Other serious toxic effects in patients taking the drug have been described by Kline and Jacob (1955), three of whose group developed atonic bladders and bowels when on intramuscular therapy. One of these actually showed symptoms of an autonomic bladder and required catheterization.

Finally, Werenberg (1955), in his series, reports three further deaths: one apparently from cardiovascular collapse; one from embolism of the pulmonary artery, thrombosis of the common iliac vein, and myocardial degeneration, associated with severe constipation; and the third from embolism of the pulmonary artery and thrombosis of the plexus parametrialis together with a large uterine fibroma.

On the other hand, Bowes (1956) reports no serious toxic results in a series of 50 cases, some of whom received up to 600 mg. of pacatal daily.

However, the findings of Werenberg (1955), of Kline and Jacob (1955), and of the present investigation suggest that pacatal should be used only with extreme caution. Chlorpromazine is equally effective in the treatment of chronic regressed female psychotic patients and its toxic effects are much less serious. It seems to us that if either drug is to be used chlorpromazine is the drug of choice.

A reference to the pharmacology of phenothiazine itself shows that liver damage and jaundice, tachycardia, and sensitization of the skin to ultra-violet light are amongst the side-effects which brought it to be regarded as too toxic for use in humans (Martindale, 1952). It is clear that the derivatives of phenothiazine at present in use have toxic side-effects which are by no means negligible and which in some respects are similar to those of the parent substance. Further research is required in an effort to eliminate this unfortunate toxicity in drugs which otherwise seem to be valuable in mental hospital practice.

Summary and Conclusions

A controlled investigation into the effectiveness of "pacatal" in reducing the incidence of incontinence, noisiness, and aggression in chronically regressed psychotic female in-patients is described.

Pacatal was effective in reducing the number of noisy, aggressive, and incontinent acts in these patients, most of whom were suffering from schizophrenia.

Unfortunately, the high incidence of toxic side-effects in this group of patients suggests that the widespread use of pacatal is unjustifiable, at least until considerable evidence to the contrary is available. The toxicity of chlorpromazine, while not negligible, does not seem to be so serious, and it would appear to be the drug of choice. But where sensitivity to chlorpromazine has developed and where a drug of the phenothiazine type is strongly indicated, it would seem justifiable to use pacatal so long as close supervision of the white-blood-cell picture and of bowel and bladder function is maintained.

Acknowledgment is due to William R. Warner and Co. Ltd., who made supplies of pacatal freely available; to Dr. J. D. Silverston, medical superintendent of Lancaster Moor Hospital, for permission to perform the investigation; to Mr. H. Lewty, hospital pharmacist, for his assistance; and to the nursing staff, without whose help this investigation could never have been made.

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NICOTINYL ALCOHOL TARTRATE IN INTERMITTENT CLAUDICATION

BY

R. O. GILLHESPY, M.D., F.[redacted]C.P.Ed.
Physician, Dudley Road Hospital, Birmingham

The purpose of this investigation was to assess the value of nicotinyl alcohol tartrate ("ronicol") in the treatment of patients suffering from severe intermittent claudication secondary to generalized arteriosclerosis.

Nicotinyl alcohol tartrate is the alcohol corresponding to nicotinic acid, and has essentially the same vasodilator properties as the latter. However, its action is more sustained than that of nicotinic acid, probably because, in addition to the vasodilator properties of the alcohol itself, partial metabolism of it in the body results in the gradual release of nicotinic acid. The vasodilator effect of nicotinyl alcohol tartrate is mainly on the small arteries and arterioles. A number of investigators in the United States and in Europe have reported encouraging results with its use in the treatment of peripheral vascular disorders.[1-10] However, although the drug is widely used in Great Britain, no report has yet been published describing a controlled investigation of its use in intermittent claudication.

Plan of Present Trial

The investigation was carried out on the "blind" principle; the majority of the patients had previously been admitted to hospital for full investigation and all had been treated previously with other compounds alleged to be of value in intermittent claudication. For inclusion in the trial, patients had to fulfil the following criteria: *(a)* There had been present for at least two months a severe gripping pain lasting for more than one minute in one or other of the calf muscles, coming on after a constant amount of exercise and relieved by a few minutes' rest. *(b)* Pulsation was absent in one or other of the palpable arteries in the affected limbs. *(c)* The skin of the extremity was blue or gangrenous and distinctly colder than that of the less affected limb.

Patients were excluded from the series if they were suffering from any other serious disease, correction of which might have influenced the assessment of the results. Congestive heart failure, when present, was always corrected by appropriate treatment in hospital before the patient was included in the series.

Once the diagnosis had been established all treatment was withheld for a period, in order to prevent any "overlap" of therapeutic effects. Patients were then treated with either nicotinyl alcohol tartrate, one 25-mg. tablet four times daily, or with dummy tablets of identical appearance. Treatment was allotted by random selection by an independent person in the pharmaceutical department and I did not know the distribution of the patients until after the results of the trial had been assessed. The treated and control groups were comparable in respect of age and sex.

The series originally contained 50 patients, but by the end of the trial only 30 remained for final assessment. Of the remaining 20 patients, 15 died before the end of the trial, three moved to another area, and two refused to complete the course of treatment. It must be appreciated that, when organizing a trial using such poor clinical material over a fairly prolonged period, deaths from coronary thrombosis, cerebral haemorrhage, or renal complications, as a result of the generalized arteriosclerosis, are inevitable. All the case records of patients who died were studied, and it was decided to exclude them from the assessment of results because the duration of their treatment was too variable for useful assessment. The losses by death did not affect the comparability of the treated and control groups.

Assessment of Results

In order to achieve a high degree of standardization a form was prepared and completed for each patient. In each case the results were assessed, after at least 18 months' treatment, by analysis of the information contained in these forms. The results of treatment were classified as follows: "No benefit" means that the patient's condition had remained stationary or had become worse, as shown by a significant reduction in the walking distance before the onset of claudication, progression of the skin changes, or the presence of gangrenous ulceration. "Slight improvement" was considered to have taken place if the progress of the disease appeared to have been halted and if there was a slight but definite increase in the number of yards traversed before the onset of claudication. "Moderate improvement" means that after treatment the patient was able to walk at least half a mile further than had been possible before treatment.

The measurement of walking distance was carried out by the patients themselves, because experience has shown that this type of patient knows fairly accurately the distance that can be walked before claudication begins. It was impressed on all these patients that they must measure this distance (at their ordinary walking speed) in paces, each pace being taken as one yard.

After the trial had been in progress for about two and a half years, and all patients had received at least 18 months' treatment, it was closed and the result in each patient was assessed. Only then was I given the key to which patients had been on nicotinyl alcohol tartrate and which on placebo therapy. The results are shown in the table.

Results of Trial

Treatment	No. of Patients	Moderate Improvement	Slight Improvement	No Benefit
Nicotinyl alcohol tartrate ..	17	10	3	4
Dummy tablets ..	13	0	4	9

Side-effects.—The only side-effect observed was mild flushing of the face in two of the 20 patients excluded from the final assessment of results.

Discussion

Intermittent claudication marks the beginning of the final stages of a slowly progressive arterial disease. After a given amount of exercise the intensity of the pain is so impressive and its onset so constant that the alleviation of this symptom is an obvious way of assessing the value of any drug used in treatment.

Because of the difficulty of making an unbiased assessment of "improvement" in such a chronic condition, it was felt to be essential to carry out a "blind" control trial, comparing the effect of nicotinyl alcohol tartrate with that of a placebo. In this disease it is difficult to compare the effect of any one drug with that of another by the application of the "blind" method, because of the large number of patients who would be required, so no such attempt was made. Further, with the use of such poor clinical material a large percentage of "rejects" can be expected, and thus relatively large numbers must be included initially, even when comparing one drug with placebo therapy, in order to obtain final figures which are sufficient for analysis. In the present trial it was found possible to include 50 patients within a relatively short time, and by these means it was hoped that a sufficient number would remain at the end of the trial to give significant results.

When comparing the numbers of patients who improved on nicotinyl alcohol tartrate with those on dummy tablets there can be no doubt that the patients on the active drug improved to a greater extent than did those on the placebo. The converse was also true—that is, the number of patients failing to derive benefit from the active tablets was significantly smaller than the number of those who failed to receive benefit from the placebo.

It should be noted that statistical analysis takes no account of the fact that this is a progressive disease and is therefore no substitute for clinical experience. In the eyes of the clinician, a drug which halts the inevitable downward progress of the patient would be considered "beneficial," although, in the eyes of the statistician, a patient whose condition was unchanged at the end of 18 months would be considered to have received "no benefit."

Summary

A "blind" controlled trial is described in which 50 patients with severe intermittent claudication secondary to generalized arteriosclerosis were treated with nicotinyl alcohol tartrate or dummy tablets. Patients whose condition was complicated by the presence of other pathological processes were excluded. By the end of the trial the results of at least 18 months' treatment with nicotinyl alcohol tartrate (17 patients) and dummy tablets (13 patients) were available for comparison.

It was found that the results in those patients on the active drug were significantly better than in those who had received the placebo. It is therefore concluded that nicotinyl alcohol tartrate is a useful drug in the control of intermittent claudication.

The value of the "blind" method in a trial of this nature is discussed.

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INTRAMEDULLARY NAILING FOR RECENT FEMORAL SHAFT FRACTURES

BY

A. E. STEVENS, M.B., F.R.C.S.Ed.

Consultant Surgeon, Redhill County, Horsham, and Dorking Hospitals

AND

J. PETT TURNEY, M.B., F.R.C.S.

Formerly Senior Surgical Registrar, Redhill County Hospital

During the past 16 years the insertion of intramedullary nails into the shafts of long bones has been done with increasing frequency. The method is not a new one, and in an extensive review of the difficulties of this form of treatment Watson-Jones and others (1950) discussed medullary nailing "after 50 years." They point out that Nicolayson in 1897 writes of the method, and Hey Groves (1918–19), in this country, described a number of cases, mostly of battle casualties from the first world war, treated in this way in 1916 and 1918. More recently, Küntscher (1940) has reintroduced the method, and there is now a vast amount of literature on the subject both on the Continent and in America. Böhler (1948) published his monograph on the method, dealing with 600 cases treated in his clinic, and the American Academy of Orthopaedic Surgeons (1951) surveyed 700 cases treated by 15 surgeons.