THE TREATMENT OF INTERMITTENT CLAUDICATION 1

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Since its first description in the horse by Bouley (1831), and in man by Brodie (1846), intermittent claudication has been associated with obstruction of the main limb arteries, a conclusion firmly established by Erb (1898). Subsequent experience has fully confirmed this view of intermittent claudication, apart from its occurrence in severe anaemia (Pickering and Wayne, 1934). Lewis, Pickering, and Rothschild (1931) showed that pain is due to the release of a substance, 'Factor P', from muscle-fibres during contraction, and the accumulation of this substance, normally removed by the circulation, above the threshold for the pain nerves in muscle. The conception has accordingly arisen that the amount of exercise necessary to produce pain in intermittent claudication is a measure of the extent to which the normal increase in muscle blood-flow with exercise is restricted by organic arterial obstruction. In this way intermittent claudication may be regarded as an index of the degree of restriction of blood-flow to the affected muscles. Treatment may be prescribed with the object of increasing blood-flow to the muscles by dilating temporarily, or enlarging permanently, the vessels which chiefly limit flow, presumably in this case the collateral vessels which carry blood past the obstruction in the main channel. Treatment is usually prescribed on a theoretical basis, and there have been relatively few attempts critically to assess its worth. Such an attempt is made in this paper. In selecting a test we have chosen the simplest, that of asking the patient to walk at his ordinary pace over a pair of steps 18 inches high, as originally introduced by Wayne and Laplace (1933) in investigating angina pectoris. While this test has the disadvantage that not all factors are under full control, it has the great advantage of familiarity to the patient, and the results are not affected by variations in the skill of performance, which are a major and uncontrolled factor in more complicated procedures. At each attendance the following observations were made on each patient:

1. Any treatment given since the previous visit.
2. The site of pain experienced.
3. The number of circuits over the steps which the patient completed before pain developed.
4. The time taken to walk the number of circuits.
5. The average rate at which each circuit was completed.
6. The time taken for the pain to subside with the patient standing still.
7. The room temperature.

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At each visit at least two recordings of the exercise-tolerance were made, and between tests the patient rested on a chair for a period of at least 10 minutes. A longer period of rest did not significantly improve subsequent performance. The possible sources of error in this method of investigating exercise-tolerance must be considered. The end-point of the exercise test is entirely subjective, and there is no method of ascertaining that the patient can be relied upon to stop when pain develops. Furthermore, the patient himself may count the circuits, and this knowledge may influence his decision as to when to stop. We have guarded against this factor as far as possible by informing the patient that
we are primarily interested in timing the exercise. Again, the duration of the
pain after exercise cannot readily be estimated by the patient, and we have
found that a true improvement in exercise-tolerance is accompanied by a
decrease in the duration of the pain, in spite of the longer period of exertion.
The patient was given no information regarding the times.

Before undertaking any investigation into the results of treatment it is
essential to appreciate the variation in exercise-tolerance occurring naturally

![Diagram](https://example.com/diagram.png)

**Fig. 2.** Spontaneous improvement occurring in Case 40 while receiving
inert tablets for 300 days. The improvement was shown by an increased
exercise-tolerance and a decreased duration of pain. The rate of walking,
as reflected by the mean time per circuit, did not alter significantly.

in the course of the disease (Silbert, 1938). A group of 10 patients was accord­
ingly observed over periods of several weeks, without any treatment being
given. Remarkable fluctuations in exercise-tolerance were seen in many of
these cases. The results showed that on any one day the variations in exercise­
tolerance were small, though, as will be pointed out later, on a single day the
exercise-tolerance might be conspicuously affected by procedures involving
therapeutic suggestion. On different days the variations in exercise-tolerance
were usually much greater, though the rate of walking remained remarkably
constant. The observations in one case are shown in Fig. 1, and the results in
all 10 cases are summarized in Table I. Variations from the mean individual
exercise-tolerance were occasionally as great as \( \pm 45 \) per cent., and in the series
the coefficient of variation was between 12 and 28 per cent. In the majority of
cases the fluctuations in exercise-tolerance were not consistently associated with
the slight changes in the rate of exercising. Furthermore, the patients showing
most variability in the speed of walking (for example, Cases 22 and 23 in Table I)
did not show the greatest variations in exercise-tolerance. We have accordingly
regarded these small alterations in the rate of walking as of little importance in
the assessment of results. The fluctuations in exercise-tolerance did not neces­
sarily represent any general tendency towards deterioration or improvement.
From these considerations it is obvious that no valid conclusions can be based
on single observations before and after any treatment. The difficulties in
assessing therapeutic effects are thus apparent, and are further illustrated by
Case 40 (Fig. 2). This patient, a man of 51 years, received inert tablets over a
period of 300 days, and during that time, despite fluctuations, there was a
remarkable increase in his exercise-tolerance, which was noticeable within six
weeks of his first attending the hospital. This increase continued steadily
throughout the following three months, though the rate of exercise remained
constant. If one of the treatments under investigation had been given, the
spontaneous improvement might easily have been attributed to the specific
action of the drug. It has too readily been assumed in previous investigations
that spontaneous changes do not occur.

The subjects of our investigation consisted of 40 non-diabetic male patients,
aged between 40 and 70 years, whose main complaint was of pain in the calf, or
calves, appearing on exertion and relieved by rest, for which they were referred
to hospital. The treatments given to these 40 patients were divided into two
groups.

1. **Long-term treatments** given continuously for several weeks, the effect upon
   the exercise-tolerance being observed after that period (Table II).
2. **Short-term treatments**: a drug, usually given intravenously, which produces
   a rapid effect, the patient being exercised while the effect is at a maximum.
   In all cases the efficacy of these short-term treatments was assessed by
   comparison with the effect of a control injection of some inert substance
   given previously at the same visit.

Although the number of patients treated by any one method is small, all these
patients have been seen at frequent intervals throughout a period of two years.
Before any long-term treatment was started, each patient was seen at weekly
intervals for a period of at least seven weeks, in order to establish an adequate
base-line on which to assess the value of future therapies. This was essential in
view of the fluctuation in exercise-tolerance which occurs even in untreated
patients, and to which we have already referred.

**Long-Term Treatments**

1. **Intermittent venous occlusion.** Lewis and Grant (1925) demonstrated that
   a marked increase in arterial flow follows the release of venous occlusion, the
   amount of increase depending upon the degree and duration of application of
   venous congestion. Collens and Wilensky (1936) utilized these observations in
   devising a machine which produced intermittent venous occlusion, and in 1937
   they reported the results of treatment of 124 cases of arterial disease by this
   machine. Brown and Arnott (1937) described another machine, and in the
   following year recorded good results in 12 out of 13 cases treated (Brown and
   Arnott, 1938). Evoy and de Takats (1948) recommended this treatment, if
given for very prolonged periods, in certain types of obliterative vascular disease. In spite of these encouraging reports Allen, Barker, and Hines (1946) considered that intermittent venous occlusion was of very limited value, but that it might be a useful adjunct to other treatments. The intermittent venous occlusion machine which we have used is similar to that described by Brown and Arnott (1937). The treatment is given in stretches of four hours throughout the 24. Between the four-hour stretches, during which the machine runs continuously, it has been disconnected for half an hour. This break serves two purposes: it allows the patient out of bed to the lavatory and bathroom, and we find that the machines tend to run better if allowed these fairly frequent periods of inactivity. This treatment has been given on 19 occasions to 16 patients, one patient receiving the treatment on three separate occasions and another on two separate occasions. In two cases the period of treatment was only 50 hours. One of these two patients discharged himself before the course was completed; the other developed gangrene, and the treatment was discontinued. In the other 14 patients the average length of treatment was 272 hours. Of these 16 patients only five have shown any improvement. The remaining 11 have shown no change, although the amount of treatment given was at least as great as in the case of those who improved. The progress of four of the patients who improved with this treatment was as follows:

Case 26, a man aged 63 years, was first investigated as an in-patient, and six observations were made over a period of one week. His average exercise-tolerance for this week was 29 circuits over the steps, with extremes of 25 and 32 circuits. He was treated with a total of 252 hours' venous occlusion, and then was discharged, his maximum number of circuits completed while receiving the treatment being 47. During the following two months he was seen on six occasions. His exercise-tolerance averaged 35 circuits. During the past 18 months he has persistently failed to keep his appointments.

Case 7, aged 60 years, maintained improvement for six months after his discharge from hospital, and then developed a fungus infection of the toes with a superadded pyogenic infection, and was readmitted. The infection could not be controlled, an area of ulceration and cellulitis developed, and eventually the leg was amputated above the knee. This man’s exercise-tolerance was as follows:

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>17</td>
<td>7 weeks</td>
</tr>
<tr>
<td>After eight days’ rest in bed</td>
<td>3 (in one day)</td>
<td></td>
</tr>
<tr>
<td>After 23 days’ rest in bed and 260 hours’ I.V.O.</td>
<td>2 (in one day)</td>
<td></td>
</tr>
<tr>
<td>After discharge from hospital</td>
<td>24</td>
<td>5 months</td>
</tr>
</tbody>
</table>

Case 30, aged 60 years, maintained his improvement after treatment for nine months, after which Achilles tenotomy was performed. He has been completely free of pain since the operation.

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>21</td>
<td>3 months</td>
</tr>
<tr>
<td>After 23 days’ rest in bed and 290 hours’ I.V.O.</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>After discharge from hospital</td>
<td>9</td>
<td>2 months</td>
</tr>
</tbody>
</table>
Case 14, aged 58 years, died from a myocardial infarction 17 days after his discharge, but his performance before and immediately after treatment was as follows:

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>27</td>
<td>5 months</td>
</tr>
<tr>
<td>After 21 days' rest in bed and 270 hours' I.V.O.</td>
<td>2</td>
<td>27.0</td>
</tr>
</tbody>
</table>

The chief difficulty in assessing such beneficial effects as may accrue from this form of treatment is to determine how much of the improvement is due to the venous occlusion and how much is due merely to rest in bed or the lapse of time. In order to clarify this point all patients except the first four were put to bed for a week before this treatment was started. In three of the five patients who were benefited by venous occlusion there was an appreciable increase in exercise-tolerance after the period of rest in bed, and this improvement continued for the following two weeks, during which time the patient stayed in bed and also received intermittent venous occlusion. In one of the patients there was no increase in exercise-tolerance after eight days in bed, but a very striking increase after 272 hours' venous occlusion. The fifth patient had not been seen before admission to hospital, so that there was no base-line on which to found a comparison. An increase in exercise-tolerance as a result of rest alone was demonstrated in two other patients, as shown in the following tables.

Case 17 (aged 62 years)
- Before rest in bed
- After 14 days' rest in bed at home
- One month later

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>2 months</td>
<td>9.3</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

Case 16 (aged 57 years)
- Before rest in bed
- After 11 days' rest in bed in hospital

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>15 days</td>
<td>16.2</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>29.5</td>
</tr>
</tbody>
</table>

In Case 17 the exercise-tolerance had reverted to its former state within two weeks of getting up; Case 16 has remained improved for over eight months.

From these observations we were left with little doubt that the improvement which resulted in patients treated with intermittent venous occlusion might equally well be the result of rest in bed. To confirm this belief we arranged for two patients to receive treatment with venous occlusion at home, for 380 hours and 150 hours respectively. Both continued their normal occupation during the day, and used the machine only during their normal resting times. In neither patient was there any significant increase in exercise-tolerance. Finally, the fifth patient to show improvement with intermittent venous occlusion was a man of 52 years who suffered from pain affecting both calves equally. After eight days' rest in bed there was a definite increase in exercise-tolerance. He was then given treatment with intermittent venous occlusion to one leg only. The subsequent increase in his exercise-tolerance was shared by both legs, and the patient continued to develop pain simultaneously in the calves of the treated and untreated legs. After 100 hours' venous occlusion to the left leg, a
further 100 hours’ venous occlusion was given to the right leg, no further treatment being given to the left. Again the improvement continued equally in both legs. This observation was repeated on another patient, aged 69 years, who showed slight improvement with rest in bed, and who was subsequently treated with 100 hours’ venous occlusion to the left leg only, in spite of claudication in both calves. The subsequent improvement was shared equally by both legs. But in both patients the increase of exercise-tolerance which occurred with treatment was such as might well have occurred spontaneously. The observations made in these four cases support our belief that the advantage of intermittent venous occlusion lies in the enforced bed rest, and that venous occlusion alone is valueless in the condition.

2. Vitamin E. Shute, Vogelsang, Skelton, and Shute (1948) treated a small series of cases of peripheral vascular disease with vitamin E, and considered that this substance had therapeutic value. Ratcliffe (1949) treated 41 cases of intermittent claudication with vitamin E in a dose of 400 mg. daily, and found that 34 of these patients were improved. He recommended that treatment should be continued for at least three months. Boyd, Ratcliffe, Jepson, and James (1949) treated 81 cases of claudication with vitamin E; in 32 cases the results were classified as good, and in another 32 as an improvement, while the remaining 17 patients were unrelieved. We have treated six cases of intermittent claudication with vitamin E. All the patients were given 400 mg. of synthetic vitamin E daily, two patients for a period of six weeks, two for a period of seven weeks, one for a period of eight weeks, and one for a period of five months. In only one case was there an increase in exercise-tolerance; the details of this case are as follows:

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>14</td>
<td>5 weeks</td>
</tr>
<tr>
<td>After vitamin E for one month</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>After vitamin E for two months</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Three weeks after stopping vitamin E</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Four months after stopping vitamin E</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Seven months after stopping vitamin E</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

The maximum improvement occurred four months after the vitamin E had been discontinued. In this patient there was obviously considerable variation, and the improvement cannot be definitely related to the vitamin E therapy. In none of the other five patients treated with vitamin E was there any increase in exercise-tolerance.

3. 2-Benzyl-4,5-imidazoline hydrochloride (tolazoline, ‘priscol’). In 1946 Chess and Yonkman showed that ‘priscol’ is both sympatholytic and adrenolytic in reference to the control of blood-pressure and salivation. Grimson, Reardon, Marzoni, and Hendrix (1948) treated five patients, all suffering from arterial disease with skin changes, and considered that ‘priscol’ was a useful adjunct to treatment in many cases of peripheral vascular disease. Douthwaite and Finnegan (1950) treated 24 male patients suffering from intermittent claudication with 50 mg. of ‘priscol’ by mouth, four times daily, for an unspecified
period. In 12 of their patients the exercise-tolerance was more than doubled. We have treated two groups of patients with 'priscol'. The first group consisted of 10 patients treated with 25 mg. of 'priscol' four times daily by mouth for varying periods of three weeks (six patients), four weeks (one patient), five weeks (one patient), six weeks (one patient), and two months (one patient). Not one of these 10 patients showed any increase in exercise-tolerance as a result of treatment. The second group consisted of eight patients treated alternately with inert tablets and with 'priscol', for two to four weeks at a time, over a period ranging from three to six months. Throughout this time all these patients were seen at fortnightly intervals, when an exercise-tolerance test was performed. In these cases the experiments were controlled with 'dummy' tablets identical in appearance with the true 'priscol' tablets, and administered so that neither the patient nor the observer knew when the changes were made from control to 'priscol' tablets and vice versa. None of the patients in the second group showed any increase in exercise-tolerance while taking the 'priscol' as compared with the control tablets.

4. Nicotinic acid. Abramson, Katzenstein, and Senior (1940) found that nicotinic acid, administered orally in doses of 100–300 mg., more than doubled the amount of blood flowing to the hand. We have given this substance to 10 patients by mouth, in a dose of 100 mg. four times daily, over periods of three to six weeks. None of the 10 patients has shown any significant increase in exercise-tolerance.

5. Methyl testosterone. Edwards, Hamilton, and Duntley (1939) administered testosterone propionate in peanut oil by intramuscular injection two to three times a week, and found an increase in exercise-tolerance, with relief of pain when at rest and a feeling of well-being. Our interest in this substance was aroused by one of our patients who was sent some methyl testosterone by a relative. His exercise-tolerance tests for the three months before and after taking this drug were as follows:

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Duration of observations</th>
<th>Mean number of circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three months before treatment</td>
<td>14</td>
<td>3 months</td>
</tr>
<tr>
<td>One week after starting treatment</td>
<td>2</td>
<td>.</td>
</tr>
</tbody>
</table>

When the testosterone was finally discontinued after two months' continuous administration, we were unable to produce the pain of claudication in this patient, who was still free from pain when last seen six months after the administration of methyl testosterone was discontinued. In this patient a sudden improvement occurred after taking methyl testosterone in a dose of 10 mg. per day for a week. It was difficult to imagine that this amount of testosterone had been responsible for such a dramatic change. We accordingly gave this substance, in the same dose of 5 mg. twice daily by mouth, to nine other patients for periods of three weeks to six weeks, without effecting any increase in the exercise-tolerance.

6. Papaverine hydrochloride. Allen, Barker, and Hines (1946) stated that papaverine improves the peripheral arterial circulation, and Mulinos, Shulman,
and Mufson (1939) found the drug of value in the treatment of Raynaud's disease. We have given this drug by mouth in a dose of two grains four times daily to 10 patients for periods of three to eight weeks. Two patients showed slight increases in exercise-tolerance while taking papaverine; these increases fell within the range of spontaneous improvement noted in Table I. None of the remaining eight patients showed any improvement.

7. Tobacco. Maddock and Coller (1932) studied 20 patients, and found that there was a rise in pulse-rate and blood-pressure, and a fall in skin temperature, while the patients smoked tobacco. Wright and Moffat (1934) and Barker (1933) confirmed the fall in skin temperature, and attributed the change to the nicotine inhaled while smoking. Seven of our patients who were heavy smokers (over 15 cigarettes a day) gave up smoking completely and suddenly. In none was there any increase in exercise-tolerance in the two months after smoking was stopped, during which time no other treatment was given. On the other hand, one patient treated with testosterone, in whom the most conspicuous improvement was seen, had stopped smoking four months before treatment with testosterone was started, but during those four months his exercise-tolerance had remained stationary, subject to normal variation. Similarly, the patient who showed the spontaneous improvement illustrated in Fig. 1 stopped smoking at the time when the observations began.

8. Aminophylline. Although Scupham (1934) considered that theobromine improved the peripheral circulation, subsequent observers (McGovern, McDevitt, and Wright, 1936) failed to confirm this impression. We have up to date treated seven patients with aminophylline by mouth, in a dose of 0.2 gm. four times daily. One patient showed a slight increase in exercise-tolerance, which was within normal variation, but no effect was observed in the remaining six.

9. Dihydroergotamine. Nickerson (1949), reviewing the pharmacology of adrenergic blocking agents, found considerable discrepancies in the value of ergot preparations in the treatment of peripheral vascular diseases. Hayes, Wakim, Horton, and Peters (1948) found an increase in the peripheral blood-flow in the lower extremities after the intravenous injection of dihydroergocornine. Bluntschli and Goetz (1948) considered the effect of dihydroergotamine on the peripheral circulation in normally innervated limbs to be like that of ergotamine, a mixture of the direct effect on the peripheral vessels and a paralysis of sympathetic impulses, but thought the direct effect on the vessels to be less marked with dihydroergotamine than with the original compound. We have treated 10 patients with a 15 per cent. solution of dihydroergotamine by mouth, in a dose of 0.7 to 1.0 ml. three times daily, for periods of from three to seven weeks in nine cases, and only two weeks in one. In none of these patients was there any increase in exercise-tolerance.

10. Lumbar sympathectomy. Allen, Barker, and Hines (1946) and Adson and Brown (1932) considered lumbar sympathectomy to be of considerable value in the treatment of thromboangiitis obliterans. Boyd, Ratcliffe, Jepson, and James (1949) treated 63 patients with intermittent claudication by lumbar sympathectomy; 37 were reported as showing 'good improvement', 15 as
5. *Tolazoline* (‘priscol’), given by intravenous injection in a dose of 25 mg. to 16 patients.

6. *Dihydroergotamine*, given in a dose of one mg. by intravenous injection to 16 patients.

7. *Padutin*, given in a dose of four to six units by intravenous injection to 16 patients.

On each occasion the administration of the substance under test has followed the trial of an inert control substance, such as one ml. of normal saline, glucose solution, or 2 per cent. procaine, by injection, or, as a control for glyceryl trinitrite, an inert chocolate-coated tablet of similar appearance and size given by mouth. In all cases an interval of at least 10 minutes has elapsed between the administration of the control (and the subsequent exercise-tolerance test) and the administration of the active substance, and during this time the patient has been at rest, sitting on a chair. In no case were we able consistently to produce an increase in exercise-tolerance which we could attribute to the action of the drug. On several occasions the injection of normal saline, given as a control procedure, produced a greater effect than the substance under investigation (Fig. 3).

**Discussion**

The purpose of the present investigation was to decide whether a selected few of the treatments which have been described as effective in the treatment of intermittent claudication did, in fact, increase the exercise-tolerance of patients suffering from this complaint. With this aim in view we have given a total of 200 individual treatments to patients; and of this total number of treatments given 107 have been what we have called ‘short-term treatments’, that is, a single dose of a drug given on one occasion only, at one visit. The poor results achieved are hardly surprising, since it is hard to imagine any one drug, given on one occasion only, producing an appreciable increase in blood-flow through limb-vessels which are sufficiently obstructed to cause claudication. At the time that the pain develops, the vessels in the muscles are under the influence of local metabolites which are powerful vasodilators, and it is improbable that any drug will produce further vasodilatation in such circumstances. In these experiments one important point was demonstrated, namely, the large psychological effect which may be produced by any treatment involving intravenous injection. In some cases normal saline so given led to a threefold improvement in the exercise-tolerance. This effect was noted even in severe cases of peripheral arterial disease, and it is a factor which must be taken into account whenever any spectacular form of treatment is employed. On the other hand, the failure of the long-term treatments to be effective is more surprising, and is certainly depressing. Of all the patients who received long-term treatments, improvement has been noticed only in two patients treated with intermittent venous occlusion, in one patient treated with vitamin E, and in one patient treated with methyl testosterone. Three other patients improved under treatment with venous occlusion, but we demonstrated that their improvement was due to the rest in bed. In the patients who received intermittent venous occlusion and
improved, the sites of arterial obstructions, as determined by the absence of palpable pulses, oscillometry, and reactive hyperaemia tests, were not consistently different from those found in the patients who did not improve. This leaves us with only four instances in which improvement might be attributed to the treatment which we have given. We have described the fluctuations in exercise-tolerance which are so typical a feature of this disease, and have given as an illustration one case in which a spontaneous recovery occurred while the patient was taking inert tablets. It is possible, and we think highly probable, that the increased exercise-tolerance in these four patients was due to a spontaneous recovery, and was unrelated to the treatment given. In the two patients who improved after taking vitamin E and methyl testosterone we consider that treatment with the drug was started shortly after a recent arterial obstruction. It is well recognized (Silbert, 1938; Boyd, Ratcliffe, Jepson, and James, 1949) that for three to six months after such an obstruction the exercise-tolerance shows progressive improvement; it seems more probable that the improvement which we observed in these two patients was that which may follow an arterial obstruction, rather than a response to therapy.

Whether the patients who improved did so as a result of treatment or for some quite irrelevant reason, our results certainly differ from those of other workers. There are several possible explanations for this discrepancy, namely, that our assessment of therapeutic action may be faulty, that the treatments have been given for inadequate periods, that we have given the treatments to the wrong type of patient, and that, as we suspect, these treatments are in fact ineffective. These possibilities will be considered in order.

1. Assessment of effects, and duration of treatment. The only two criticisms which can be raised against our technique of assessing therapeutic activity are directed against the method of estimating exercise-tolerance. The first is that we have had no control over the rate at which the patient walks; this we consider unimportant, since the variation in the rate of walking of any one patient was so slight as to be insignificant, as we have already shown. The second criticism is that suggested by Shepherd (1950), that by simple exercise-tolerance tests it is impossible to decide whether any improvement which results from treatment is due to an increased blood-flow or to an analgesic effect of the drug; but since the treatments used failed to relieve the pain of claudication, this criticism does not apply. Ratcliffe (1949) and Boyd, Ratcliffe, Jepson, and James (1949), in discussing treatment with vitamin E, stated that in every case which responded to vitamin E therapy there was noticeable objective improvement after two months. The only patient of our series who improved while taking vitamin E showed increases in exercise-tolerance which could not be strictly correlated with the taking of the drug. Furthermore, an undoubted spontaneous improvement of a greater order subsequently occurred in this patient when he was receiving no treatment. Although most of our patients who received vitamin E did so for periods of only six to eight weeks, they were all seen at frequent and regular intervals, so that, had any subjective or objective improvement occurred, it would have been noticed, and the treatment
would have been continued. Since no improvement was observed except in the one patient mentioned above, we did not proceed with courses longer than those stated. But in view of the discrepancy between our results and those of Ratcliffe (1949), further trials over longer periods are being carried out. Such prolonged treatment raises the difficulty that the longer a treatment is given, the greater is the possibility of a spontaneous change. This argument may be applied to treatment with any drug, and for this reason we have in general restricted the treatment to periods not exceeding two months, since we consider that if the drug is effective some improvement should be noticed within that time.

2. **Type of patient.** Boyd, Ratcliffe, Jepson, and James (1949) classified their cases according to the response to continued exertion once pain has developed: in Group 1 the pain disappears if exertion be continued; in Group 2 the pain reaches a maximum intensity, and maintains a steady level until exercise ceases; in Group 3 the pain, once developed, rapidly increases in severity with continued exertion, bringing the patient to a halt. They regarded the patients in Group 1 as having a minimal interference with arterial flow, those in Group 3 as being grossly affected, and those in Group 2 as intermediate. They maintained that the treatment should be different for each group: patients in Group 1 would be relieved by 'almost anything', for patients in Group 2 they found both vitamin E and lumbar sympathectomy effective, and the majority of patients in Group 3 required an Achilles tenotomy for the relief of their pain.

We classified the majority of our patients similarly by making them continue walking after the development of pain. In no case did the pain disappear with continuation of the exercise over the steps. Nine patients were able to proceed with the walking without the pain becoming more severe. In 24 the pain eventually stopped the exercise test. In the few cases in which improvement occurred, it did so equally in the two groups. Similarly there was no correlation between the severity of the initial restriction of exercise-tolerance and any subsequent improvement. The above considerations force us to accept the fourth explanation for the failure of our patients to respond to treatment, namely, that the medical treatments which we have given are ineffective in increasing the exercise-tolerance of patients suffering from intermittent claudication.

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**Summary**

1. The treatment of 40 patients suffering from intermittent claudication, and the method of assessing results, are described. Considerable fluctuations in exercise-tolerance, and spontaneous improvement, may occur and must be taken into account before any success is attributed to specific therapy.

2. The treatments consisted of 11 different therapies given over a prolonged
period, in addition to single administrations of seven different drugs. The effects of vitamin E, tolazoline ('priscol'), methyl testosterone, nicotinic acid, dihydroergotamine, papaverine, and aminophylline were investigated, in addition to treatment by intermittent venous occlusion, lumbar sympathectomy, and tenotomy.

3. The vast majority of these 40 patients failed to show any improvement as a result of treatment.

4. None of the forms of drug therapy used has shown an increase in exercise-tolerance beyond that occurring naturally in the course of the disease, or beyond that produced by inert preparations.

5. Tenotomy, performed on four patients, has given relief of pain to all, although leaving a residual disability. In one patient this disability was as severe as that due to the original claudication.

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