Clinical, Haemodynamic, Rheological, and Biochemical Findings in 126 Patients with Intermittent Claudication

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Summary

Increased blood viscosity has been shown to be an important factor in reducing blood flow in a review and analysis of the history, clinical findings, and haemodynamic, rheological, radiological, and biochemical measurements in 126 patients with intermittent claudication. In some patients increased viscosity seemed to be the determining cause of claudication. A raised plasma fibrinogen was the most common single biochemical abnormality. The results of conventional serum lipid and lipoprotein estimations were abnormal in the series as a whole but did not correlate with clinical findings or flow measurements at individual patient level. There was, however, a significant correlation between some clinical findings and the susceptibility of the red cells to autoxidation.

Introduction

Intermittent claudication is one of the commonest causes of disability in the middle-aged and elderly. It is also one of the commonest regional manifestations of degenerative arterial disease. In most cases the aetiology is unknown; and, apart from a few patients suitable for reconstructive surgery, there is no effective treatment. Moreover, except for postoperative series, the natural history of lower limb ischaemia still rests almost entirely on clinical studies, uncorrelated with physiological measurements or biochemical data. Such series are of limited value as guides to prognosis in individual patients. Three years ago we decided to assess and follow up in detail a group of patients suffering from this condition. We here summarize the presenting clinical, haemodynamic, radiological, rheological, and biochemical findings in 126 patients.

Patients

Because the patients were unselected and referred from a variety of sources there was no consistent relation between the duration or severity of their disease and our initial studies. We divided them, retrospectively, into three groups—those who had been clinically improving during the previous six to 12 months (group 1), those whose condition had been more or less stationary (group 2), and those who had been steadily deteriorating (group 3). Their average age was 62.5 years (range 35-85 years)

with a 4.5:1 preponderance of men over women. The lapse of time since their first symptom varied from one month to 14 years (average two years and four months). Thirty-one patients remembered that the onset of their symptoms had been acute.

Patients were excluded from the series if they had undergone reconstructive surgery during the previous year; but 18 had had operations more than a year earlier.

At their initial visit all patients were carefully screened for other diseases which might influence the progress of their claudication or which might be relevant to the interpretation of the rheological, haemodynamic, and biochemical findings. Thirty-three patients (26%) had evidence of ischaemic heart disease. The blood pressure readings were not significantly higher than would be expected in a healthy group of the same age (average 154/88 mm Hg). Six patients (5%) were diabetic, all well controlled on diet or oral hypoglycaemic drugs or on both forms of treatment. Sixty-seven per cent. of the patients smoked cigarettes, about half of them more than 15 a day.

Investigations

Blood Flow Measurements.—The calf blood flow was measured in all patients at every visit by using mercury-in-rubber strain-gauge plethysmography. In order to assess the ability of the circulation to respond to stress, measurements were carried out both at rest and after a standard stepping exercise. The detailed interpretation of the postexercise patterns has been described (Dormandy *et al.*, 1972). A recent improved technique of plethysmography is based on selective femoral vein occlusion by means of a specially designed pressure pad. In patients with arterial disease this gives more accurate readings than the traditional occlusion cuff around the thigh (Colley and Dormandy, 1973). It also permits the positioning of a second strain gauge around the thigh. By using this technique in the last 30 patients simultaneous calf and thigh blood flow determinations were made both at rest and after standard exercise.

Radiological Assessment.—Arteriography had been performed in 82 cases. It was performed in new patients if they were potential candidates for surgical treatment. The limitations of this investigation are familiar to vascular surgeons. To make the results more functional and meaningful a new method of "stress arteriography" was used over the past year (Mackintosh *et al.*, 1973). In this technique the patient is asked to perform isometric leg exercises after insertion of the arterial catheter, and the dye is injected only when the patient complains of claudication pain. The method improves the visualization of collateral vessels and may show channels distal to a block not shown on conventional arteriograms.

Blood Viscosity.—Blood viscosity measurements were carried out regularly on all patients. Venous blood samples were collected without the use of tourniquets and anticoagulated with lithium heparin. The viscosity was measured within four hours at two shear rates, 23 and 230 sec⁻¹, with a Brookfield microviscometer. The different viscosities at the two shear rates reflect to some extent the non-Newtonian behaviour of blood. The red cell volume was determined on the same sample of blood since this is the most critical determinant of whole-blood viscosity. The relation between red cell volume and viscosity is approximately log-linear within the physiological range of the packed cell volume (Begg and Hearn, 1966; Dormandy, 1970,

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1973). The regression equation for this semi-log relation was calculated with the data from the whole patient group. It was then used to "correct" the measured viscosity of each sample to the theoretically expected viscosity at a standard red cell volume of 45%. Comparisons of such corrected viscosities largely eliminate differences due to variations in red cell volume.

Plasma Fibrinogen.—This was measured in all patients on venous blood samples withdrawn at the same time as the samples collected for viscosity measurements and for serum lipid and other biochemical estimations. Edetic acid was used as the anticoagulant, and estimations were performed within three hours of the venepuncture. The method of estimation is based on the precipitation of fibrinogen from a sample of plasma diluted with buffer by heating to 56°C for 15 minutes as originally described by Stirland (1956). The precipitated fibrinogen is estimated nephelometrically (Stone *et al.*, 1971). The results are in good agreement with measurements made by thrombin precipitation (Millar *et al.*, 1971).

Serum Lipid and Lipoproteins.—The patients were instructed to fast for 12 hours before the test. The separated sera were kept at 4°C for up to 24 hours. Cholesterol was measured on an autoanalyser by Technicon Method N 24a. Triglycerides were measured on an autoanalyser with the method of Noble and Campbell (1970) as modified by McLellan (1971). Total lipids were measured by the sulphophosphoalvin reaction (Woodman and Price, 1972). Lipoprotein electrophoresis was performed on cellulose acetate which was stained with oil-red-O (Dangerfield, 1971). The fractions were quantitated visually. The concentration of S., M., and L. (small, medium, and large) particles was estimated nephelometrically as described by Stone and Thorpe (1966). "Lipoprotein profiles" were based on the classification of Fredrickson but taking the S.M.L. scores into account (Fredrickson *et al.*, 1967; *Bulletin of the World Health Organization*, 1970; Stone *et al.*, 1970).

Red Cell Malonyldialdehyde.—This measurement reflects a property of red cell lipids. Polyunsaturated lipids, which include all the essential fatty acids, have an inherent tendency to autoxidize (rancidify) in the presence of oxygen (Dormandy, 1969). Cells *in vivo* are actively protected against this by antioxidant mechanisms which are imperfectly understood but highly effective. Despite these mechanisms it is possible to measure the susceptibility of tissues to autoxidation by exposing them to standardized oxidative stress (Dormandy, 1971 b; Stocks and Dormandy, 1971). In the case of red cells the results can be expressed in terms of nanomoles of malonyldialdehyde, a secondary breakdown product of lipid peroxides, generated in the course of a two-hour assay. Our normal range between the ages of 2 and 70 years is 60-300 nmol/g Hb (Stocks, 1972; Stocks *et al.*, 1972). Above 60 years of age the normal mean rises and the scatter becomes progressively wider.

Results

CLINICAL

The distribution of the claudication distances at the initial visits is shown in fig. 1. There was no correlation between this distance and the length of the past history ($r = 0.01$). On the other hand, the claudication distance of patients who also complained of rest pain was significantly less (average 106 yd—97 m) than the claudication distance of those who had no rest pain (average 329 yd—301 m). The type of onset also had some bearing as expected, those with a history of acute onset had a longer claudication distance (average 347 yd—317 m) than those with a gradual onset (213 yd—195 m).

The principal clinical sign of lower limb ischaemia is the disappearance of pulses. Though subject to considerable observer error it was a more reliable measure of the underlying disease process than claudication distance. In particular the absence of peripheral pulses was related to the length of history,

FIG. 1—Distribution of claudication distances in 126 patients complaining of intermittent claudication. Distance scale is logarithmic.

being 13% more common among those who had had symptoms for more than a year.

BLOOD FLOW

The resting blood flow, though more objective a measure than clinical symptoms and signs, is still subject to wide and seemingly random variations. In the present series the mean resting blood flow was 3 ml/100 ml/min (S.D. 0.76). This was only slightly less than the normal mean of 4.3 ml/100 ml/min (S.D. 1.02), and the two ranges widely overlapped. Much more meaningful was the pattern of response to a standard exercise. The normal and four abnormal patterns are shown in fig. 2. The four types of pattern are correlated with the symptoms and signs in fig. 3.

FIG. 2—Normal and four types of abnormal patterns of calf blood flow after exercise. N = Normal response with a return to resting blood flow within one minute after exercise. Type 1 abnormal pattern = Lower than normal blood flow after exercise with period of hyperaemia lasting up to three minutes (17% of our patients). Type 2 abnormal pattern = Hyperaemia after exercise for more than three minutes (46% of patients). Type 3 abnormal pattern = No significant increase in blood flow after exercise (25% of our patients). Type 4 abnormal pattern = Decreased blood flow after exercise (probably due to "steal" phenomenon) with a delayed increase (12% of our patients).

RADIOLOGICAL FINDINGS

Disease (as shown by radiography) was widespread in most cases. The commonest site for a complete block was the superficial femoral artery (table I). (Twelve patients in whom this was an isolated lesion with a good "run in" above the block and a good "run-off" below it are considered further below.)

TABLE 1—Radiological Findings in 82 Patients

Vessel	Narrowing by 50% or More	Complete Block
Aorta	24	0
External iliac and common femoral	23	5
Superficial femoral and popliteal	10	38
Profunda femoral	7	2
Tibial	11	20

FIG 3—Correlation between pattern of calf blood flow after exercise and (A) claudication distance, (B) rest pain, and (C) palpable peripheral pulses.

BLOOD VISCOSITY

The overall initial rheological results are summarized in table II. At both shear rates the measured blood viscosity of the patients was significantly higher than the measured viscosity of a control series of 100 normal subjects of the same age group (mean 57 years; S.D. 25 years). The difference in corrected viscosity between patients and controls was less but still significant.

TABLE II—Rheological Findings

		Mean Viscosities (Centipoises)			
		Shear Rate 23 sec ⁻¹		Shear Rate 230 sec ⁻¹	
		Measured	Corrected	Measured	Corrected
Patients (n = 126)	..	7.87 (s.d. 1.12)	6.99 (s.d. 0.67)	4.74 (s.d. 0.54)	4.35 (s.d. 0.30)
Controls (n = 100)	..	6.86 (s.d. 1.09)	6.60 (s.d. 0.76)	4.29 (s.d. 0.49)	4.15 (s.d. 0.35)
Significance of difference	..	P < 0.001	P < 0.001	P < 0.001	P < 0.001

TABLE III—Correlation between Rest Pain, Claudication Distance, and Viscosity. Figures in parentheses are S.D.

	No. of Patients	Mean Viscosities (Centipoises)			
		Shear Rate 23 sec ⁻¹		Shear Rate 230 sec ⁻¹	
		Measured	Corrected	Measured	Corrected
With rest pain	24	8.02 (1.03)	7.07 (0.53)	4.86 (0.63)	4.45 (0.30)
Without rest pain	102	7.80 (1.09)	6.97 (0.63)	4.70 (0.52)	4.30 (0.28)
Claudication distance less than 100 yd (91 m)	35	7.95 (0.93)	7.03 (0.54)	4.83 (0.57)	4.40 (0.27)
Claudication distance more than 100 yd (91 m)	91	7.80 (1.03)	6.92 (0.70)	4.70 (0.49)	4.30 (0.29)

Within the patient series the blood viscosity was higher in those with rest pain than in those without; and it was higher in those with a claudication distance of less than 100 yd (91 m) than in those less severely disabled (table III). These differences are not statistically significant, but consistent at both shear rates and for both measured and corrected viscosities.

In an attempt to decide whether the raised blood viscosity was more likely to be a cause or an effect of the disability, the viscosity readings of patients with a history of less than six months were compared with the results in the series as a whole. There was no significant difference between the two groups.

The 33 patients with definite evidence of ischaemic heart disease as well as peripheral arterial disease had a significantly higher measured blood viscosity than those with peripheral arterial disease alone (fig. 4).

FIG. 4—Correlation between measured blood viscosity (at 230 sec⁻¹) intermittent claudication (I.C.) alone, and intermittent claudication with evidence of ischaemic heart disease. (Viscosity measured in centipoises.)

TABLE IV—Serum Lipoprotein Patterns in 106 Patients

Type*	No. of Patients
Normal	52
I	0
II/a	27
II/b	11
III	1
IV	15

*Criteria as recommended by memorandum of World Health Organization.

PLASMA FIBRINOGEN

As shown in fig. 5 60% of patients had a plasma fibrinogen concentration above the upper limit of our normal range (400 mg/100 ml). There was a significant positive correlation between blood viscosity (measured at 230 sec⁻¹) and the plasma fibrinogen concentration, $r = 0.39$; $P < 0.01$.

FIG. 5—Distribution of (A) plasma fibrinogen, (B) serum cholesterol, and (C) serum triglyceride concentrations. Upper limits of our normal ranges (normal mean +2 S.D.) in a non-aged-matched population are indicated.

SERUM LIPIDS

The distribution of serum cholesterol and serum triglyceride concentrations in the series as a whole are shown in fig. 5. One or other or both concentrations were outside the normal range in 46% of patients; the serum triglycerides alone were raised in 28% and the serum cholesterol alone was raised in 7%. The distribution of lipoprotein abnormalities are given in table IV. The pattern was normal in just under half the cases. Detailed statistical analysis failed to show any correlation at the individual patient level between any of these serum lipid or lipoprotein measurements on the one hand and the clinical history, symptoms and signs, radiological disease, blood flow pattern, or blood viscosity readings on the other.

Discussion

A group of patients with intermittent claudication has now been followed up clinically and by detailed laboratory studies for up to three years. The present analysis is concerned with correlations between the clinical, haemodynamic, rheological, and biochemical findings at the time they were referred to us. In the light of the follow-up results we shall consider separately later

TABLE VI—"Rheological Claudication"

	Average Claudication Distance in Yards (Metres)	Rest Pain (No. of Patients)	Mean Viscosities (Centipoises)			
			Shear Rate 23 sec ⁻¹		Shear Rate 230 sec ⁻¹	
			Measured	Corrected	Measured	Corrected
(A) Correlation between Clinical and Rheological Findings in 12 Patients with Similar Arteriographic Appearance*						
Six patients with shorter claudication distance ..	85 (78)	3	8.20 (S.D. 0.40)	7.20 (S.D. 0.61)	5.00 (S.D. 0.37)	4.45 (S.D. 0.31)
Six patients with longer claudication distance ..	1,200 (1,097)	1	7.40 (S.D. 0.99)	6.35 (S.D. 0.55)	4.70 (S.D. 0.53)	4.20 (S.D. 0.32)
Significance of difference ..			P = 0.1	0.02 < P < 0.05	0.1 < P < 0.2	0.1 < P < 0.2
(B) Correlation between Clinical and Rheological Findings in 33 Patients with Similar Major-vessel Disease†						
18 patients with shorter claudication distance ..	180 (165)	6	8.05 (S.D. 0.96)	7.00 (S.D. 0.54)	4.80 (S.D. 0.43)	4.45 (S.D. 0.24)
15 patients with longer claudication distance ..	1,500 (1,372)	1	7.35 (S.D. 0.80)	6.70 (S.D. 0.54)	4.45 (S.D. 0.45)	4.20 (S.D. 0.25)
Significance of difference ..			P < 0.05	0.1 < P < 0.2	P < 0.05	P < 0.01

*Isolated superficial femoral block with good "run-in" and "run-off."
†At least one palpable ankle pulse on the affected side.

the prognostic significance of the various clinical and laboratory investigations and the response to treatment.

Review of the patients' past history and clinical symptoms and signs lends support to the traditional view of two parallel processes—progressive obstruction in the major arteries accompanied by the gradual development of a more or less adequate collateral circulation. This is reflected by the lack of correlation between the duration of the disease and claudication distance on the one hand and the time-related decrease in the number of patients with palpable distal pulses on the other. Since claudication distance can be expressed in yards it is, on the face of it, one of the most easily quantitated symptoms in clinical medicine; but in fact it is as much influenced by psychological and external variables (and therefore as imprecise a measure of the underlying disease process) as any other kind of pain. From the point of view of objective functional assessment the need is clearly for a reliable method for measuring the blood supply to the limb in exercise. Measurement of pressure gradients after exercise—for example, from arm to ankle—have been advocated and have been used with some success (Lewis *et al.*, 1973). This indirect approach has the merit of comparative technical simplicity, but it depends on the assumption of a more or less constant pressure-gradient/flow relation. Neither in theory nor in practice is this assumption always justified. The plethysmographic determination of calf blood flow after exercise, though a more complicated technique, provides a more direct and therefore more reliable measure of the adequacy of the combined main vessel and collateral blood supply.

Of the three variables which determine blood flow—the radius of the vessels, the pressure gradient, and viscosity of the blood—disproportionate attention has been paid in the past to vessel narrowing at the expense of viscosity. Though Poiseuille's (1846) equation remains after more than 100 years one of the most-quoted statements in cardiovascular physiology, and though a significant relation in normals between blood flow and viscosity has now been established (Dormandy, 1971 a), viscosity changes have not been previously measured in patients with intermittent claudication. In the present series the blood viscosity was significantly raised compared with age-matched normal controls. A combined comparative review of the arteriographic, clinical, and rheological evidence suggests, moreover, that in a proportion of cases the increased viscosity is the critical factor responsible for the symptoms. Because the degree of arterial narrowing still cannot be accurately measured this concept of "rheological claudication" remains to be proved;

TABLE V—Correlation between Red Cell Malonyldialdehyde, Claudication Distance, and Immediate Past Progress

	Claudication Distance		Clinical Past Progress	
	100 yd (91 m) or Less	1,000 yd (914 m) or More	Getting Worse	No Change or Improving
Red cell malonyldialdehyde (nmol/g Hb) ..	353	281	372	292
No. of patients (S.D.) ..	19 (103)	13 (110)	23 (108)	44 (115)
Significance of difference	$0.05 < P < 0.1$		$P < 0.01$	

but the existence of such a state is strongly supported by the findings summarized in table VI. The 12 patients reviewed in table VI (A) showed the same arteriographic lesion (a localized superficial-femoral block) but had widely differing claudication distances. The six with a shorter claudication distance (average 85 yd—78 m) had a higher blood viscosity than the six with a longer claudication distance (average 1,200 yd—1,097 m). The 33 patients reviewed in table VI(B) include all those in whom at least one palpable ankle pulse on the affected side suggested comparatively mild large vessel disease. When these patients were subdivided into two groups according to their claudication distance the 18 with a shorter claudication distance (six of whom also had rest pain) had a significantly higher blood viscosity than the remaining 15.

FIG. 6—Correlation between red cell malonyldialdehyde (MDA) and patients' clinical progress over preceding six months. (MDA is expressed in nmol/g Hb after our standard two-hour assay.)

Of the biophysical and biochemical factors which govern blood viscosity (other than the packed cell volume) plasma fibrinogen has been shown to be a critical determinant both in vitro and in vivo (Merrill, 1969; Weaver *et al.*, 1969). Plasma fibrinogen is believed to affect viscosity by increasing red cell aggregation (Rosenblum, 1969). This effect is increasingly pronounced at lower shear rates and is therefore at least partly responsible for the non-Newtonian behaviour of whole blood though it does not interfere with the Newtonian behaviour of plasma. A raised plasma fibrinogen was the commonest single biochemical abnormality in our series as a whole; and individual values correlated closely not only with the corrected viscosity—that is, the viscosity adjusted to a standard packed cell volume—but also with our initial clinical grouping of patients according to their immediate past progress (fig. 7).

The serum-lipid "profile" of the series as a whole is in general agreement with two recently published biochemical studies (Greenhalgh, 1971; Newall, 1971). Because minor degrees of claudication are probably neither complained of nor detected in many elderly people, there remains an element of uncertainty about any "age-matched normal" control group. But both published evidence and our own suggests that the prevalence of hyperlipidaemia—in particular a raised serum triglyceride and a raised serum cholesterol level—is higher in intermittent claudicants than in those without claudication. There is also a higher prevalence of types II and IV (Fredrickson *et al.*, 1967) hyperlipoproteinaemia. On the other hand, correlation analysis of our data clearly showed that in the assessment of individual patients serum lipid profiles as currently obtained have no diagnostic value: in particular, they bear no relation to the duration of the disease, to the severity of the symptoms, to the main physical signs, to the measured blood flow, or to the blood viscosity. This probably reflects not a true lack of connexion between degenerative peripheral arterial disease and lipid metabolism but the inadequacy of current serum lipid and lipoprotein measurements as a means of insight into metabolic changes. The evaluation of non-fasting or apparently non-fasting specimens remains one intractable difficulty. There can be no doubt that whereas normal people can provide good fasting blood samples

FIG. 7—Correlation between patients' immediate past clinical progress and (A) flow pattern, (B) blood viscosity (in centipoises), and (C) plasma fibrinogen concentration. In (A) postexercise flow patterns 1 and 2 and postexercise flow patterns 3 and 4 are grouped together as indicated.

after a conventional 10 to 12-hour fast, many patients with hyperlipidaemia never have "fasting" serum lipids in the course of their ordinary everyday life. It is as unreasonable to reject such "non-fasting" samples as it is to compare them with fasting samples from normal controls. In so far as serum lipids can ever yield individually useful diagnostic information, the need is clearly for a procedure which will measure the response to a standard load over a set period of time rather than one which aims at an unattainable baseline ideal.

The measurement of red cell malonyldialdehyde was included in our series of routine investigations with two possibilities in mind. The susceptibility of cells to autoxidation has now been shown to be closely related to the percentage composition of cell lipids and in particular to the percentage concentration of the polyunsaturated fatty acids (Gutteridge and Dormandy 1973). This, it was felt, might influence the physical properties of red cells which, in turn, might affect whole-blood viscosity. More important, changes in red cell lipids provide a far more reliable guide to tissue lipids than serum lipid measurements; and the changes reflected by an increased susceptibility to autoxidation might be particularly relevant to degenerative arterial disease (Harman, 1956; Barber and Berheim, 1967; Slater, 1972). Our findings give no support to the first possibility—that is, to a direct relation between whole-blood viscosity and red cell autoxidation, though such a relation might be apparent at lower shear rates than were used with the present study. On the other hand, the unexpected possible link between red cell malonyldialdehyde and the patients' symptoms and progress may represent the only significant correlation so far between clinical manifestation and blood lipid changes.

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Prognostic Significance of Rheological and Biochemical Findings in Patients with Intermittent Claudication

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Summary

To assess the prognostic significance of clinical and laboratory findings in intermittent claudication a group of 62 untreated patients was followed up in detail for periods of from one to three years. There was a significant correlation between progressive deterioration of the peripheral circulatory disturbance and the initial blood viscosity, the plasma fibrinogen level, and the susceptibility of red cell lipids to autoxidation.

Introduction

We recently reviewed the clinical, haemodynamic, rheological, and biochemical findings in 126 patients with intermittent claudication (Dormandy *et al.*, 1973). Sixty-two of these patients have now been followed up for periods of from one to three years. During this time all were assessed clinically and had their baseline investigations repeated at regular intervals of one or two months. We here consider the prognostic significance of our initial findings in the light of the patients' subsequent progress.

Patients

Our series as a whole has been described in our previous paper. Of the 62 patients who are included in the present study none

had undergone reconstructive arterial surgery during the follow-up period or for a minimum of a year before their first visit. (Thirteen had had arterial surgery and five had had a lumbar sympathectomy at an earlier date.) The average age of the patients at the beginning of the follow-up was 64 years (range 46-85 years). Twenty-six patients had definite evidence of ischaemic heart disease, 21 had a blood pressure above 160/100 mm Hg, and three were well-controlled diabetics on oral hypoglycaemic drugs. There had been a history of intermittent claudication for an average of just over two years before their first visit. Seven of the patients died during the follow-up period, six of them known cases of ischaemic heart disease.

Methods

INVESTIGATIONS

Our methods and our interpretation of results have already been described (Dormandy *et al.*, 1973). The patients' calf blood flow was measured at rest and after a standard exercise by using a mercury-in-rubber, strain-gauge plethysmograph. More recently the thigh blood flow was also measured simultaneously with a new technique of selective femoral vein occlusion (Colley and Dormandy, 1973). Whole-blood viscosity was measured at two shear rates, 23 and 230 sec⁻¹. The red cell volume was also determined and the corrected viscosity (based on a theoretical "standard" packed cell volume of 45%) was calculated. Blood was collected at the same time for plasma fibrinogen estimation and for serum lipid and lipoprotein studies. The latter included measurements of serum cholesterol, total lipids, triglycerides, lipoprotein electrophoresis, and the nephelometric estimation of small, medium, and large particles (S. M. L. scoring). The susceptibility of the red blood cells to autoxidation was assessed by measuring the generation of malonyldialdehyde under standard oxidative stress (Dormandy, 1971; Stocks *et al.*, 1972).

ASSESSMENT OF PROGRESS

We have already considered the difficulty in assessing objectively the severity of intermittent claudication, and similar difficulties arise when assessing progress over a period of time. The shorten-

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