References

- Barber, A. A., and Bernheim, F. (1967). *Advances in Gerontological Research*, 2, 355.
- Begg, T. B., and Hearn, J. B. (1966). *Clinical Science*, 31, 87.
- Bulletin of the World Health Organization, 1970, 43, 891.
- Colley, J., and Dormandy, J. A. (1973). To be published.
- Dangerfield, W. G. (1971). *Proceedings of the Royal Society of Medicine*, 64, 896.
- Dormandy, J. A. (1970). *Annals of the Royal College of Surgeons*, 47, 211.
- Dormandy, J. A. (1971 a). *British Medical Journal*, 4, 716.
- Dormandy, J. A. (1973). *British Journal of Surgery*, 60, 187.
- Dormandy, J. A., Kenefick, J., and Hoare, E. (1972). In *Blood Flow Measurement*, ed. C. Roberts. London, Sector Publishing Ltd.
- Dormandy, T. L. (1969). *Lancet*, 2, 684.
- Dormandy, T. L. (1971 b). *British Journal of Haematology*, 20, 457.
- Fredrickson, D. S., Levi, R. I., and Lees, R. S. (1967). *New England Journal of Medicine*, 276, 34, 94, 148.
- Greenhalgh, R. M., et al. (1971). *Lancet*, 2, 947.
- Gutteridge, J. M. C., and Dormandy, T. L. (1973). To be published.
- Harman, D. (1956). *Journal of Gerontology*, 11, 298.
- Lewis, J. D., Papathanasiou, C., Yao, S. T., and Eastcott, H. H. G. (1972). *British Journal of Surgery*, 59, 418.
- Mackintosh, C. E., Dormandy, J. A., and Waite, D. H. (1973). *Lancet*, 1, 1477.
- McLellan, G. H. (1971). *Clinical Chemistry*, 17, 535.
- Merrill, E. W. (1969). *Physiological Reviews*, 49, 863.
- Millar, H. K., Simpson, J. G., and Staller, A. L. (1971). *Journal of Clinical Pathology*, 24, 827.
- Newall, R. G. (1971). *Clinica Chimica Acta*, 32, 185.
- Noble, R. P., and Campbell, F. M. (1970). *Clinica Chimica Acta*, 16, 166.
- Poiseuille, J. L. M. (1846). *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, 9, 433.
- Rosenblum, W. I. (1969). *Nature*, 221, 365.
- Slater, T. (1972). *Free Radical Mechanisms in Tissue Injury*. London, Pion.
- Stirland, R. M. (1956). *Lancet*, 1, 672.
- Stocks, J. (1972). *Autoxidation of Human Red Blood Cells*. M.Sc. Thesis, London University.
- Stocks, J., and Dormandy, T. L. (1971). *British Journal of Haematology*, 20, 95.
- Stocks, J., Offerman, E. L., Modell, C. B., and Dormandy, T. L. (1972). *British Journal of Haematology*, 23, 713.
- Stone, M. C., and Thorpe, J. M. (1966). *Clinica Chimica Acta*, 14, 812.
- Stone, M. C., Thorpe, J. M., Mills, G. L., and Dick, T. B. S. (1970). *Clinica Chimica Acta*, 30, 809.
- Stone, M. C., Thorpe, J. M., Mills, G. L., and Dick, T. B. S. (1971). *Clinica Chimica Acta*, 31, 333.
- Weaver, J. P. A., Evans, A., and Walder, D. N. (1969). *Clinical Science*, 36, 1.
- Woodman, D. D., and Price, C. P. (1972). *Clinica Chimica Acta*, 38, 39.

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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TABLE II—Prognostic Significance of Initial Plasma Fibrinogen Concentrations

	Fibrinogen (mg/100 ml)	
Change in claudication distance:		
Longer	401	N.S.
Same	417	} P < 0.01
Shorter	561	
Change in flow pattern:		
Better	382	P < 0.05
Same	468	} P < 0.01
Worse	543	
Overall progress group:		
Group 1	398	N.S.
Group 2	433	} P < 0.001
Group 3	605	

N.S. = Not statistically significant.

FIG. 2—Distribution of initial viscosities, plasma fibrinogen levels, and red cell malonyldialdehyde (MDA) values among the three progress groups. (Plasma fibrinogen in mg/100 ml; MDA in nmol/g haemoglobin; viscosity in centipoises.)

neither the initial pattern nor the changes were related to progress.

Red Cell Lipids.—The susceptibility of the red cell lipids to autoxidation (red cell malonyldialdehyde) increased with a worsening prognosis as assessed by any single criterion (table III). However, the correlation was statistically significant only when the mean malonyldialdehyde of the patients who showed overall improvement was compared with the mean malonyldialdehyde of patients who deteriorated (table III, fig. 2).

TABLE III—Prognostic Significance of Initial Serum Cholesterol, Serum Triglycerides, and Red Cell Malonyldialdehyde

	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Malonyldialdehyde (nmol/g Hb)
Change in claudication distance:			
Longer	275	178	276
Same	268	196	312
Shorter	262	174	377
Change in flow pattern:			
Better	286	170	296
Same	238	191	313
Worse	266	208	375
Overall progress group:			
Group 1	274	169	301
Group 2	231	199	313
Group 3	280	193	395

There was no statistically significant difference between any of the mean cholesterol and triglyceride values.

Discussion

Though there is wide agreement that peripheral arterial disease is rarely a cause of death and that intermittent claudication tends to improve (Singer and Rob, 1960; Begg and Richards, 1962; Taylor and Calo, 1962; Schatz, 1967), previously reported series give no indication about the presenting features which, in an important minority, point to a progressively downhill course. Even the two clinical clues suggested in the literature—a history of acute rather than gradual onset (Bloor, 1961) and the presence of diabetes (Dry and Hines, 1941; Schadt *et al.*, 1961)—have had no prognostic value in our smaller series. The only biochemical factor which has been studied in the past in relation to outlook has been the serum cholesterol (Juergens *et al.*, 1960), and this has proved to be totally unrelated to the progress of the leg symptoms. There has been a similar lack of correlation in our own series between progress and other serum lipid and lipoprotein measurements. In contrast to these negative findings the initial blood viscosity, the initial plasma fibrinogen, and to a less extent the initial red cell lipid findings correlated significantly with the subsequent clinical course.

Since plasma fibrinogen is a critical factor which determines whole-blood viscosity, it is likely that the effect of a raised fibrinogen on blood flow and on the course of the claudication is indirect. Whether or not this is so, the downhill course in a proportion of patients appears to be essentially a function of the rheological properties of blood. The prognostic significance of a raised red cell malonyldialdehyde is less easy to interpret; but a number of possible explanations can be envisaged. Firstly, it is possible that depletion of the red cells of polyunsaturated fatty acids (the source of malonyldialdehyde) may alter the physical character of the cells sufficiently to affect their internal viscosity or "deformability." (It may be recalled that the number of double bonds in a mixture of long-chain fatty acids is one of the variables which determines the melting point or "liquidity" of the material.) This in turn could influence the viscosity of whole blood. Secondly, the raised red cell malonyldialdehyde could reflect a more fundamental change in cell lipids which might be related to the severity of the underlying degenerative arterial disease. Though serum lipid measurements as currently performed have been shown to be of little or no value in assessing the severity and outlook of arterial degeneration in individual patients, it is possible that changes in red cell lipids reflect this process more accurately. Thirdly, if an increased red cell malonyldialdehyde reflects an increased susceptibility to lipid autoxidation in other tissues, one must consider the possible "pharmacological" effects of the secondary products of autoxidation both on blood vessels and on the causation of the pain itself.

References

- Begg, T. B., and Richards, R. L. (1962). *Scottish Medical Journal*, 7, 341.
- Bloor, K. (1961). *Annals of the Royal College of Surgeons*, 28, 36.
- Colley, J., and Dormandy, J. A. (1973). To be published.
- Dormandy, T. L. (1971). *British Journal of Haematology*, 20, 457.
- Dormandy, J. A., Hoare, E., Colley, J., Arrowsmith, D. E., and Dormandy, T. L. (1973). *British Medical Journal*, 4, 581.
- Dry, T. J., and Hines, E. A. (1941). *Annals of Internal Medicine*, 14, 1893.
- Fredrickson, D. S., Levi, R. I., and Lees, R. S. (1967). *New England Journal of Medicine*, 276, 34, 94, 148.
- Juergens, T. L., Barker, N. W., and Hines, E. A. (1960). *Circulation*, 21, 188.
- Schadt, D. C., Hines, E. A., Juergens, J. L., and Baker, N. W. (1961). *Journal of the American Medical Association*, 175, 937.
- Schatz, I. T. (1967). In *Atherosclerotic Vascular Disease*, ed. A. N. Brest and J. H. Moyer. New York, Appleton.
- Singer, A., and Rob, C. (1960). *British Medical Journal*, 2, 633.
- Stocks, J., Modell, C. B., Offerman, E. L., and Dormandy, T. L. (1972). *British Journal of Haematology*, 23, 713.
- Taylor, G. W., and Calo, A. R. (1962). *British Medical Journal*, 1, 507.