial as they became available. The statistical method, an open sequential procedure as described by Armitage (1960), determined its design and the assessment of results.

For admission it was necessary for the patient's angina to be regarded clinically as due to coronary artery disease and to be of at least moderate severity with relief by trinitrin. Severity was recorded on the criteria of Wood (1956), and the following grades were accepted: II, pain on walking on level at average speed; III, pain on walking slowly, and IV, pain at rest.

In addition, the patient's angina had to be static for at least three months, and so far as was possible neurotic and unreliable witnesses were excluded at the outset. A history of cardiac infarction less than six months

previously was not acceptable. Cardiographic abnormalities were regarded as necessary for the diagnosis only in clinically doubtful cases. Before and after treatment each patient had blood-pressure estimations and an electrocardiogram. Patients taking nitrites had their drugs continued but barbiturates and tranquillizers were omitted.

A series of 63 patients began the trial, but eight of them failed to finish for varied reasons—development of cardiac infarction, non-cooperation, and death. The remaining 55 were considered for analysis. The trial was conducted on the double-blind basis, using control tablets identical in appearance to isocarboxazid, and the crossover-within-patient technique was employed, each patient acting as his own control. The treatment given was one tablet three times daily before meals, and was unknown to both patient and observer. The total daily dosage of isocarboxazid was 30 mg. For administrative purposes patients were placed in groups of five, the key for which was opened and the group assessed after completion of both treatments. Each treatment was given for four weeks with a three-weeks interval between, so as to eliminate any possible prolongation of affect from one to the other. The initial treatment was allocated randomly. After each treatment the patients were interviewed and asked to state if they felt any change in their angina, and, if so, was this definite or slight. Minor degrees of help claimed were counted as failures, and only definite statements of marked improvement were accepted as a success.

The statistical plan had to satisfy the power $1 - \beta = 0.95$ of detecting a difference between the two treatments with a two-sided significance level $2\alpha = 0.05$ when the following success rates were adopted. It was expected there would be a favourable response to the control in 40% of patients, $p_1 = 0.4$, and it was thought that if 68% responded favourably to isocarboxazid, $p_2 = 0.68$, the trial could be accepted as a success for this treatment. With these two proportions Fig. 2 of Armitage (1954) gives a value for $\theta = 0.75$; that is, the proportion of united pairs which must be obtained in the trial to indicate success for isocarboxazid. For this critical value of θ the limits of the boundaries in an open sequential design were obtained from Table 3.1 of Armitage (1960).

Results

Table I gives details of the response of the groups to treatment, the untied pairs of which are plotted on the sequential design. A significant preference for isocarboxazid was obtained in spite of a large proportion of failures with both treatments.

As expected the milder cases of angina showed more reaction to the placebo, and tied pairs in whom both treatments were successful were all in this group. In grades III and IV 40% of patients showed a preference for isocarboxazid, whereas in grade II only 27% did so. Males responded more favourably than females—37% to 23%. Neither the patient's age nor the duration of angina had any effect on the outcome, the averages of all groups lying inside the standard deviation of the series. The height of systolic blood-pressure was likewise unimportant, there being little difference between the proportion of patients responding in the upper or lower ranges, percentages being 39 and 36.4 respectively. Analysis of the cardiographic patterns showed that patients with major ischaemia but without definite infarction obtained benefit in 58% of cases. This is a

TABLE I.—Response to Treatments

	Untied Pairs		Tied Pairs		Total
	Isocarboxazid Only Successful	Control Only Successful	Both Successful	Both Failures	
No. of patients	18	5	7	25	55
Grade of angina:					
II	8	2	7	13	30
III	8	3	0	9	20
IV	2	0	0	3	5
Males	14	3	5	16	38
Females	4	2	2	9	17
Average age in years	58.7	57	60.4	59.2	59 ± 8.9
Average duration in years	4.4	3.3	3.2	4.1	4 ± 3.6
Systolic B.P.:					
Under 151	7	3	1	7	18
151–180	4	0	2	5	11
181–210	3	2	2	8	15
Over 210	4	0	2	5	11
Abnormal E.C.G. pattern:					
Normal	3	1	1	4	9
Minor	3	1	2	6	12
Major	7	1	2	2	12
Post infarct	5	2	2	13	22
History of coronary thrombosis:					
No	11	3	5	16	35
Yes	7	2	2	9	20

much higher proportion than in the other groups combined, where only 34% preferred isocarboxazid, and is notable. There was, however, little difference in the response to isocarboxazid so far as history of coronary thrombosis was concerned: accuracy of diagnosis depended on the patient's history.

Sequential of graph of trial: isocarboxazid versus control.

Side-effects were insignificant and no changes were found in either blood-pressure or cardiogram. Malaise and insomnia were complained of by two patients on isocarboxazid and lasted a few days. A few patients had minor gastric upsets with both treatments. In only three of the eight patients withdrawn from the trial was this because of cardiovascular disease; these had cardiac infarctions—two while on the drug and the other while on the control. No conclusions could be drawn from so small a number, but the patient who died while on isocarboxazid had had very severe angina and a previous infarction. His relapse was not unexpected. Of the remaining five patients, three would not co-operate and did not finish the first bottle of tablets or reattend for assessment; no reason could be ascertained for their failure to carry out treatment. Another patient was admitted to hospital elsewhere with an exacerbation of

a gastric ulcer while on the first bottle of placebo and for this reason did not continue the trial. The last patient, with grade IV angina and a previous history of coronary thrombosis, had in addition severe emphysema. He stated that the first tablets, which were isocarboxazid, had given him nausea and he had to stop them after one week. He refused to continue with the trial.

Discussion

A major criticism of many of the early reports on the use of M.A.O. inhibitors in angina is that controls were not used. Overoptimistic results occurred through ignoring the long-established fact that remarkable subjective benefit is produced by an inert substance. Evans and Hoyle's (1933) figure for placebo improvement in these cases was 38%. It is obvious that most of the reports of investigations in which there was no attempt at control are of little value and tend only to confuse. This is borne out by the report of Murphy *et al.* (1961) on pivazide ("tersavid"), in which their experience with a controlled trial was completely contradictory to their previous results.

A controlled trial does not, however, solve all the difficulties in obtaining a useful decision. Patients can be matched in pairs by age, sex, and severity, and a different treatment be allocated to each member of the pair. This method may be statistically ideal, but from clinical experience it seems difficult to regard any two cases of angina as exactly the same under all circumstances. The present investigation therefore used the double-blind crossover technique where each patient was his own control. This method has been used by most workers on angina with apparent satisfaction.

In the actual assessment of subjective response a preliminary experience of daily report cards on frequency of attacks as used by Fife *et al.* (1960) in their trial reporting poor results with iproniazid was not satisfactory. Many patients seemed quite incapable of co-operating to this extent, so that final assessment had to be made on a general feeling of improvement in angina over the month's treatment. Even on this basis I was careful to avoid accepting anything other than a really definite claim of considerable relief with a treatment.

Subjective assessments have themselves come under criticism, and Mitchell's (1961) observations on the discrepancy between a patient's observed exercise tolerance and subjective assessment of it can give rise to no real satisfaction in our methods of evaluating angina. In a trial on pheniprazine Sandler (1961) reassessed this drug by checking the number of trinitrin tablets used, and carried out exercise-tolerance tests with cardiographic control. He found he could not, on these objective criteria, confirm the previous promising results of a subjective controlled trial by Mackinnon *et al.* (1960). Objective methods as described are themselves somewhat artificial and, being not without danger, may not always be considered either justifiable or conclusive.

It would seem, therefore, that while the present trial gave moderately encouraging results, optimism should be tempered with caution in making claims for isocarboxazid. Previous results of a personal trial of the related compound pivazide were disappointing (Grant, 1960). Isocarboxazid, however, produced few side-effects and appeared to react much more favourably. Published reports on this compound in the American literature (Griffith, 1959; Abrams *et al.*, 1960; Bloom,

1960; Halprin, 1960; Hollander *et al.*, 1960; Russek, 1960; Winsor and Zarco, 1960; Wolffe, 1960) claim excellent results, and it is noted that these are all clinical impressions and lack any adequate control. The results of published double-blind trials with other M.A.O. inhibitors summarized in Table II make sober reading.

TABLE II.—Summary of Double-blind Trials with M.A.O. Inhibitors

Authors	Drug	Result	No. of Cases
Dewar <i>et al.</i> (1959)	Iproniazid	Failure	20
Snow and Anderson (1959)	"	"	41
Fife <i>et al.</i> (1960)	"	"	51
Shoskes <i>et al.</i> (1959)	"	Success	23
Mackinnon <i>et al.</i> (1960)	Pheniprazine	Failure	27
Sandler (1961)	"	Failure	12
Phear and Walker (1960)	Pivazide	"	19
Murphy <i>et al.</i> (1961)	"	"	30
Allanby <i>et al.</i> (1961)	Nialamide	Partial success	28

In the present report more patients were assessed than previously, and a significant number of them found symptomatic benefit from isocarboxazid. The proportion of patients favouring the drug was higher in the severer grades of angina, and if the trial had contained more of the milder cases it is possible that a negative result might have been obtained. It is suggested that further trials should consider only severe grades of cardiac pain. The cardiograph appeared important only in the group with gross ischaemic change short of infarct. The danger of producing infarcts in such persons has precluded any attempt to find out whether aemeliomeration of anginal pain can be of benefit to them. This danger has, of course, been a source of anxiety to many people and requires further investigation.

Summary and Conclusions

In a double-blind trial of isocarboxazid, using the cross-over technique, patients were randomly treated with both the drug and placebo. The trial was conducted sequentially, and was stopped when a decision was reached. In the 55 patients whose responses were recorded isocarboxazid was more effective in a dosage of 10 mg. three times daily than the placebo, 18 cases of moderate to severe angina claiming a marked preference to the drug alone and five with the control. Over half the patients (25 out of 55) did not appear, however, to obtain significant relief with either treatment. Factors suggestive of help from isocarboxazid were: male sex; major ischaemia rather than actual post-infarction changes in the electrocardiogram; and severer grades of anginal pain.

Side-effects were insignificant, and isocarboxazid may be of symptomatic help in some cases of angina pectoris.

I am indebted to Dr. Evan Fletcher for assessing the results on some of his patients and to Dr. P. Gorman and Dr. W. D. Linehan for their valuable assistance. My thanks are also due to Dr. M. Corbett, of Messrs. Roche Products Limited, for supplies of "marplan" and placebo, and to Dr. P. C. Elmes for helpful criticism.

REFERENCES

- Abrams, W. B., Becker, M. C., Lewis, D. W., and Killough, J. H. (1960). *Amer. J. Cardiol.*, **5**, 634.
 Allanby, K. D., Cox, A. G. C., Maclean, K. S., Price, T. M. L., and Southwell, N. (1961). *Lancet*, **1**, 138.
 Armitage, P. (1954). *Quart. J. Med.*, **23**, 255.
 — (1960). *Sequential Medical Trials*. Blackwell, Oxford.
 Bloom, N. (1960). *Virginia med. Monthly*, **87**, 23.
Brit. med. J., 1960, **1**, 257.
 Dewar, H. A., Horler, A. R., and Newall, D. J. (1959). *Brit. Heart J.*, **21**, 315.

- Evans, W., and Hoyle, C. (1933). *Quart. J. Med.*, **26**, 311.
 Fife, R., Howitt, G., and Stevenson, J. (1960). *Brit. med. J.*, **1**, 692.
 Grant, A. P. (1960). *Irish J. med. Sci.*, **418**, 466.
 Griffith, G. C. (1959). *Clin. Med.*, **6**, 1555.
 Halprin, H. (1960). *Angiology*, **11**, 348.
 Hollander, W., Chobanian, A. V., and Wilkins, R. W. (1960). *Amer. J. Cardiol.*, **6**, 1136.
 Mackinnon, J., Anderson, D. E., and Howitt, G. (1960). *Brit. med. J.*, **1**, 243.
 Mitchell, J. R. A. (1961). *Ibid.*, **1**, 791.
 Murphy, F. M., Barber, J. M., and Kilpatrick, S. J. (1961). *Lancet*, **1**, 139.
 Phear, D., and Walker, W. C. (1960). *Brit. med. J.*, **2**, 995.
 Russek, H. I. (1960). *Angiology*, **11**, 76.
 Sandler, G. (1961). *Brit. med. J.*, **1**, 792.
 Shoskes, M., Rothfeld, E. J., Becker, M. C., Finkelstein, A., Smith, C. C., and Wachtel, F. W. (1959). *Circulation*, **20**, 17.
 Snow, P. J. D., and Anderson, D. E. (1959). *Brit. Heart J.*, **21**, 323.
 Winsor, T., and Zarco, P. (1960). *Angiology*, **11**, 67.
 Wolffe, J. B. (1960). *Amer. J. Cardiol.*, **5**, 719.
 Wood, P. H. (1956). *Diseases of the Heart and Circulation*, 2nd ed., p. 711. Eyre and Spottiswoode, London.

COMA AS PRESENTING SIGN OF ADRENAL FAILURE AFTER STEROID WITHDRAWAL

A REPORT OF THREE CASES

BY

ERIC D. SILOVE, M.B., B.Ch.

Lately of Johannesburg General Hospital and University of the Witwatersrand, Johannesburg

Patients with latent adrenal insufficiency may suffer an unexpected adrenal crisis when subjected to stress (Williams, 1955). As a consequence of the therapeutic use of the corticosteroids and the resultant depression of the patients' adrenocortical function, this has become a fairly common occurrence. A surgical procedure has classically been cited as the stress factor, and there have been numerous reports of post-operative collapse, sometimes fatal, in patients who have been on corticosteroid therapy (Fraser *et al.*, 1952; Salassa *et al.*, 1953; *Lancet*, 1957; *Brit. med. J.*, 1959; Smyth *et al.*, 1960).

The purpose of this paper is to record the case histories of three patients who, while on long-term corticosteroid therapy, were admitted to hospital in a semi-comatose state with an acute infection, having concomitantly stopped their therapy. Only one of these presented with features more typical of an adrenal crisis.

Case 1

A 68-year-old white woman first developed bronchial asthma in 1940 and continued to have attacks each year, but these were never severe and were easily controlled. In 1952 corticosteroid therapy was first begun in the form of cortisone in a dosage which varied from 50 to 100 mg. daily. In 1955 cortisone was replaced by hydrocortisone for a few months and then by prednisone in equivalent doses. On this treatment the asthma was well controlled until August, 1958, when she was admitted to hospital in severe status asthmaticus. With the use of steroids, bronchodilators, antibiotics, and sedatives, the attack gradually subsided after six days. After her discharge in September she was maintained on triamcinolone, 12 mg. daily, and remained well until March 16, 1959, when she was again admitted to hospital. She had on that morning developed an acute pharyngitis with a temperature of 103° F (39.4° C.), had vomited, and, as a consequence, had failed to take her usual dose of triamcinolone. Later she had become drowsy,