A STUDY OF SOME ASPECTS OF THE EPIDEMIOLOGY AND TREATMENT OF PERIPHERAL VASCULAR DISEASE

by

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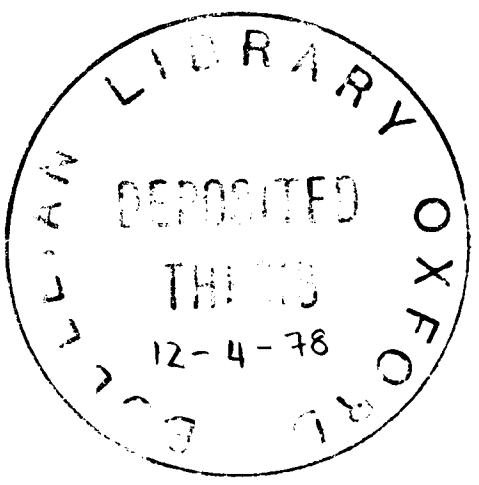
A Thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

in the University of Oxford



St. Peter's College
and
Department of Social & Community Medicine

Trinity Term

1977

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INTRODUCTION AND ACKNOWLEDGEMENTS

In this thesis I have attempted to review the relevant literature concerning the epidemiology and treatment of peripheral vascular disease and have described five studies which were carried out in the hope of making some contribution to knowledge in this field. A summary of this research is presented in the Abstract.

Many people have helped in this work. I have been extremely fortunate in having Dr. Jim Mann as my supervisor. His advice and encouragement at all stages has been invaluable, and I am very grateful. I would like to thank Professor Martin Vessey for having me as a member of his department. In addition to advising me on many aspects of the research itself, he also provided the technical support and friendly working atmosphere which made life very much easier. My sincere thanks are due to Mrs. Adrienne Garrod who assisted me for most of this period and who was responsible for collecting the data which formed the basis of the study presented in Chapter 6.

I would like to thank the general practitioners and staffs of the Sonning Common and Donnington Health Centres who were so helpful in allowing me to conduct the prevalence survey and case-control study described in Section 2 of the thesis. Dr. Frank Woods and Dr. Ivan Walton were the original investigators of the patient group described in Chapter 5, and kindly allowed me to use their data in a follow-up study. Professor Peter Morris and Mr. David Tibbs were helpful in allowing me to examine their patients, and Mr. Howard Steer and Miss Patricia Franklin assisted me in the drug trial presented in Chapter 7.

As a novice in the analysis of data I have needed frequent advice, and this has been provided with great patience by Dr. Klim McPherson. Other statistical help has come from Mr. Richard Peto, Mr. Julian Peto, and Mr. Peter Smith, and I am grateful to Mr. Peter Wiggins for help with the computing.

I have had technical assistance from many people, but my special thanks go to Mr. Dick Jelfs for the lipid analyses and also for many of the drawings. Mrs. Audrey Maxwell has helped with the references, and Mrs. Diana Collinge has typed my correspondence. Mr. Alf March has helped me on many occasions with administrative problems. I would like to thank Mrs. Ann Read for her skill in the typing and checking of the draft and final manuscript.

Financial assistance has been provided by the Department of the Regius Professor of Medicine, the Regional Health Authority, the Rhodes Trust, Imperial Chemical Industries, and Janssen Pharmaceuticals.

Finally, I am grateful to the patients, for without their co-operation this work would not have been possible.

ABSTRACT

Prior to starting the research described in this thesis I had completed the first year of a residency programme in internal medicine. During this time I became interested in epidemiology and wished to learn more about how this approach could be used to examine problems in clinical medicine. When the opportunity arose to study in Oxford I considered a number of possible topics for my research but decided to study some aspects of atherosclerotic vascular disease because this was an important subject and also relevant to a possible future career in cardiovascular medicine.

A preliminary review of the literature revealed that there was a vast amount of information concerning coronary artery and cerebral vascular disease. In contrast, few data were available concerning the epidemiology of peripheral vascular disease (PVD), possibly because this condition was rarely a primary cause of death, symptoms of PVD were often tolerated by patients who did not seek medical attention, or because serious complications such as amputation were infrequent. Another reason for this lack of data may have been the assumption that the factors leading to an increased risk of developing PVD were the same as those which caused coronary artery and cerebral vascular disease. It seemed that research concerning risk factors for PVD, and the natural history of this condition, might provide new information of clinical importance, and would at the same time permit me to learn some of the techniques of epidemiology.

When I began I felt that there were several basic questions which needed to be answered. The first concerned the frequency of PVD. Few studies had attempted to determine the prevalence

of PVD or that of its most common symptom, intermittent claudication (IC). Most data came from selected groups of people which were not representative of a general population. The techniques used to identify cases were poorly standardized, and few studies included an examination of the peripheral circulation. I decided, therefore, that the first stage of my research would be to determine the frequency of IC in a general population using a standardized questionnaire to identify cases and a physical examination to confirm the diagnosis. One advantage of starting with a prevalence survey was that the cases identified could then be compared with controls selected at random from the same population, and a second important question could then be answered: what factors are associated with an increased risk of developing IC?

A survey to determine the prevalence of IC and a case-control study to examine risk factors for this condition are presented in Section 2 of the thesis. The prevalence of IC in men aged 45 to 70 years was 3.0 per cent, and that of women 50 to 70 years was 0.8 per cent. A total of 54 cases of IC were identified, and the over-all prevalence in the population was 2.0 per cent. Factors associated with an increased risk of developing IC were age, smoking, a history of diabetes mellitus, hypertension or hyperlipidaemia, and elevations of blood pressure, serum triglyceride, plasma fibrinogen, and serum uric acid. Of these factors, smoking was associated with the greatest relative risk of IC and was the main risk factor for this condition. Elevated blood pressure, the chief risk factor for cerebral vascular disease, did not have the same degree of importance in the aetiology of PVD. Serum cholesterol, which is one of the main risk factors for coronary artery disease,

was not elevated in the patients with IC compared with their controls. Nor was the blood glucose elevated in the cases despite a higher prevalence of diabetes. There was significant synergism among the risk factors, and the relative risk of developing IC rose sharply in people with multiple risk factors. Evidence of coronary artery disease was found very frequently among the patients with IC.

In addition to defining risk factors for IC, I also wanted to examine the natural history of patients with PVD. Data was available from a number of studies which had examined series of patients referred to hospital, but few of these had investigated the effect on prognosis of removing correctable risk factors such as smoking and hypertension. I was fortunate in having the opportunity to examine a group of 60 patients with IC referred to hospital in 1971 and 1972 who had been extensively investigated to determine risk factors for PVD. I undertook a follow-up study of these patients in order to determine whether any of the risk factors identified at the initial examination had had a significant effect on prognosis. The results of this investigation are presented in Chapter 5.

A number of the patients had died since the first referral for IC, and, in agreement with other studies, the chief causes of death were coronary artery and cerebral vascular disease. The only correctable risk factor which significantly affected prognosis was smoking. Most of the patients who stopped or reduced smoking after referral completed the follow-up period without significant complications from their PVD, whereas the majority of patients who continued to smoke had a deterioration in their symptoms and a clinical course which was punctuated with frequent hospital admission, reconstructive surgery,

amputation, and death. This effect was not due to other risk factors since the smoking groups were comparable with respect to age, severity of PVD at referral, and the prevalence of other medical conditions such as ischaemic heart disease. Thus the improved prognosis associated with abstinence from tobacco could reasonably be attributed to elimination of this risk factor. Elevated blood pressure did not significantly worsen the prognosis except in those who continued to smoke, suggesting a synergistic effect of smoking and blood pressure. The only other factor which had a significant effect was a history of stroke; these people had a very high mortality rate. Patients with elevated glucose, cholesterol, or triglyceride, did not have a worse prognosis than people with normal levels.

The follow-up study described in Chapter 5 examined a small number of patients for a relatively short period of time. In order to provide further information about the prognosis of patients with PVD, I decided to identify a larger patient group and follow them for as long as possible. The presence of a unique computer-based information system, the Oxford Record Linkage Study (ORLS), enabled me to identify all people admitted for the first time to hospitals in the Oxford area in 1965 and 1966 because of PVD and to determine the frequency of subsequent hospital admissions, operations and death by means of the linked records maintained by the ORLS. This study is described in Chapter 6.

The 160 patients included in this study had a five-year mortality rate which was twice that of the general population, controlling for age and sex. Factors which worsened the prognosis were increasing age at referral, ischaemic heart disease, cerebral vascular disease, and diabetes. The patients

had frequent and prolonged admissions to hospital because of deterioration in their condition, and many had reconstructive surgery or amputations. The degree of morbidity associated with PVD was striking, and the disease had a great impact not only on the patients but also on the financial resources of the health services. Thus the observation made in Chapter 5 that patients who stop or reduce smoking have a better prognosis than those who continue to smoke was seen to be relevant not only to the individual with PVD but also to have practical significance for the community as a whole.

The final chapter of my thesis contains the results of a trial of Cinnarizine in the treatment of 18 patients with IC. I chose to investigate this drug because other studies have shown an improvement in the symptoms and blood flow (measured by plethysmography) of patients with PVD who were treated with Cinnarizine. Unlike most of the drug preparations being investigated at the time, Cinnarizine was not a vasodilator and did not cause changes in blood pressure, pulse, or cause the "steal" effect which is so often reported. The trial protocol included measurements of blood flow using a mercury strain gauge plethysmograph. This enabled me to compare the plethysmograph with another objective variable, the ankle systolic blood pressure measured with a Doppler ultrasound flow meter, and to determine their usefulness in the evaluation of patients with PVD.

It was planned initially to treat 20 patients with IC for four months and then to proceed with a double-blind trial if the results were promising. Unfortunately there was little evidence of subjective improvement in patient symptoms at the end of the preliminary study and no evidence of improved blood flow to the

legs as measured by plethysmography. Thus it was decided that a double-blind trial was not indicated. The objective measurement which was most strongly correlated with patients' symptoms was the ankle systolic pressure measured after exercise, and since this test was far easier to perform than plethysmography I concluded that the Doppler flow meter was the better method of evaluating PVD.

In summary, I have found that intermittent claudication occurs in approximately two per cent of adults. Peripheral vascular disease is, therefore, a fairly common disorder, and since it is associated with significant morbidity and mortality its prevention and treatment are major concerns for the medical profession. Peripheral vascular disease, coronary artery disease, and cerebral vascular disease have several risk factors in common, but smoking seems to be particularly important in promoting atherosclerosis in the peripheral circulation. Every effort should be made to encourage patients with peripheral vascular disease to stop smoking, since continuation of this habit significantly worsens the prognosis and may increase the likelihood of costly medical intervention. At the present time surgical correction of arterial lesions is the only accepted form of treatment for peripheral vascular disease. Since atherosclerosis is a generalized process, it is possible that removal of correctable risk factors may be a more effective way of preventing ischaemic complications. The peripheral circulation is uniquely accessible to examination with non-invasive techniques, and I believe that further investigations in which patients with peripheral vascular disease are observed and the effect of risk factor control are evaluated may provide new information concerning the aetiology and treatment of atherosclerosis.

SECTION 1

CHAPTER 1

A REVIEW OF THE LITERATURE

Chapter 1 A REVIEW OF THE LITERATURE

A. INTRODUCTION

Throughout this thesis I have used the term 'intermittent claudication'(IC) to describe the symptom of leg pain associated with walking which is one of the consequences of atherosclerosis affecting the arterial circulation of the legs. Though the symptom of IC may be due to conditions other than atherosclerosis such as narrowing of the neuro-spinal canal (Silver et al, 1969), pheochromocytoma (Scharf et al, 1971), and obstruction of major leg veins (Bjordal, 1970), and has been described in patients with normal arterio-grams (Yao et al, 1972), atherosclerosis is by far the most common cause of IC. Some of the studies in this review of the literature have included patients who had symptoms such as rest pain and severe ischaemia with gangrene. Others have included only people with uncomplicated IC. It has not always been possible to determine the criteria used by the authors of these studies to select patients, so that their use of the terms peripheral vascular disease (PVD) and IC was confusing. When possible, in describing these studies I have used the term IC specifically to mean the symptom of leg pain on walking, and have used the term PVD in a more general sense to mean atherosclerosis affecting the arterial circulation of the legs.

In this chapter I have mentioned briefly the historical aspects of IC and then reviewed the major studies which provide the information currently available concerning the epidemiology of PVD. I have included a short discussion of the pathology of atherosclerosis in order that the effects of certain risk factors on the incidence, prevalence, and prognosis of PVD can

be considered in terms of their effects on the circulation. Measurement of the severity of PVD is discussed since this is relevant not only to my research but also the data from other studies.

B. HISTORICAL ASPECTS OF INTERMITTENT CLAUDICATION

Burns, in 1809, was one of the first to describe the symptoms of impaired circulation to the leg in man:

> "In health, when we excite the muscular system to more energetic action than usual, we increase the circulation in every part, so that to support this increased action, the heart and every other limb has its power augmented. If, however, we call into vigorous action a limb, round which we have with a moderate degree of tightness applied a ligature, we find that then the member can only support its action for a very short time; for now its supply of energy and its expenditure do not balance each other; consequently, it soon, from a deficiency of nervous influence and arterial blood, fails and sinks into a state of quiescence".
>
> (Burns, 1809, pp. 138)

The term intermittent claudication was first used by Bouley in 1831. It described a condition of lameness in the horse developing after a period of exercise, and accompanied by obliteration of the main artery to the limb. Brodie, in 1846, and Charcot, in 1859, described a similar condition in humans due to senile arteritis or aneurysm of the popliteal artery.

The cause of limping in intermittent claudication was thought initially to be due to failing power of the limb. Burns, however, had noted that the pain remained constant even when the patient was not moving if the circulation remained occluded:

> ".... we witness an induction of an extreme degree of debility, and we hear the person complaining of an unusual painful feeling in the limb, but its muscles are in a state of inactivity".
>
> (Burns, 1809, pp. 142)

Charcot, in 1887, wrote that loss of blood supply led to cramp of the muscles, and compared this to cadaveric rigidity. Later observers found pain in the absence of cramp to be more common. Erb, in 1898, established that obstructive arterial disease was the anatomical lesion usually found, and concluded that limping was caused by pain rather than by weakness or cramp.

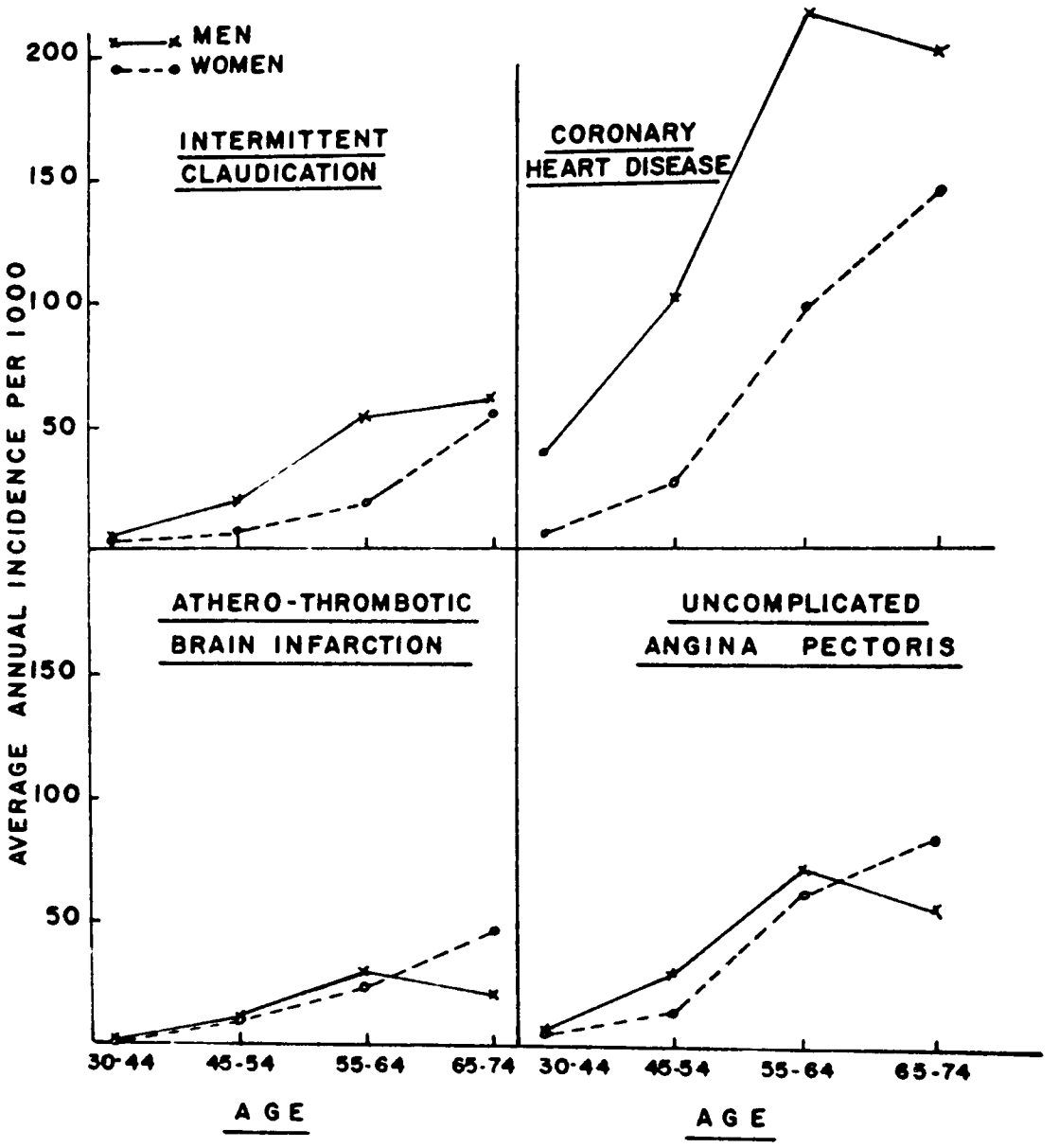
Zak postulated in 1921 that the pain was due to arterial spasm. Lewis, in 1931, demonstrated that, far from being in spasm, the arteries in ischaemic muscle were maximally dilated. He postulated a chemical "Factor P" which was produced when exercise took place. In the presence of a poor circulation, a critical level of Factor P built up in the tissues, and pain occurred. With rest the circulation was able to clear the muscles of this factor, and pain subsided. Lewis demonstrated that the pain of intermittent claudication was not due to a direct lack of oxygen. He showed that arrest of the circulation resulted in cyanosis of the skin in 10 to 15 minutes but, in the absence of exercise, pain did not occur. He believed that the "physico-chemical stimulus" responsible for the pain was located in the interstitial spaces of tissues, since prompt cessation of pain with the restoration of circulation made an intracellular substance unlikely. Despite a number of subsequent experiments the Factor P invoked by Lewis has not yet been clearly defined, and the mechanism of ischaemic pain in the limbs is poorly understood.

C. THE INCIDENCE AND PREVALENCE OF INTERMITTENT CLAUDICATION

Few data are available concerning the incidence and prevalence of intermittent claudication (IC) in a general

FIGURE 1.1

AVERAGE ANNUAL INCIDENCE OF ATHEROTHROMBOTIC EVENTS BY SEX AND AGE. FRAMINGHAM STUDY, 14-YEAR FOLLOW-UP.



From: Kannel et al (1970a)

population.

A prospective study was begun in Framingham, Massachusetts, in 1949 to determine the incidence and prevalence of a number of cardiovascular diseases (CVD), and to study the risk factors associated with these diseases. At the initial examination 5,209 subjects aged 29 to 62 years were screened for CVD. They were followed with biennial examinations, and 4,030 completed the eighth examination, providing 14 years of follow-up. The diagnosis of IC was based on a history of leg pain associated with exercise and not on physical examination or laboratory investigations. During 14 years of follow-up, 79 men and 46 women developed the initial symptoms of IC. Figure 1.1 illustrates the effect of age and sex on incidence, and demonstrates the relative incidence of other cardiovascular diseases in this population (Kannel et al, 1970).

Hobson and Pemberton (1955) investigated the health of elderly people living at home. The population of 474 people (192 men and 282 women) aged 60 years and older was selected from a previous social survey of the elderly made by the Sheffield Council of Social Service in 1948.

A full medical history was obtained and enquiry was made about 30 listed symptoms, including intermittent claudication. There were 20 males (10.4%) and nine females (3.2%) who had this symptom in some degree. The details of the examination of the peripheral circulation were not given. The incidence of intermittent claudication in this study was reported to be about 1.5 per cent, though it is not clear how this calculation was made since the design of the study did not include long-term follow-up to identify

new cases of IC.

Widmer et al (1964) invited the employees of several pharmaceutical companies in Basle to participate in a study to determine the prevalence of peripheral arterial occlusions. The volunteer rate was 53 per cent (6,437 people) for the whole population, but response was particularly poor in those aged 40 to 55 years (approximately 30%). Each subject was given a screening examination including a cardiovascular history, palpation and oscillographic recording of foot and wrist pulses, weight, height and blood pressure measurements. A further detailed examination including electrocardiogram, walking test, aortography (83 subjects) and muscle blood flow (Na^{24} clearance) was performed on 294 people with a history and palpatory or oscillographic findings suggesting pathology. Occlusions of peripheral arteries were found in 101 limbs in 75 subjects (11 of 1,550 women, 0.7%; 64 of 4,887 men, 1.3%). The prevalence rate rose from 0.1 per cent in men aged 30 to 39 to 8 per cent in men 60 to 64 years of age. Two-thirds of the patients with arterial occlusion were unaware of the condition; one-third were largely free of pain, and one-third had no pain at all. Only 35 of the 64 men (55%) with arterial occlusion complained of intermittent claudication, resulting in a prevalence of IC in men of 0.7 per cent in this population. (Data were not provided for the women).

A study of men aged 60-64 years living in Prague found a prevalence of IC of 10.6 per cent (Fodor et al, 1968). The electoral list was used to determine the population, and a one-in-six sample was invited to appear for investigation. Two-thirds of those invited appeared voluntarily. The remainder were followed up in person, and 443 of the 473 men (93.7%) were

examined. This study focused primarily on coronary artery disease, and no examination of the peripheral circulation was performed. The diagnosis of IC was based solely on the medical history, and the questions used to elicit patient symptoms were not discussed.

A questionnaire designed to identify people with IC (Rose, 1962) and recommended for use by the World Health Organization, was administered to 487 people aged 62 years and older randomly selected from a population of 27,000 older people living in a defined area of Edinburgh (Milne and Williamson, 1972). Physical examination was limited to palpation of the foot pulses and the authors disagreed on the findings in 11 per cent of cases. The prevalence of IC, defined as a positive questionnaire response and absent foot pulses, was 10.4 per cent in men and 2.6 per cent in women.

A random sample of 1,000 men in Moscow and 622 men in Berlin were asked to participate in a screening programme for cardiovascular disease (Bothig et al, 1976). The response rate was 77 per cent in the Moscow men, and 89 per cent in those from Berlin. The study focused on coronary artery disease, and the peripheral circulation was not examined. The diagnosis of IC was based solely on the response to the Rose questionnaire mentioned earlier. The prevalence of IC, using Rose's criteria, was 6.9 per cent in Moscow and 3.4 per cent in Berlin. No attempt was made to compare the technique of questionnaire administration in the two cities, so the difference in the prevalence rates could not be explained. Between-centre differences in the interpretation of electrocardiograms were examined, and disagreement occurred in 24 per cent of cases. It is possible, therefore, that there were considerable

differences in the methods used in the two centres.

In summary, most of the investigations described above have been unsatisfactory. They have investigated selected populations (Widmer et al, 1964), have had poor response rates leading to possible bias in the results (Widmer et al, 1964; Bothig et al, 1976), have used poorly standardized methods to elicit the symptoms of IC (Hobson and Pemberton, 1955; Fodor et al, 1968), or have not sought the presence of PVD with a physical examination and laboratory investigations (Kannel et al, 1970; Fodor et al, 1968; Bothig et al, 1976). A study which examined a general population, using a standardized questionnaire to identify people with symptoms of peripheral vascular disease, and in which the diagnosis was confirmed by physical examination and appropriate investigations, would be helpful in accurately determining the frequency of the condition.

D. THE AETIOLOGY OF PERIPHERAL VASCULAR DISEASE

During the course of this discussion I shall use the term 'risk factor' to describe hereditary, biological and environmental characteristics which have been shown to be associated, either directly or through interaction with other risk factors, with an increased risk of developing peripheral vascular disease. Before discussing the evidence implicating individual risk factors I should like, briefly, to review the normal anatomy of the arterial wall and the pathology of atherosclerosis. The discussion of risk factors will then be made in the context of this pathology and in relation to the major theories of the pathogenesis of atherosclerosis.

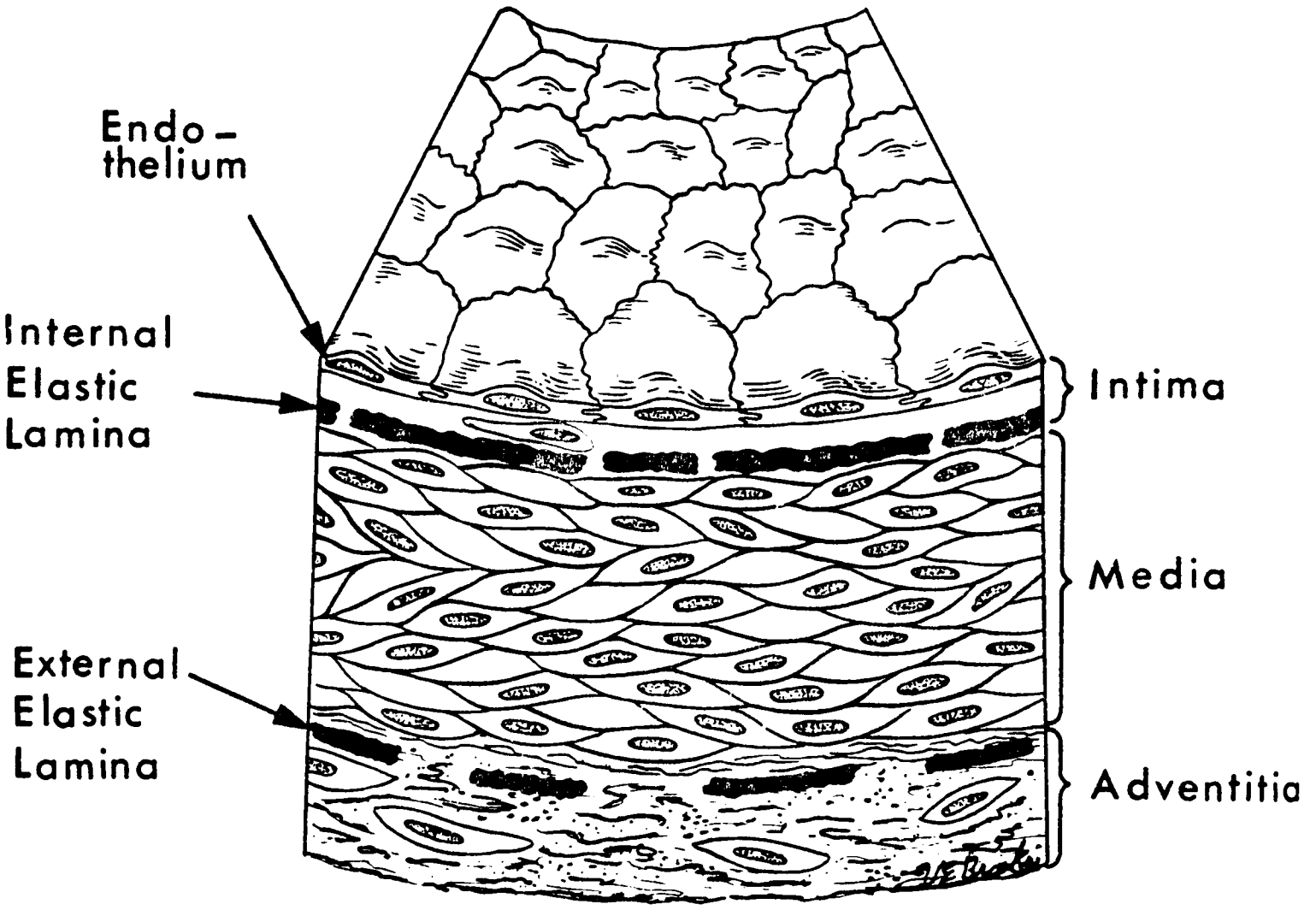
1. THE PATHOLOGY OF ATHEROSCLEROSIS

(a) Structure of the normal artery wall

There are three morphologically distinct layers in the

FIGURE 1.2

STRUCTURE OF THE NORMAL MUSCULAR ARTERY



From: Ross and Glomset (1976)

wall of muscular and elastic arteries (Figure 1.2). A continuous layer of endothelial cells forms the intima, and recent studies have demonstrated highly-interdigitated cell junctions which preclude penetration of the intima by large molecules such as plasma proteins. The media, bounded on either side by the internal and external elastic laminae, consists of smooth muscle cells surrounded by a tissue matrix of collagen, elastic fibres, and complex mucopolysaccharides called proteoglycans. The adventitia consists of a connective tissue matrix of collagen and proteoglycans containing loosely-arranged smooth muscle cells and collagen.

The cells of the intima and a variable proportion of the media derive oxygen and metabolites from the lumen of the vessel. Cells in the outer layers are supplied by small vessels called the vasa vasorum. Passage of macromolecules from the lumen into the wall is effected by pinocytosis, and this may be an important mechanism in controlling the milieu surrounding arterial smooth muscle cells (Ross and Glomset, 1976).

(b) The pathology of atherosclerotic lesions

There are three types of lesion commonly recognized in atherosclerotic vascular disease. These are the fatty streak, the fibrous plaque, and the complicated lesion.

Pathological examination of the arterial vasculature has shown the presence of fatty streaks in the intima of nearly all humans beyond the third year of life (Holman et al, 1958; McGill et al, 1963). These consist of focal accumulations of cells, now identified as smooth muscle cells, in the media containing and surrounded by deposits of lipid. These lesions develop in childhood and adolescence and are found both in western countries and in Africa and Asia where adult atherosclerosis

is rare (Gotto et al, 1976). Fatty streaks occur approximately ten years before more advanced lesions are found. The distribution of fatty streaks in the arterial system differs from that of the advanced lesions, and definitive evidence for the progression of fatty streaks to plaques is lacking (Strong et al, 1958; Strong et al, 1959).

Some authors make a distinction between atherosclerosis and another commonly used term, arteriosclerosis. Steele (1952) describes arteriosclerosis as:

> "additional morphological changes such as the laying down of connective tissue about the fatty plaque and in the surrounding tissues".

This addition of fibrous tissue to the early cellular lesion of the intima results in a grossly whitish lesion which protrudes into the lumen of the artery. The fibrous plaque consists primarily of lipid-laden cells surrounded by a matrix of collagen, elastic fibres, proteoglycans, and cellular debris. Free lipid is also present, primarily as cholesterol and cholesterol ester.

The complicated lesion is an extension of the processes operating to form the fibrous plaque. The disruption of the normal architecture of the artery wall leads to secondary events such as intramural haemorrhage, cell necrosis, and mural thrombosis with ensuing calcification and further fibrosis (Ross and Glomset, 1976).

(c) Theories of the pathogenesis of atherosclerosis

In 1852 Rokitansky postulated that the initial step in the development of an atherosclerotic plaque was the formation of a thrombus on the arterial wall:

> "In a highly developed form of this affection, we find the inner surface of a large artery, as the aorta, covered with a foreign substance spread over it at

> separate points, or in large patches, and forming a stratum varying in thickness, by which the inner surface of the vessel is commonly rendered uneven....
>
> ...."The deposit is an endogenous product derived from the blood, and for the most part from the fibrin of the arterial blood. Its formation demonstrates the pre-existence of a peculiar crasis of the blood, which is intrinsically arterial.... It is the most frequent form of disease affecting the arteries, and is on that account of the greatest importance".
>
> (Rokitansky, 1852, pp. 261)

Duguid (1949) supported the thrombosis hypothesis and refuted the assumption that arteriosclerosis was a reaction secondary to degeneration of fatty deposits in the arterial wall.

> ...."it is important to note that while the expansion (of the arterial wall) is a movement imposed on the arteries by the blood pressure, the recoil is a function of their own elasticity; and therefore anything which reduces this property will diminish their powers of recoil, or, in other words, cause them to remain more or less dilated.
>
> ...."A fibrous overgrowth would from its inception have to conform to the normal expansion of the vessel at each systole or be torn asunder as it formed, and it therefore would not be likely to offer much resistance to that movement. It would, on the other hand, by reducing the elasticity of the vessel, be likely to interfere with the recoil, and, were it to increase indefinitely, it would ultimately tend to fix the vessel rigidly in the expanded position....
>
> "The process is almost the reverse of what has usually been pictured, for instead of there being a gradual encroachment on the lumen.... there is a sudden and total occlusion by a mass of blood.... The blood pressure is eliminated and movements cease, and it is not until the circulation is re-established that these factors again come into play. They then, as would be expected, lead to a gradual widening of the new lumen; but a long time must presumably elapse before the vessel regains its original internal diameter, and it is not to be wondered that narrowing is a common feature of the lesions....
>
> "The thrombus first becomes covered with endothelium so that it is incorporated in the intima.... if it is thin.... the fibrin, which forms a shallow layer under the endothelium, (becomes) condensed and hyaline in appearance.... if thick.... the subendothelial layers undergo a direct transformation like that just described,

> the deeper ones may become vascularised.... In the large deposits fatty changes also appear.... and thus foci of the atheroma are formed".

The second major theory originated in 1856 when Virchow noted the similarity between atherosclerotic lesions in humans and those produced by experimental injury to arteries in animals. He suggested that changes in the arterial wall were a primary response to injury:

> "In the last place, it is a question where the seat of fatty degeneration really is.... it may be imagined that the fat is deposited in spaces intervening between the lamellae.... The enlargement which the part undergoes in consequence of the process and which we call sclerosis, depends upon this; the cellular elements of the coat increase in size and a multiplication of their nuclei takes place, so that spaces are not unfrequently found in which whole heaps of nuclei are lying.... These afterwards become the seat of the fatty degeneration, and then really perish. Thus we have here an active process, which really produces new tissues, but then hurries on to destruction in consequence of its own development".
>
> (Virchow, 1856, pp. 403)

In 1904 Marchand suggested that lipids found in plaques were derived from blood by a process similar to filtration. This lipid-filtration theory has since been propounded by a large number of workers.

Accumulation of lipid-rich cells in the subendothelial region is the first structural alteration seen in experimental atherosclerotic plaques. Altschul (1950) proposed that they were smooth muscle cells of the media which had invaded the intima. Electron microscopy confirmed the presence of smooth muscle cells in aortic plaques of cholesterol-fed rabbits (Buck, 1962), and recent reviews have focused on the key role of smooth muscle cell proliferation in atherosclerosis.

Intimal smooth muscle cells accumulate slowly and at a fairly uniform rate with increasing age in man. The reasons

for this proliferation are not clear, though the response-to-injury hypothesis of Virchow is supported by recent experimental evidence. Smooth muscle cells can be observed within the fenestrae of the internal elastic lamina, apparently in the process of migrating into the intima, five to seven days after balloon-catheter injury of an artery, and within one to three months the intima contains several layers of smooth muscle cells. Other types of mechanical, chemical and immunological injury result in the same smooth muscle cell response (Ross and Glomset, 1976).

Another reason for smooth muscle cell proliferation was suggested by the monoclonal hypothesis (Benditt and Benditt, 1973). This theory was based on the concept that only one of the two X-chromosomes in the cells of adult females is active. The two chromosomes can be electrophoretically distinguished by a marker gene for glucose-6-phosphate-dehydrogenase (G6PD). A piece of normal artery wall taken from a woman contains a mixture of the two types of G6PD, indicating a heterozygous smooth muscle cell component. The G6PD of an atherosclerotic plaque is, in contrast, solely or predominantly of one type, indicating that the smooth muscle cells arose from a single type of cell. A recent study has shown that intramuscular injection of carcinogenic substances caused an increase in aortic atherosclerosis in chickens (Albert et al, 1977). It is possible that genetic or environmental factors may cause mutation of arterial smooth muscle cells and subsequent cell proliferation.

Martin and Sprague (1973) suggested that smooth muscle cell proliferation was the result of a failure in the feedback system which normally inhibits cell division. They postulated the existence of "chalones" secreted by the cells to inhibit

replication. With age, the number of stem cells in the artery wall decreased, and the concentration of chalones fell. This effect was more pronounced in the intima where there were fewer cells initially, and the disinhibition of cells here resulted in the early atherosclerotic lesion. A similar theory of stem cell failure in the endothelium could explain the initial break in the endothelial layer proposed by the response-to-injury hypothesis (Ross and Glomset, 1976).

In summary, the focal lesions of atherosclerosis are characterized by three fundamental phenomena: proliferation of smooth muscle cells, deposition of intracellular and extracellular lipid, and accumulation of extracellular matrix. To be plausible, any hypothesis invoking a risk factor for peripheral vascular disease must take these pathological changes into account.

2. FACTORS ASSOCIATED WITH AN INCREASED RISK OF DEVELOPING INTERMITTENT CLAUDICATION

(a) Age

The annual incidence rate of IC is very low in people under the age of 30 years, and increases with age in men and women (see Figure 1.1). The prevalence of IC has been shown to increase from about 0.1 per cent in young men to approximately 10 per cent in people 65 years and older (Widmer et al, 1963; Milne and Williamson, 1972). This increase of incidence and prevalence with age is also seen in coronary artery and cerebral vascular disease. The major theories of pathogenesis are all compatible with this observation, since it can be explained in terms of biological senescence with failure of normal cell control and repair mechanisms (failure of stem cells, monoclonal hypothesis, response-to-injury hypothesis) and the cumulative

effect of continued exposure to risk factors (lipid filtration theory, thrombogenic theory).

(b) Sex

All major series of patients with IC have shown a greater proportion of men than women afflicted with the disease. The ratio of men to women varies from as low as 1.6:1 (Widmer et al, 1963) to as high as 11:1 (Jeurgens et al, 1960). The incidence of IC in the Framingham study was higher in men than women at all ages, a pattern not present in uncomplicated angina and stroke (Figure 1.1). The incidence in women was approximately equal to that of men 10 years older, though after the age of 60 the rate rose to approach that of the men.

The increased susceptibility of men to IC may be due to a greater prevalence of risk factors. In the Tecumseh study, men had significantly higher mean triglyceride and systolic blood pressure values than women in young and middle ages (Ostrander and Lamphiear, 1976). The prevalence of smoking, and the amount of tobacco smoked, is also greater in men than women at all ages (Lee, 1976). The increase in incidence after the menopause may be due to a withdrawal of hormonal protection. Oestrogens block the stimulating effect of low-density lipoproteins on smooth muscle cells in culture (Gresham et al, 1976), and it is known that women who are subjected to bilateral ovariectomy or who have a spontaneous premature menopause are more prone to develop ischaemic heart disease (Oliver and Boyd, 1959; Sznajderman and Oliver, 1963).

(c) Smoking

Pathological studies have shown a relationship between cigarette smoking and atherosclerosis. Strong and Richards

(1976) obtained the smoking history of 1,320 autopsied men by interviews with first-degree relatives. The cases were divided into non-smokers, light to moderate smokers (1 to 24 cigarettes daily), and heavy smokers (25 or more cigarettes daily). The coronary arteries and aorta were examined visually and with an X-ray technique to determine the degree of atherosclerosis and calcification. With few exceptions, the extent and severity of atheroma increased with the amount of tobacco smoked at all ages. The magnitude of difference was greater in the abdominal aorta than in the coronary arteries, and raised lesions covered approximately twice as much of the intimal surface area of the aortae of heavy smokers compared with non-smokers. Other post-mortem studies have reached similar conclusions (Wilens, 1962; Auerbach et al, 1965).

Jeurgens et al (1960) found that 97.5 per cent of the patients in a series of 520 claudicants were smokers at the onset of symptoms, and 33 per cent smoked 20 or more cigarettes a day. A similar prevalence of smoking in patients with IC has been found in other studies (Eastcott, 1962; Lord, 1965; Lithell et al, 1975). In the Framingham study a higher incidence of IC was found with increasing levels of cigarette smoking, and, in comparison with other risk factors, it was concluded that "the cigarette habit is second to none as a contributor to intermittent claudication risk in both sexes" (Kannel and Shurtleff, 1973).

The type of tobacco smoked and the amount of smoke inhaled and absorbed may also affect the risk of developing IC. Janzon (1975) compared the smoking habits of 17 newly-referred claudicants with those of 55 healthy smokers, and found that the cases reported inhaling the smoke more commonly than the

controls. It has been shown that pipe and cigar smokers are less likely to develop ischaemic heart disease than cigarette smokers, though similar data is not available concerning the risk of PVD (Kannel et al, 1968; Kesteltoot et al, 1976).

Cigarette smoke is a complex mixture of particles and gases with a large number of chemical components (Wynder and Hoffman, 1965). Attempts have been made by many workers to determine the component responsible for arterial disease in the hope of producing a "safer" cigarette. One of the components examined, carbon monoxide (CO), constitutes about four per cent of cigarette smoke by volume, and smoking is the most important single source of exposure to CO in man, frequently leading to carboxyhaemoglobin (COHb) levels above eight per cent (Wald et al, 1973). The level of COHb reached in the blood depends on a number of factors including the type of cigarette smoked, the depth of inhalation, the number of puffs per cigarette, and the physical activity of the individual. There is considerable variation in the COHb level achieved by different people smoking under standard conditions, but the COHb increment per cigarette may be typical for each person (Wald et al, 1975).

The cigarette smoking habit and consequent COHb level were examined in 1,085 volunteers working in Copenhagen. In the age group 30 to 69 years, a person with a COHb level of five per cent or more was 21 times as likely to be affected by certain atherosclerotic diseases (including IC) as another person of the same age and sex with a similar smoking history and current smoking habits but with a COHb level of less than three per cent (Wald et al, 1973). The COHb yield of filter cigarettes is significantly higher than that of plain cigarettes

due to the use of unventilated paper in the former (Wald et al, 1977), and it has been postulated that the increased use of filter cigarettes, while causing a reduction in the number of deaths due to lung cancer, may be responsible for the continued rise in deaths due to cardiovascular disease (Wald, 1976).

A number of animal experiments have shown that intimal and subintimal injuries indistinguishable from early atherosclerosis can be produced after exposure to CO (Wanstrup et al, 1969; Thomsen, 1974; Astrup et al, 1967; Webster et al, 1970). The primary effect of CO on the cardiovascular system is increased endothelial permeability which leads to oedema of the endothelial cells, and may trigger the pathological changes discussed earlier (Kjeldsen, 1969; Ross and Glomset, 1976).

In addition to the potential long-term effect of CO on the circulation, there is an acute effect. Aronow et al (1974) demonstrated that the exercise tolerance of people with IC fell significantly after exposure to CO. This was not due to a reduction in calf blood flow (Coffman and Javett, 1963), and may have been caused by reduced oxygen transport due to the displacement of oxygen by CO on the haemoglobin molecule.

The relationship between CO and vascular disease is not yet firmly established. Jones and Sinclair (1975) studied a group of blast furnace workers, and found no significant difference in the prevalence of arterial disease among those exposed to high levels of atmospheric CO and others working away from the furnaces. It may be that COHb is simply an indicator of the absorption of some other toxic component of cigarette smoke.

The other major constituent of tobacco smoke to be invoked as a potential risk factor for atherosclerosis is

nicotine. Intravenous injection of nicotine causes cutaneous vasoconstriction and a decrease in digital blood flow and temperature in the extremities (Roth and Shick, 1958). This may explain part of the detrimental effect of continued smoking on the amputation rate of patients with IC (Jeurgens et al, 1960). Shepherd (1963) found that at the ordinary rate of smoking (one puff every 66 seconds in his study) the change in digital blood flow could not be attributed to the direct effect of nicotine on the smooth muscle cells of arteries, and concluded that the effect was mediated primarily via the sympathetic nervous system.

Intravenous nicotine also causes an increase in circulating free fatty acids (FFA), and it has been shown that this effect is mediated by the release of catecholamines from the adrenal glands. Kershbaum et al (1961) demonstrated a rapid and consistent rise in FFA in humans after cigarette smoking, and in a later study demonstrated an exaggerated FFA response in patients with healed myocardial infarction (Kershbaum et al, 1962). The FFA response to smoking is much less marked with cigars than cigarettes due to decreased inhalation and absorption of nicotine in cigar smokers (Kershbaum et al, 1966a; Kershbaum et al, 1966b). Certain free fatty acids are known to enhance thrombus formation and can influence blood coagulation (Connor and Poole, 1961; Poole, 1958). As discussed earlier, this effect on the coagulation system may have detrimental effects on the circulation. The effect of nicotine on cholesterol and triglyceride is not clear. There seems to be no acute effect of cigarette smoking on these lipids in humans (Page et al, 1959), though impaired fat tolerance (elevated triglyceride and chylomicrons after a standard meal) in smokers compared with non-

smokers has been demonstrated (Kershbaum and Bellett, 1964; Marder et al, 1952).

In addition to the direct toxic effects of cigarette smoke on the circulation, the smoking habit may be associated with other risk factors for peripheral vascular disease. In the Stockholm Prospective Study the cholesterol and triglyceride concentrations of men who smoked were found to be higher than those of men who did not smoke, up to 55 years of age (Carlson and Lindstedt, 1968). Women who smoked had elevated triglyceride in all age classes, and a tendency to elevated cholesterol levels in the older age groups compared with women who did not smoke. In the Oslo study the levels of cholesterol, triglyceride, blood glucose, and systolic and diastolic blood pressure, rose with increased smoking (Leren et al, 1975). This effect was more pronounced in younger men, and there was no effect on these variables of cigar or pipe smoking. Serum cholesterol was higher in those with a longer duration of smoking, though it is not clear whether the amount smoked was the same in the groups compared.

Not all studies have found that smoking has an adverse effect on risk factors. The relationship between cigarette smoking and other physical characteristics was studied in a population of 8,641 people living in Tecumseh, Michigan (Higgins and Kjelsberg, 1967). Cigarette smokers of both sexes weighed significantly less than the rest of the population, and skinfold measurements indicated that the differences in weight were at least partly due to reduced body fat in smokers. There was no significant difference in the systolic blood pressure, cholesterol, or blood glucose of smokers compared with non-smokers, and smokers had significantly lower diastolic blood pressure and serum uric

acid levels. Cigar and pipe smoking had no effect on these variables. Kesteltoot et al (1976) also found a small but significant lowering of blood pressure in cigarette smokers compared with life-long non-smokers. After 16 years of follow-up in the Framingham study there were only small correlations, all negative, between the number of cigarettes smoked per day and systolic blood pressure, diastolic blood pressure, cholesterol, and blood glucose (Kannel and Shurtleff, 1973).

In summary, a number of studies have shown that smoking has direct and indirect effects on the arterial system which result in an increased prevalence of atherosclerosis. Pathological and epidemiological studies have shown that the severity of atherosclerosis and the frequency of IC increase with the amount of tobacco smoked, though the exact mechanism by which smoking promotes atherosclerosis is not completely understood. The effect of carbon monoxide on endothelial cells, and of nicotine on the coagulation system, are consistent with the response-to-injury and the thrombogenic theories of atherosclerosis, respectively. Carcinogens present in tobacco smoke may cause mutations in smooth muscle cells, leading to proliferation as described in the monoclonal hypothesis of Benditt and Benditt (1973). Finally, the interaction of smoking with other factors, such as blood pressure or serum lipids, may place a smoker at increased risk of developing IC.

(d) Blood pressure

A number of studies have demonstrated that elevated blood pressure is associated with an increased risk of IC. Jeurgens et al (1960) found that 25 per cent of patients with IC had a systolic blood pressure (SBP) greater than 150 mm Hg and a diastolic blood pressure (DBP) greater than 90 mm Hg

compared with only nine per cent of control patients with pressures above these arbitrary levels. Taylor and Calo (1962) defined hypertension as SBP greater than 180 mm Hg, and found this risk factor in 28 per cent of a series of 454 patients referred to hospital for PVD. Begg and Richards (1962) chose to use DBP as the measure of hypertension, and in a review of 198 claudicants, found that 29 per cent had a DBP greater than 100 mm Hg. In the Framingham study blood pressure readings (SBP, DBP, or both) more than two standard deviations above the mean were associated with an increased risk of IC at all ages (Gordon et al, 1972).

Hypertension is associated with pathological changes in arterial walls including the deposition of hyaline, proliferation of smooth muscle cells, and, with severe elevation, necrotizing arteriolitis (Robbins, 1967). It was postulated in 1958 that vibrational injury of haemodynamic origin was a major factor in atherosclerosis, and that the degenerative compensatory thickening of the intima was the consequence of mechanical failure of the vessel wall (Stehbens, 1975). It has been demonstrated that haemodynamic injury can affect highly specific sites on the arterial wall (Ross and Harker, 1976). Experimental arteriovenous fistulae in sheep resulted in diminished cohesion of endothelial and smooth muscle cells, with patchy separation of the basement membrane and loss of elastic tissue. Examination of the connective tissue protein revealed a defect at the level of the cross-linking amino acids. Cellular debris accumulated at the site of vibrational injury, and it was postulated that the lipid in the atherosclerotic vessel was derived from biochemical alteration of this debris (Stehbens, 1975). It can be seen that these mechanical stresses will be accentuated in the

presence of raised arterial pressure.

There is an interaction of blood pressure with other risk factors. Leren et al (1975) found a small but significant positive correlation among blood pressure, cholesterol and triglyceride. Vogelburg et al (1975) found a significant increase in the degree of PVD demonstrated by arteriography in patients with type IIa and type IIb hyperlipoproteinaemia who had hypertension, compared with normotensive hyperlipidaemic patients. Hypertension also increased the degree of arteriosclerosis in diabetic patients in this study. Several population studies have found a positive correlation between blood pressure levels and blood glucose (Leren et al, 1975; Garcia et al, 1974; Epstein et al, 1965). In the Framingham study, diabetics were found to have an increased incidence of hypertension, and the presence of elevated blood pressure resulted in increased mortality due to cardiovascular diseases in these patients compared with normotensive diabetics (Garcia et al, 1974). Keen (1976) acknowledged the relationship between glucose and blood pressure, but stated that with few exceptions there was no systematic elevation of blood pressure in populations of established diabetics when compared with proper age and sex-matched normal controls. An increased risk of death from cardiovascular disease in smoking hypertensives compared with non-smoking hypertensives has been demonstrated (Dorn, 1959; Hammond, 1964; Doyle et al, 1964). The effect of smoking on blood pressure has been discussed.

In summary, elevated blood pressure causes mechanical stresses on the arterial wall which may lead to increased atherosclerosis. Patients with IC have elevated blood pressure compared with the general population, and prospective studies

have shown that the risk of IC (and other ischaemic events such as stroke and myocardial infarction) mounts with increasing levels of blood pressure (Kannel and Dawber, 1974). There is also evidence that elevated blood pressure acts synergistically to increase the damage caused to the arterial system by other risk factors such as hyperlipidaemia, diabetes, and smoking.

(e) Serum lipids

The relative importance of cholesterol and triglyceride in the pathogenesis of PVD is not clear. Some studies have found an elevation in the concentration of triglyceride to be the most common lipid abnormality in patients with IC (Kremer et al, 1973; Vyden et al, 1975), while hypercholesterolaemia has been found more commonly in other series (Sloan et al, 1971; Leren et al, 1971).

Slack (1969) identified 104 patients with Frederickson's type II hyperbetalipoproteinaemia (elevated cholesterol, level not defined), and 41 patients with hyperlipoproteinaemia associated with hypertriglyceridaemia (Frederickson's types III, IV, V) (Frederickson et al, 1967). The life experience (from date of birth) was examined using a life-table method, and patients with elevated triglyceride had an increased incidence of PVD while those with elevated cholesterol suffered mainly from ischaemic heart disease.

Greenhalgh et al (1971) examined the serum lipids of 116 patients referred to hospital with PVD, and compared them with a control group of 50 age-matched hospital in-patients admitted for non-vascular diseases. The upper limit of normal was taken as the mean level plus two standard deviations found in the controls. The most common lipid abnormality was an elevated triglyceride with normal serum cholesterol (30%). In 11 cases

(9.5%) both triglycerides and cholesterol were elevated, while six (5%) had hypercholesterolaemia only. A total of 44 per cent of those with PVD had lipoprotein abnormalities.

Skrede and Kvarstein (1975) reviewed 110 non-diabetic patients with radiologically-proven PVD and compared their lipid levels with those of 548 normal individuals. The 95th percentile of the values found in the control group was used as the upper limit of normal. The most common abnormality found was combined elevation of cholesterol and triglyceride (21%), while raised cholesterol with normal triglyceride was found in 17.9 per cent, and raised triglyceride alone in 12.6 per cent.

Vogelburg et al (1975) studied the distribution and severity of atherosclerotic lesions in patients with PVD and known lipid abnormalities. The degree of PVD, as measured by arteriography, was more severe in those with raised cholesterol, and no correlation was found between serum triglyceride levels and the degree of PVD. There was a tendency for the pelvic vessels to be involved in those with raised cholesterol, while distal vessels were commonly affected in those with raised triglyceride.

Several studies have concentrated on the role of cholesterol in PVD and have not examined triglyceride. Elevated cholesterol was found to be a risk factor for IC in the Framingham study (Gordon and Kannel, 1972). Jeurgens et al (1960) compared the cholesterol values of 520 claudicants with those of 194 patients free of PVD. Using an arbitrary value of 250 mg/100 ml as the upper limit of normal, 48 per cent of the men and 74 per cent of the women with PVD had elevated cholesterol compared with only eight per cent of the controls. The mean cholesterol level was 50 mg higher in the men with PVD compared

with male controls, and the mean level in the women with PVD was 35 mg higher than that of the male claudicants. Bliss et al (1972) used the same cut-off point, and found that 25 claudicants in a series of 50 exceeded this value for serum cholesterol.

Marchand (1904) first put forth the theory that the lipids found in an atherosclerotic plaque were derived from the blood by a process not unlike filtration. Anitschkow (1913) demonstrated that rabbits fed a diet high in cholesterol developed lipid-containing intimal plaques in their aortae, and it has been shown by radioisotope techniques that lipids move from the blood into the arterial wall (Brest and Moyer, 1967). Ross and Harker (1976) found that monkeys who had been fed increased amounts of cholesterol for a period of nine to 18 months showed a focal loss of approximately seven per cent of their arterial endothelial surface. In contrast, the endothelium of normocholesterolaemic monkeys matched for age and weight was intact. Further experiments showed delayed healing of endothelial injuries caused by a balloon catheter in the hypercholesterolaemic monkeys. The authors postulate that chronic elevation of serum cholesterol may cause similar endothelial injury with delayed healing in man.

The recent development of cell culture techniques has permitted in vitro experiments to study factors which promote smooth muscle cell proliferation. If five per cent serum is added to smooth muscle cells in culture, they will maintain their differentiated appearance and grow logarithmically for 10 to 14 days. If serum from which the fraction containing low-density lipoproteins (LDL) has been removed is used, cell growth is considerably less. High-density lipoprotein (HDL) binds to

the surface of arterial smooth muscle cells as effectively as LDL, but is taken into the cell and degraded much more slowly. Thus HDL blocks the uptake of LDL by the cells and has been shown to inhibit their growth in cell culture (Carew et al, 1976; Ross and Harker, 1976). HDL is also important in the removal of cholesterol from the peripheral tissues, and it has been postulated that a low level could lead to an imbalance in the normal flux of lipid in and out of the arterial wall, with an accumulation as described in the lipid-filtration theory of atherosclerosis (Berg et al, 1976). It has been shown that patients with evidence of arteriosclerosis (myocardial infarction or PVD) have significantly lower levels of HDL than patients free of these complaints (Berg et al, 1976; Erickson and Carlson, 1974). The concentration of HDL in healthy women is significantly higher than that of men, and thus HDL may be partly responsible for the lower incidence of IC in women (Farish et al, 1975).

One of the components of the arterial extracellular matrix is glycosaminoglycan. An important constituent, dermatan sulfate, is present in high concentrations in primate aortae, and strongly binds LDL at physiologic pH and ionic strength. This interaction may lead to extracellular deposition of lipids during plaque formation (Ross and Glomset, 1976).

In summary, serum lipids affect endothelial and smooth muscle cells and play an important role in the initiation and growth of the atherosclerotic lesion. It is not known whether cholesterol or triglyceride is more important in the pathogenesis of PVD, but it seems likely that marked elevation of either is associated with increased severity of arterial lesions. Most studies have examined the serum lipids of patients after symptomatic PVD was established, and few data are available from

prospective studies such as Framingham. Thus the degree of risk of developing IC associated with increased levels of serum lipids has not been clearly defined. As discussed in previous sections, the presence of other risk factors such as hypertension and smoking increases the damage caused to the arterial system by hyperlipidaemia.

(f) Diabetes and glucose intolerance

The relationship between PVD and glucose metabolism is unclear, partly because of difficulties in the definition and diagnosis of diabetes. Adult-onset diabetics may tolerate symptoms for many months before seeking medical advice, and for each person in the general population with known diabetes there are several others with unrecognized hyperglycaemia (Sharp et al, 1964; Keen et al, 1965; Royal College of General Practitioners, 1963). The prevalence of diabetes in clinical series of claudicants varies with the population selected, but several large studies found that approximately four per cent of their patients were known diabetics (Bloor, 1960; Begg and Richards, 1962; Silbert and Zazeela, 1958).

In the Framingham study, there was an increased risk of coronary artery disease, stroke, and IC with increasing glucose levels (Kannel and Shurtleff, 1971). Keen et al (1965) found an increased prevalence of ischaemic symptoms (angina, pain of possible infarction, or IC assessed by questionnaire) with increasing blood glucose at levels below those needed to establish the diagnosis of diabetes. Kingsbury (1966) studied 338 male non-diabetic patients with PVD, and found a significant correlation between the degree of arterial irregularity and narrowing shown on arteriogram and the level of fasting blood glucose. The relationship was also evident after a 50 gram

glucose tolerance test. Other studies which have examined diabetic patients have found no correlation between the degree of glucose intolerance and the frequency of complications such as gangrene and skin ulceration (Dry and Hines, 1941; Albrink, 1961).

Vogelburg et al (1975) found that abnormal glucose tolerance did not affect the degree of arteriosclerosis shown on the arteriograms of 121 patients with PVD, but diabetics tended to have preferential involvement of the distal leg arteries. Strandness et al (1964) used a mercury strain gauge plethysmograph to study PVD, and found that diabetic patients had a significantly higher incidence of involvement in the anterior tibial, posterior tibial, and peroneal arteries than did non-diabetics. The location of arterial narrowing may be of importance in the subsequent development of collateral circulation, and affects the choice of reconstructive surgical procedures. This may explain the observation that diabetics with IC have a worse prognosis than non-diabetic claudicants (Silbert and Zazeela, 1958; Schadt et al, 1961).

The mechanism by which the altered glucose metabolism of diabetes leads to atherosclerosis has not been clearly established. Hyperglycaemia may activate the sorbitol pathway (Morrison et al, 1970). The necessary enzymatic apparatus is present in the aortic endothelium, and accumulation of the poorly diffusible alcohol, sorbitol, may cause endothelial swelling and increased permeability, initiating the mechanisms discussed earlier. The complex glycosaminoglycans present in the interstitial matrix of the artery wall are produced in excess in diabetics, and this may lead to the accumulation of lipoprotein by physicochemical forces (Gero et al, 1973; Ross

and Glomset, 1976).

In the adult-onset form of diabetes, there is often a normal or raised level of insulin present in the blood (Turner and Holman, 1976). The consequences of hyperinsulinaemia include increased production of triglyceride-rich lipoprotein, inhibition of tissue lipolysis, and stimulation of in-situ lipogenesis. Insulin may also stimulate the proliferation of smooth muscle cells (Keen, 1976). With further loss of beta cells, hypoinsulinaemia may occur. This is associated with decreased lipoprotein lipase activity, resulting in slow removal of lipoproteins from the circulation. Increased hepatic triglyceride synthesis results because of the rise in circulating fatty acid levels, and cholesterol mobilization and transport may also be affected by reduction in the activity of lecithin cholesterol acyl transferase, an enzyme which esterifies cholesterol. Increased free fatty acid levels may also result in activation of platelets and the clotting mechanism (Keen, 1976).

Several epidemiological studies have demonstrated a positive correlation between elevated blood glucose and serum cholesterol (Epstein et al, 1965; Garcia et al, 1974; Leren et al, 1975). Abrams et al (1969) demonstrated a strong correlation between glucose and triglyceride, and Keen (1976) states that hypertriglyceridaemia is the characteristic abnormality of lipids in diabetics. Diabetes is very often associated with obesity, and this may account for much of the association of hyperlipidaemia, hyperinsulinaemia, and hyperglycaemia. Obesity may also contribute to the reported increase in the incidence of hypertension in hyperglycaemic people (Leren et al, 1975), though the relationship between diabetes and hypertension remains

unclear (Garcia et al, 1974; Keen et al, 1975).

The effect of nicotine on catecholamine release could result in transient hyperglycaemia. Leren et al (1975) found a small but significant rise in glucose with increased smoking. In the Framingham study a small negative correlation was found between smoking and glucose, consistent with the fact that smoking is associated with decreased body weight (Kannel and Shurtleff, 1973; Higgins and Kjelsberg, 1967). Smoking does increase the risk of IC in diabetics compared with non-smoking diabetics (Weinroth and Herzstein, 1946).

From this discussion it can be seen that the disruption of normal glucose and insulin homeostasis has profound effects on the metabolism of the artery wall. Small and medium-sized arteries are often affected, leading to an increased incidence of serious complications. The circulation of diabetics is susceptible to the effects of other risk factors, such as smoking and hypertension, which accelerate the atherosclerotic process.

(g) Blood viscosity

Dormandy et al (1973a) examined 126 patients with IC and found that their blood viscosity was significantly higher than that measured in a series of 100 age-matched controls. Within the patient series, the viscosity was higher in those with a claudication distance of less than 100 yards and in those with rest pain. Thirty-three patients with definite evidence of ischaemic heart disease as well as PVD had significantly higher blood viscosity than those with PVD only. The most common single biochemical abnormality in the cases was a raised plasma fibrinogen; 60 per cent had a concentration greater than the upper limit of normal. There was a significant positive

correlation between viscosity and fibrinogen. The claudication distance and peripheral blood flow measured by plethysmography of 62 untreated patients taken from this series was observed for a period of one to three years. Patients with a high level of viscosity and fibrinogen at referral had a signicantly greater risk of deterioration than patients whose viscosity was normal (Dormandy et al, 1973b). Other studies have also demonstrated increased viscosity or plasma fibrinogen in patients with coronary artery disease or PVD compared with normal controls (Rosenblatt et al, 1965; Dintenfass et al, 1966; Thompson, 1976).

Blood is a suspension of cells in an aqueous solution of electrolytes, plasma proteins and other substances. At rest it forms a continuous structure which must be disrupted before flow begins. The measurement of the force required to initiate flow determines the internal friction, or viscosity. The two components of blood, plasma and cells, are both important determinants of viscosity and also interact with each other.

The effect on viscosity of the plasma proteins varies with the type of protein considered. An increase in the concentration of globulin from 10 to 40 grams/1 increases the viscosity by about 50 per cent. Albumin, however, does not appear to have a significant effect. Blood serum has a viscosity 20 per cent less than plasma, and it has been suggested that fibrinogen is the plasma protein which most affects viscosity, perhaps by promoting red blood cell (RBC) aggregation (Woodcock, 1976; Merrill and Pelletier, 1967; Merrill, 1969; Bottiger and Svedberg, 1967).

Blood viscosity increases with increasing levels of haematocrit, and the range of viscosities in normal people can largely be accounted for by the normal range of haematocrit

(Dintenfass et al, 1966). The flexibility of the RBC is also important, and conditions such as acidosis, hypoxia, and sickle cell anaemia which make the RBC more rigid than normal are associated with increased viscosity (Dintenfass, 1968; Chien et al, 1970). A filtration technique was used to determine the RBC flexibility of 44 patients with PVD and 44 age- and sex-matched controls (Reid et al, 1976). The ability of the RBC's to deform and pass through the filter was significantly reduced in the cases, and significantly less in those with rest pain and gangrene than in those who only had IC. Reid et al did not find a relationship between RBC flexibility and whole blood viscosity. Nor was there a clear relationship between fibrinogen and the ability of the RBC's to pass through the filter.

Blood is a thixotropic substance, and its viscosity decreases as the flow velocity increases. This indicates that RBC aggregation, a reversible phenomenon, is an important factor affecting viscosity. Antigen-antibody reactions, excess fibrinogen, acidosis, and stasis increase RBC aggregation, and result in abnormally high blood viscosity. Aggregates may intermittently plug the entrance to arterioles, resulting in localized stasis and hypoxia (Dintenfass et al, 1966). Thus a vicious cycle may be established in which tissue hypoxia (as in IC) leads to increased viscosity, which in turn results in decreased tissue perfusion.

In addition to peripheral resistance, blood viscosity also affects cardiac output. Dormandy (1970) demonstrated a 40 per cent increase in the cardiac output of anaesthetized dogs whose blood viscosity was decreased by 15 per cent with exchange transfusions of normal saline. There was no change in the heart rate, and increased cardiac output was due to an increase

in the stroke volume. There was also a decrease in the peripheral resistance which was less than the rise in cardiac output. The author pointed out that this surprising effect on cardiac output could have a significant effect on patients with PVD who also have an elevated viscosity, since correction of the abnormality could improve flow to the limbs, quite apart from any treatment of the arterial lesions.

Thompson (1976) studied the relationship of plasma fibrinogen and smoking in 288 smokers and 506 non-smokers attending a clinic in Manchester. He found a significant elevation in the mean fibrinogen concentration of the smokers compared with non-smokers, controlling for age and sex. Goldbourt and Medalie (1977) compared the characteristics of smokers, ex-smokers and non-smokers in 10,000 Israeli men, and found a significant increase in the haematocrit of the smokers. Thus it is possible that one of the mechanisms by which smoking causes a deterioration in patients with IC is through its effects on blood viscosity. Elevated fibrinogen has been found in diabetics (Keen, 1976), but no significant correlation has been shown between serum lipids and blood viscosity (Rosenblatt et al, 1965; Woodcock, 1976).

In summary, viscosity is unique as a risk factor in that its proposed mechanism of action does not involve the arterial wall, but the fluid within. The studies described have all examined the viscosity in patients with symptomatic atherosclerotic vascular disease, and so it is not known whether the relationship between viscosity is a consequence of atherosclerosis or is due to other risk factors associated with PVD. I am not aware of a prospective study which has demonstrated an increased risk of developing IC in people with elevated viscosity,

possibly because of the great care and precision required in the measurements which would make this a very difficult project.

(h) Other factors

Included in this section are obesity, physical activity, platelets and the coagulation system, and serum uric acid. Though there are few data which implicate these factors in the aetiology of peripheral vascular disease, there is evidence that they may act either directly or indirectly through association with other risk factors to damage the arterial system.

(i) Obesity and physical activity

The mean weight of men and women increases with age. This weight change has been examined in the Framingham study, and is correlated with a rise in serum cholesterol, blood pressure, blood glucose, and serum uric acid (Ashley and Kannel, 1974). Serum triglyceride also increases with increasing relative body weight (Leren et al, 1975; Hartmann, 1976). In the Tecumseh study, the level of serum lipids, glucose, and the systolic blood pressure were highly correlated with adiposity as determined by relative weight and skinfold thickness (Ostrander and Lamphiear, 1976). Reporting on the same population, Epstein et al (1965) found obesity and systolic blood pressure to be independent risk factors for coronary artery disease. Jeurgens et al (1960) and Bothig et al (1976) found no increase in the prevalence of obesity in patients with IC compared with normal people, and I am unaware of any evidence that obesity acts as an independent risk factor for PVD.

Physical activity has been shown to affect risk factors for PVD. Carlson and Lindstedt (1968) found a marked effect of

leisure activity on serum triglyceride in 3,624 men studied as part of the Stockholm Prospective Study. Systolic and diastolic blood pressure and relative body weight were also lower in men reporting physical activity at leisure, whereas these parameters changed in the opposite direction in men and women reporting moderate to hard physical activity during working hours. Leren et al (1975) examined 17,965 men in Oslo to determine the prevalence of cardiovascular disease. He found that increased physical activity at work and at leisure was associated with a fall in serum cholesterol, blood pressure, and over-all risk score for cardiovascular disease. Most studies which have examined the role of physical activity have found that differences in the level of activity of groups of people are often associated with differences in such things as diet, body weight, smoking, and alcohol consumption. It seems likely that people who exercise regularly have a lifestyle which is different from that of the general population, and this may affect their risk of developing cardiovascular disease. None of the major series has examined the physical activity of patients with IC prior to the onset of symptoms, and I am not aware of evidence that lack of exercise acts as an independent risk factor for PVD. Physical exercise has been shown to benefit people with established IC, and this will be discussed in a later section.

(ii) Platelets and the coagulation system

The coagulation system involves the interaction of the arterial wall, platelets, and circulating proteins in a complex relationship containing several control mechanisms. It is over 300 years since the initial suggestion of systemic hyper-coagulability (Wiseman, 1676) and our knowledge of this system is still far from complete.

When the endothelial layer is damaged, sub-intimal collagen is exposed and causes the adherence of platelets, resulting in the release of platelet ADP which in turn induces reversible platelet aggregation. Collagen is also believed to activate Hageman factor (Factor XII), thus starting the sequential reactions leading to thrombin formation. Thrombin itself is responsible for converting the loose and reversible ADP-induced platelet plug into a consolidated or irreversible phase, and the aggregate then contracts. The concentration of thrombin necessary to make platelet aggregation irreversible is believed to be much less than that required for fibrin formation. Thrombin is also responsible for the conversion of fibrinogen to fibrin, which further reinforces the platelet plug to yield what is classically known as the white thrombus (Wessler, 1971).

Platelet adhesiveness is increased in diabetes (Keen, 1976), and with elevations of serum lipids (Wessler, 1971). Diabetes is also associated with increased concentrations of fibrinogen and Factor VIII. Cigarette smoking is associated with catecholamine release (Westfall and Watts, 1964), resulting in a rise in serum free fatty acids (Kerschbaum and Bellett, 1964), which is in turn associated with enhanced thrombus formation (Connor and Poole, 1961), blood coagulation (Poole, 1958), increased platelet activation, and decreased platelet survival (Mustard, 1963). Dintenfass (1968) has shown that platelet aggregation is increased at high shear rates in vitro, and points out that blood flow through arterial stenoses in vivo results in a high velocity gradient which simulates experimental conditions of high shear stress. Flow through capillaries depends on cell size and flexibility, and since platelet

aggregates are larger and more rigid than red blood cells, the presence of increased numbers of platelet aggregates could affect tissue perfusion.

In vitro studies of cultured arterial smooth muscle cells have examined the role of platelets in cell proliferation. In the presence of serum derived from cell-free plasma (as opposed to whole blood) the arterial smooth muscle cells remain healthy but quiescent. However, if serum derived from whole blood is added to the cells, they begin to proliferate. This effect is caused by a factor released by platelets during clotting. In baboons, the addition of dipyrimadole to inhibit platelet function prevented smooth muscle cell proliferation after arterial injury. Another study used antiplatelet serum with the same effect (Ross and Glomset, 1976).

There is recent evidence that the arterial wall generates a substance, prostacyclin, which is a potent inhibitor of platelet aggregation (Moncada et al, 1977). It is believed that the substrate for prostacyclin is a prostaglandin endo-peroxide produced by platelets. Thus a homeostatic mechanism exists which controls platelet aggregation (Editorial, Lancet, 1977).

Antithrombin is a protein which interacts with thrombin and other clotting enzymes to inhibit thrombosis. This substance acts with the plasmin system, and a deficiency of antithrombin is associated with an increased risk of venous thrombosis and increased severity of coronary artery disease (Editorial, Lancet, 1976b). Browse et al (1977) found a deficiency of tissue and blood fibrinolytic activity to be associated with certain vascular diseases, including athero-sclerosis, though this study was later critized because of

inappropriate controls (Meade et al, 1977).

There is at present no prospective study which has shown that patients with increased platelet activity or hyper-coagulability are more prone to develop IC than people with a normal coagulation system. It can be seen, however, that abnormalities in the mechanisms discussed above could act to promote atherosclerosis as described in the thrombogenic theory of Rokitansky (1852) and Duguid (1949).

(iii) Serum uric acid

An association between atherosclerotic vascular disease (coronary artery disease and IC) and elevated serum uric acid (SUA) levels has been found in several studies, though the reason for this association is not understood (Wollenweber et al, 1971; Goldstein et al, 1973; Lewis et al, 1974; Medalie et al, 1975). Men have a higher SUA than women until the fifth and sixth decade of life, when the SUA level of women rises to equal that of men (Bengtsson and Tibblin, 1974). There is no association of SUA with smoking, and no correlation of blood sugar and lipid levels with SUA in studies of general populations (Hall, 1965; Mikkelson, 1965). Hyperuricaemia is associated with obesity, and physical training reduces SUA (Ashley and Kannel, 1974; Busco et al, 1970).

Hyperuricaemia is often found in hypertension and is sometimes attributed to renal damage or drug therapy. However, about one-fourth of untreated, non-azotemic hypertensive patients have elevated SUA, and the incidence of coronary and cerebral arterial disease is greater in the hyperuricaemic hypertensives than in normouricaemic hypertensives (Breckenridge, 1966). The Coronary Drug Project Research Group (1976) examined the SUA in 2,789 men, and concluded that, when prescription of diuretic

drugs (some of which raise SUA) was taken into account, SUA had little independent predictive power for total mortality. There was a small positive correlation between SUA and blood pressure, cholesterol, triglyceride, blood glucose and relative body weight in this study.

In addition to its association with other risk factors, SUA may have a direct effect on platelet aggregation. Newland (1975) postulated that SUA, a final metabolite in the enzymatic degradation of ADP, could inhibit this process if present in excess, resulting in more stable platelet aggregates (induced by ADP release), increased blood viscosity, and a greater tendency to thrombosis. This hypothesis was supported by Winocour et al (1977) who induced hyperuricaemia in rats by feeding them diets rich in nucleic acid. The platelet aggregation induced either by ADP or thrombin was significantly greater in the hyperuricaemic rats compared with normal controls.

E. THE PROGNOSIS OF PATIENTS WITH PERIPHERAL VASCULAR DISEASE

The natural history of peripheral vascular disease has been studied in a few major series of patients whose intermittent claudication was severe enough to require medical attention. Selvaag (1956) studied 233 patients (192 men and 41 women) referred to hospital for peripheral arterial insufficiency. Diagnosis was based on the history, a clinical examination, and in most cases, arteriography. A total of 64 patients (27.5%) had a history of myocardial infarction (MI), angina, or electrocardiogram (ECG) evidence of coronary insufficiency or old infarction at first referral, and a further 26 patients (11%) developed clinical manifestations of coronary artery disease (MI, angina, or ECG) during a follow-up period of six months to four and a half years. Twenty-one of the 25 patients who died

in the follow-up had a history of coronary artery disease, and all but two of the deaths were due to coronary artery or cerebrovascular disease. Hypertension (BP>155/95) did not affect the mortality rate. This study focused on the incidence of ischaemic heart disease in claudicants, and the effect of other risk factors such as smoking and diabetes on the course of the disease was not examined.

A similar prevalence of angina (20%) and myocardial infarction (10%) was found in a series of 108 patients referred to hospital for IC (Spalding, 1956). Eighty-six patients had electrocardiograms, and 40 (47%) had evidence of ischaemia or infarction. The patients were selected from a diagnostic index, and follow-up consisted of a case history review. There were 32 deaths in a follow-up period of one to 15 years, with an average annual mortality rate of four per cent after onset of claudication. Twenty-one of the 32 deaths (66%) were due to coronary artery or cerebrovascular disease.

An early age of onset (<50 years) was associated with a lower mortality and amputation rate. Hypertension (BP>150/90) was present in 17 (53%) of the 32 patients who died (compared with 37% of the patient series), but there was no effect of hypertension on the amputation rate. Twenty-seven patients (25%) had amputations. The effect of other risk factors on the course of the disease was not examined.

Silbert and Zazeela (1958) reviewed 942 men and 256 women referred as private patients because of IC. All patients who had evidence of cerebrovascular or coronary artery disease were excluded. Progress was followed by repeat examination, or by correspondence with the referring physician. The authors stated that 399 patients (33%) were diabetic, 353 (29%) were

hypertensive, and 851 (71%) were smokers. Unfortunately, the criteria used to define diabetes and smoking were not described.

The life expectancy of patients with IC uncomplicated by diabetes or severe hypertension (BP>200/110) was not significantly different from an age-matched group of normal people. The authors did not state whether patients with evidence of coronary artery or cerebrovascular disease were excluded from the control group. The ten year mortality rate was 38 per cent in diabetics compared with 11 per cent in non-diabetic patients and diabetics had a higher amputation rate (34%) than non-diabetics (8%). Severe hypertension also shortened life expectancy.

Of particular interest was the observation that smokers who were able to stop had a mortality rate of about one-half that experienced by those who continued to smoke, and also had a lower amputation rate. Approximately 73 per cent of those who stopped smoking reported improved or unchanged symptoms compared with 56 per cent of those who continued smoking. Unfortunately no information was provided concerning the age and sex distribution, smoking history prior to referral, duration and severity of PVD at referral, or the prevalence of hypertension of those who stopped or continued to smoke. It is possible, therefore, that the difference in mortality and amputation rates was related to factors other than smoking.

Life-long non-smokers who developed IC had mortality and amputation rates equal to people who continued to smoke, leading the authors to postulate that other factors, "possibly hereditary", were operating in those cases. Patients with an acute onset of symptoms had a better prognosis than those with a gradual onset. No patients in this series underwent

reconstructive arterial surgery, and only 39 had a sympathectomy. In this small group there was no evidence that sympathectomy had a favourable effect on the amputation rate. The known cause of death in the majority of cases was coronary thrombosis (42%) or cerebral thrombosis (12%).

A series of 1,508 patients, referred to the Manchester Royal Infirmary between 1947 and 1953 for assessment of PVD was followed for a period of four to ten years (Bloor, 1960). At the first visit the sites of arterial lesions were determined by clinical examination and oscillometry, and the claudication distance measured on a treadmill. Symptoms of coronary or cerebral ischaemia were present in 7.9 per cent at first referral.

There were 673 deaths in the follow-up period, of which 59.5 per cent were due to coronary and 16.6 per cent to cerebral vascular disease. Peripheral vascular disease accounted for 8.1 per cent of the deaths, and only 15.6 per cent of the patients died of non-vascular diseases. The five-year survival was 79 per cent, and the ten-year survival 54 per cent. Compared with the general population, those with PVD had a survival rate approximately equal to people ten years older. Twenty per cent of those surviving five years had non-fatal coronary or cerebral symptoms, and approximately 25 per cent had further occlusion of the leg vessels. Pre-gangrene and gangrene occurred in 8.3 per cent of the patients in the first year after onset, and less frequently thereafter. Despite this, the amputation rate remained fairly constant at one to two per cent per year. A man surviving five years had a seven per cent chance of losing a leg, and if he survived ten years, a 12 per cent chance. Those patients with common iliac or

aortic blocks had a 2.5-fold increased risk of amputation.

No patients in this series underwent direct arterial surgery. Lumbar sympathectomy was performed in 278 patients, and there was little evidence of therapeutic benefit. A sudden onset of symptoms was associated with a better prognosis. Only four per cent of the patients were diabetic, and their death rate was only slightly higher than that of non-diabetics. The prevalence of smoking and its effect on outcome was not examined in this series.

Jeurgens et al (1960) reviewed 520 non-diabetic patients less than 60 years of age referred to the Mayo Clinic because of IC. Initial assessment included a fasting serum cholesterol and clinical examination, and arteriography was not done. Eighty-five patients (16.3%) had rest pain due to local tissue ischaemia when referred, and 55 (10.6%) had ischaemic ulceration or gangrene. Previous myocardial infarction or angina pectoris was present in 16 per cent. Follow-up information was obtained from clinic notes and letters written to the patients, and 464 (89.2%) were traced five years after referral.

The five-year survival of all patients was 77.2 per cent, falling to 58.6 per cent in those with coronary artery disease and 61.1 per cent in patients with cerebrovascular disease. Approximately three-fourths of the deaths were due to coronary artery disease. Those with femoral artery occlusions had a better five-year survival (80.1%) than those with aorto-iliac disease (73.0%). In contrast to the series reviewed by Bloor (1960) patients with aorto-iliac blockages had a lower amputation rate than those with femoral occlusions. Twenty-one patients required amputation of a leg soon after referral, and a further 23 patients (4.9%) had an amputation during five years

of follow-up.

Hypertension (BP>150/90) and elevated serum cholesterol ($\geq$250 mg) had no significant effect on survival. There was, however, an effect of smoking on the amputation rate. Of 88 patients who continued to smoke after diagnosis, ten (11.4%) had an amputation within five years. There were no amputations in 71 people who stopped smoking in the same period. Unfortunately no information was provided concerning the duration or severity of PVD at referral, the smoking history prior to referral, the age and sex distribution, or the prevalence of hypertension or hyperlipidaemia of the two groups. Nor was any information provided about the 305 patients (66%) in the follow-up who were not considered in this analysis. Differences in these factors may, therefore, have accounted for the higher amputation rate in those who continued to smoke. The death rates of the two groups were not compared.

Schadt et al (1961) included many of the patients studied by Jeurgens et al in a series of 422 patients referred to the Mayo Clinic for PVD. Patients with diabetes were not excluded, and all patients in this series had femoral artery occlusion (determined by physical examination). Sixty-four were diabetic, and the prevalence of hypertension (BP>160/90), angina, myocardial infarction, ischaemic skin ulceration and gangrene was higher in this group than in the non-diabetic patients. The five-year survival was 75.7 per cent in the non-diabetic and 54.4 per cent in the diabetic patients, and at the end of nine years the comparable figures were 59.1 per cent and 37.9 per cent, respectively. The cause of death was determined in only 66 of the 201 patients (33%) known to have died, and 54 (82%) of the deaths were due to cardiovascular diseases. During the

nine-year follow-up 27 per cent of the diabetics had amputations compared with 7.3 per cent of the non-diabetics. Unfortunately the effect of smoking was not examined in this study.

Singer and Robb (1960) selected 359 patients referred to hospital for IC and followed them for a minimum period of two years. Diagnosis was based on history and physical examination, and 205 arteriograms were performed. Patients were divided into those with femoro-popliteal (250 cases) or aorto-iliac disease (109 cases). The prevalence of myocardial ischaemia and cerebrovascular disease was approximately the same in the two groups, but the mortality rate of patients with aorto-iliac blockages was higher (32%) than that of patients with femoral-popliteal blockages (19%). This difference in the mortality rate was due to a high proportion of post-operative deaths (12 patients) in the aorto-iliac group. The mortality rates of both groups were significantly higher than that of the general population, controlling for age and sex, and, as in other studies, the majority of deaths were due to coronary artery (53%) or cerebrovascular (14%) disease.

Begg and Richards (1962) reviewed 184 men and 14 women referred to a vascular clinic for IC, and found a five-year mortality rate of 25.3 per cent. They estimated the ten-year mortality rate to be 58.3 per cent, which was significantly higher than that of the general population, controlling for age and sex. Fifty-one (55%) of the 92 deaths were due to myocardial infarction, and only 11 deaths (12%) were from non-vascular diseases.

The only factor which had a statistically significant effect on mortality was hypertension (diastolic BP>100).

Bilateral arterial disease, ischaemic heart disease, and advanced age at onset worsened the prognosis, but the effects of these factors were not statistically significant. Most patients received vasodilator drugs, but these agents and lumbar sympathectomy did not affect the death rate or the severity of IC. There were only seven amputations (3.6%) during the follow-up period. The effects of serum lipids, glucose intolerance, and smoking on prognosis were not examined.

Taylor and Calo (1962) followed for three to 12 years a group of 454 patients referred to hospital for PVD. Only 4.5 per cent were diabetic and 28 per cent were hypertensive (systolic BP>180). Angina was present in 71 (17%) patients. The incidence of leg amputation was ten per cent, and it is of interest that the amputation rate of hypertensives was only one-half that of normotensive patients. Prognosis for limb survival was poor in patients presenting initially with rest pain, and 17 of 29 limbs (59%) came to amputation (compared with eight per cent when IC was the presenting symptom). Incidence of rest pain and gangrene was highest in limbs with lesions in the popliteal artery and below (determined by clinical examination) and limb survival was best in those with aorto-iliac blockages.

In the first part of this study, uncomplicated IC was considered an adequate indication for lumbar sympathectomy. This practice stopped, and in later years only those with severe ischaemia were treated in this way. Though selection was non-random, a comparison was made between those presenting with uncomplicated IC in the first and second halves of the study. Sympathectomy did not seem to affect the severity of symptoms (graded as improved, stationary or worse) of patients presenting

initially with uncomplicated IC. Sympathectomy did seem to improve those with rest pain and minor tissue necrosis.

The mortality rate was 21 per cent, with an average survival of eight years in those younger than 50 years, and four years in patients above that age. Coronary and cerebrovascular disease accounted for 51 per cent of the deaths. Factors such as smoking, serum lipids and diabetes were not considered in this study.

Data were collected on 466 patients referred to hospitals in Stockholm for PVD, and 366 were followed for an average period of five years (Tillgren, 1965a). Initial examination included a medical history, inspection and palpation of the legs, oscillometry to determine the sites of occlusion, digital plethysmography, walking tolerance, electrocardiography, and arteriography (271 patients). The mortality rate of patients with total occlusion of the femoral artery was the same as those who had only stenoses. Nor was there any difference in survival of those with and without amputations. The data was analyzed according to the life-table method, and the presence of coronary artery disease (a history of myocardial infarction and an ECG positive for ischaemia or infarct) at referral was associated with a significant adverse effect on survival (Tillgren, 1965b). Patients who did not have coronary artery disease at referral had approximately the same life expectancy as that of the general population, controlling for age. There were 109 deaths (30%) during the follow-up, the majority (70%) due to coronary or cerebrovascular disease. The effect of smoking on outcome was not examined.

Imparato et al (1975) studied 104 patients who had an arteriogram in the course of investigation for PVD. The follow-up

period was six months to eight years, with a mean of 2.5 years. During this time 5.8 per cent had an amputation. The major factor determining prognosis was involvement of vessels below the knee. Of those with below-knee involvement, 12.5 per cent had amputations. Unfortunately the prevalence of smoking, diabetes and hypertension was not presented so that it is not possible to examine the effect of these risk factors on the severity and distribution of arterial lesions.

In the Framingham study, the men who had or developed IC had an annual mortality of 39 per 1,000 compared with ten deaths per 1,000 men free of the affliction (Kannel and Shurtleff, 1971). Women with IC had an annual death rate of 20 per 1,000 compared with five per 1,000 without IC. After adjustment for age, a two-fold increased risk of death remained for both men and women. Approximately three-fourths of the deaths were attributed to cardiovascular diseases, whereas only one-half the deaths among persons without IC were so ascribed. It is of interest that almost 45 per cent of patients had a spontaneous remission of their symptoms for four years or more, though it was not known whether this improvement was due to the adoption of a sedentary lifestyle, lack of vitality due to other cardiovascular diseases, or to the development of collateral circulation.

The effect of factors such as smoking and diabetes on the risk of developing IC in the Framingham study will be discussed in later sections. I am not aware that the effect of continued smoking on the outcome of patients with IC has been analyzed in this study.

In summary, intermittent claudication is associated with significant morbidity and mortality. Most deaths are due, not

to peripheral vascular disease, but to coronary artery and cerebral vascular disease. Once IC is established there is little conclusive evidence that risk factors other than diabetes worsen prognosis, though smoking and blood pressure have been implicated. With the exception of Framingham, the studies discussed have examined series of claudicants referred to hospital. These patients may not be representative of people with PVD in a general population, many of whom have mild symptoms and do not receive medical attention.

F. THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

1. SURGICAL TREATMENT

There are many surgical procedures which have been used to treat PVD, each with its own technique, indications and advocates. My research has not dealt with the surgical management of IC, and I will not attempt to review in detail the vast literature on the subject. Some aspects of surgical treatment, particularly as they affect the clinical course of PVD, are relevant, and I will focus on these areas.

It is generally accepted that uncomplicated intermittent claudication is not an indication for surgery, since serious complications are uncommon, and the amputation rate in untreated IC is only one to two per cent a year (Jepson and Harris, 1969). The patient's lifestyle, type of employment, and alternative means of transport are factors taken into account before deciding on an operation. Some patients are not unduly inconvenienced by a very short claudication distance, while the economic livelihood of others may be threatened by relatively mild symptoms. Even when IC is a considerable handicap, a period of observation before surgery is justified, since significant improvement or complete remission of symptoms will

occur in approximately 40 per cent of patients (Bloor, 1960; Kannel and Shurtleff, 1971; Editorial, British Medical Journal, 1976d).

The main surgical techniques currently used to treat PVD are sympathectomy (either surgical or chemical), and direct arterial reconstruction. Reconstructive operations include endarterectomy, local arterioplasty (in which a vein patch or synthetic patch is used to widen a stenosis), and bypass procedures using either a reversed vein graft or Dacron. Other procedures such as transluminal recanalization have specific indications (Brahme et al, 1969), and destructive operations (calf denervation, section of Achilles tendon) have largely been abandoned (Pollock and Jackson, 1970; Brahme et al, 1969).

The effect of sympathectomy on blood flow has been reviewed by Shepherd (1963). Following sympathectomy there is an increase in flow to the foot which is greatest two to three days post-operatively. With time this diminishes, so that several months later the blood flow, while still greater than pre-operatively, is much less than in the immediate post-operative period. Despite diminishing flow, many patients report persistence of warm feet. This may be due to an absence of sweating, or the fact that when the blood flow is sufficient to give a skin temperature of 31 to 32°C a further increase in blood flow results in only small changes in skin temperature.

The effect of sympathectomy on the prognosis of patients with IC has been reviewed by Owens (1973). He states that the wide range of improvement rates after sympathectomy (from 5% to 85%) reported by different centres is probably due to a lack of standardized measurement techniques and that there is no evidence that lumbar sympathectomy is warranted in uncomplicated

IC. Sympathectomy is effective in relieving causalgia-type pain and the improved blood flow to the skin (muscle circulation is altered only slightly) following ablation may relieve foot symptoms and increase walking tolerance in patients with severe PVD. Part of the improvement is due, however, to the strong placebo effect associated with this procedure (Fyfe and Quin, 1975).

The outcome of direct arterial surgery is affected by the severity of atherosclerosis and the distribution of the lesions, by the age and fitness of the patient, and by the skill and experience of the surgeon. Aorto-iliac blockages are associated with a significant risk of amputation (Bloor, 1960), and operations such as endarterectomy or a Dacron bifurcation bypass graft can produce dramatic relief of symptoms with good long-term patency rates (approximately 75%). These are major procedures, however, with an estimated mortality of approximately five per cent (Gardham, 1976).

Operations on the smaller vessels of the femorol-popliteal system often yield good results in the immediate post-operative period, but at five years the patency rate is only about 50 per cent. Furthermore, a failed operation carries a significant risk of amputation (Taylor, 1973). Of key importance is the state of the distal vessels, since poor run-off makes a successful long-term result less likely (Kaminski et al, 1972).

When medical and surgical attempts fail to improve the circulation to a severely ischaemic limb, and no further intervention is feasible, amputation is the inevitable result. It is now increasingly recognized that an early amputation combined with intensive rehabilitation may be preferable to protracted abortive attempts at reconstruction which debilitate

the patient (Gardham, 1976). The life expectancy of amputees has been shown to be similar to that of claudicants who avoid amputation (Tillgren, 1965a).

2. NON-SURGICAL TREATMENT

(a) Vasodilating drugs

The role of vasodilating drugs in the treatment of occlusive vascular disease was reviewed by Gillespie in 1966. His conclusion was that blood flow measurements do not justify the use of vasodilators given by any route by which their effects are generalized. This is because of the "steal" effect of vasodilators which results in a redistribution of blood flow from arteriosclerotic vascular beds, which are unable to vasodilate due to fixed stenoses, to normal areas which decrease their resistance in response to the drug. This often results in an actual decrease in blood flow to the diseased sites. Ten years later the position has not changed, and in a recent review the conclusion was that "the eagerness of the drug firms to promote the latest vasodilator suggests their awareness of the need to get another drug on the market before the last has been found to be ineffective. There is, indeed, no good evidence that any vasodilator is pharmacologically active in occlusive vascular disease". (Editorial, British Medical Journal, 1976d).

(b) Vitamin E

Vitamin E in large doses has been recommended as a treatment for a wide variety of cardiovascular disorders including intermittent claudication, angina pectoris, coronary occlusion and thrombophlebitis (Olson, 1973). Boyd et al (1949) found that 28 of 71 claudicants (40%) treated for six months with 600 to 800 I.U. of Vitamin E improved, but subsequent double-blind

studies have been subject to criticism or produced negative results (Livingstone and Jones, 1958; Baer and Heine, 1949; Hamilton et al, 1953). The mode of action at the molecular level is not understood, but it has been suggested that Vitamin E may act as an antioxidant (protecting polyunsaturated fatty acids), as part of the electron transport mechanism in mitochondria, or in the transfer of genetic information (Olson, 1973). Most advocates admit that the patient must wait for three months before an effect can be expected, a time interval which could allow spontaneous recovery. Vitamin E is not widely used at present, though it is still being studied and prescribed in some centres, particularly in patients with severely diseased distal vessels (Williams and Fenna, 1971; Haeger, 1974).

(c) Drugs which lower plasma fibrinogen and blood viscosity

The report by Dormandy et al (1974) that the fibrinogen-lowering action of clofibrate was associated with clinical evidence of improvement in patients with IC has raised the possibility that drugs which lower fibrinogen (and hence blood viscosity) may be useful in the treatment of PVD. Objective evidence of improved peripheral circulation after treatment with clofibrate was provided by Postlethwaite and Dormandy (1975) who showed a significant increase in the post-exercise ankle systolic pressure index (ankle SBP/arm SBP) and a shortening of recovery time in claudicants with elevated fibrinogen who were treated for 11 months with two grams of clofibrate a day. This was also associated with an increase in the claudication distance. A large multi-centre trial of clofibrate in the treatment of IC is currently nearing completion, and the results will provide further evidence for or against the efficacy of

this drug.

In 1958 it was noted that people bitten by the Malayan pit viper developed a bleeding tendency due to incoagulable blood, but otherwise showed no harmful effects (Reid and Chan, 1968). The mode of action was later shown to be an enzyme which converted fibrinogen into an unstable form of fibrin which was rapidly removed by the fibrinolytic system. As a result an isolated deficiency of fibrinogen developed without depletion of other coagulation factors. Intravenous and subcutaneous administration of a purified derivative has been used to lower fibrinogen in a controlled study of ten patients with severe PVD and was shown to significantly reduce rest pain and analgesic consumption (Wolf, 1976). Another study using the same drug demonstrated significant improvements in pre- and post-exercise ankle systolic blood pressure indices, recovery time, and exercise tolerance after a three-week course of treatment (Dormandy et al, 1977). Unfortunately, antibodies soon form which destroy the activity of the venom so that in six to eight weeks it is no longer active. It may still prove useful in the post-operative period, however, since it has been shown to improve the patency rates of Dacron vascular grafts in the arteries of rabbits and may, by inference, improve the prognosis after femoro- or popliteal-tibial bypass procedures where early occlusion is a frequent occurrence (Postlethwaite et al, 1977).

Heparin, oral anticoagulants, and anti-platelet drugs have also been used to treat PVD, without proven efficacy (Prentice and McNicol, 1971; Singer and Robb, 1960). It is perhaps significant that in a recent extensive review of the role of these drugs in a wide variety of cardiovascular disorders intermittent claudication was not considered (Rogers

and Sherry, 1976).

(d) Exercise therapy

A structured programme of physical exercise and walking has been shown to benefit patients with IC (Tse, 1971; Zetterquist, 1970; Larsen and Lassen, 1969). Possible mechanisms of action include more efficient utilization of energy by muscle cells (Holm et al, 1973), a redistribution of blood flow from inactive to exercising muscles, and improved muscular co-ordination (Schoop, 1973). An inverse relationship has been shown between physical fitness categories and parameters such as body weight, per cent body fat, cholesterol, triglyceride and systolic blood pressure, and exercise may simply serve to reduce these risk factors (Cooper et al, 1976). The major disadvantage of exercise treatment is that it requires long-term co-operation of the patients: the beneficial effect is lost within two or three weeks if training stops, and exercise tolerance reverts to pre-treatment levels. Because of the effort needed to maintain patient motivation, and the lack of a permanent effect on walking distance, exercise programmes are used in only a few centres, primarily in the Scandinavian countries.

(e) The treatment of risk factors

Certain risk factors for PVD and their effect on prognosis have been discussed earlier. Control of these factors may prevent the onset of intermittent claudication in an individual, but there is less evidence that their removal or reduction will either halt progression or cause regression of peripheral atherosclerosis when IC is already present.

In 1924 Aschoff proposed that atherosclerosis was a reversible disease. He attributed the lower incidence after the

First World War to reduced intake of dietary fat. Since then a large body of experimental evidence has accumulated, indicating that atherosclerotic lesions induced in animals can be made to regress if the atherogenic stimulus is withdrawn. The concept of lipid "pools" has been introduced to describe the exchange of lipids between the plasma and an atherosclerotic plaque. This exchange has been studied, using isotope methods, and a reduction of the lipid content of lesions after a low-lipid diet has been demonstrated. It has been more difficult to determine the fate of the fibrous tissue component of plaques, and the results are inconclusive (Gresham, 1976). While early lesions may regress in man, there is no clear evidence that clinically significant human lesions of the raised or complicated type can regress at all (Editorial, British Medical Journal, 1976a).

Dietary manipulation, with substitution of polyunsaturated fats for animal fat and a reduction of caloric intake, can reduce the level of serum triglyceride and, to a lesser extent, serum cholesterol. Barndt et al (1977) demonstrated regression of early femoral atherosclerosis in nine of 25 patients with hyperlipidaemia treated with a lipid-lowering diet, sometimes supplemented with clofibrate. Weight loss after dieting also reduces blood pressure and uric acid, and improves glucose tolerance (Ashley and Kannel, 1974; Ostrander and Lamphier, 1976). Tetranicotinolyfructose and clofibrate (which reduce serum triglyceride) have been used to treat claudicants. The results of these studies showed a modest improvement of symptoms which was attributed by the authors not to the hypolipidaemic effect of these drugs, but to other pharmacological actions (Dormandy et al, 1974; Postlethwaite and Dormandy, 1975; Benaim

and Dewar, 1975). I am unaware of any studies which have shown a reduction in the death or amputation rates of claudicants who have had long-term treatment to lower serum lipids.

The effect of continued smoking on the prognosis of IC has been discussed (Silbert and Zazeela, 1958; Jeurgens et al, 1960). Birckenstock et al (1975) treated 390 patients with IC who were not considered eligible for surgery by advising careful foot care, walking exercises, a low cholesterol diet, and Vitamin E. Follow-up was from four to 72 months, and change in the patient's condition was evaluated by reported claudication distance, severity of rest pain, ulcer healing, demarcation or progression of gangrene, and palpation of pulses. Detailed information about smoking was not obtained initially, but the patients were later classified as smokers or non-smokers. At the end of the study the authors concluded that the most striking feature of the trial was the correlation between smoking and failure to improve. Patients who did not smoke had an 85 per cent chance of improvement, whereas only 20 per cent of smokers improved. Unfortunately the severity of PVD, prevalence of other risk factors, and effect of other treatments in smokers and non-smokers was not compared, so that the difference in prognosis may not have been due to smoking. The effect of smoking on surgically-treated patients was examined by Robicsek et al (1975) who found a significantly higher occlusion rate after Dacron bypass grafting in smokers and concluded that "failure to promise to stop the smoking habit should be regarded as a relatively strong contraindication for surgery in patients not directly threatened with loss of an extremity".

Treatment of hypertension may result in decreased perfusion of an ischaemic limb, and may produce intermittent claudication

in an asymptomatic patient or aggravate the symptoms of a claudicant (Rodger et al, 1976). Taylor and Calo (1962) found the amputation rate of hypertensive claudicants to be less than that of normotensives, and Stephensen (1973) induced hypertension with a mineralo-corticoid preparation to treat patients with gangrenous skin lesions with improvement in half the cases. The risk of coronary or cerebral vascular events mounts with elevation of the blood pressure, and most clinical decisions to treat hypertension in patients with PVD are made for this reason. Antihypertensive therapy may help to prevent rupture of an aortic aneurysm, but I am unaware of any large trial which has demonstrated an improvement in the amputation rate or symptoms of claudicants treated for hypertension.

Although diabetes is known to be a risk factor for PVD, there are conflicting views as to the degree of correlation between the severity of glucose intolerance and the prognosis of PVD (Dry and Hines, 1941; Keen et al, 1965). Several authors have stated that there is no objective evidence that strict control of diabetes will prevent or retard peripheral arterio-sclerosis, and I am unaware of a prospective study which has shown a beneficial effect on the prognosis of claudicants of controlling blood glucose (Knowles, 1970; Schatz, 1971).

Dormandy et al (1973a) found a significant correlation between whole blood viscosity and severity of PVD. Treatment which lowered plasma fibrinogen and blood viscosity was shown to improve patients' symptoms (see pp. 53).

In summary, reconstructive surgery is the only form of treatment currently available which, when successful, results in prompt and significant relief of the symptoms of PVD. There are many patients whose arterial lesions cannot be surgically

corrected, however, and a medical treatment which would arrest or reverse peripheral atherosclerosis or improve the blood flow to ischaemic limbs is badly needed.

G. THE MEASUREMENT OF THE SEVERITY OF PERIPHERAL VASCULAR DISEASE

1. QUALITATIVE METHODS OF ASSESSMENT

The medical history provides information about the degree to which activity is limited by IC. There is, however, no correlation between the patient's reported walking distance and that measured on a treadmill or standardized walking test (Sigaard-Andersen and Petersen, 1968; Thomas and Quick, 1976).

On physical examination, the appearance of the skin may indicate gross abnormalities of the blood flow in the limb. Pallor distal to an acute arterial block, cyanosis in an area of stasis, ulceration, and gangrene are all manifestations of disordered blood flow which can be detected at the bedside. The accuracy of the examination can be enhanced by reactive hyperaemia tests in which the flushing of the skin after a period of arterial occlusion or exercise is observed and its progress to the toes timed (Hillestad, 1962 I). Palpation of leg pulses is useful in detecting blockages in the main arteries of the leg, but is subject to intra- and interobserver variation (Milne and Williamson, 1972).

2. QUANTITATIVE METHODS OF ASSESSMENT

(a) Exercise tolerance tests

Pain originating during exercise is the most common symptom of PVD, and the amount of exercise required to precipitate pain has been used as an index of severity. Walking distance measured on a treadmill, though an objective test, requires patient co-operation and motivation. It varies, depending on

pain tolerance, treadmill speed and incline, body weight, and the presence of other diseases such as arthritis or coronary artery disease (Ebel and Kuo, 1967; Petersen, 1967; Colt, 1971). The coefficient of variation is less (approximately 10%) when the distance at which pain begins is recorded rather than the distance at which the patient is forced to stop (coefficient of variation approximately 20%), since the latter measurement is related more to motivation (Hillestad, 1963 iv). The relationship between walking distance and leg blood flow has been studied using plethysmography to determine resting and peak blood flow to the leg. The correlation coefficient between walking distance and these flow parameters is not strong ($r \approx 0.5$), indicating that exercise tolerance depends on factors other than blood flow (Dahn, 1965).

The treadmill is an expensive and often cumbersome machine and it requires some time to train the patients to use it. A set of steps can be made easily, and though climbing stairs requires the action primarily of hip and thigh muscles rather than the gastrocnemius, the step-test of exercise tolerance has been shown to equal treadmill walking in its variability (Kissin et al, 1950). Other methods used to measure exercise tolerance include the foot treadle (Fisher et al, 1939), and ergometers which record plantar flexion with varying resistances (Simmons, 1936). These devices are portable and their coefficient of variation is approximately the same as other methods. For this reason they are still used in the follow-up of patients with IC. Treadles can also be used in conjunction with plethysmography (when the patient is immobile, connected to the machine) to study the haemodynamic response to exercise.

(b) The venous occlusion plethysmograph

Venous occlusion plethysmography was introduced by Brodie and Russell (1905) and is based on the principle that the veins draining a limb segment can be occluded without significant narrowing of the arteries, and consequently the segment begins to swell at a rate equal to the arterial inflow (Hewlett and Van Zwaluenberg, 1909). The limb is sealed into a closed plastic or metal box which is filled with either air or water, and the venous occluding cuff is wrapped around the limb proximal to the plethysmograph. The cuff is then inflated and deflated at regular intervals and the volume of air or water displaced during occlusion is recorded. The variables usually measured are the flow at rest and the peak flow and duration of hyperaemia after a period of arterial occlusion or exercise. The choice of stimulus depends on the type of plethysmograph used, but arterial occlusion for two minutes or more is an adequate and reproducible way of causing reactive hyperaemia and is the method preferred in most centres (Myers, 1964; Hillestad, 1963 vii).

The rest flow of patients with PVD is normal unless the arterial blockages are extensive and severe (Shepherd, 1950; Hillestad, 1963 v). Follow-up of stable claudicants over a period of months showed a coefficient of variation for an individual of approximately 20 per cent and a coefficient of variation for the group of approximately ten per cent in this measurement (Hillestad, 1963 v). Patients with normal circulation reach peak flow within a few seconds after arterial occlusion and flow returns to normal within two to three minutes. Patients with IC take longer to achieve peak flow, and hyperaemia is prolonged, often lasting five to ten minutes or more (Shepherd,

1950). Measured over a period of months, peak flow has a coefficient of variation of approximately five per cent (Hillestad, 1963 v). The effect of age on reactive hyperaemia has been examined, and there is no significant difference in rest flow, peak flow or duration of hyperaemia in different age groups (Myers, 1964; Sigaard-Anderson, 1965).

Volume plethysmographs are difficult to use, and the procedure is time-consuming. The strain gauge plethysmograph employs a thin rubber or Silastic tube filled with mercury to measure the change in limb girth during venous occlusion (Whitney, 1953). The gauge serves as a mercury "wire", and the increased resistance of the mercury column as the gauge is stretched is transformed into an easily recorded electrical signal. Arterial inflow can be recorded as a per cent volume increase over a period of time or converted into ml of blood per minute. There is a linear relationship between the flow rates produced by conventional volume plethysmography and the strain gauge method with correlation coefficients varying from 0.80 to 0.95 (Whitney, 1953). The strain gauge plethysmograph is quicker and easier to use, and can be applied to several sites on the same limb simultaneously, providing information about segmental blood flow.

(c) The Doppler ultrasonic flowmeter

In 1842 Doppler stated that the frequency of sound emitted or reflected from a moving object varied with the velocity of the object. When sound waves are directed toward the blood flowing in a vessel, they are reflected by moving cells, and the frequency of the reflected sound waves is altered from that of the source beam. The Doppler effect was first used in medicine by Satomura in 1957 to study heart structure and function, and

in 1966 Rushmer, and then Strandness, used a transcutaneous ultrasonic blood velocity meter to study arterial and venous blood flow (Nayman, 1974; Rushmer et al, 1966; Strandness et al, 1967).

The flowmeter operates by transmitting an ultrasound beam from a ceramic crystal toward a blood vessel. The reflected waves are received by a detector crystal, and the flowmeter filters out all the waves with an unaltered frequency, transmitting only those reflected from moving blood cells.

If a directional Doppler meter is used, phasic flow velocity curves can be produced. The normal pattern is triphasic: the major deflection represents forward flow during systole; the second smaller negative deflection is caused by reversal of flow during diastole; and the small third signal represents the return of forward flow. This flow velocity pattern is the same as that produced by an electromagnetic flowmeter placed around the artery. Patients with occlusive or stenotic lesions lose the triphasic pattern (which is quite distinctive when the signal is transmitted through earphones) and have a monophasic pattern with slow systolic acceleration and absence of the second and third components (Yao, 1970).

If a blood pressure cuff is placed above the ankle, the flowmeter can be used to measure ankle systolic blood pressure (ASBP) in the same manner that the stethoscope is used in the arm. The ASBP measured in this way was compared with the ASBP measured with a microneedle inserted into the foot arteries and showed a high correlation ($r=0.87$) with differences never exceeding 15 mm Hg (Bollinger et al, 1976). In patients with normal arteries the ASBP at rest is greater than the brachial systolic pressure, and the pressure ratio (ankle SBP/arm SBP) is

therefore greater than one (Mackereth and Lennihan, 1970; Myrhe, 1973; Yao et al, 1972a). Patients with PVD often have a resting pressure ratio less than one, and Yao et al (1972b) have demonstrated that maximal walking distance is more closely correlated to the pressure ratio ($r=0.44$, $p<0.001$) than to muscle blood flow measured by plethysmography ($r=0.15, p>0.05$).

With exercise the ASBP remains constant or increases slightly in healthy legs, but decreases in legs with significant arterial stenoses. This drop is due to vasodilation in proximal muscle groups which "steal" available blood at the expense of the foot and ankle (Mackereth and Lennihan, 1970; Bollinger et al, 1973). After exercise the sensitivity of the Doppler flowmeter increases (probably due to increased flow velocity), allowing detection of post-exercise pressures as low as 20 mm Hg (Bollinger et al, 1973). The degree of ASBP drop after exercise and the recovery time during which the ASBP returns to resting levels have been related to the severity of arterial lesions demonstrated on arteriogram (Chamberlain et al, 1975). With extensive disease, particularly in the iliac and femoral arteries, there is a sharp drop in ASBP and a slow return to resting levels. The Doppler flowmeter is now the most widely accepted non-invasive method of investigating the peripheral circulation of claudicants because the results are more reproducible than other methods (Strandness et al, 1967), and the speed and ease of measurement facilitates clinical examination and follow-up.

(d) Other non-invasive methods

These include digit or extremity calorimetry and thermography (Reece, 1974), local clearance methods using non-toxic radioisotopes (Alpert et al, 1969; Coffman and Mannick, 1965;

Cutajar et al, 1971), and oscillometry (Greenfield et al, 1963). I will not attempt to describe these methods in detail, since I have not used them in the course of my research and they do not play a prominent part in the relevant literature.

(e) Arteriography

A detailed description of the techniques and interpretation of arteriograms is beyond the scope of this review. Despite the increasing sensitivity of new non-invasive techniques such as the ultrasound flow detector, the arteriogram remains an integral part of the investigation of patients with PVD for whom reconstructive arterial surgery is being considered. They provide precise information about arterial lesions, and correlate well with operative and pathological findings (Lindbom, 1950). There is also a correlation between arteriography and patient symptoms though, as with other methods discussed, the relationship is imprecise. A patient with radiologically severe disease may have no, or minimal, symptoms, and the converse is also true (Wolfe and Beven, 1971).

SUMMARY

In this review of the literature I have tried to summarize the information currently available concerning the epidemiology of peripheral vascular disease and to explain the effects of risk factors in terms of the physiology of the arterial wall and the major theories of the pathogenesis of atherosclerosis. Most data have come from studies of patients with established PVD referred to hospital, and little information is available concerning PVD in a general population. The prognosis of people with PVD has been described, but the effect of many risk factors on the outcome is unclear. Surgical treatment, while helpful in some patients, has limitations, and there is need for a successful non-invasive form of therapy.

SECTION 2

INTERMITTENT CLAUDICATION:

PREVALENCE AND RISK FACTORS

CHAPTER 2

METHODS USED IN THE POSTAL SURVEY AND PATIENT EXAMINATION. CRITERIA USED IN THE DIAGNOSIS OF INTERMITTENT CLAUDICATION, AND SELECTION OF CONTROLS

Chapter 2 METHODS USED IN THE POSTAL SURVEY AND PATIENT EXAMINATION. CRITERIA USED IN THE DIAGNOSIS OF INTERMITTENT CLAUDICATION, AND SELECTION OF CONTROLS

A. INTRODUCTION

Little information is available concerning the prevalence of intermittent claudication (IC). As discussed in the review of the literature, most investigations have examined selected samples which may not be representative of a general population. Patients' symptoms, elicited by questionnaires or screening programmes, have been used to identify cases of IC, but in only a few studies has a systematic physical examination been undertaken as well (Hobson and Pemberton, 1955; Widmer, 1963; Milne and Williamson, 1972).

In order to obtain information about the prevalence of IC in the general population, it was decided to begin a screening programme using a questionnaire designed by Rose (1962), and recommended for use by the World Health Organization. Those people identified as having symptoms compatible with IC were examined, and the diagnosis confirmed by measuring the ankle systolic blood pressure. Thus it was possible to identify false-positive cases and to test the specificity of this widely-accepted questionnaire.

A second objective was to determine risk factors for IC. Cases of IC identified in the screening programme were matched for age and sex with control patients selected at random from the survey population. A number of tests were performed on cases and controls in order to determine the risk factors for IC and to study the interaction of those risk factors.

To test the feasibility of the methods, a pilot study was begun in February, 1975, using a population of 298 people taken from the patient list of an Oxford general practitioner. This study was completed in June, 1975, and it was decided to expand the project. Sonning Common, a community of 10,000 people, was chosen because of its proximity to Oxford, the presence of an age-sex register, and because the general practitioners in the community agreed to co-operate fully. This study was completed in March, 1976. In order to increase the number of cases of IC, a further survey was then carried out on the Oxford practice which had been used in the pilot study. This was completed in November, 1976.

B. METHODS USED IN THE POSTAL SURVEY AND PATIENT EXAMINATION

1. THE POPULATION

The people screened for IC were patients of two general practices, one in Oxford and the second in Sonning Common. These practices participate in the Oxford Community Health Project (OCHP), which is a computer system that maintains patient listings for 26 practices (Evans et al, 1975). The OCHP provided the names and addresses of men aged 45 to 70 years and women aged 50 to 70 years who were registered with the participating doctors on January 1st, 1975. These age groups were chosen because the incidence of IC is very low in younger men and women (Kannel, 1970a) and there were few patients over the age of 70 on the lists of these doctors.

The Oxford practice is located in the Donnington Health Centre, and consists of four general practitioners serving a population of approximately 10,000 people living in east Oxford. Sonning Common is located 20 miles south-east of Oxford, and its population of approximately 10,000 people is

TABLE 2.1

THE SOCIAL CLASS DISTRIBUTION OF THE SONNING COMMON AND DONNINGTON HEALTH CENTRE POPULATIONS

Social Class	Sonning Common No. (%)	Donnington Health Centre No. (%)
I	9 (12)	4 (5)
II	26 (33)	10 (12)
III	28 (36)	48 (57)
IV	15 (19)	22 (26)
V	0	0
Total	78 (100)	84 (100)

served by four general practitioners working in a well-equipped health centre. Both practices gave me access to their patients' records and allowed me to use their facilities for interviews and examinations.

The social class structure of the two communities was examined using the 1971 Census of Great Britain. In this census, the socioeconomic classification of each person was determined, using the type of work performed as the main criterion. Appendix 2.1 presents the socioeconomic group distribution of people living in the parishes surrounding the two health centres. Though this information is undoubtedly imprecise due to changes in the populations since 1971, it seems that the Sonning Common population may contain a greater proportion of people in the higher social classes. This impression was strengthened when the occupations of the cases and controls in the two surveys were examined and the social class of the individuals determined using the Classification of Occupations (1970). Table 2.1 presents the social class distribution of the patients (cases and controls combined) from the two health centres who formed the population examined in the case-control study described in Chapter 4. It can be seen that a greater proportion of the patients from the Sonning Common practice were in social classes I and II.

2. THE POSTAL SURVEY

A questionnaire, two explanatory letters, and a reply-paid envelope were sent to each person in the appropriate age groups. The letters sent with the questionnaire are shown in Appendix 2.2. One was signed by me, and explained the purpose of the questionnaire. The second letter, from the general practitioners, encouraged the patient to co-operate.

Experience in the pilot study suggested that the majority of replies could be expected within three weeks of mailing the questionnaires. After this period a second questionnaire with a reply-paid envelope was sent with a reminder letter to those who had not responded. A third mailing was sent to non-responders after a further three weeks. The mailing in which each questionnaire was returned was recorded, so that it was possible to compare early responses with those of later mailings.

3. THE QUESTIONNAIRE

The questionnaire used in this survey was designed by Rose and recommended for use by the World Health Organization (Rose and Blackburn, 1968). The questions were modified slightly for self-administration, and three questions dealing with medical treatment were added at the end (see Appendix 2.3). A COMMENTS section was used in the pilot study to obtain suggestions on ways to improve the survey technique. This section was retained in the main survey because people often used the space to clarify the nature of their complaint.

4. CLASSIFICATION OF THE QUESTIONNAIRES

In its original form, the questionnaire was administered by a nurse, and the interview was structured carefully to avoid bias (Rose, 1962). A self-administered version of the same questionnaire was used to study a population of male civil servants, and yielded results similar to the original form (Rose et al, 1977). These men, very familiar with form-filling, were also interviewed, and questionnaire responses were checked by a nurse.

Rose has stipulated very precise criteria for the diagnosis of IC using his questionnaire, and requires complete and consistent responses to all the questions. Unfortunately,

questionnaires returned by post often contain errors or omissions and there is no opportunity to discuss these with the patient. If the Rose criteria are applied strictly to these forms, a number of patients with symptoms similar to IC must be excluded. The Rose criteria also exclude information which may be written on the form by the patient.

Many people in the pilot study returned forms that were partially answered or which had inconsistent responses. Some of these forms fulfilled the Rose criteria except for one or two questions. I felt that some of these people might have IC, but did not have the skills necessary to complete the form properly. To investigate this possibility I decided to allow one or two discrepancies from the Rose criteria and to examine all those whose questionnaires indicated the following.

1. Presence of leg pain 2. Clear association between exercise and pain 3. Relief of pain with cessation of exercise	All three were present
AND	
4. Pain did not begin sitting or standing 5. Pain was in the calf 6. Pain never disappeared when walking 7. Pain disappeared in less than ten minutes 8. Patient stopped or slowed down when having pain	At least three of the five were present

The questionnaires were also coded according to the Rose criteria for IC, and the two methods were compared (Rose stipulates that all eight of these statements are positive in people with IC).

According to the questionnaire response, people were

classified in the following way:

1. Positive for IC.

2. Negative for IC.

3. Questionably positive - these responses were consistent in most respects with the diagnosis of IC. Many included in this category did not answer all the questions on the form.

4. Refusal to participate - a small number of people returned the form and stated that they did not wish to answer the questions.

5. Dead or Disabled - some patients on the lists had died, and the form was returned by relatives. Others were immobile due to illnesses such as arthritis, stroke with hemiplegia, severe emphysema, etc. and returned the form to us indicating that they did not walk far enough to develop IC.

6. Emigrated - the computer listing is updated monthly when the OCHP is informed of deletions or additions to the lists. In spite of this, a number of people had moved from the address given on the listing. The form was then returned to us by the Post Office, or by the new occupant.

7. Questionnaire error or inconsistency - there were many examples of inconsistent replies. In most cases it was possible to determine the nature of a complaint and to categorize the questionnaire as positive or negative. In a small number of cases, however, the answers were confusing and no decision could be made.

8. Other missing data - some people neglected to turn the form over and fill in the reverse side. Others answered consistently, but left out so much information that no diagnosis was possible.

9. Miscellaneous - in a few cases the form, intended for one person in the family, was filled in by the wrong person. The most common mistake was to have an elderly parent, troubled with pain, fill in the form instead of the son or daughter for whom the form was intended.

5. DATA PROCESSING OF THE QUESTIONNAIRES

When the questionnaires had been received and coded, the data were punched on 80-column cards. All cards were checked twice against the original form to ensure the accuracy of punching. The internal consistency of the responses was

checked by computer programme. For example, if a person denied leg pain in Question 1 and then described calf pain in Question 3, an error message was printed and the form re-examined. When checking was completed and all errors corrected, other computer programmes were used to analyse the data.

6. FOLLOW-UP OF THE QUESTIONNAIRE RESPONSES

All those coded positive or questionably positive for IC were invited to come to the health centres for an interview and examination. After two letters (Appendix 2.2) and a home visit, two-thirds of the patients agreed to come for examination. The remainder were seen in their homes. No attempt was made to approach those people who had expressed reluctance to participate. Occasionally we received a strongly-worded reply, or a complaint was made directly to the general practitioner. When this happened, I either telephoned or wrote a letter to the patient explaining the purpose of the research and the way in which the data was to be used. This explanation always met with a positive response, and in many cases the patient then agreed to return the form.

When a form was returned indicating that the patient had died, the practice was notified and the death confirmed in their records. In no instance was the practice unaware of the death; the problem was a failure to communicate the information to the OCHP. A letter was then sent by me to the family apologising for any upset that our enquiry had caused. When a patient was too ill to walk, the practice records were checked to establish the cause of immobility. Very often the patient explained his infirmity in the COMMENTS section of the form.

Change of address was a common occurrence in the population

despite frequent updating of the listings. A number of our forms were forwarded to the new address of the patients, and then returned. When a form was returned by the Post Office or the new occupant, a check was made with the practice records. Again the chief problem was a failure to notify the OCHP.

Whenever a form was returned with incomplete or inconsistent answers, another form was mailed with a letter outlining in greater detail the proper procedure for filling in the form and stressing the need for complete and accurate responses to all the questions. In several cases where there were language or intellectual difficulties the general practitioner helped the patient to complete the form. When the wrong member of the family returned the form, another was sent with a letter specifying the date of birth (very often the problem was identical names of father and son) of the person from whom we wanted a reply.

7. FOLLOW-UP OF NON-RESPONDERS

In order to establish that the non-responders did not differ appreciably from those who returned the questionnaire, an effort was made to contact all non-responders in the pilot study to determine the presence or absence of IC. Some had telephones, but most did not and were visited at home. When contacted, the standardized technique recommended by Rose was used to administer the questionnaire.

If the person had moved, and the new occupant had no forwarding address, neighbours on either side of the original address were asked about the patient's location. The practice notes were also reviewed, and if a new address was available, a questionnaire was sent with an appropriate letter. In the

main survey, the same techniques were used to follow up a one-in-five sample randomly selected from the non-responders.

8. PATIENT INTERVIEWS

The interview was structured and the data recorded using the form in Appendix 2.4. The past medical history dealt with those risk factors thought to be associated with atherosclerosis. The patient was asked about specific disease entities and symptoms. Questionnaires recommended by the World Health Organization were used to elicit the symptoms of angina, possible infarction, respiratory disease, and IC (Rose and Blackburn, 1968). The general practice, and, where appropriate, hospital notes of the patients were also examined to confirm a diagnosis.

9. PHYSICAL EXAMINATION

The examination focused on the peripheral circulation, and no attempt was made to perform a complete physical examination.

(a) Height and weight

Height (cm.) without shoes, and weight (kgm.) after removal of external garments were recorded.

(b) Blood pressure

The blood pressure (diastolic 5th phase) was taken in the right arm with the patient supine after a rest of at least five minutes. The pressure was measured twice, at the beginning and end of the examination, and the lowest value recorded to the nearest 5 mm Hg.

(c) Palpation of peripheral pulses

The patient was covered with a blanket, and the room temperature was controlled by central heating in both practices to a temperature of approximately 19 to 20°C. The

legs were, therefore, usually warm, and the femoral, popliteal, dorsalis pedis and posterior tibial pulses were palpated in both legs. The pulses were recorded as present, diminished, or absent.

(d) Visual examination of the legs

The legs and feet were inspected to determine the adequacy of tissue nutrition. Trophic changes such as loss of hair, thin or shiny skin, and thickened toenails, were recorded.

(e) Ankle systolic blood pressure (ASBP)

A blood pressure cuff was placed around the lower leg above the malleoli, and blood flow was detected in the dorsalis pedis and posterior tibial arteries with a Doppler ultrasound recorder supplied by Parks Electronics Laboratory (Model 801-A). The cuff was then inflated so that no flow was heard. The ASBP was recorded at that point when flow was detected as the cuff was slowly deflated.

After recording the resting ASBP, the blood pressure cuffs were left on the legs (the cuff tubing securely taped), and the patient was instructed to traverse a set of three nine-inch high steps. A metronome was used to ensure a uniform rate, and the patient was instructed to exercise at a rate of one step/second for 60 seconds. On completion of this, the patient returned quickly to the examining couch, the sphygmomanometer cuff was reconnected, and the ASBP was measured. It was usually possible to measure the ASBP in both legs within 30 seconds after exercise.

The ratio of the ASBP (highest value recorded) divided by the brachial systolic blood pressure (lowest value) was calculated for both legs at rest and after exercise.

TABLE 2.2

LABORATORY INVESTIGATIONS

	Name of test	Method
1.	Routine haematology	Coulter Counter Model S (Britten and Johnson, 1969)
2.	Blood glucose	Bergmeyer and Bernt (1965)
3.	Serum cholesterol	Technicon N24a
4.	Serum triglyceride	Cramp and Robertson (1968)
5.	Biochemical screen (uric acid)	SMA 12/60
6.	Carboxyhaemoglobin	Commins and Lawther (1965)
7.	Plasma fibrinogen	Ratnoff and Menzie (1951)

(f) Electrocardiogram

The electrocardiograms were coded by one observer, Dr. J. I. Mann, who was unaware of the medical history of the patients. The Minnesota Code for Resting Electrocardiograms was used to classify the ECG's as normal, positive for infarction (codes 1.1 to 1.3), or positive for ischaemia (codes 4.1 to 4.4, 5.1 to 5.3, 7.1) (Rose and Blackburn, 1968).

10. LABORATORY INVESTIGATIONS

A sample of blood was drawn after a twelve-hour fast with a minimum of venous occlusion. The tests performed and the methods used are summarized in Table 2.2. The technicians performing the tests were unaware of the medical history of the patients. The carboxyhaemoglobin determinations were performed by me.

C. THE DIAGNOSIS OF INTERMITTENT CLAUDICATION

In order to establish the diagnosis of intermittent claudication due to arterial insufficiency, the following criteria were used in this study and were present in each patient:

1. A history of pain in the muscles of the legs precipitated by exercise and relieved by rest. The location of pain varied in individuals, but the calf was the most common site. In some patients it was possible to confirm the diagnosis with hospital records, including arteriograms.

2. Diminished or absent leg pulses in the affected leg. The palpation of leg pulses is inexact and subject to intra- and interpersonal variation (Milne and Williamson, 1972). Absence of a foot pulse, particularly the dorsalis pedis, can also be a normal variant (Silverman, 1946). Nevertheless, the presence of good volume leg pulses makes the diagnosis of

peripheral vascular disease unlikely, and the clinical examination is an accepted part of the assessment of IC.

The possibility of examining the patients before taking the history (i.e. "blind") was considered, but the need to establish some sort of rapport with an essentially volunteer population made this impractical. All examinations were performed by me, thus eliminating inter-observer variation.

3. Doppler ankle systolic blood pressure ratio. A resting pressure ratio (ankle SBP/brachial SBP) below 0.75 in one leg was needed to make the diagnosis of peripheral vascular disease. In those cases with borderline pressure ratios, a drop to below 0.60 after exercise was used to confirm the diagnosis.

At the present time there is no widely accepted level of the pressure ratio below which a diagnosis of peripheral vascular disease is certain. The arbitrary cut-off points used in this study were set after discussion with experienced workers in the field. It would have been preferable to time the post-exercise pressure response to derive a pressure-time curve as described by Yao (1970). The nature of the research (with frequent home-visiting in a volunteer population) and manpower required (at least two people, one for each leg) made this impossible.

D. THE SELECTION OF CONTROLS

When a diagnosis of IC had been made in a patient, two control patients matched for sex and age (within five-year age groups) were selected as follows from among those not complaining of this symptom. The name of the patient with IC was located on the alphabetical computer listing provided by the Oxford Community Health Project. A search was then made

up the listing until a person of the same sex and within the same five-year age group was found. This person was chosen as a control, provided his questionnaire was coded as negative. A search was made down the listing in the same manner until a second control was found.

One of the purposes of this study was to determine the ability of the questionnaire to discriminate between IC and other non-vascular causes of leg pain. The questionnaires returned by the control patients often reported leg pains, and a pain-free questionnaire was not required in the selection of a control.

A letter was sent to the controls asking them to come to the health centre for an interview and examination (see Appendix 2.2). There was an understandable reluctance on the part of many people with no leg pain or trivial complaints to participate, and only one-third of the controls responded after two letters had been sent. The remainder were then visited at home, and after careful explanation most agreed either to come to the health centre or to be examined in their homes.

Nine people (8%) refused to be interviewed or examined as control patients. When this happened, an alternate control was selected by continuing the search of the OCHP listing up (or down) as described earlier. The general practice notes of those people who refused to serve as controls were carefully checked for any evidence of atherosclerotic vascular disease, and none was found.

CHAPTER 3

THE RESULTS OF THE POSTAL SURVEY.

THE PREVALENCE OF INTERMITTENT CLAUDICATION IN A GENERAL POPULATION

TABLE 3.2

THE QUESTIONNAIRE RETURN RATE OF THE COMBINED POSTAL SURVEY POPULATION

	No. mailed	No. returned	Cumulative return rate (%)
First mailing	3303	1802	54.6
Second mailing	1501	752	77.3
Third mailing	749	313	86.8
Patient follow-up	-	112	90.2
Total returns		2979	90.2

TABLE 3.1

THE AGE AND SEX DISTRIBUTION OF THE POSTAL SURVEY POPULATION

Age group (yrs)	No. Men (%)	No. Women (%)	Total (%)
<45	19 (1.1)	2 (0.1)	21 (0.6)
45-49	437 (25.1)	26 (1.7)	463 (14.0)
50-54	433 (24.9)	449 (28.7)	882 (26.7)
55-59	277 (15.9)	368 (23.5)	645 (19.5)
60-64	292 (16.8)	376 (24.0)	668 (20.2)
65-69	277 (15.9)	342 (21.8)	619 (18.7)
70+	3 (0.2)	2 (0.1)	5 (0.2)
Total	1738 (100)	1565 (100)	3303 (100)

Chapter 3 THE RESULTS OF THE POSTAL SURVEY. THE PREVALENCE OF INTERMITTENT CLAUDICATION IN A GENERAL POPULATION

A. THE RESULTS OF THE POSTAL SURVEY

1. THE POPULATION

The age and sex distribution of the patient lists provided by the OCHP for the pilot study (298 patients), the Sonning Common survey (1,800 patients), and the Donnington Health Centre survey (1,205 patients), were very similar. Table 3.1 combines these populations and presents the age and sex distribution of all the people who were sent a questionnaire. A small number of people on the listings provided by the OCHP were outside the age limits requested, a fact discovered after completion of the postal survey. None of these people returned a questionnaire which was positive for IC. Of the 3,303 people in the survey, 1,738 (52.6%) were men, and 1,565 (47.4%) were women. The mean age of the men was 56.2 years, and that of the women was 59.3 years.

2. THE QUESTIONNAIRE RETURN RATE

Table 3.2 summarizes the questionnaire return rate, combining the results of the pilot study with those obtained from the two larger general practice surveys. The return rates in the pilot study (88.9%) and the Donnington Health Centre survey (92.0%) were similar. The lowest return rate (83.0%) was in the Sonning Common survey. The return rate from the combined population (86.8%) was enhanced by the follow-up of non-responders so that a total of 2,979 (90.2%) people from the original population participated in the survey.

The response rate was slightly higher in women than men

TABLE 3.4

CLASSIFICATION OF QUESTIONNAIRES DIVIDED BY MAILING OR FOLLOW-UP

	First mailing	Second mailing	Third mailing	Follow-up	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (100%)
Positive	24(75)	7(22)	1 (3)	0	32(100)
Negative	1597(61)	650(25)	255(10)	104(4)	2606(100)
? Positive	35(65)	13(24)	6(11)	0	54(100)
Refusal	20(65)	4(13)	5(16)	2(6)	31(100)
Dead or disabled	16(53)	9(30)	5(17)	0	30(100)
Emigrated	101(48)	64(30)	40(19)	6(3)	211(100)
Questionnaire error	1(100)	0	0	0	1(100)
Missing data	8(62)	5(38)	0	0	13(100)
Miscellaneous	0	0	1(100)	0	1(100)
Total	1802(60)	752(25)	313(11)	112(4)	2979(100)

TABLE 3.3

CLASSIFICATION OF THE QUESTIONNAIRES IN THE POSTAL SURVEY POPULATION

	Men	Women	Total
	No. (%)	No. (%)	No. (%)
Positive for IC	25 (1.6)	7 (0.5)	32 (1.1)
Negative for IC	1333(85.8)	1273(89.3)	2606(87.5)
Questionably positive	31 (2.0)	23 (1.6)	54 (1.8)
Refusal	15 (1.0)	16 (1.1)	31 (1.0)
Dead or disabled	18 (1.2)	12 (0.8)	30 (1.0)
Emigrated	125 (8.0)	86 (6.0)	211 (7.1)
Questionnaire error	0	1 (0.1)	1 (0.03)
Missing data	5 (0.3)	8 (0.6)	13 (0.4)
Miscellaneous	1 (0.1)	0	1 (0.03)
Total	1553 (100)	1426 (100)	2979 (100)

in most age groups. With the exception of the small group of people less than 45 years of age, none of the age groups in either sex in any of the three surveys had a response rate of less than 80 per cent after three mailings. The response rate of elderly people was quite high, and more than 90 per cent of those 65 years and older returned the form (see Appendix 3.1).

3. THE CLASSIFICATION OF THE QUESTIONNAIRES

The questionnaires were coded and classified as discussed earlier. Table 3.3 presents the results of the classification, divided by sex, in the combined surveys. Included in this table are the 112 non-responders who were telephoned or visited at home. Table 3.4 divides the results by the mailing (or follow-up) in which they were obtained. The effect of age on classification is presented in Appendix 3.2.

There were a total of 32 questionnaires which I felt were positive for IC, and 54 which were questionably positive. Of these questionnaires, 59 (69%) were returned in the first mailing, and 20 (23%) in the second mailing. This pattern may reflect an increased motivation to respond to the questionnaire in those with significant leg pain.

Thirty-one people (1%) refused to answer the questionnaire despite attempts to emphasize the confidential way in which the data would be handled. A common problem in this survey was a change in the mailing address, and 211 (7%) of the population were not living at the address given by the OCHP. Thus no information about IC was obtained from 242 people (8.1%) of those included in Tables 3.3 and 3.4. Partial information was obtained from a total of 14 people in the Questionnaire Error, Missing Data, and Miscellaneous categories. Thirty people (1%)

TABLE 3.5

PROVEN CASES OF IC COMPARED TO QUESTIONNAIRE CLASSIFICATION

	IC found No.(%)	IC not found No.(%)	Total No.(%)
Positive for IC	29(91)	3(9)	32(100)
Questionably positive	25(46)	29(54)	54(100)
Total	54(63)	32(37)	86(100)

in the postal survey population were coded as dead (24) or disabled (6). Two of the disabled were hemiplegic after a stroke, two suffered from severe obstructive pulmonary disease, and two were mentally handicapped.

As shown in Appendix 3.2, the number of people who were dead or disabled and the number of positive and questionably positive questionnaires increased with age. The younger people in the population were more likely to have moved than the older people. The proportion of people who refused to participate or who gave incomplete responses was relatively constant in all the age groups. I have examined these trends separately in men and women, and there was no difference between the sexes.

4. THE SPECIFICITY OF THE QUESTIONNAIRE: RESULTS OF THE PATIENT INTERVIEW AND PHYSICAL EXAMINATION

All people returning a positive or questionably positive questionnaire were interviewed and examined to establish the presence of IC. The criteria used to diagnose IC have been discussed. Seven cases of IC were found in the pilot study, and 47 cases were found in the two larger surveys. The ability of the questionnaire to identify people with IC, as measured by the number of true cases compared with the number of false positives, is summarized in Table 3.5. Thirty-two questionnaires were coded as positive, and 29 (91%) of the people examined were found to have IC. Of those classified as questionably positive, 25 (46%) were found to have IC on examination. Taken together, the questionnaires coded as Positive and Questionably Positive resulted in the correct diagnosis in 63 per cent of the people examined.

The Rose criteria for IC have been described earlier.

TABLE 3.7

QUESTIONNAIRE RESPONSES DIFFERING FROM THE ROSE CRITERIA IN PEOPLE WITH PROVEN IC

Question discrepances	Number of responses
Pain begins when sitting or standing	9
Pain not in calf	3
Pain may disappear when walking	18
Pain takes more than ten minutes to disappear	3
I carry on walking when I have the pain	10
TOTAL	43

TABLE 3.6

A COMPARISON OF THE STUDY CRITERIA AND THE ROSE CRITERIA FOR IC IN CLASSIFYING THE 54 CASES OF IC

	ROSE CRITERIA			
	All questions correct	One question incorrect	Two questions incorrect	Total
Hughson criteria	No. (%)	No. (%)	No. (%)	No. (%)
Positive	18(62)	8(28)	3(10)	29(100)
Questionably positive	4(16)	13(52)	8(32)	25(100)
Total	22(41)	21(39)	11(20)	54(100)

A total of 25 questionnaires in the pilot study and the main survey fulfilled these criteria. On examination, 22 (88%) were found to have IC. Of the 32 remaining cases, 21 fulfilled the Rose criteria except for one question, and 11 differed on two questions. A comparison of my classification with the Rose criteria appears in Table 3.6.

On four occasions I coded as Questionably Positive a form which fulfilled the Rose criteria for IC. In each instance this discrepancy was due to information written on the form by the patient which led me to suspect another diagnosis.

There were 32 cases of IC whose responses differed from those of the Rose criteria (21 cases in one question, and 11 cases in two questions). These discrepancies are summarized in Table 3.7. Eighteen people reported on the questionnaire that the pain could disappear while they were walking. Many of these had only mild symptoms, and would carry on walking with pain. Nine people stated that the pain could begin when they were sitting or standing, though questioning at the patient interview confirmed that in the vast majority of instances pain was associated with walking. Some patients also confused muscle cramp with the pain of IC when filling in the form. Three patients reported that the pain was not in their calf. On further questioning all of these people did have calf pain, though two reported predominantly foot pain, and one had thigh pain. Three people stated that the pain took more than ten minutes to stop. One of these had severe PVD with rest pain, and in the other two questioning revealed that the pain stopped on most occasions in less than ten minutes.

It was possible to establish the cause of leg pain in 19 of the people who returned false-positive questionnaires, and a

TABLE 3.9

THE EFFECT OF VARYING THE POPULATION AT RISK ON THE PREVALENCE OF IC

Population description	No. at risk	No. cases	Prevalence
(1) Total population	3303	54	1.63%
(2) All who participated in the postal survey	2979	54	1.81%
(3) Postal survey population with dead, disabled and emigrated people removed	2738	54	1.97%
(4) Postal survey population plus all non-responders with estimated deaths and emigrations removed	3150	54	1.71%

TABLE 3.8

CAUSES OF LEG PAIN IN PEOPLE RETURNING FALSE-POSITIVE QUESTIONNAIRES

Diagnosis	No. people
Varicose veins	6
Osteoarthritis	5
Sciatic nerve pain	4
Residual effect of trauma	2
Stroke with hemiplegia	1
Diabetic neuropathy	1
No firm diagnosis	17
TOTAL	36

summary of these diagnoses appears in Table 3.8. I did not assign a diagnosis to a false-positive patient unless there was documentation in the notes of a definite disease entity, and this accounts for the large number with no firm diagnosis.

B. THE PREVALENCE OF INTERMITTENT CLAUDICATION

A total of 3,303 people were sent questionnaires and 54 cases of IC were discovered. If the total survey population is used as the denominator, a rough estimate of the prevalence is 1.6 per cent.

A number of people in the survey population were not at risk for IC due to death, disability, or emigration. Of the 2,979 people who participated in the survey either by returning the form or in the follow-up of non-responders, 241 were dead, disabled, or had moved (Appendix 3.2). Thus 2,738 people in the postal survey were at risk, and the prevalence rate using this population as the denominator is 1.97 per cent. A further 31 people refused to participate in the study, and if they are excluded, the prevalence rises to 1.99 per cent.

No cases of IC were found in the sample of non-responders who were followed up, though it is possible that some cases were missed in the 324 people who were not contacted. Of the 112 who were followed up, six (5.4%) were not at risk for IC due to emigration. If this sample was representative, it can be estimated that 24 people (5.4% of 436) people in the non-responder group were not at risk for IC. Thus 412 people in the non-responder group were at risk. Assuming that there were no cases of IC in this group, a total of 3,150 people (2,738 + 412) in the study were at risk, and the minimum prevalence of IC is 1.71 per cent. Table 3.9 summarizes the prevalence rates of IC which can be calculated using the

TABLE 3.12

THE AGE DISTRIBUTION OF WOMEN WITH IC AND THE AGE-SPECIFIC PREVALENCE RATE

Age (yrs)	No. at risk	No. cases	Prevalence (%)
<45	1	0	-
45-49	25	0	-
50-54	378	0	-
55-59	309	2	0.6
60-64	314	3	1.0
65-69	299	6	2.0
70+	2	0	-
Total	1328	11	0.8

TABLE 3.11

THE AGE DISTRIBUTION OF MEN WITH IC AND THE AGE-SPECIFIC PREVALENCE RATE

Age (yrs)	No. at risk	No. cases	Prevalence (%)
<45	12	0	-
45-49	349	3	0.9
50-54	351	10	2.8
55-59	222	3	1.4
60-64	240	10	4.2
65-69	233	17	7.3
70+	3	0	-
Total	1410	43	3.0

TABLE 3.10

THE AGE DISTRIBUTION OF PATIENTS WITH IC AND THE AGE-SPECIFIC PREVALENCE RATE

Age (yrs)	No. at risk	No. cases	Prevalence (%)
<45	13	0	-
45-49	374	3	0.8
50-54	729	10	1.4
55-59	531	5	0.9
60-64	554	13	2.3
65-69	532	23	4.3
70+	5	0	-
Total	2738	54	2.0

different denominators I have discussed. The fact that most positive questionnaires arrived in the first mailings seemed to indicate a greater motivation to answer the questionnaire in those with IC. I have therefore included the people who refused to answer the questionnaire in the populations at risk in Table 3.9, since this group may be less likely to have IC.

The age distribution of the people with IC, and the age-specific prevalence rate for IC is summarized in Table 3.10. The population used to calculate these rates is the postal survey population plus the followed-up group of non-responders (see Appendix 3.2). I have removed those who were dead, disabled, or emigrated in calculating the population at risk. The age specific rates for men and women are presented in Tables 3.11 and 3.12, respectively. It can be seen that the prevalence of IC increased with age (except for men aged 55 to 59 years), and that IC was more common in men than women at all ages.

C. DISCUSSION

Factors which can influence the return rate in a postal survey include the length and layout of the questionnaire, the number or spacing of reminders, the colour and size of envelopes and whether they are typed or hand-written, the number or denomination of stamps, the tone of the accompanying letter, and the season of the year in which the questionnaires are sent out (Cartwright and Ward, 1968; Newland et al, 1977). People from the higher social classes with a higher level of education or with a special interest in the subject of the questionnaire may be more likely to return the form (Bennett and Ritchie, 1975).

It was not the object of this study to investigate the

factors influencing postal returns, but it is possible to make some observations. The questionnaire and mailing methods used have remained the same throughout the pilot study and the main survey, so that factors such as questionnaire length, type of envelope, etc. will not have altered the return rates. The social class distributions of the Sonning Common and Donnington Health Centre practices have been discussed in an earlier section. Despite the fact that Sonning Common had a greater proportion of people in the higher social classes (as determined in the 1971 Census of Great Britain), the questionnaire return rate in this survey was lower than that of the Donnington Health Centre. Therefore the results of this study do not support the premise that a higher level of education leads to a better response rate.

The questionnaires in the pilot study were mailed from February to April, 1975, while those of the Donnington survey were mailed in the same months one year later. The Sonning Common questionnaires were sent out from June to August, 1975. It is possible that more people in Sonning Common were away on holiday during the three mailings, and this may have lowered the return rate.

The letters in the pilot study were impersonal and unsigned, while those in the two main surveys were addressed individually and signed in ink. At the advice of the general practitioners in the Donnington Health Centre, the letters used in that survey were less complex in their description of the purpose of the questionnaire, and more direct in tone when asking the patient to respond (Appendix 2.2). This may have helped to improve the response rate.

The pattern of mailing returns was reasonably consistent

in the three surveys. Those with symptoms returned the questionnaire promptly, with only a few positive questionnaires in the third mailing. Of the 54 cases, 53 were identified in the first two mailings, and there were no cases of IC identified in the follow-up of non-responders. If one postulates a greater motivation to return the form in those with symptoms, it may be that those who refused to answer the form were unlikely to be afflicted with IC, and were therefore not motivated to respond. The practice notes of all refusals were examined, and no evidence of IC was found. For these reasons I would include the refusals as part of the population at risk when calculating the prevalence of IC.

If the Rose criteria for IC had been strictly applied in the interpretation of the questionnaires, 22 cases of IC would have been discovered, resulting in a prevalence of 0.8 per cent. Of the Rose-positive questionnaires, 13 occurred in men 45 to 64 years of age, resulting in a prevalence of IC of 1.1 per cent in this age group. This compares with the prevalence of IC of 0.7 per cent in the group of male civil servants, 40-64 years of age, who were screened with a postal questionnaire (Rose et al, 1977). The age distribution of the civil servant study was not described in detail, though many men retired at the age of 60 and thus were not included. The difference in the prevalence of Rose-positive questionnaires may, therefore, have been due to different age distributions in the two populations. There may also have been a "survivor effect" in the civil servant study, since those men with health problems such as atherosclerotic vascular disease may have retired prematurely.

Thirty-two cases of IC were discovered in people whose

questionnaires did not fulfil all the Rose criteria. Unlike the civil servant study described earlier, there was no opportunity in my study to check all the questionnaires with the patients. This resulted in inconsistent and incomplete answers on some questionnaires, and necessitated a more flexible approach. The patient interviews clarified the nature of the complaint, and in most cases the patient's symptoms were consistent with the Rose criteria.

The IC questionnaire was originally designed and validated using a group of hospital patients with undoubted IC, most of whom had had arteriograms (Rose, 1962). Of the 54 cases in my study, only 29 had complained to their general practitioners, and only eight had been referred for hospital treatment. Many of the cases had only mild symptoms and adjusted to their limitation by using public transport or walking slowly. Of the 18 people who stated on the questionnaire that the pain could disappear while they walked, most in fact simply slowed their pace and carried on. It is likely that the hospital patients used to design the questionnaire had more severe arterial disease than the patients identified in my study, and this probably accounts for many of the questionnaire discrepancies.

The prevalence of IC increased with age, except for men aged 55-59 years, where there was a fall in prevalence. This drop may have been due to a random fluctuation, and has not been found by other studies. It is possible, however, that the increase in cerebro- and cardiovascular disease which occurs in men at this age (see Figure 1.1) may result in a high death rate in those with generalized atherosclerotic disease, and therefore a decrease in the number of men

complaining of IC. Those atherosclerotic patients who escape death from myocardial infarction or stroke and develop IC in later life may represent a subgroup of individuals whose arterial lesions are different in distribution and severity from those who die at younger ages.

No cases of IC were found in women under the age of 55 years, and the prevalence of IC was greater in men than women at all ages. The prevalence of IC in men rose from 0.9 per cent in those 45-49 years of age to 7.3 per cent in those 65-69 years of age. Taking all age groups into account, the prevalence of IC in men was 3.0 per cent. The prevalence of IC in women was 0.8 per cent, so that IC was 3.8 times more common in men than women.

The prevalence rates found in this study were generally lower than the rates found in the studies reviewed in Chapter 1. Milne and Williamson (1972) found a prevalence of 10.4 per cent in men and 2.6 per cent in women greater than 62 years of age. Their study did not measure the ankle systolic pressure, however, and relied solely on the palpation of foot pulses to confirm the diagnosis of IC. Fodor et al (1968) found a prevalence of IC of 10.6 per cent in men aged 60-64 years. The criteria for the diagnosis of IC were not described in this study, and there was no examination of the peripheral circulation. Bothig et al (1976) found a prevalence of IC in men 50-54 years of age of 6.9 per cent and 3.4 per cent in Moscow and Berlin, respectively. Again there was no examination of the peripheral circulation. It is likely that all these studies included people whose symptoms were compatible with IC but who would not have had objective evidence of PVD on physical examination.

Widmer et al (1964) examined the circulation using an oscillograph and found a prevalence of arterial occlusion which rose from 0.1 per cent in men aged 30-40 years to 7.5 per cent in men aged 60-64. Of these men, approximately one-third had symptoms. Widmer et al did not define the criteria used to diagnose IC, nor did they give the age-specific prevalence. If the proportion of symptomatic arterial lesions was uniform in all ages, then approximately 2.5 per cent of the men aged 60-64 would have had symptoms (unspecified) and objective evidence of arterial disease. This compares with a prevalence of IC of 4.2 per cent in men 60-64 years of age in my study. The population studied by Widmer consisted of factory workers. It is possible that those men who continue to work after the age of 60 enjoy better health than people of the same age drawn from a general population, and this may account for the lower prevalence rate in this study. The different methods used to examine the circulation may also have resulted in different estimates of the prevalence.

Hobson and Pemberton (1955) found 29 cases of IC in people greater than 60 years of age. They performed a physical examination, though the criteria used to establish a diagnosis of IC were not defined. The prevalence in this study was 6.1 per cent with a male-to-female prevalence ratio of 2.2:1. The prevalence of IC in men and women greater than 60 years of age was 3.3 per cent in my study, with a male-to-female prevalence ratio of 3.9:1. The population studied by Hobson and Pemberton included a number of people older than 70 years of age, and this probably contributed to the higher prevalence in this study. The age-specific prevalence of IC was not given.

D. SUMMARY

The strict criteria defined by Rose for use with his questionnaire were not appropriate when the form was self-administered in a postal survey of a general population. Strict adherence to these criteria would have resulted in an underestimate of the prevalence of IC, since many questionnaires were returned with incomplete or inconsistent responses. With repeated mailings it was possible to obtain questionnaires from most of the population, and the response rate was particularly good in the older age groups. If the purpose of the survey had simply been to identify cases, two mailings would have been sufficient (and more efficient), since those people with symptoms tended to return the form promptly. It was not possible to test the sensitivity of the questionnaire, since only those with positive responses (and their controls) were examined. There may, therefore, have been people with IC who were not identified in the survey. The specificity of the questionnaire was good when strict criteria for the diagnosis of IC were applied, but fell to approximately 60 per cent when questionably positive forms were included. Complete follow-up of non-responders in the pilot study, and a one-in-five sample of non-responders in the larger surveys did not identify any further cases of IC. Thus it is likely that the prevalence of IC found in the people who returned the questionnaire was not significantly different from that of the general population. A total of 54 cases of IC were identified. The prevalence was 3.0 per cent in men and 0.8 per cent in women.

CHAPTER 4

A CASE-CONTROL STUDY TO DETERMINE RISK FACTORS FOR INTERMITTENT CLAUDICATION

Chapter 4 A CASE-CONTROL STUDY TO DETERMINE RISK FACTORS FOR INTERMITTENT CLAUDICATION

A. INTRODUCTION

There are only a few studies that have investigated the risk factors for intermittent claudication. Most of these have examined highly-selected populations such as patients hospitalized due to severe arterial disease. Such groups are not representative of people who suffer from IC, since many patients with mild symptoms do not come to medical attention (Widmer et al, 1964). Of the 54 claudicants identified in the postal survey described in Chapter 3, approximately one-half had not complained to their doctor, and only 15 per cent had been referred to hospital. They are, therefore, more likely than a series of hospitalized patients to be representative of people with symptomatic peripheral vascular disease as it exists in the general population.

The purpose of this investigation was to determine those characteristics which place an individual at increased risk of developing IC in the hope that such knowledge may be applied to prevent the disease. A description of the risk factors present in the patients identified in Chapter 3 (compared with age- and sex-matched controls) is likely to resemble closely the spectrum of risk factors which are present in the general population and which result in an increased risk of intermittent claudication.

The methods used to identify cases and select controls and to perform the interview, examination, and laboratory investigations have been discussed in Chapter 2.

B. STATISTICAL ANALYSES

For continuous variables, the statistical significance of

differences between the case value and the mean value of the two age- and sex-matched controls were analyzed using a paired t-test. Because cholesterol and triglyceride are log-normally distributed, the logarithm of the concentration was calculated before performing the t-test on these variables (Truswell and Mann, 1972).

Relative risks were calculated without regard to individual matching and also according to the method described by Pike and Morrow (1970) which considers the matching. Standardized relative risks correcting for possible confounding variables were calculated according to the method of Mantel and Haenzel (1959). The levels used when standardizing are presented in Appendix 4.1.

C. A DESCRIPTION OF THE PATIENTS WITH INTERMITTENT CLAUDICATION

The age and sex distribution of the cases has been discussed and is presented in Tables 3.11 and 3.12. Forty people complained of bilateral IC. The 14 patients with unilateral symptoms were evenly divided, with seven having pain in the right leg and seven with pain in the left (see Appendix 4.2). The average duration of symptoms was 36 months in patients with bilateral IC and 27 months in those with one leg affected. Onset of symptoms was gradual in all but three of the 54 cases, and average walking distance before pain started was 450 yards at onset of the disease.

Three patients stated that the pain sometimes occurred at rest. One of these was a man who had previously undergone an amputation and since developed severe ischaemia in the other leg. The other two patients also had significant arterio-sclerosis on physical examination, but in addition to PVD one was an insulin-dependent diabetic with peripheral neuropathy

TABLE 4.2

THE PREVALENCE OF ISCHAEMIC HEART DISEASE IN CASES AND CONTROLS

	Cases (54) No. (%)	Controls (108) No. (%)
Myocardial infarction (no angina)	3 (6)	0
Myocardial infarction (with angina)	2 (4)	2 (2)
Angina (no myocardial infarction)	18 (33)	5 (5)
Positive ECG with no symptoms	6 (11)	8 (7)
Total	29 (54)	15 (14)

TABLE 4.1

THE CAUSES OF RESTRICTED ACTIVITY IN THE PATIENTS WITH INTERMITTENT CLAUDICATION

	No.	%
IC	31	(57)
IC and angina	11	(20)
IC and respiratory disease	4	(7)
IC and stroke	3	(6)
IC and arthritis	3	(6)
IC and poor vision	2	(4)
Total	54	(100)

and the other had mild hemiparesis after a stroke. Involvement of the nervous system may have contributed to their symptoms.

The patients were asked whether their IC had progressed in the year prior to the interview. Nineteen said their symptoms had worsened, six felt they could walk further, and 29 said their condition had not changed. The three patients with a sudden onset of IC all reported a deterioration. Average walking distance before pain started was 200 yards at the time of interview.

Patients of the Donnington and Sonning Common Health Centres had ready access to their general practitioners. Despite the availability of medical care, 25 of the 54 cases (46%) with symptoms of IC did not consult their doctor. Reasons for this may include the mild symptoms of many patients and the insidious onset of the complaint. Only ten patients said that IC resulted in a severe limitation of their activity, while 17 patients said they were slightly restricted. The presence of other medical illnesses such as coronary artery disease and angina served to limit the movement of some so that the addition of IC did not result in a significant change in their activities. Table 4.1 summarizes the causes of restricted activity in the patients with IC.

Twenty-nine patients had complained of IC to their doctor. Analgesics had been prescribed for two, and five had been given vasodilating drugs. Eight patients had been referred to hospital and examined by arteriography, and six had undergone surgery. The arteriographic findings and operative procedures used in these patients are presented in Appendix 4.3.

D. THE PREVALENCE OF CORONARY ARTERY AND CEREBROVASCULAR DISEASE IN THE CASES AND CONTROLS

Table 4.2 summarizes the prevalence of ischaemic heart

disease in the cases and controls. It is of interest that nine of the 11 women with IC also complained of angina. There were only three patients in this study who had suffered a stroke, and all were cases.

E. THE EXAMINATION OF THE PERIPHERAL CIRCULATION OF THE CASES AND CONTROLS

As discussed in Chapter 2, all cases had absent or diminished pulses in at least one leg. In fact most of the patients with unilateral IC also had evidence on palpation of PVD in their asymptomatic leg. In contrast, the majority of the control patients had peripheral pulses which were normal in volume (see Appendix 4.4). Similarly, tissue wasting, ulceration and gangrene were found more commonly in the cases (Appendix 4.5).

The mean ankle systolic blood pressure ratios (ASBP) of cases and controls at rest and after exercise are presented in Appendices 4.6 and 4.7. There was no effect of age on the pressure index, and when the data for men and women were analyzed separately, there was no significant difference in this measurement between the two sexes. The step-test was often quite difficult for elderly patients because it required a moderate amount of co-ordination, balance and physical fitness. Some could not do the exercise test at all because of angina, arthritis, or other illnesses. For these reasons the step-test was used in this study to stress the circulation and to measure the ASBP response to exercise, and not as a measure of the work capacity of the legs. As discussed in Chapter 2, all patients with the diagnosis of IC had a resting ASBP ratio of less than 0.75 or an exercise ratio less than 0.60, or both, in at least one leg.

TABLE 4.4

THE DIASTOLIC BLOOD PRESSURE OF CASES AND CONTROLS

	Cases	Controls	Significance
Mean DBP	88.3	82.9	
Std. error	1.6	1.0	t = 2.68 on
Minimum	70	60	53 d.f.
Maximum	120	110	p<0.01
No. observations	54	108	

FIGURE 4.2

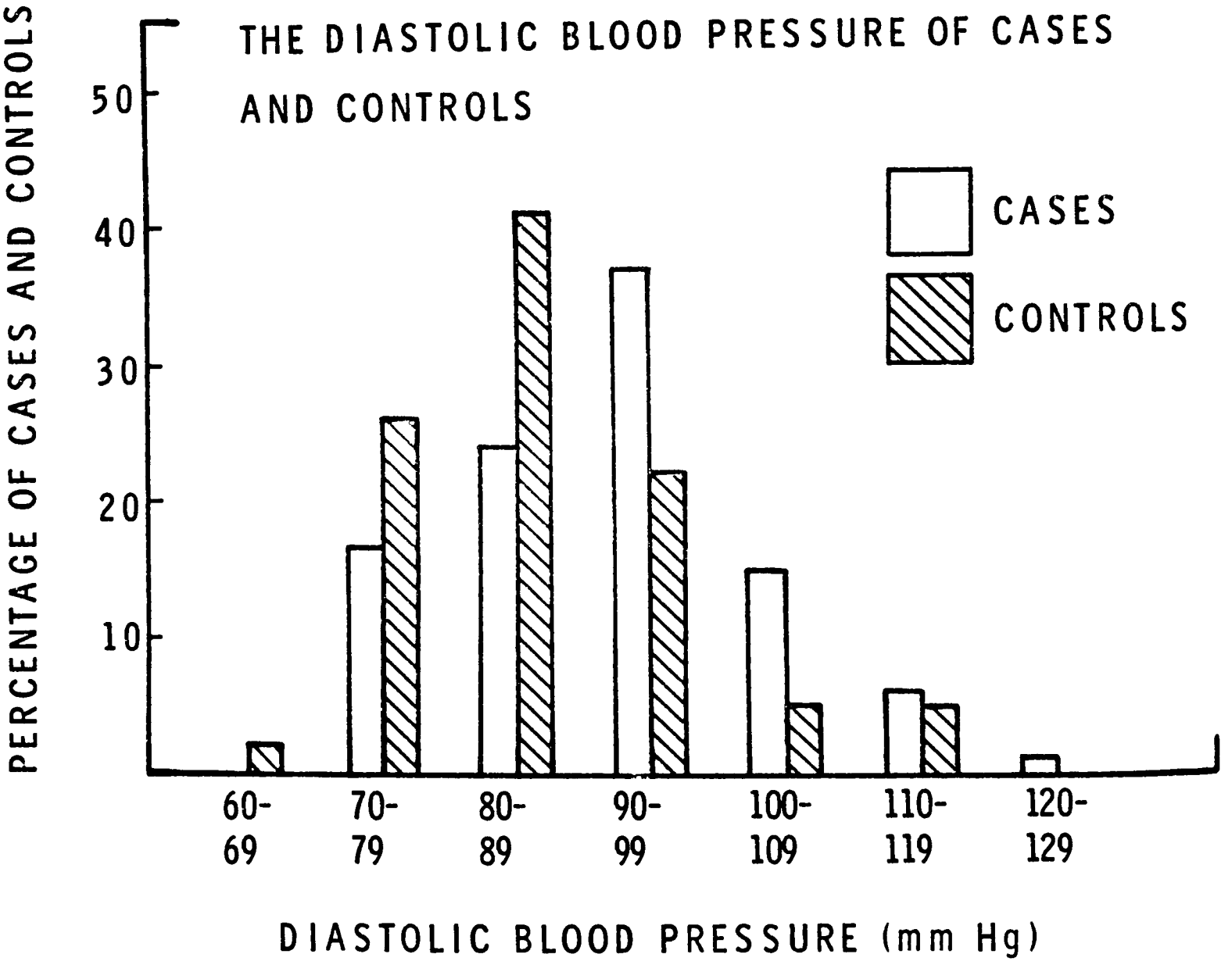
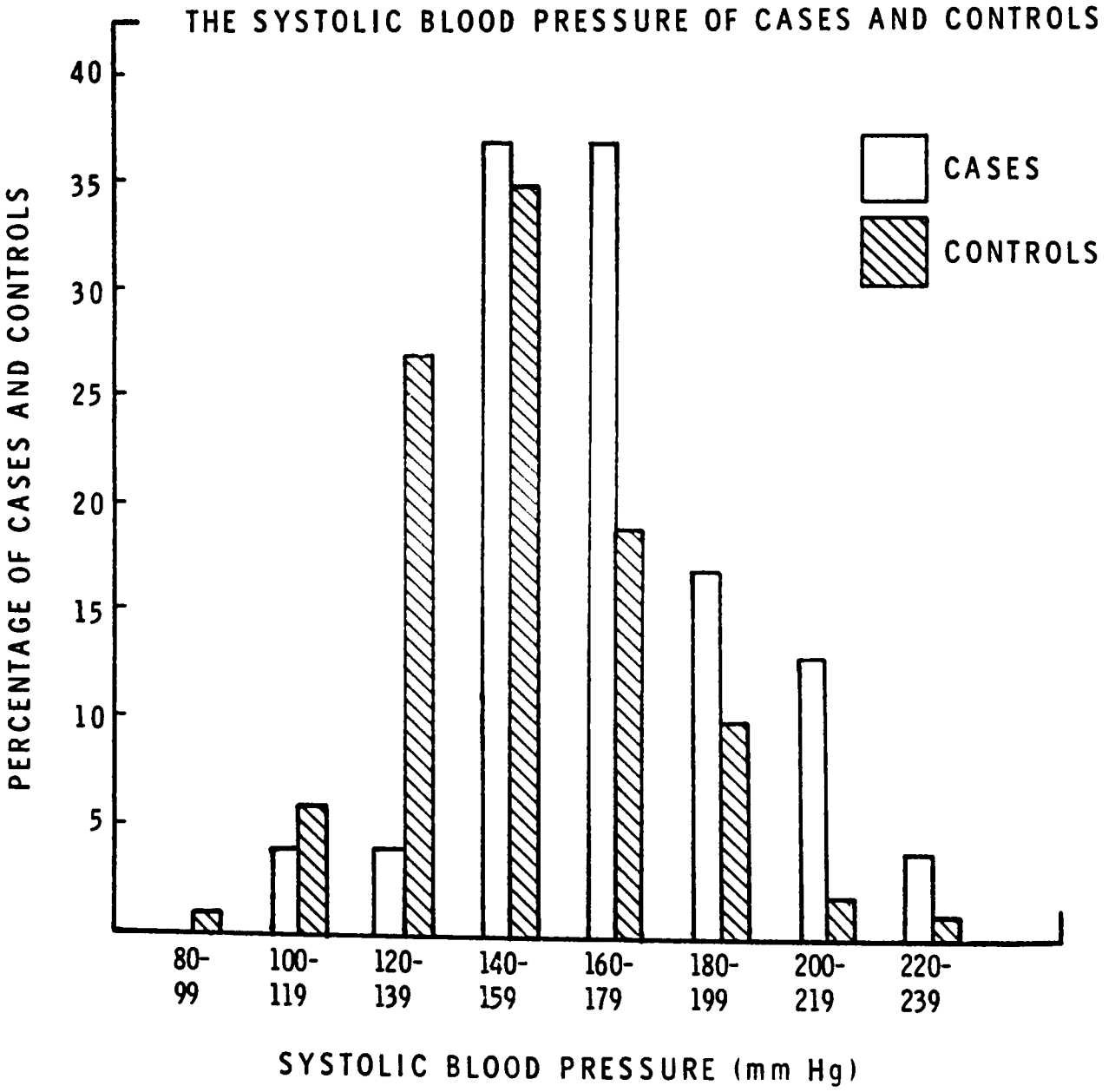


TABLE 4.3

THE SYSTOLIC BLOOD PRESSURE OF CASES AND CONTROLS

	Cases	Controls	Significance
Mean SBP	164.4	147.2	
Std. error	3.5	2.3	t = 4.03 on
Minimum	110	95	53 d.f.
Maximum	220	230	p<0.001
No. observations	54	108	

FIGURE 4.1



F. RISK FACTORS FOR INTERMITTENT CLAUDICATION

1. THE BLOOD PRESSURE OF THE CASES AND CONTROLS

Eighteen of the 54 cases (33%) had been treated for hypertension compared with nine controls (8%). The mean systolic (SBP) and diastolic (DBP) pressures are presented in Tables 4.3 and 4.4, respectively, and the distributions are shown in Figures 4.1 and 4.2. The cases had significantly elevated systolic ($p<0.001$) and diastolic ($p<0.01$) pressures compared with the controls. At the time of examination, 15 cases (28%) were receiving antihypertensive drugs compared with six of the control patients (6%). This treatment may have reduced the difference between the two groups.

The mean systolic and diastolic pressures of the cases and controls, divided by age and sex, are presented in Appendices 4.8 and 4.9. If the men are examined separately, there was a significant elevation of SBP ($p<0.001$) and DBP ($p<0.01$) of the cases compared with their controls. There was, in contrast, no significant difference between the women with IC and their controls. Thus the difference in the mean SBP and DBP between cases and controls was attributable almost entirely to elevated blood pressure in the male claudicants.

Systolic and diastolic pressure increased with age in the control patients, but this trend was not seen in the cases. Differences between cases and controls were, therefore, greater in the younger age groups.

Thirty-three cases (61%) had a SBP greater than or equal to 160 mm Hg, compared with 34 controls (31%). The relative risk of IC was 3.4 to 1 (95% confidence limits 2.3 to 6.9) for SBP at or above this level. This relative risk was statistically significant when the matching was considered ($X^2_1 = 11.8$, $p<0.001$,

TABLE 4.6

ESTIMATED RELATIVE RISK OF IC IN PATIENTS WITH A DIASTOLIC BLOOD PRESSURE GREATER THAN OR EQUAL TO 90 mm Hg AFTER STANDARDIZATION FOR POSSIBLE CONFOUNDING VARIABLES

Variable standardized	Relative risk estimate	Chi-Square	Significance level
None	3.2	10.4	$p<0.005$
Systolic B.P.	1.9	3.1	$p<0.10$
Cholesterol	2.7	7.9	$p<0.01$
Triglyceride	2.3	5.8	$p<0.025$
Glucose	3.2	11.4	$p<0.001$
Uric acid	3.1	8.6	$p<0.005$
Fibrinogen	2.8	8.6	$p<0.005$
Quetelet's index	3.2	11.3	$p<0.001$
Amount smoked	3.6	12.7	$p<0.0005$

TABLE 4.5

ESTIMATED RELATIVE RISK OF IC IN PATIENTS WITH A SYSTOLIC BLOOD PRESSURE GREATER THAN OR EQUAL TO 160 mm Hg AFTER STANDARDIZATION FOR POSSIBLE CONFOUNDING VARIABLES

Variable standardized	Relative risk estimate	Chi-Square	Significance level
None	3.4	11.8	$p<0.001$
Diastolic B.P.	3.0	8.6	$p<0.005$
Cholesterol	2.9	9.2	$p<0.005$
Triglyceride	3.2	10.5	$p<0.005$
Glucose	3.4	12.7	$p<0.001$
Uric acid	3.4	11.9	$p<0.001$
Fibrinogen	3.3	11.1	$p<0.001$
Quetelet's index	3.4	12.8	$p<0.001$
Amount smoked	3.6	12.7	$p<0.0005$

pike and Morrow (1970)), and when cases and controls were compared without regard to individual matching (X^2_1 = 11.8, $p<0.001$). Table 4.5 presents the relative risk of IC associated with SBP of 160 mm Hg or more, controlling for other risk factors. When cases and controls were divided according to age, the risk of IC associated with SBP greater than or equal to 160 mm Hg was greater in those less than 60 years of age (R.R. = 6.3) than in those 60 years and older (R.R. = 2.8).

Similar estimates of relative risk can be calculated for diastolic blood pressure. Thirty-two cases (59%) had a DBP greater than or equal to 90 mm Hg, compared with 34 controls (31%), and the relative risk of IC was 3.2 to 1 (95% confidence limits 1.9 to 11.6) for DBP at or above this level. This risk was significant when the matching was considered (X^2_1 = 10.3, $p<0.005$) and when individual matching was ignored (X^2_1 = 10.4, $p<0.005$). Table 4.6 presents the standardized relative risk, correcting for possible confounding variables. As for SBP, the relative risk of IC associated with elevated DBP ($\geq$90 mm Hg) was greater in those less than 60 years of age (R.R. = 6.8) than in those 60 years and older (R.R. = 2.2).

There was a reduction in the risk associated with DBP when correction was made for SBP. However, because these variables were strongly correlated (r = 0.74, $p<0.001$), it would not be correct to conclude that the risk of IC associated with an elevated blood pressure was due solely to the systolic component. It is possible that with larger numbers of patients the diastolic component of blood pressure would emerge as an independent risk factor for IC.

It should be noted that the choices of 160 mm Hg and 90

TABLE 4.8

THE FASTING TRIGLYCERIDE CONCENTRATION (MMOL/L) OF CASES AND CONTROLS

	Cases No. (%)	Controls No. (%)	Significance
Mean (mmol/l)	2.32	1.92	$p<0.05$
Std. error	0.19	0.06	$t = 2.10$ on
Minimum	0.93	0.66	49 d.f.
Maximum	10.25	4.75	
No. observations	50	101	

Conversion factor from S.I. units to traditional units

Triglyceride 1 mmol/l $\approx$ 88.5 mgm/100 ml

FIGURE 4.4

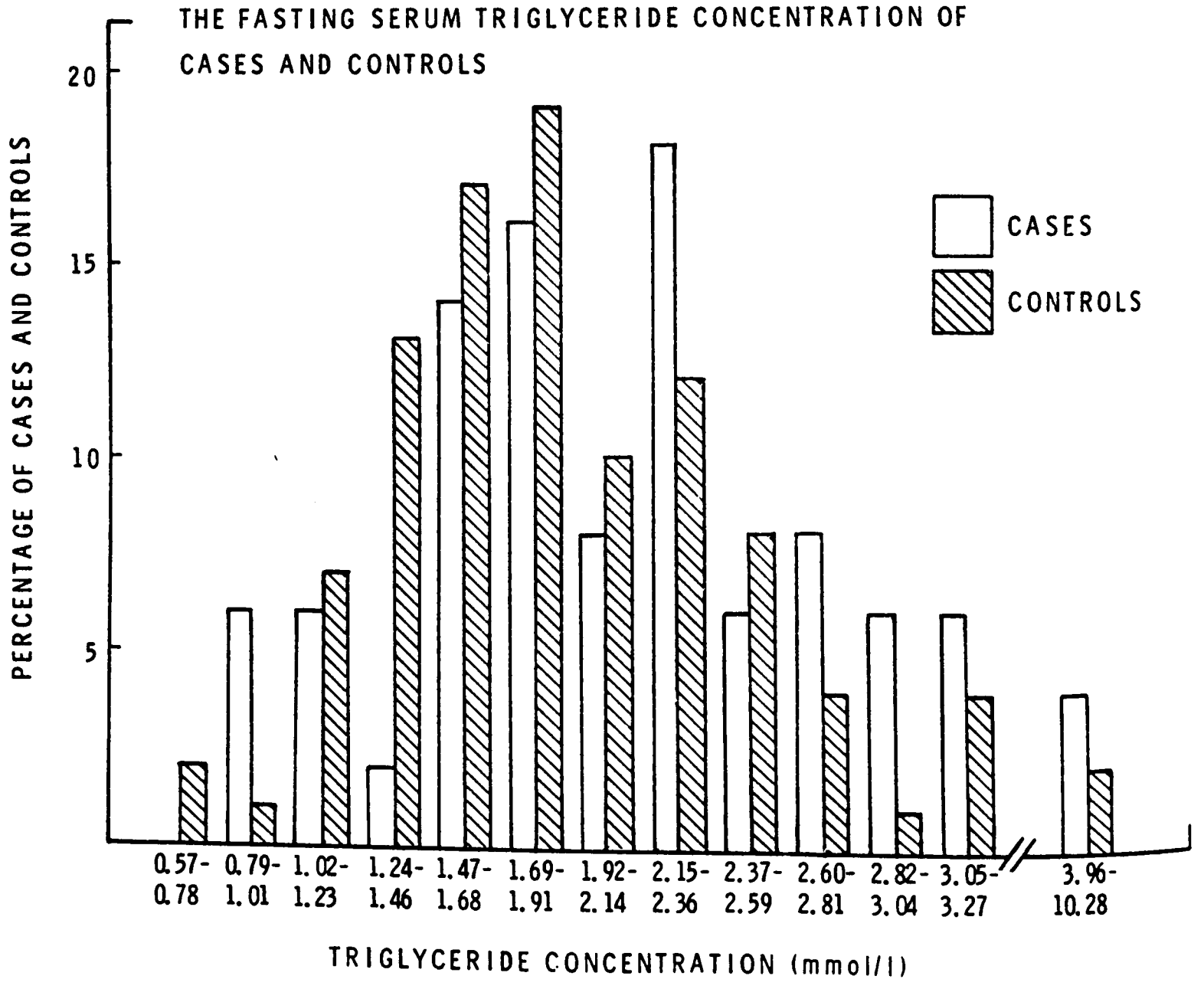


TABLE 4.7

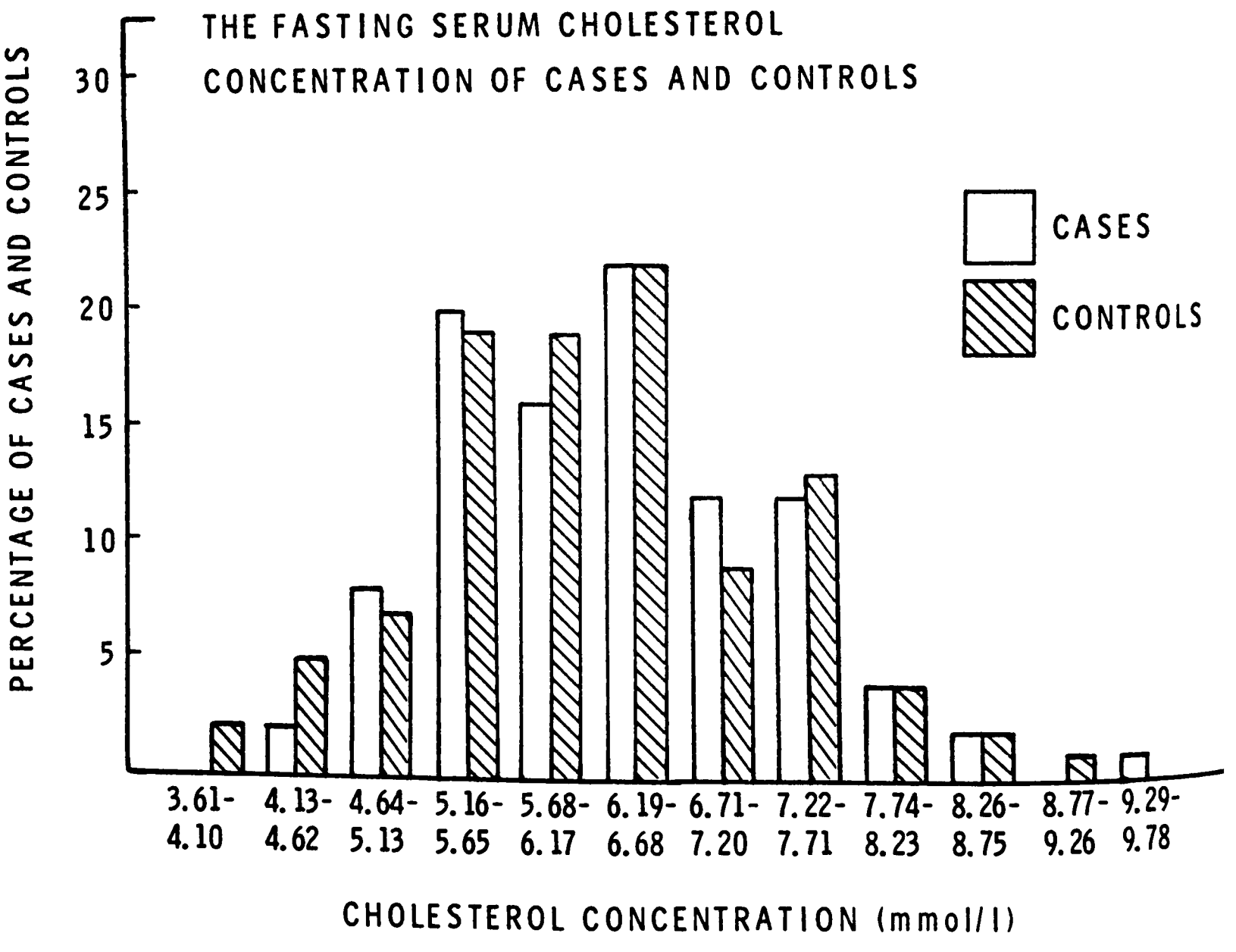
THE FASTING CHOLESTEROL CONCENTRATION (MMOL/L) OF CASES AND CONTROLS

	Cases No. (%)	Controls No. (%)	Significance
Mean (mmol/l)	6.3	6.2	N.S.
Std. error	0.2	0.1	
Minimum	4.4	4.1	
Maximum	9.7	9.2	
No. observations	50	101	

Conversion factor from S.I. units to traditional units

Cholesterol 1 mmol/l≈38.6 mgm/100 ml

FIGURE 4.3



mm Hg as arbitrary cut-off points for SBP and DBP, respectively, were not made simply because these levels were associated with a significant risk. These levels were selected because they have been examined in other studies and are considered to be of clinical significance. Also the constraints of small numbers necessitated the choice of levels with sufficient numbers of cases and controls above and below so that standardization for other risk factors was possible.

2. THE SERUM LIPIDS OF THE CASES AND CONTROLS

Twelve patients in the study had been told of elevated serum lipids by their doctor. Nine of these were claudicants (17%), and three were controls (3%). Eight of the nine cases and two of the three control patients with a history of hyperlipidaemia were receiving treatment with diet or clofibrate at the time of the examination. The mean fasting cholesterol of these patients was 7.0 mmol/l, and the mean fasting triglyceride concentration was 2.71 mmol/l.

Tables 4.7 and 4.8 present the mean fasting cholesterol and triglyceride concentrations, respectively, of the cases and controls. The cholesterol levels were similar in the two groups, but the concentration of triglyceride was significantly higher in the patients with IC than in the controls ($p<0.05$). The distributions of the lipid concentrations are presented in Figures 4.3 and 4.4.

The mean concentrations of cholesterol and triglyceride, divided by age and sex, are presented in Appendices 4.10 and 4.11, respectively. As with blood pressure, there was a tendency for the serum lipids to increase with age in the control patients, but this trend was not evident in the cases. The concentration of cholesterol was significantly higher in

the women than the men in both cases and controls (t-test, $p<0.01$). There was no significant difference between men and women in the concentration of triglyceride.

The overall difference in cholesterol between cases and controls was not significant, and indeed the mean concentrations were very similar. There was, however, some indication that cholesterol may have been a risk factor for IC in the younger age groups. The mean level of cholesterol in the cases less than 60 years of age was 6.2 mmol/l compared with 5.7 mmol/l in their age-matched controls ($t = 1.84$ on 16 d.f., $p<0.10$). In contrast, the mean concentrations were almost identical in the cases (6.4 mmol/l) and controls (6.5 mmol/l) who were 60 years and older. The relative risk associated with elevated cholesterol when all the cases were considered was 1.2 to 1 (for a concentration $\geq$ 6.7 mmol/l), but if the cases less than 60 years of age were examined separately, a concentration greater than or equal to 6.7 mmol/l was associated with a relative risk of IC of 2.3 to 1.

There were 24 cases (44%) and 32 controls (30%) whose fasting triglyceride concentration was greater than or equal to 2.15 mmol/l. The relative risk of IC associated with a triglyceride concentration at or above this level was 2.0 to 1 (95% confidence limits 0.93 to 4.3). This risk was statistically significant when individual matching was considered ($X^2_1 = 3.9$, $p<0.05$), but fell below the level of statistical significance when matching was ignored ($X^2_1 = 3.15$, $p<0.10$). Once again, the relative risk was greater in the patients less than 60 years of age (R.R. = 6.0, $X^2_1 = 6.6$, $p<0.025$) than in patients 60 years and older (R.R. = 1.2, N.S.).

There was some evidence of an increased risk of IC with

TABLE 4.9

ESTIMATED RELATIVE RISK OF IC IN PATIENTS WITH A FASTING SERUM TRIGLYCERIDE CONCENTRATION GREATER THAN OR EQUAL TO 2.15 MMOL/L AFTER STANDARDIZATION FOR POSSIBLE CONFOUNDING VARIABLES

Variable standardized	Relative risk estimate	Chi-Square	Significance level
None	2.0	3.2	$p<0.10$
Systolic B.P.	2.3	4.4	$p<0.05$
Diastolic B.P.	2.1	3.9	$p<0.05$
Cholesterol	1.9	3.4	$p<0.10$
Glucose	1.9	3.4	$p<0.10$
Uric acid	1.9	3.3	$p<0.10$
Fibrinogen	1.8	2.4	$p<0.20$
Quetelet's index	2.1	4.5	$p<0.005$
Amount smoked	2.5	6.2	$p<0.025$

increasing levels of triglyceride. For example, at a concentration greater than or equal to 2.71 mmol/l, the relative risk of IC was 2.9 to 1 (95% confidence limits 1.1 to 8.2), which was significant both when matching was considered (X^2_1 = 4.6, $p<0.05$) and when cases and controls were compared without regard to matching (X^2_1 = 3.9, $p<0.05$). Unfortunately, there were too few cases to allow a detailed analysis of this trend.

Table 4.9 presents the standardized relative risk of IC, controlling for possible confounding variables, associated with a triglyceride concentration greater than or equal to 2.15 mmol/l. I have chosen this level even though the uncorrected relative risk was not great because the distribution of triglyceride concentrations did not allow standardization at more significant cut-off points (too few controls had markedly elevated levels). It can be seen that none of the variables standardized had a marked effect on the relative risk.

When all patients with a history of treatment for diabetes were removed from the analysis, the difference between cases and controls in the concentration of triglyceride decreased, but was still statistically significant (t = 2.02 on 43 d.f., $p<0.05$).

3. THE BLOOD GLUCOSE LEVELS OF THE CASES AND CONTROLS

Six of the patients with IC (11%) had received treatment for diabetes compared with only one control patient (1%). All were adult-onset diabetics, and at the time of examination, four cases were being treated with diet and an oral hypoglycaemic drug, one was on diet and insulin, and one was not receiving treatment. The mean fasting glucose concentration of the diabetic cases was 8.2 mmol/l. The diabetic control was on a

TABLE 4.11

THE SMOKING HABITS OF CASES AND CONTROLS

		Cases (54) No. (%)	Controls (108) No. (%)
Non-smokers		4 (7)	30 (28)
Ex-smokers		13 (24)	41 (38)
Pipe and cigar smokers		7 (13)	8 (7)
Current cigarette smokers	1-14/D	9 (17)	11 (10)
	≥15/D	21 (41)	18 (17)
Total		54(100)	108(100)

TABLE 4.10

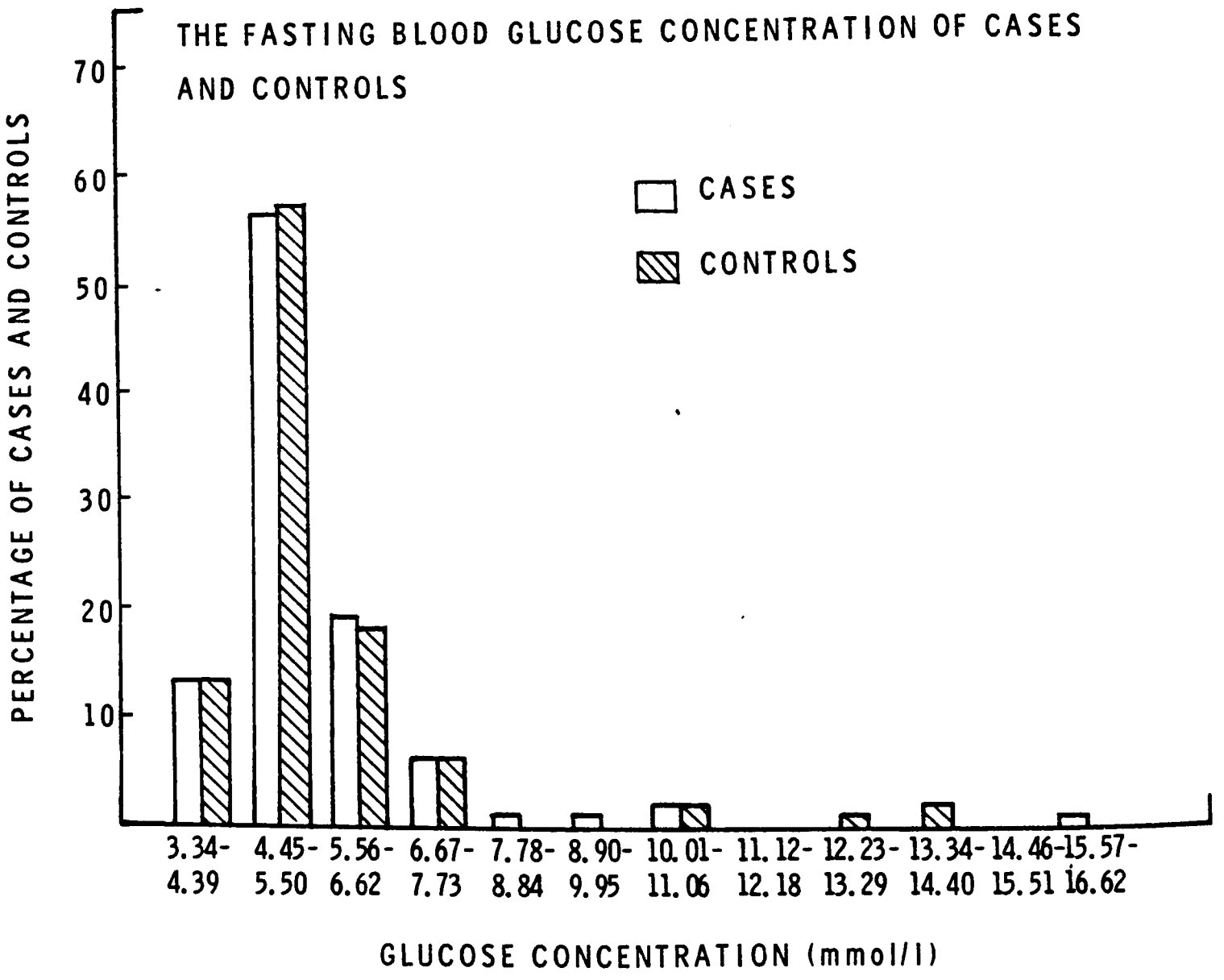
THE FASTING BLOOD GLUCOSE CONCENTRATIONS (MMOL/L) OF CASES AND CONTROLS

	Cases No. (%)	Controls No. (%)	Significance
Mean (mmol/l)	5.6	5.5	N.S.
Std. error	0.3	0.2	
Minimum	3.6	3.6	
Maximum	16.2	14.2	
No. observations	54	108	

Conversion factor from S.I. units to traditional units

Glucose 1 mmol/l≈18.0 mgm/100 ml

FIGURE 4.5



diet and an oral hypoglycaemic drug, and had a blood glucose concentration of 14.2 mmol/l.

There was no statistically significant difference in the fasting glucose concentration of cases compared with controls (Table 4.10), and the distribution of glucose concentrations was very similar in the two groups (Figure 4.5). The level tended to rise slightly with age, and the mean levels of cases and controls were similar in all age groups and in both sexes (Appendix 4.12).

There were 17 cases (31%) and 31 controls (29%) whose fasting blood glucose levels were greater than 5.6 mmol/l. Four of these patients were known to be diabetic, but the remainder gave no history of glucose intolerance. Of the 17 cases with elevated glucose, 14 (82%) were older than 60 years of age. The same was true of the hyperglycaemic controls of whom 24 (77%) were 60 years and older. The greater proportion of elderly cases and controls with elevated glucose was also present when other levels of glucose concentration were examined.

4. THE SMOKING HABITS OF THE CASES AND CONTROLS

In this study a smoker was defined as a person who had smoked at least one cigarette a day, or more than one gram of tobacco a day if a pipe or cigar smoker, for longer than a year. An ex-smoker was defined as a smoker who had stopped smoking for more than a year, and a non-smoker was a person who had never been a smoker as defined above. Table 4.11 summarizes the smoking habits of the cases and controls at the time of the examination.

Twice as many cases (69%) as controls (34%) were smokers at the time of the examination, and 50 of the 54 cases (93%) had

TABLE 4.12

RELATIVE RISK[+] OF IC ASSOCIATED WITH SMOKING COMPARED TO NON-SMOKERS

Smoking category	Relative risk	Chi-Square	Significance level
Non-smoker	1.00	-	-
Ex-smoker	2.4[*]	1.3	NS
Pipe and cigar smoker	6.6[**]	5.4	$p<0.025$
Cigarette smoker			
1-14/D	6.1[***]	5.9	$p<0.025$
$\geq$15/D	8.8[****]	16.3	$p<0.001$

[*] 95% confidence limits = 0.5 to 10.8

[**] 95% confidence limits = 1.4 to 32.2

[***] 95% confidence limits = 1.4 to 26.4

[****] 95% confidence limits = 3.0 to 25.6

[+] Individual matching has not been considered in this analysis

smoked during their lifetime. In contrast, 30 controls (28%) said they had never smoked. If the smoking habits of cases are examined when symptoms of IC first began, 45 cases (83%) were smoking. Eight cases stopped smoking on the advice of their doctors after the onset of IC. The mean age at which smoking began was approximately the same in the two groups (16.1 and 17.6 years of age in the cases and controls, respectively), but the duration of smoking, considering both current and ex-smokers, was longer in the cases (mean = 43.0 years) than the controls (mean = 36.5 years) ($p<0.001$, Mann-Whitney U test, Siegel (1956)).

The proportion of cases who were smokers was greater in all age groups in both sexes (Appendix 4.13). The difference was more marked in the older age groups, since the proportion of ex-smokers and non-smokers increased with age in the control patients. Appendix 4.14 presents the weight of tobacco smoked per day by the cases and controls who were smokers or ex-smokers. There was no difference in the mean weight of tobacco smoked by the male cases compared with their controls, but the women with IC smoked significantly more tobacco than the women controls ($p<0.01$, Mann-Whitney U test, Siegel (1956)).

The relative risk of IC associated with smoking, compared with people who had never smoked, is presented in Table 4.12. It can be seen that the risk of IC was greatest in those who smoked 15 or more cigarettes per day. Within this category, the relative risk rose to 13.5 to 1 in those smoking 15 to 24 cigarettes a day (95% confidence limits = 3.8 to 48.3, $\chi^2_1 = 16.3$, $p<0.001$). Too few cases (three) smoked more than 25 cigarettes a day at the time of the examination to allow an assessment of the risk of heavy smoking (several very heavy

TABLE 4.13

ESTIMATED RELATIVE RISK OF IC IN PATIENTS SMOKING 15 OR MORE CIGARETTES A DAY AFTER STANDARDIZATION FOR POSSIBLE CONFOUNDING VARIABLES

Variable standardized	Relative risk estimate	Chi-Square	Significance level
None	8.8	16.3	$p<0.001$
Systolic BP	9.0	15.8	$p<0.001$
Diastolic BP	8.9	16.5	$p<0.001$
Cholesterol	9.7	14.4	$p<0.001$
Triglyceride	7.3	10.8	$p<0.005$
Glucose	8.4	14.2	$p<0.001$
Uric acid	8.3	7.2	$p<0.01$
Fibrinogen	8.7	13.3	$p<0.001$
Quetelet's Index	9.6	15.9	$p<0.001$

smokers had stopped or reduced on the advice of their doctors. The relative risk of IC associated with any amount of cigarette smoking compared with non-smokers was 7.8 to 1 (95% confidence limits = 2.5 to 24.0, X^2_1 = 12.6, p<0.001).

Table 4.13 presents the standardized relative risk, controlling for possible confounding variables, associated with smoking 15 or more cigarettes a day. The same analysis was performed for the other smoking categories, and in no instance did standardization for other variables significantly alter the relative risks shown in Table 4.12.

A sample of blood was drawn from those cases and controls who had smoked on the day of the interview, and the carboxy-haemoglobin (COHb) concentration (per cent saturation of haemoglobin) was determined. The amount of tobacco smoked, and the time of smoking on that day was also recorded. The distribution of COHb concentrations was quite similar in cases and controls, and there was no indication that cases had a higher COHb level per gram of tobacco smoked (Appendix 4.15).

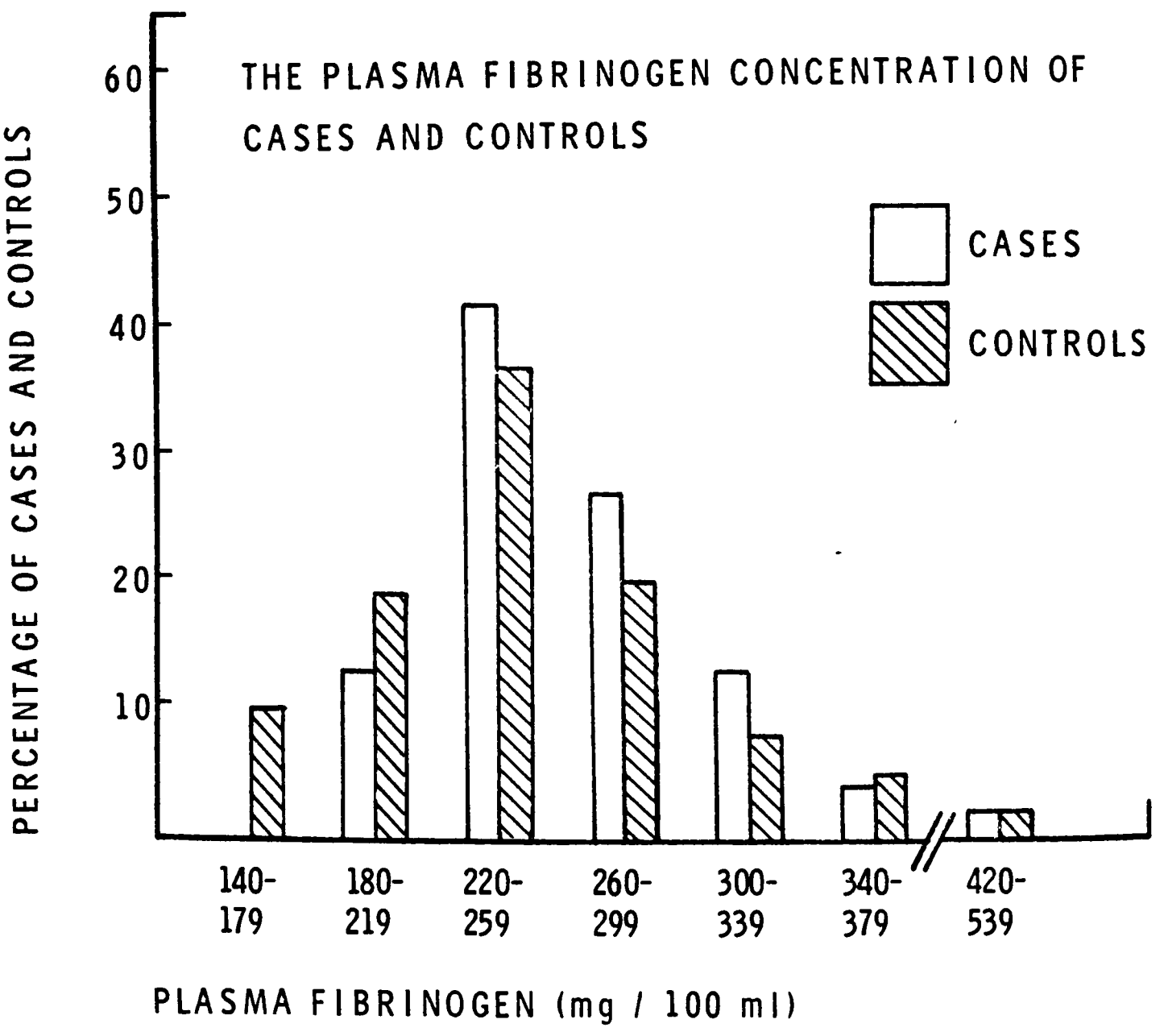
Smokers and ex-smokers were asked whether they inhaled the tobacco smoke. Compared with controls, a larger proportion of cases reported moderate or deep inhalation (Appendix 4.16). The difference was particularly marked in the pipe and cigar smokers, where six of the seven cases (86%) admitted inhaling compared with three of the eight controls (38%). The COHb concentration of smokers was examined in order to compare reported inhaling habits with the absorption of tobacco smoke by the lungs. There was a significant correlation between COHb and the weight of tobacco smoked on the day of the interview ($r = 0.73$, $p = 0.001$). However, there was only a small correlation between COHb and reported depth of inhalation,

TABLE 4.14

PLASMA FIBRINOGEN CONCENTRATION OF CASES AND CONTROLS

	Cases No. (%)	Controls No. (%)	Significance
Mean concentration (mgm %)	264.2	248.3	t = 2.89 on 47 d.f. p<0.01
Std. error	6.5	5.8	
Minimum	180.0	143.0	
Maximum	420.0	530.0	
No. observations	48	102	

FIGURE 4.6



controlling for the weight of tobacco smoked prior to venepuncture ($r = 0.18$, $p = 0.09$).

The effect of smoking on certain risk factors for PVD is presented in Appendix 4.17. Non-smokers and ex-smokers (cases and controls) had a higher relative body weight than smokers. This increase in weight was associated with increased levels of blood pressure, glucose, and cholesterol in the non-smoking controls compared with smoking controls, but this trend was not seen in the cases. The blood pressure of smoking cases, in contrast to the trend shown in the controls, was higher than that of cases who were ex-smokers or non-smokers.

5. THE PLASMA FIBRINOGEN CONCENTRATION OF THE CASES AND CONTROLS

The mean plasma fibrinogen concentration of the cases and controls is presented in Table 4.14 and the distribution of the concentrations is shown in Figure 4.6. The cases had a significantly higher concentration of fibrinogen than the controls ($t = 2.89$ on 47 d.f., $p<0.01$).

The mean fibrinogen concentrations were higher in the women with IC than in the male claudicants, but this difference was not statistically significant (Appendix 4.18). There was no significant effect of age on fibrinogen. Despite the fact that fibrinogen was significantly elevated in cases (paired t-test), the distribution of the concentrations was such that no arbitrary cut-off point could be chosen at which a statistically significant relative risk could be calculated.

6. THE SERUM URIC ACID CONCENTRATION OF THE CASES AND CONTROLS

None of the patients had a history of gout, and only a few had elevated serum levels of uric acid. The cases had significantly higher concentrations of uric acid than their

TABLE 4.17

THE MEAN QUETELET'S INDEX OF CASES AND CONTROLS

	Cases No. (%)	Controls No. (%)	Significance
Mean Quetelet's Index	2.47	2.47	N.S.
Std. error	0.05	0.07	
Minimum	1.88	1.40	
Maximum	3.96	3.49	
No. observations	54	108	

FIGURE 4.8

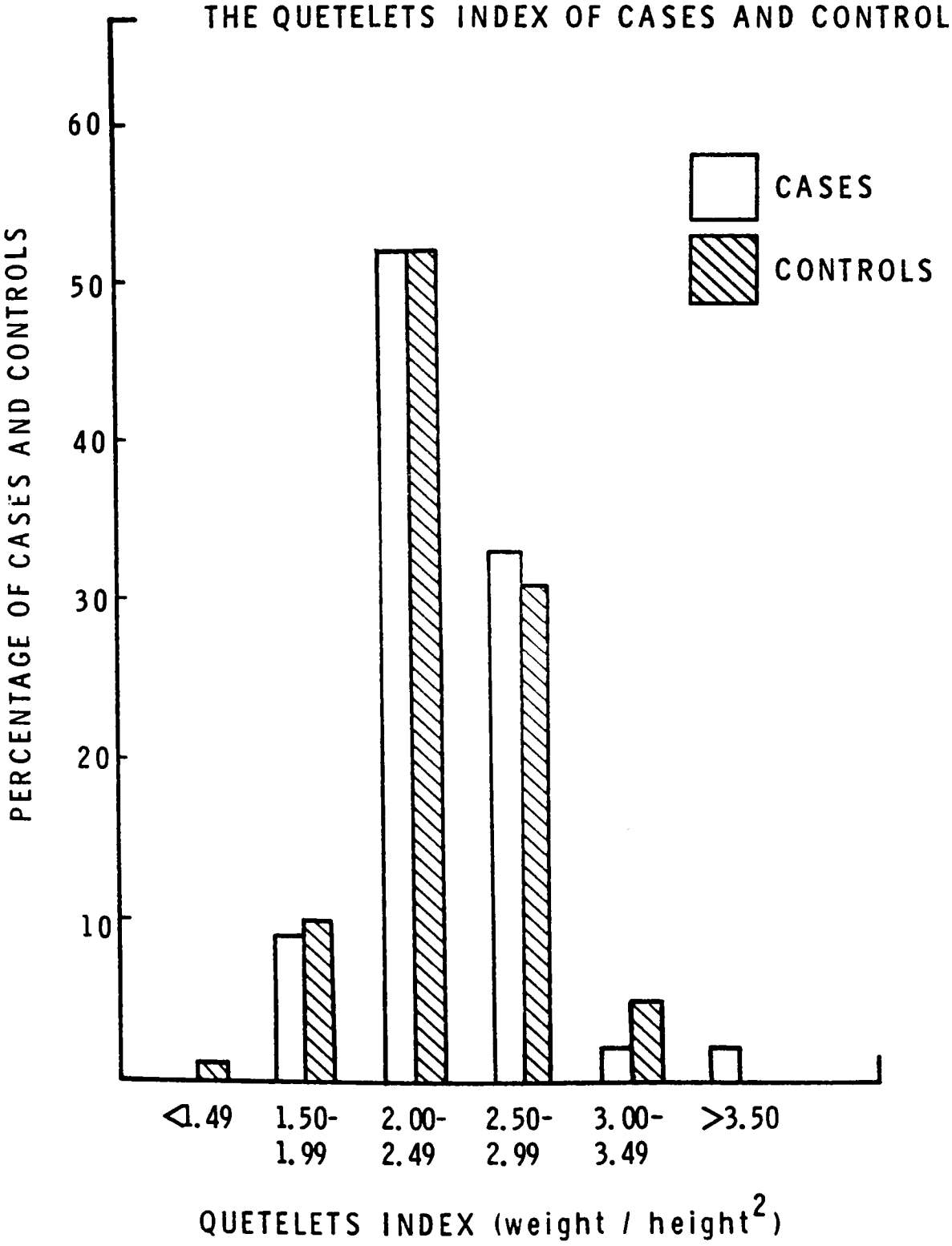


TABLE 4.16

ESTIMATED RELATIVE RISK OF IC IN PATIENTS WITH A SERUM URIC ACID CONCENTRATION GREATER THAN OR EQUAL TO 0.357 MMOL/L AFTER STANDARDIZATION FOR POSSIBLE CONFOUNDING VARIABLES

Variable standardized	Relative risk estimate	Chi-Square	Significance level
None	2.6	6.8	$p<0.01$
Systolic BP	2.4	5.8	$p<0.025$
Diastolic BP	2.4	6.5	$p<0.025$
Cholesterol	2.6	7.2	$p<0.01$
Triglyceride	2.6	6.8	$P<0.01$
Glucose	2.6	7.6	$p<0.01$
Fibrinogen	2.1	4.2	$p<0.05$
Quetelet's index	2.5	7.6	$p<0.01$
Amount smoked	2.4	4.4	$p<0.05$

TABLE 4.15

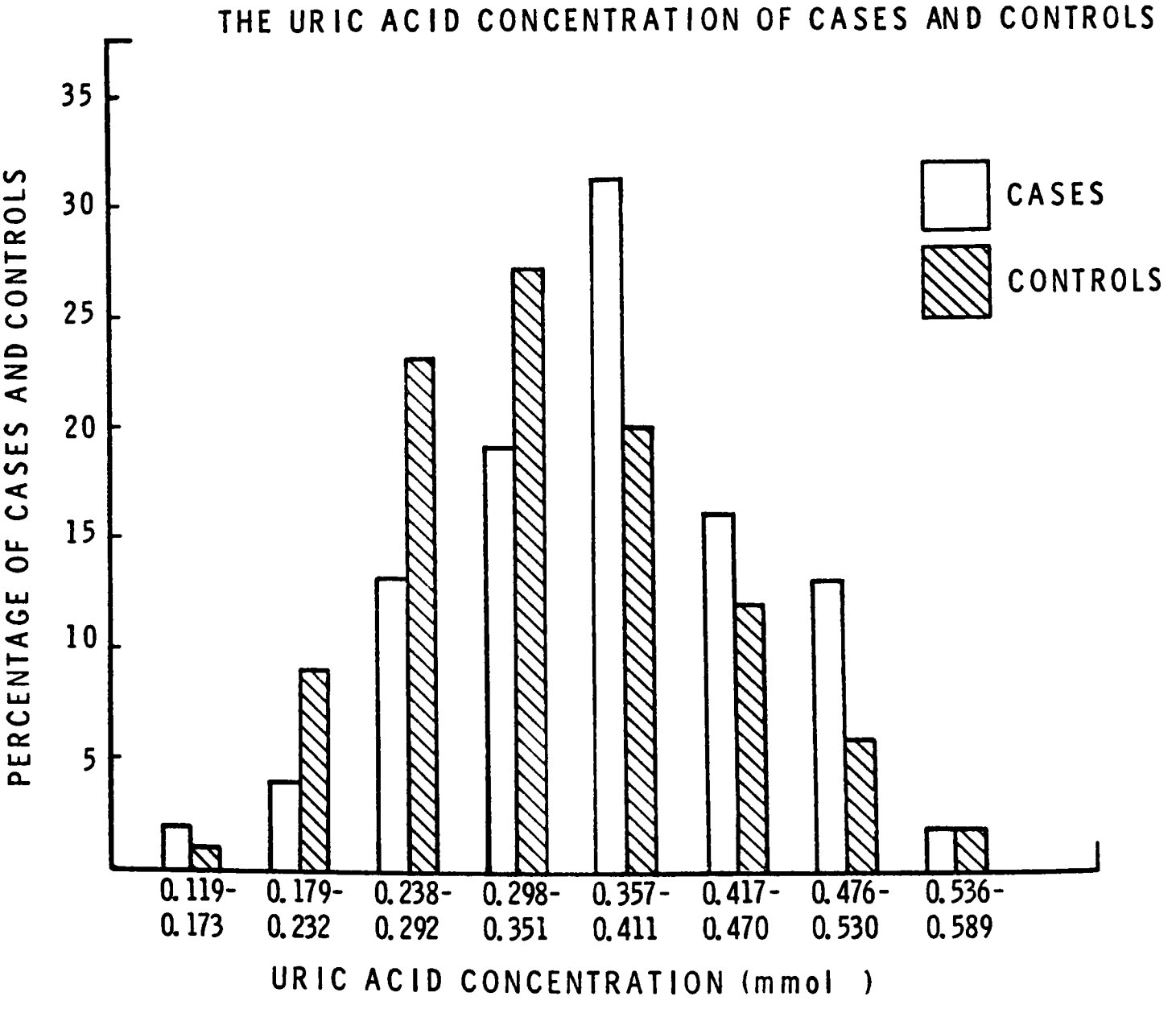
THE MEAN URIC ACID CONCENTRATION (MMOL/L) OF CASES AND CONTROLS

	Cases No. (%)	Controls No. (%)	Significance
Mean	0.363	0.339	t = 2.64 on
Std. error	0.012	0.006	53 d.f.
Minimum	0.155	0.173	p<0.02
Maximum	0.553	0.565	
No. observations	54	108	

Conversion factor from S.I. units to traditional units

Uric acid 1 mmmol/l≈16.8 mgm/100 ml

FIGURE 4.7



controls (Table 4.15). There was no significant effect of age or sex on the uric acid concentration (Appendix 4.19).

Diuretics are known to cause elevated uric acid concentrations in some patients, and since more cases (10) than controls (seven) were receiving diuretics, the observed difference in the mean uric acid levels might have been due to these drugs. To examine this possibility, the cases and controls who were receiving diuretics were separated from those not on treatment. The mean uric acid concentrations of the patients receiving diuretics was higher than those not receiving these drugs (0.361 and 0.349 mmol/l, respectively), but this difference was not statistically significant (t-test). When the patients receiving diuretics were removed from the analysis, the difference in uric acid concentrations between cases and controls was smaller, but still statistically significant ($p<0.05$).

Thirty-four cases (63%) and 43 controls (40%) had uric acid concentrations greater than or equal to 0.357 mmol/l. The relative risk of IC associated with a concentration of uric acid at or above this level was 2.6 to 1 (95% confidence limits 1.3 to 5.3, $X^2_1 = 6.8$, $p<0.01$), and this was not significantly affected by standardization for other risk factors (Table 4.16). Unlike other variables, the relative risk of IC associated with elevated uric acid ($\geq$0.357 mmol/l) was greater in those 60 years and older (3.6 to 1) than in the younger patients (1.4 to 1).

7. THE RELATIVE BODY WEIGHT OF THE CASES AND CONTROLS

There was no difference in the Quetelet's index (weight/height^2, Goldbourt and Medalie (1974)) of the cases compared with the controls (Table 4.17, Figure 4.8). Nor was there a consistent increase in the mean relative body weight with age

TABLE 4.18

THE PROPORTION OF CASES AND CONTROLS WITH MULTIPLE RISK FACTORS AND THE RELATIVE RISK OF IC ASSOCIATED WITH MULTIPLE RISK FACTORS

Number of risk factors[+]	Cases No. (%)	Controls No. (%)	Relative risk of IC compared to those with no risk factors
None	2 (4)	23 (21)	1.0
One	12 (22)	50 (46)	2.76[*]
Two	19 (35)	24 (22)	9.10[**]
Three or more	21 (39)	11 (10)	21.95[***]
Total	54(100)	108(100)	

[+] Risk factors were defined as follows:

Systolic BP $\geq$160 mm Hg or DBP$\geq$90 mm Hg
Triglyceride $\geq$2.15 mmol/l
Uric acid $\geq$0.357 mmol/l
Smoking $\geq$15 grams of tobacco/day
A history of diabetes mellitus

[*] $X^2_1 = 0.96$, N.S.

[**] $X^2_1 = 8.08$, $p<0.005$, 95% confidence limits 2.0 to 41.8

[***] $X^2_1 = 17.04$, $p<0.0005$, 95% confidence limits 4.4 to 65.4

in men or women (Appendix 4.20). There were several very obese women controls aged 65 to 69 years, which accounts for the high mean value in this group.

8. OTHER VARIABLES

The social class distribution (Appendix 4.21) and the alcohol consumption reported by the cases and controls (Appendix 4.22) were similar. The women were asked about their reproductive history including the age of menarche and menopause (Appendix 4.23). Four of the eight women with IC (50%) who had had children gave a history of hypertension and oedema during pregnancy which required medical treatment compared with only one control (6%).

9. THE INTERACTION OF RISK FACTORS

The correlation coefficients between the risk factors discussed are presented separately for cases and controls in Appendices 4.24 and 4.25, respectively. A non-parametric method, Spearmann's r, has been used to calculate the coefficients, and the significance levels are two-tailed p values.

There were few strong correlations, but a significant positive correlation between age and systolic pressure, diastolic pressure and cholesterol was found in the controls which was not evident in the cases. There was a significant positive correlation between the Quetelet's Index and systolic pressure, triglyceride, and glucose in the controls, and between Quetelet's Index and glucose in the cases. Fibrinogen and uric acid were significantly correlated in the cases, but not in the controls.

Table 4.18 presents the proportion of cases and controls having one or more risk factors. The cut-off points used to define a risk factor are the same as those discussed in earlier sections. The relative risk of IC increased with the number of risk factors present, and in those with four or more risk

factors (five cases, one control) the relative risk of IC was 57.5 to 1 ($X^2_1 = 11.69$, $p<0.001$).

G. DISCUSSION

A total of 26 patients with IC had a history of coronary artery or cerebrovascular disease, and if those with an abnormal ECG but no cardiac symptoms are included, 32 cases (59%) had evidence of arteriosclerosis in sites other than the legs. In contrast, only 15 controls (14%) had evidence of arteriosclerotic vascular disease.

Jeurgens et al (1960) found a history of previous myocardial infarction or angina in 16 per cent of patients at the time of diagnosis of IC, and Begg and Richards (1962) and Taylor and Calo (1962) found clinical evidence of ischaemic heart disease in 19 and 17 per cent, respectively, of claudicants attending their clinics for the first time. The patients in these series were, on average, ten years younger than those in my study, and the criteria used to diagnose ischaemic heart disease were not described. Widmer et al (1964) found symptoms of coronary artery disease in 27 per cent of the factory workers in his study who had occlusions of peripheral arteries (with or without IC), and evidence of generalized atherosclerosis (occlusions in more than one site) in about 90 per cent of these people. In the Framingham study the examining physician, at the time of diagnosing IC, encountered evidence of cardiovascular disease, cerebrovascular disease, or congestive heart failure in one case out of three (Kannel and Shurtleff, 1971).

The prevalence of generalized atherosclerosis among claudicants in my study was higher than that found in the studies described above despite the fact that many cases had mild IC and had not consulted their doctor. The age distribution

of the cases may account for this, since 23 of the 54 cases (43%) in my study were 65 years or older. It is also possible that younger patients, still actively employed, may seek medical attention for IC earlier, before cerebrovascular or coronary artery disease is evident.

There were 11 women with IC in my study, and nine of these complained of angina pectoris. This high rate of angina in the female claudicants is striking, and may indicate that the distribution and degree of arterial occlusions in atherosclerotic women differ from those of men with atherosclerosis. All the female claudicants were post-menopausal when their symptoms began, and all but two were more than 60 years of age. This may indicate that decline of ovarian function is an important factor in the development of PVD, but there was no difference in the mean age of menarche or menopause between the cases and controls, and the reproductive history of the two groups was similar. Four of the 11 cases (36%) had been hospitalized for pre-eclampsia compared with only one control (5%). Despite this fact, there was no significant difference in the blood pressures of the female cases compared with their controls.

Hypertension was a common finding in the patients with IC. More than one-third had a systolic pressure greater than 160 mm Hg or a diastolic pressure greater than 100 mm Hg, or both. The prevalence of hypertension among claudicants in my study was similar to that found in other series (Jeurgens et al, 1960; Taylor and Calo, 1962; Begg and Richards, 1962).

Studies of general populations have shown that blood pressure tends to increase with age and with increasing body weight (Hamilton et al, 1954; Ashley and Kannel, 1974). In

this study the mean blood pressure of the cases did not increase with age, though this trend was evident in the controls. It is possible that elevated blood pressure is an early feature of IC, either as a causative factor or as a consequence of atherosclerosis in the arterial system, and thus an effect of age on blood pressure was not seen in the claudicants. There was a positive correlation between relative body weight and blood pressure, and this may have been partly responsible for the fact that female controls (who had a higher Quetelet's Index than the female cases) had blood pressures similar to the women with IC.

There was no significant difference in the serum cholesterol concentration of the cases and controls, and the mean levels were quite similar to those found in the general population (Brown and Daudiss, 1973; Lewis et al, 1974). This is in contrast to the known association of serum cholesterol and ischaemic heart disease (Kannel et al, 1971), and may indicate that the two types of serum lipids have different effects on the coronary and peripheral circulations. It was of interest that patients with IC who were younger than 60 years of age had a higher mean cholesterol concentration than their controls. The difference between cases and controls was not statistically significant, possibly because of small numbers. Preliminary analysis of a larger series of patients referred to the Radcliffe Infirmary for IC showed a high proportion of younger patients with hypercholesterolaemia, and further work needs to be done in order to clarify the role of serum cholesterol in the aetiology of PVD (Mann, 1977).

The triglyceride concentration of cases was significantly higher than that of the controls, and 22 cases (41%) had a

triglyceride concentration greater than 2.26 mmol/l. This finding is in close agreement with a number of other studies of IC where 2.26 mmol/l has been used as the upper limit of normal (Kremer et al, 1973).

The mean fasting triglyceride concentration of the control patients was higher than that reported by studies of general populations, leading to the suspicion that some of the controls had not fasted adequately or that the method of triglyceride determination was not calibrated correctly (Patterson and Slack, 1972; Lewis et al, 1974; Leren and Haabrekke, 1971a). A number of cases and controls with elevated triglyceride and glucose concentrations were contacted and questioned about the length and completeness of the fasting period prior to the blood tests. All were quite certain that they had fasted properly. When possible, another fasting sample of blood was obtained (26 patients), and the lipid and glucose measurements repeated. The mean level of triglyceride of these patients found on repeat testing (mean = 1.51 mmol/l, S.D. = 0.75) was lower than the mean level of the tests performed at the patient interview (mean = 2.45 mmol/l, S.D.= 0.96 mmol/l). Since the 26 people tested all had elevated levels on the first determination, it was not surprising that the repeat tests showed a regression toward the mean. Those patients with very high initial levels also had elevated repeat levels, and when the two sets of results were compared (Mann-Whitney U test), the degree of regression was not statistically significant. I cannot explain the high fasting levels, but I do not believe they were due to a lack of patient co-operation. All the lipid determinations were performed by one technician under the supervision of Professor Barry Lewis (St. Thomas' Hospital, London) and the method was checked at

frequent intervals against known standards. There were no difficulties in the laboratory methods during the time when my samples were analyzed.

The prevalence of known diabetes in the control patients (1%) was the same as the estimated prevalence in the general population (Jarrett and Keen, 1976). Six cases (11%) were known to have diabetes, a higher prevalence than that of other series of claudicants (Bloor, 1960; Begg and Richards, 1962; Silbert and Zazeela, 1958). All were maturity-onset diabetics.

The mean fasting glucose concentration found in the cases of IC was higher than that reported in other series (Leren and Haabrekke, 1971a; Bliss et al, 1972). Compared with studies of normal populations, the fasting glucose of the controls was also elevated (Lewis et al, 1974). The elevated means may have been due to the age distribution of the patients (67% were 60 years or older), since the proportion of people with asymptomatic hyperglycaemia is known to increase with age (Jarrett and Keen, 1976). As discussed earlier, the possibility of inadequate fasting was examined in 26 patients. The mean level of glucose at the initial examination was 6.8 mmol/l, S.D. = 2.6 mmol/l, and the mean repeat level was 6.1 mmol/l, S.D. = 2.6 mmol/l. The method of glucose determination is unlikely to have been at fault, since it was checked against a known standard at frequent intervals. All samples were treated in the same manner under standardized conditions, and since not only the mean levels but also the distribution of glucose concentrations were very similar, the elevated means do not alter the conclusion that there was no difference between the cases and controls.

There was no significant correlation between fasting glucose and serum cholesterol or triglyceride. The six diabetic

claudicants had a normal mean serum cholesterol (6.0 mmol/l), but their mean serum triglyceride (5.0 mmol/l) was more than twice that of the other patients with IC. This finding is in agreement with other studies (Keen, 1976), and may be one of the mechanisms by which diabetes increased the risk of developing IC.

The high prevalence of smoking found in the cases has been described in other series of patients with IC (Lithell et al, 1975; Jeurgens et al, 1960). The prevalence of smoking in the controls was similar to that found in the general population, controlling for age and sex (Kannel and Shurtleff, 1973; Higgins and Kjelsberg, 1967; Lee, 1976). Approximately three-fourths of women over the age of 50 in these studies reported that they were non-smokers, compared with 15 of 22 non-smoking women controls (68%) in my study. In contrast to the controls, eight of the 11 women with IC (73%) were smokers or ex-smokers. The women with IC also smoked significantly more tobacco than the women controls who smoked.

The proportion of smokers who were pipe and cigar smokers was similar in the cases and controls, and similar to that found in the general population (Higgins and Kjelsberg, 1967). This observation does not support the premise that pipe and cigar smokers are less likely to develop symptoms of arterio-sclerosis than cigarette smokers (Kannel et al, 1968; Kesteltoot et al, 1976). The risk of IC may have been due in part to the fact that the cases who were pipe and cigar smokers tended to inhale, and several of the higher COHb levels came from these patients.

There was no evidence in this study that cases received a greater COHb increase per gram of tobacco smoked than the controls.

However, since many of the blood samples were drawn in the early morning, the amount of tobacco smoked on the day of the venepuncture was often small. As a result, the COHb level was quite low in many people, and an accurate estimate of the COHb yield per cigarette could not be calculated. The COHb level achieved by a smoker depends on a number of variables such as depth of inhalation, number of puffs per cigarette, and physical activity. Because of this variability, more cases would probably be needed to demonstrate an increased COHb level in patients with IC compared with controls. More cases (57%) than controls (40%) who smoked cigarettes preferred filter cigarettes (which produce more COHb than plain cigarettes), providing some support for the premise that filter cigarettes may increase the risk of arterial disease (Wald, 1976).

No direct measurement of blood viscosity was made in this study, but the presence of elevated plasma fibrinogen in the cases is consistent with the observation that blood viscosity is increased in patients with IC (Dormandy et al, 1973a). (There was no significant difference in the haemoglobin or haematocrit of cases compared with controls). The finding of elevated uric acid in the cases is in agreement with other studies, but the reason for the association with PVD is not understood. If platelet aggregates are stabilized in increased concentrations of uric acid (Newland, 1975), it is possible that this risk factor promotes thrombosis in patients with IC. It is of interest that there was a significant positive correlation between uric acid and plasma fibrinogen ($r = 0.42$, $p = 0.003$) in the cases which was not present in the controls ($r = -0.11$, $p = 0.28$). This may imply an interaction between the cellular and protein components of the coagulation system in patients with IC.

The differences among cases and controls in the mean values of most risk factors was greater in the younger age groups than in those 60 years or older. This may be due to a gradual increase with age in the prevalence of risk factors among normal people, or may reflect an increased prevalence and severity of risk factors among people who develop significant atherosclerosis at a young age. Though this study was not designed to examine the role of treatment in the prevention of PVD, it is possible that the early identification and treatment of young people with risk factors would reduce the incidence of IC. Of all the variables examined, smoking was associated with the greatest relative risk of developing IC. Since this factor is also the easiest to remove if people can be persuaded not to smoke, and no long-term medication or follow-up is needed for its control once smoking has stopped, correction of this risk factor may be the most efficient and efficacious form of preventive therapy.

There was a significant interaction among risk factors, and the relative risk of IC rose in an approximately geometric fashion with each additional risk factor. Similar synergistic effects of multiple factors on the risk of developing ischaemic heart disease have also been found (Goldbourt et al, 1975). Because of this relationship, it can be seen that the elimination of even one risk factor would significantly reduce the relative risk of developing IC, and would also help to prevent ischaemic heart disease, the chief cause of mortality in patients with PVD.

H. SUMMARY

Fifty-four patients with IC were identified in a postal survey of a general population. They were interviewed and examined, and certain characteristics were compared with those

of 108 age- and sex-matched controls. A history of hypertension, hyperlipidaemia, diabetes, or ischaemic heart disease was found more frequently in patients with IC than in the controls. Risk factors for IC identified were smoking, and elevations of systolic and diastolic blood pressure, triglyceride, uric acid, and plasma fibrinogen. There was no significant difference between cases and controls in the concentration of blood glucose and cholesterol.

SECTION 3

THE PROGNOSIS OF PATIENTS WITH PERIPHERAL VASCULAR DISEASE

CHAPTER 5

FOLLOW-UP STUDY OF SIXTY PATIENTS WITH INTERMITTENT CLAUDICATION

TABLE 5.1

BLOOD TESTS PERFORMED AT THE INITIAL ASSESSMENT

	Name of test	Method
1.	Routine haematology	Coulter Counter Model S (Britten and Johnson, 1969)
2.	Uric acid	Technicon SMA12/60
3.	Blood glucose	Bergmeyer and Bernt (1965)
4.	Serum cholesterol	Searcy and Bergquist (1960)
5.	Serum triglyceride	Eggstein and Kreutz (1966)

Chapter 5 FOLLOW-UP STUDY OF SIXTY PATIENTS WITH INTERMITTENT CLAUDICATION

A. INTRODUCTION

During a nine-month period from November, 1971 to July, 1972 Dr. H. F. Woods and Dr. I. Walton interviewed and examined a consecutive series of patients referred to hospital for assessment of intermittent claudication to determine the presence of risk factors for peripheral vascular disease. I undertook a follow-up study of these patients from April to July, 1976, approximately four years after the first assessment, to determine the prognostic significance of the various measurements made at the initial examination.

B. METHODS

1. THE PATIENTS

The patients in this study were referred from their general practitioners to Mr. D. J. Tibbs, a consultant surgeon at the Radcliffe Infirmary, Oxford, for assessment of peripheral vascular disease (PVD). A total of 63 consecutive referrals for PVD (48 men and 15 women) were interviewed and examined from November, 1971 to July, 1972.

2. THE INITIAL ASSESSMENT

The interview at the initial assessment consisted of a general medical history including details of previous coronary and cerebral vascular disease, and the presence of risk factors such as smoking, hypertension, and diabetes. The legs were inspected, peripheral pulses palpated, and blood pressure measured. A sample of blood was drawn after a 12-hour fast, and a number of tests performed (Table 5.1). All patients had a 12-lead electrocardiogram (ECG).

3. THE PATIENT FOLLOW-UP

A letter was sent to the patients' general practitioners (G.P.) asking for permission to re-examine the patients. If the patient had died, the G.P. was asked to provide the data and cause of death. This was then checked with the patient's death certificate. If the patient had moved, the new address was obtained from the G.P. or the Family Practitioner Committee. Permission to reassess was refused in only one case, a 65-year old aphasic man with severe Parkinson's disease. Another man, 66 years of age, suffered a myocardial infarction within a week of first referral for IC and died before the initial examination could be concluded. Incomplete data was obtained concerning a third man, 64 years of age, who died of a myocardial infarction within one month of referral. He was never admitted to hospital, and his notes could not be found.

Sixteen patients had died in the interval between the first assessment and follow-up. The remainder were contacted, and an appointment made. At interview information was collected concerning events which had occurred since referral, and the severity of symptoms. The legs were examined, and blood pressure and ankle systolic pressure taken using the methods described in Chapter 2. All patients had a resting 12-lead E.C.G., and a blood sample was drawn after a 12-hour fast. The concentration of cholesterol and triglyceride was determined by the same technician who had performed the tests in the initial assessment, and the same methods were used. A number of other blood tests were also performed (see Table 5.1).

4. ASSESSMENT OF PATIENT OUTCOME

In this small group of patients there were too few deaths

to examine the effect of risk factors on mortality. In order to investigate which factors might be predictive of an unfavourable outcome, I defined the term "adverse event". Information was obtained from the patient (if alive), the general practitioner, and the hospital notes concerning symptoms, surgery, and the development of related illnesses such as coronary artery disease. An adverse event was defined as any one of the following:

1. Death. Three patients died of causes unrelated to vascular disease (two of cancer, one after a fractured hip). These deaths were not included as adverse events.
2. Amputation. (None were performed in the first year of follow-up).
3. Onset of intermittent claudication (IC) in a previously asymptomatic leg or onset of rest pain in a leg previously free of rest pain.
4. Myocardial infarction, onset of angina, or stroke in a person with no history or evidence of coronary or cerebral vascular disease.
5. Operation for deterioriation of PVD. Surgery related to the initial referral and any post-referral re-operations for failed procedures were not included as adverse events. Subsequent operations were chosen as adverse events when it was clear that a change in the patient's condition (usually more than a year after referral) was the indication for surgery.

The adverse events were determined by one physician, Dr. Diana Gale, who was provided with details of events subsequent

TABLE 5.3

THE ADVERSE EVENTS WHICH WERE USED TO CALCULATE LIFE TABLES SHOWING THE PROGNOSIS OF PATIENTS WITH IC

Time interval	From referral to first event	From three months after referral to first event	From six months after referral to first event	From twelve months after referral to first event
Type of event	No. patients (%)	No. patients (%)	No. patients (%)	No. patients (%)
Death	11 (20)	10 (19)	9 (17)	8 (15)
Amputation	2 (4)	2 (4)	2 (4)	2 (4)
Onset of IC or rest pain	11 (20)	10 (19)	8 (15)	6 (12)
Myocardial infarction or onset of angina	2 (4)	2 (4)	2 (4)	2 (4)
Stroke	1 (2)	1 (2)	1 (2)	1 (2)
Reconstructive operation	12 (22)	13 (24)	14 (26)	14 (27)
No adverse event	16 (29)	16 (30)	17 (32)	19 (37)
Total number of patients at risk	55(100)	54(100)	53(100)	52(100)

TABLE 5.2

REASONS FOR EXCLUSION FROM THE LIFE TABLE ANALYSIS

Sex	Age at referral (yrs)	Reason for exclusion	Other characteristics
M	66	Died one week after referral of a myocardial infarction before data collection was completed.	Smoked 20 cigarettes a day at time of referral.
M	62	Severe chronic obstructive pulmonary disease. Clearly stated in the hospital notes that deterioration of PVD present, but anaesthetic risk too great in this patient and therefore no surgery.	Smoked 2 oz. tobacco/week as hand-rolled cigarettes at referral, and continued to do so. At follow-up could walk 25 yards before leg pain and shortness of breath forced him to stop. Rest pain present at night.
M	75	Stroke before referral for IC and progressive severe Parkinson's disease. General practitioner refused permission to follow-up and stated patient immobile.	Smoked 30 cigarettes per day at referral. No details available concerning smoking after referral.
M	64	Stroke in 1968. Died of myocardial infarction within one month of referral. Never an in-patient and hospital notes could not be found. Data incomplete.	No information available.
F	83	Fell and fractured hip one month after referral. Died after attempted internal fixation.	Life-long non-smoker.

to first referral but had no knowledge of initial measurements or risk factors such as smoking. After Dr. Gale had defined the adverse events, time intervals were calculated and used to produce life-tables.

Dr. Gale excluded five patients from the life-table analyses. The reasons for exclusion are summarized in Table 5.2. Incomplete data was the reason for exclusion in three patients, and one patient was excluded because severe chronic obstructive pulmonary disease present at referral prevented a surgical operation for deterioriation of PVD (defined as an adverse event). The fifth patient, the only life-long non-smoker in the series, died shortly after referral from an event unrelated to vascular disease.

Patients with a previous history or evidence of coronary artery disease could not, by definition, have as an adverse event a subsequent myocardial infarction or onset of angina. Similarly patients with bilateral IC, rest pain, or stroke at referral were "protected" by the criteria used to define an adverse event. In order to examine the magnitude of this protective effect I have listed in Table 5.3 the types of adverse events which were used to calculate lifetables (see Data Handling and Statistical Analyses below). It can be seen that death and reconstructive surgery were the most frequent adverse events, and that myocardial infarction, angina, and stroke were the adverse events defined for only three patients. Thus a history of cardio- or cerebrovascular disease would not have significantly altered the risk of an adverse event as defined in this study. Onset of IC in an asymptomatic leg (in patients with unilateral IC at referral) or rest pain was, however, a fairly frequent adverse event.

With larger numbers it would have been possible to stratify the patients according to their previous medical history and their symptoms at referral. There were, however, too few patients in this study to allow such stratification when examining the effect of risk factors such as smoking or hypertension on prognosis. When discussing the effect of smoking habits after referral on prognosis I have presented in detail the past medical history, symptoms, and prevalence of risk factors of the patients at referral so that the comparability of the patient groups (those who stopped, reduced, or continued smoking) can be observed. I have not presented this detailed information for other risk factors, though I have examined the possible protective effect afforded by the definitions of adverse events. In no instance did the criteria used to define adverse events significantly bias the analyses.

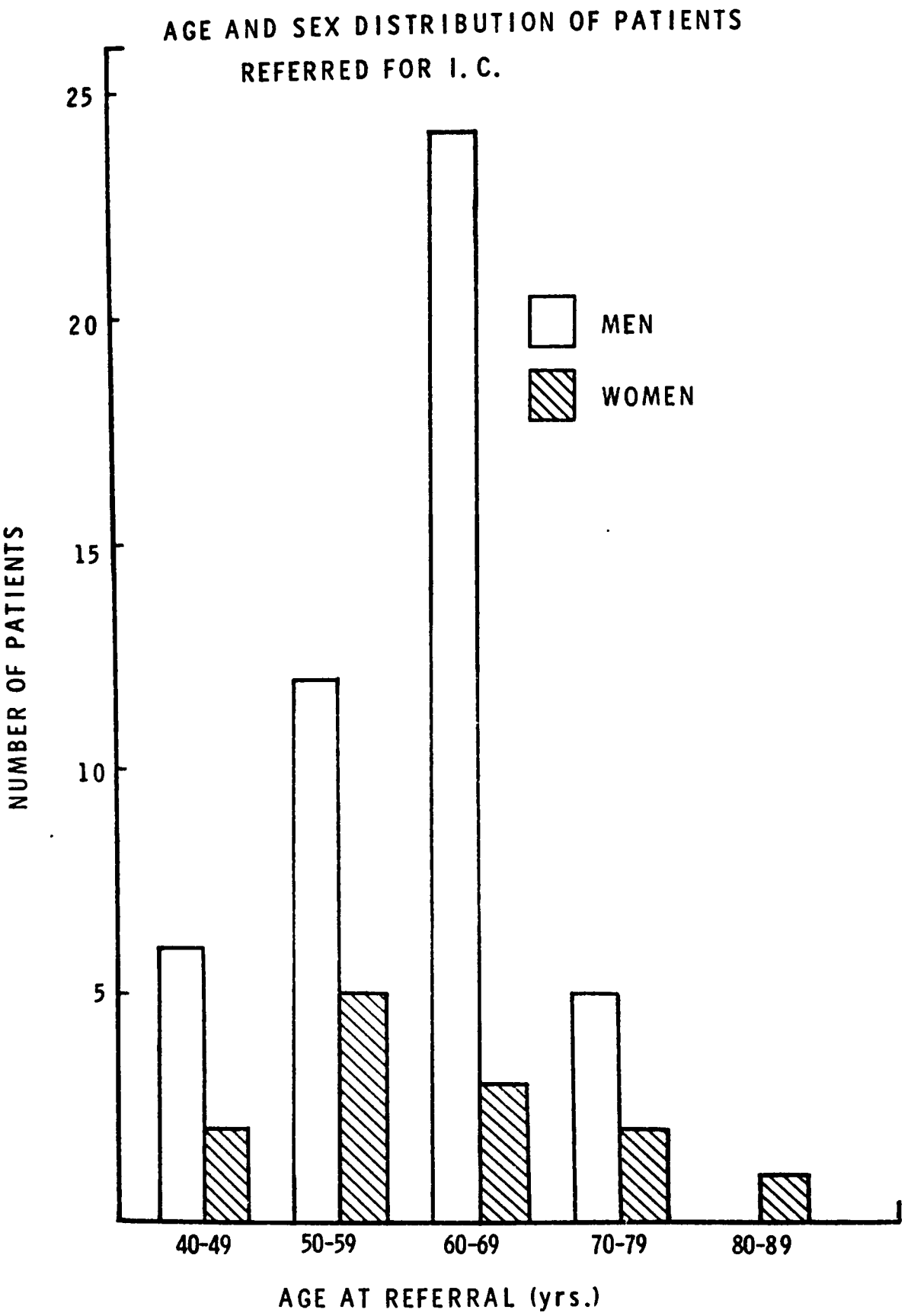
5. DATA HANDLING AND STATISTICAL ANALYSES

The data were punched on 80-column cards, and initial analyses performed using a computer programme, The Statistical Package for the Social Sciences (Nie et al, 1970). The two-tailed test of significance was used in all instances.

Life tables were computed considering the time between referral and development of the first adverse event, though, as described earlier, operations carried out as a consequence of the initial referral were excluded (Pike et al, 1976; Peto et al, 1977). Some of the patients stopped smoking at the time of referral, and in order to assess the effect of doing so further life tables were computed using the following time intervals:

1. Time interval from three months after referral (i.e. after three months non-smoking) to first adverse event. Any event occurring in the three

FIGURE 5.1


AGE AND SEX DISTRIBUTION OF PATIENTS
REFERRED FOR I. C.
NUMBER OF PATIENTS
25
20
15
10
5
MEN
WOMEN
40-49
50-59
60-69
70-79
80-89
AGE AT REFERRAL (yrs.)

months after referral was excluded, and the first event after three months was chosen.

2. Similarly, time from six months after referral to first adverse event.
3. Time from one year after referral to first adverse event.

These time intervals were entered as part of the patient data, and used to construct life tables representing the prognosis. The computer programme used enabled correction to be made for age, sex, and other factors when examining the effect of a particular risk factor on prognosis (Pike et al, 1976).

C. RESULTS

1. THE INITIAL ASSESSMENT

Three of the patients referred for intermittent claudication did not have peripheral vascular disease when examined. Two women, aged 57 and 72, were found to have severe varicose veins, and one man, 59, had an acute episode of calf pain after a deep vein thrombosis. Figure 5.1 presents the age and sex distribution of the remaining 60 patients. The mean age at referral of the 47 men was 61.2 years and that of the 13 women was 61.1 years.

The average duration of symptoms prior to referral was 14 months (range one to 72 months). Twenty-six patients (43%) complained of bilateral IC, and 34 (57%) had IC in one leg only (17 left, 17 right). Onset of symptoms was gradual in 62 (72%) of the 86 limbs affected and sudden in 15 (17%). Four patients (nine limbs) could not recall the onset of IC. The average walking distance prior to onset of pain was 150 yards at referral, and nine patients (15%) complained of rest pain. The most common site of pain was the calf, though thigh, buttock,

TABLE 5.7

OPERATIONS DURING THE FOLLOW-UP PERIOD

Type of operation	Number performed
1. Lumbar sympathectomy	15
2. Vein bypass	33
3. Dacron bypass	12
4. Endarterectomy	20
5. Amputation	
(a) Above-knee	2
(b) Through-knee	3
(c) Below-knee	4
Total number of operations	89

TABLE 5.6

NON-FATAL ISCHAEMIC EVENTS IN THE FOLLOW-UP PERIOD

	No. patients (%)
Myocardial infarction	4 (7)
Stroke	4 (7)
Onset of angina	2 (3)
Congestive heart failure	2 (3)
Arterial embolism	2 (3)
Onset of rest pain	7(12)
Total	21(35)

TABLE 5.5

THE CAUSES OF DEATH IN THE FOLLOW-UP PERIOD

Sex	Age at death	Date of death	Cause of death
M	64	6-72	Myocardial infarction
M	66	7-72	Myocardial infarction
M	65	7-72	Stroke
M	68	8-72	Myocardial infarction after R. profundo-plasty
F	82	8-72	Pulmonary embolus two days after operation for fracture of R. femur
M	71	2-73	Stroke
M	71	5-73	Congestive heart failure
M	67	5-73	Stroke
M	69	6-73	Ruptured aortic aneurysm
M	70	8-73	Ruptured aortic aneurysm
M	70	9-73	Myocardial infarction
M	66	2-74	Ruptured aortic aneurysm
M	70	2-74	Pulmonary embolus after mid-thigh amputation
M	59	5-74	Congestive heart failure
M	66	6-74	Disseminated carcinoma. Primary not found
M	71	5-76	Metastatic carcinoma of bowel

TABLE 5.4

THE PREVALENCE OF CERTAIN DISEASES AT REFERRAL

(Total patients = 60)

	No. (%)
Coronary artery disease	
(i) History of myocardial infarction (no angina)	6(10)
(ii) History of myocardial infarction with angina	8(13)
(iii) Angina without infarction	4 (7)
(iv) Positive E.C.G. with no symptoms	7(12)*
Stroke	9(15)
Diabetes	0
Hyperlipidaemia	9(15)
Hypertension	14(23)
Bronchitis	14(23)
Gout	1 (2)

* Dr. J. I. Mann interpreted the E.C.G.'s using the criteria shown on page 76

and foot pain was also reported.

The prevalence at referral of certain diseases is summarized in Table 5.4. The criteria used to define myocardial infarction, angina, stroke, and bronchitis have been described in Chapter 2 (Rose and Blackburn, 1968). The diagnosis of hypertension and hyperlipidaemia was based on the patient's history plus documentation in the hospital notes of elevated blood pressure or lipids (SBP $\geq$160 mm Hg, DBP $\geq$90 mm Hg, cholesterol $\geq$6.7 mmol/l, triglyceride $\geq$2.15 mmol/l). One patient had a history of gout and documented hyperuricaemia.

Though the patients in this study had all been referred to hospital and were therefore not directly comparable to the claudicants identified in the postal survey discussed in Chapter 4 (who were members of a general population), the proportion of patients with a history of ischaemic heart disease, hypertension, or hyperlipidaemia was reasonably similar in the two populations. There were six diabetics (11%) in the patient group described in Chapter 4, but no known diabetics in this series.

2. THE FOLLOW-UP ASSESSMENT

Table 5.5 summarizes the causes of death in the 16 patients (27%) who died in the interval between the first examination and the follow-up assessment. A number of patients had non-fatal ischaemic events, and these are summarized in Table 5.6. Thirty-three patients (55%) underwent surgery, (14 had more than one operation) either immediately after referral, or during the follow-up period. The numbers and types of operations performed are summarized in Table 5.7. Appendix 5.1 compares the values at referral of certain risk factors in the patients who died with those of patients surviving until follow-up. Appendix 5.2

FIGURE 5.2

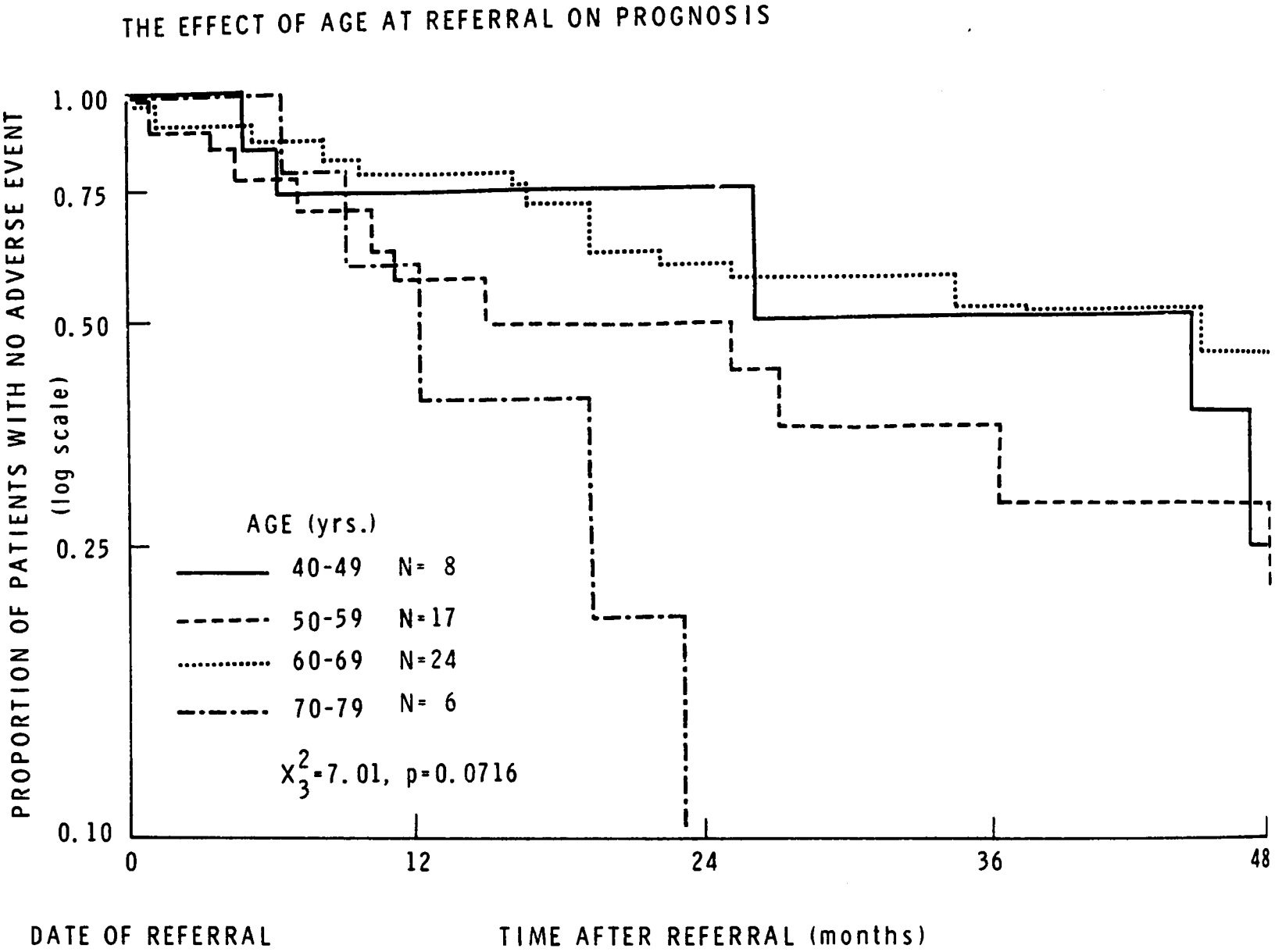

THE EFFECT OF AGE AT REFERRAL ON PROGNOSIS
PROPORTION OF PATIENTS WITH NO ADVERSE EVENT (log scale)
1.00
0.75
0.50
0.25
0.10
AGE (yrs.)
40-49 N= 8
50-59 N=17
60-69 N=24
70-79 N= 6
X^2_3=7.01, p=0.0716
0
12
24
36
48
DATE OF REFERRAL
TIME AFTER REFERRAL (months)

TABLE 5.8

THE DEGREE OF PHYSICAL DISABILITY REPORTED BY THE SURVIVING PATIENTS

Degree of disability	No. patients (%)
Severe	21(49)
Moderate	15(35)
Mild	4 (9)
None	3 (7)
Total	43(100)

TABLE 5.9

THE CHIEF CAUSE OF PHYSICAL DISABILITY IN THE SURVIVING PATIENTS

Cause of disability	No. patients (%)
Intermittent claudication	27(63)
Amputation	5(12)
Angina	5(12)
Stroke	1 (2)
Arthritis	1 (2)
Respiratory disease	1 (2)
None	3 (7)
Total	43(100)

provides the same information for those who had amputations.

Forty-three patients were interviewed and examined in the follow-up. Thirty-two (74%) were still complaining of intermittent claudication, and 11 (26%) were asymptomatic. Of those with persistent IC, 16 (50%) stated that their symptoms had worsened in the year prior to follow-up, four (13%) said they could walk further, and 12 (38%) said their condition was unchanged. At follow-up, the average walking distance before pain started was 200 yards in the patients with IC. Five patients complained of rest pain. Only four patients were receiving medical treatment for IC; three had been prescribed analgesics, and one patient was receiving physiotherapy. The degree and chief causes of physical disability reported by the surviving patients are summarized in Tables 5.8 and 5.9.

3. THE EFFECT OF INDIVIDUAL RISK FACTORS ON THE PROGNOSIS OF PATIENTS WITH PERIPHERAL VASCULAR DISEASE

(a) Age at first referral for intermittent claudication

Few patients could recall the exact date of onset of IC. For this reason, the date of first referral was chosen as the starting point to determine the effect of age on the prognosis. Figure 5.2 presents the life table of the four age groups in the study from the date of first referral until the first adverse event (as defined earlier). The prognosis of those aged 70-79 was poor, but the difference in prognosis among the age groups was not statistically significant (X^2 = 7.01 on 3 d.f., p = 0.0716).

Nine patients in the study group had an amputation. All were men, and their age distribution is presented in Appendix 5.3. Age at first referral did not have a significant effect on the amputation rate.

(b) Sex

Comparison of the prognosis of the two sexes was hampered by the small number of women in this study. Fifteen of the sixteen patients who died, and all nine amputees, were men. The mean values of certain risk factors were similar in the two sexes (Appendix 5.4), but men had a higher prevalence of symptomatic coronary artery and cerebral vascular disease at referral (Appendix 5.5). The men also had a longer duration of symptoms prior to referral (15 months) compared with the women (nine months) and seven of the 12 patients who presented with rest pain were men.

When adverse events in addition to death and amputation were included in the analysis, there was no significant difference in the prognosis of the two sexes ($X^2_1 = 1.00$, $p = 0.3169$). Correction for age ($X^2_1 = 0.87$, $p = 0.3508$) and smoking habits after referral ($X^2_1 = 0.51$, $p = 0.4768$) did not result in a significant difference.

(c) The effect of cerebrovascular or coronary artery disease on the prognosis of patients with intermittent claudication

A total of 25 patients had symptoms of coronary artery disease (myocardial infarction or angina) or a positive E.C.G. at referral. There was no significant effect of coronary artery disease on prognosis when corrected for age and sex ($X^2_1 = 0.19$, $p = 0.6621$) or smoking habits after referral ($X^2_1 = 0.01$, $p = 0.9601$). Patients with myocardial infarction or angina were examined separately, and no significant effect of these individual risk factors was found.

The presence of cerebrovascular disease, however, did appear to affect prognosis. Nine patients had suffered a stroke prior to referral, and their prognosis was considerably worse

TABLE 5.15

RISK FACTORS AT REFERRAL IN THOSE WHO STOPPED, REDUCED OR CONTINUED SMOKING

	stopped smoking (11) ($\bar{x}$ ± S.E.)	reduced smoking (9) ($\bar{x}$ ± S.E.)	continued smoking (39) ($\bar{x}$ ± S.E.)
Systolic BP (mm Hg)	162.5 ± 6.5	163.1 ± 8.3	166.7 ± 4.7
Diastolic BP (mm Hg)	96.2 ± 3.6	91.9 ± 4.0	90.8 ± 2.9
Cholesterol (mmol/l)	5.84 ± 0.30	6.33 ± 0.48	6.42 ± 0.22
Triglyceride (mmol/l)	1.77 ± 0.22	1.79 ± 0.19	1.63 ± 0.08
Glucose (mmol/l)	5.19 ± 0.49	5.93 ± 0.94	5.25 ± 0.12
Uric acid (mmol/l)	0.387 ± 0.036	0.303 ± 0.066	0.333 ± 0.012
Quetelet's index$_2$ (weight/height^2)	2.38 ± 0.13	2.24 ± 0.11	2.24 ± 0.06

TABLE 5.14

MEDICAL HISTORY PRIOR TO REFERRAL OF PATIENTS WHO STOPPED, REDUCED, OR CONTINUED SMOKING AFTER REFERRAL

	Stopped smoking (11) No. (%)	Reduced smoking (9) No. (%)	Continued smoking (39 No. (%)
Myocardial infarction	2 (18)	3 (33)	9 (23)
Angina	2 (18)	2 (22)	8 (21)
Stroke	1 (9)	2 (22)	6 (15)
Diabetes	0	0	0
Hyperlipidaemia	0	4 (44)	5 (13)
Hypertension	4 (36)	4 (44)	6 (15)
Bronchitis	3 (27)	1 (22)	10 (26)

TABLE 5.13

BILATERAL IC, REST PAIN, SKIN ULCERS, TROPHIC CHANGES AND GANGRENE IN THOSE WHO STOPPED, REDUCED, OR CONTINUED SMOKING AFTER REFERRAL

	Stopped smoking (11) No. (%)	Reduced smoking (9) No. (%)	Continued smoking (39) No. (%)
Bilateral IC	5 (45)	5 (56)	16 (41)
Rest pain at referral	2 (18)	1 (11)	6 (15)
Skin ulceration at referral	0	0	2 (5)
Trophic changes at referral	2 (18)	1 (11)	8 (20)
Tissue necrosis (toe) at referral	0	4 (44)	1 (3)

TABLE 5.11

THE SMOKING HABIT PRIOR TO REFERRAL OF THOSE WHO STOPPED, REDUCED, OR CONTINUED SMOKING AFTER REFERRAL

	Stopped smoking (11) ($\bar{x}$ ± S.E.)	Reduced smoking (8) ($\bar{x}$ ± S.E.)	Continued smoking (39) ($\bar{x}$ ± S.E.)
Weight of tobacco smoked (grams/D)	18.3 ± 10.3	27.2 ± 17.2	20.8 ± 16.9
Years smoking	48.7 ± 14.0	39.2 ± 9.7	49.1 ± 11.8
Age started smoking (yrs)	17.6 ± 7.1	18.6 ± 7.8	20.6 ± 8.5

TABLE 5.12

THE HISTORY OF INTERMITTENT CLAUDICATION IN THOSE WHO STOPPE REDUCED, OR CONTINUED SMOKING AFTER REFERRAL

	Stopped smoking (11) ($\bar{x}$ ± S.E.) (range)	Reduced smoking (8) ($\bar{x}$ ± S.E.) (range)	Continued smoking (39) ($\bar{x}$ ± S.E.) (range)
Age at onset of IC (yrs)	60.4 ± 11.2 (43-76)	56.9 ± 6.8 (48-68)	60.0 ± 7.2 (41-71)
Age at first referral	61.1 ± 11.2 (43-78)	58.0 ± 6.5 (49-68)	61.3 ± 7.7 (42-76)
Claudication distance at first referral	185 ± 115 (20-400)	200 ± 145 (50-500)	150 ± 75 (20-500)

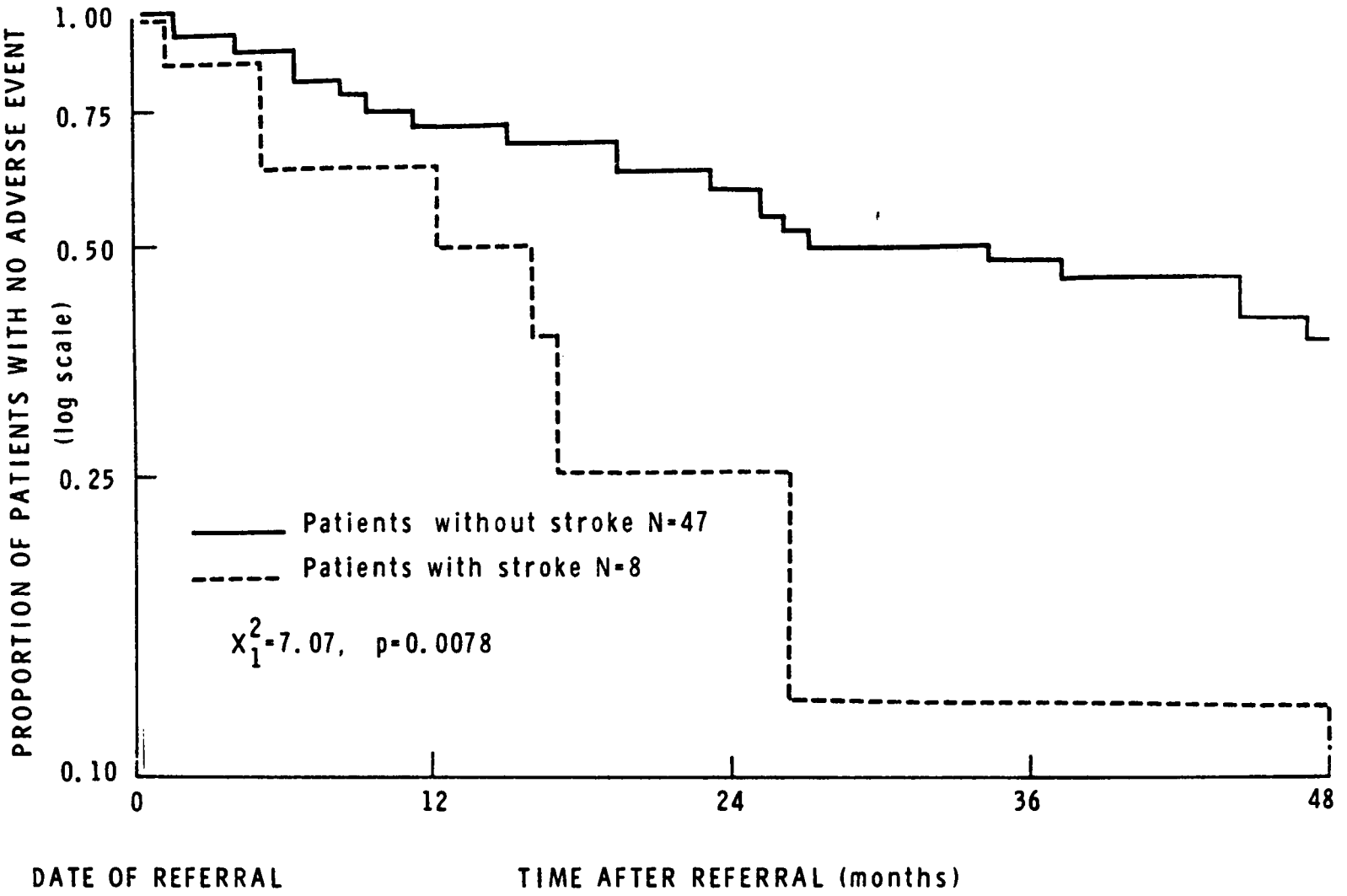
TABLE 5.10

THE SMOKING HABITS OF PATIENTS AT REFERRAL

	No. (%)
Non-smoker	1 (2)
Pipe and cigar smoker	4 (7)
Cigarette smoker	
1-14/D	24(40)
15-24/D	20(33)
$\geq$25/D	11(18)
Total	60(100)

FIGURE 5.3

THE EFFECT OF CEREBROVASCULAR DISEASE ON THE PROGNOSIS OF PATIENTS WITH PVD



than that of patients with no history of cerebrovascular disease (Figure 5.3). This effect was still significant when corrected for age and sex ($X^2_1 = 5.6$, $p = 0.0195$) and smoking after referral ($X^2_1 = 9.53$, $p = 0.0020$).

(d) Smoking

Fifty-nine of the 60 patients were smokers, and only one patient was a life-long non-smoker (Table 5.10). All were urged in the strongest terms to stop smoking, but despite this advice only eleven stopped completely after referral and a further nine patients reduced their daily consumption to fewer than 10 cigarettes. The remainder did not alter their smoking habits appreciably during the follow-up period, and continued to smoke more than 10 cigarettes a day.

There was no significant difference in the initial smoking habits of those who stopped or reduced and those who continued smoking (Table 5.11). Nor was there a significant difference in the age of onset, age at first referral, claudication distance, or prevalence of severe ischaemia at referral among the three groups (Tables 5.12 and 5.13). The medical history prior to referral, and the mean values of certain risk factors were similar, and are presented in Tables 5.14 and 5.15. The palpation of the leg pulses of the patients is summarized in Appendix 5.6. Absent or diminished pulses occurred with approximately the same frequency in the three groups. Arteriograms were performed on only 37 patients so that a comparison of the severity of arterial lesions of all patients in the three groups was not possible. The proportion of patients who had arteriograms was approximately the same in the three groups, and the degree of arteriosclerosis shown was comparable.

TABLE 5.17

REPEAT OPERATIONS FOR DETERIORATING SYMPTOMS

	Patients who stopped or reduced smoking	Patients who continued smoking	Total
One operation	12	21	33
Second operation	5	9	14
Interval* (months) between operations	21	2	28
	42	17	31
	43	18	40
	46	22	
	47	27	
		27	

* The interval between operations was significantly shorter in those who continued smoking

Mann-Whitney U test (Siegel, 1956)

$U = 6$

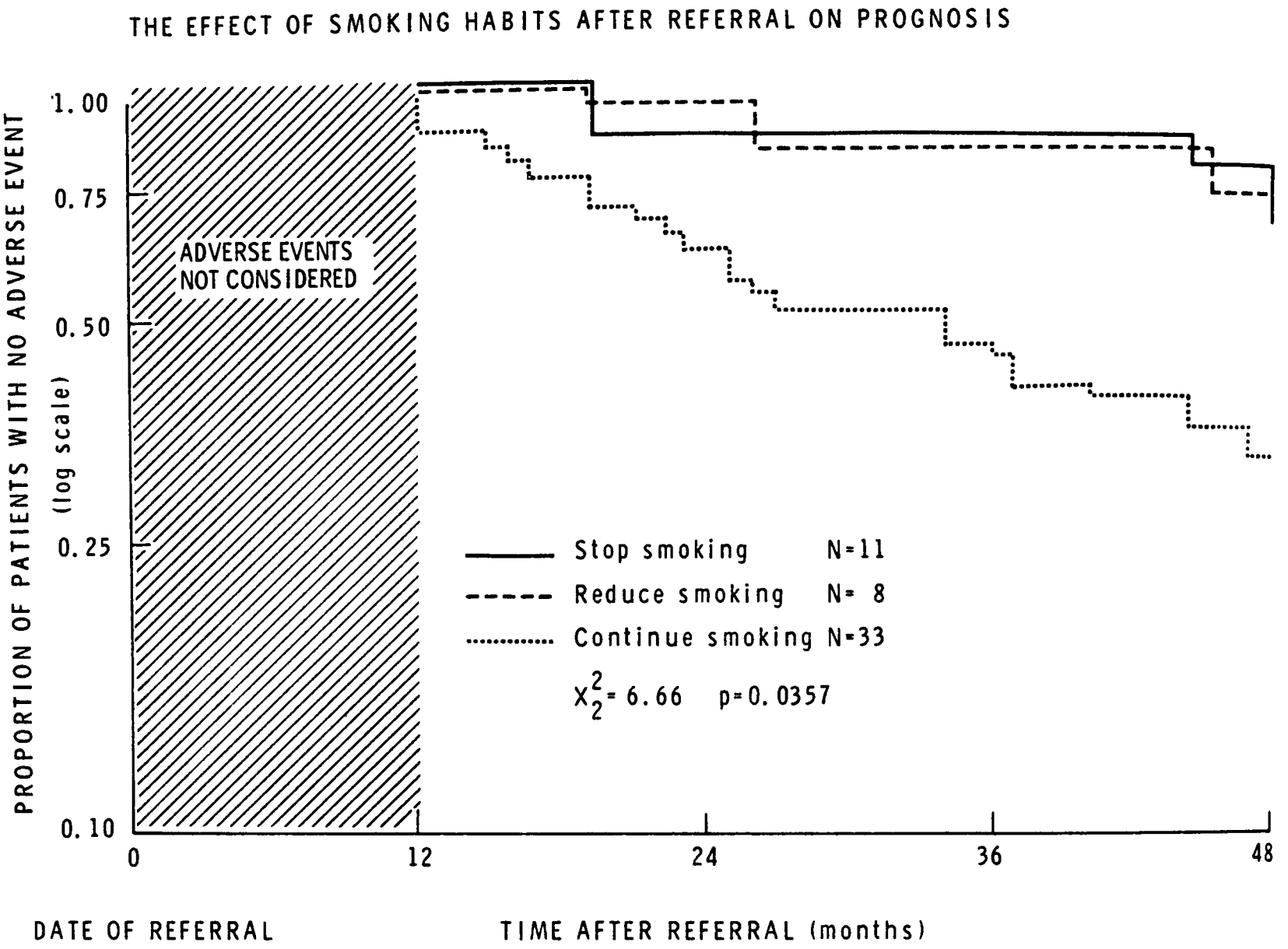
$p<0.05$

TABLE 5.16

THE DIFFERENCE IN SURVIVAL OF PATIENTS WHO STOPPED, REDUCED, OR CONTINUED SMOKING WITH DIFFERENT STARTING POINTS (TIME ZERO) FOR THE SURVIVAL CURVES

Time zero chosen	Uncorrected Significance	Significance corrected for age and sex
Date of referral	χ_2^2 1.64 p=0.4394	χ_2^2 1.72 p=0.4242
Three months after referral	χ_2^2 2.69 p≅0.2600	χ_2^2 3.13 p≅0.1191
Six months after referral	χ_2^2 4.24 p≅0.1202	χ_2^2 4.59 p≅0.1007
Twelve months after referral	χ_2^2 6.66 p≅0.0357	χ_2^2 7.07 p≅0.0296

FIGURE 5.4


THE EFFECT OF SMOKING HABITS AFTER REFERRAL ON PROGNOSIS
PROPORTION OF PATIENTS WITH NO ADVERSE EVENT (log scale)
1.00
0.75
0.50
0.25
0.10
ADVERSE EVENTS NOT CONSIDERED
Stop smoking N=11
Reduce smoking N= 8
Continue smoking N=33
X^2_2= 6.66 p=0.0357
0
12
24
36
48
DATE OF REFERRAL
TIME AFTER REFERRAL (months)

In order to assess the effect of continued smoking on the prognosis of peripheral vascular disease the prognosis curves of the patients who stopped, reduced, or continued smoking were calculated. The starting point (time zero) of the life table shown in Figure 5.4 is 12 months after referral. This starting point was chosen because it was felt that any beneficial effect of stopping smoking would take at least one year to become evident. The probability of an adverse event was considerably greater in those who continued to smoke after referral compared with those who stopped or reduced (X^2 = 6.66 on 2 d.f., p = 0.0357). When corrected for age and sex, the difference in prognosis was more significant (X^2 = 7.04 on 2 d.f., p = 0.0296).

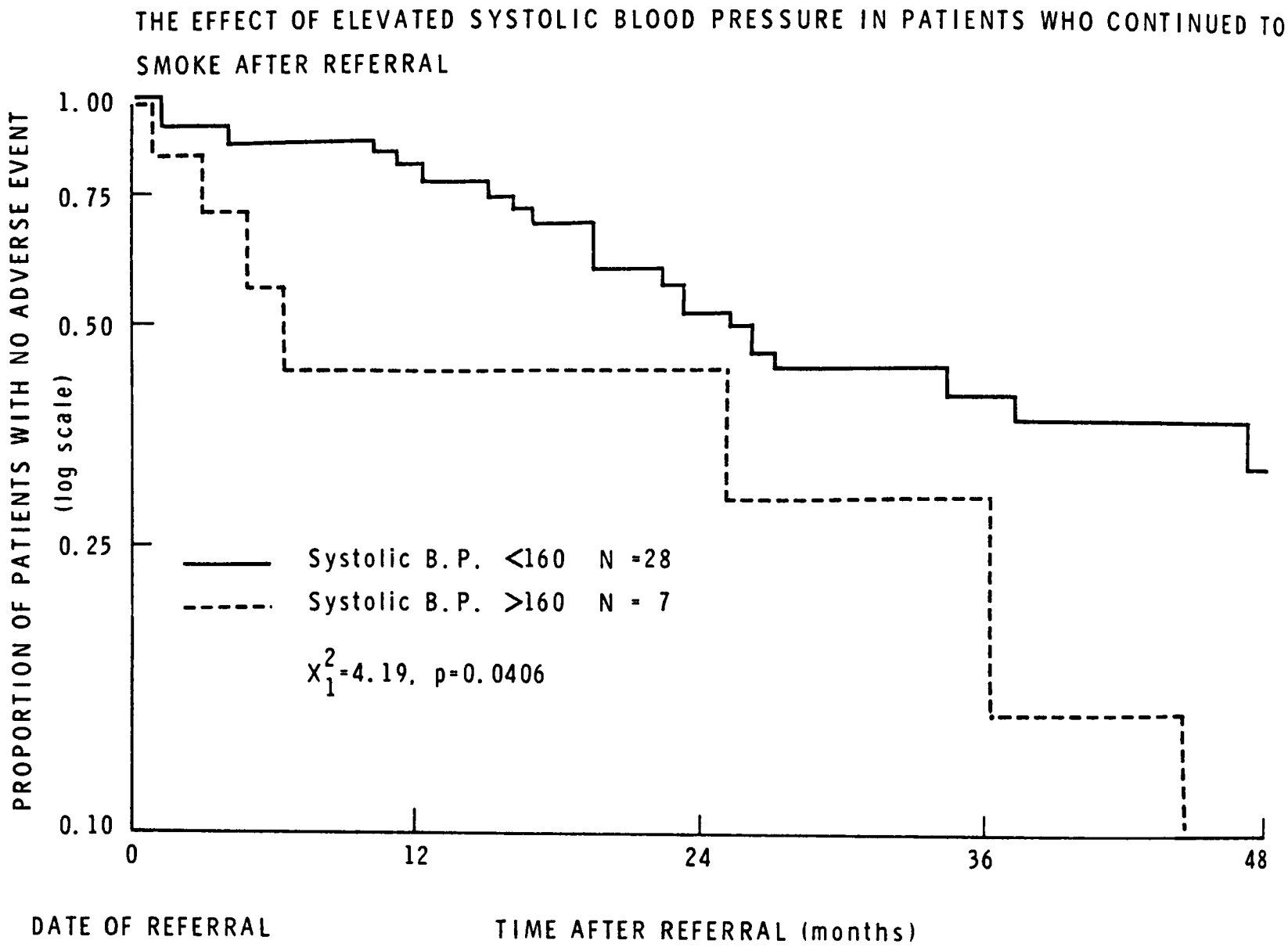
The effect of shorter intervals of non-smoking or reduced smoking is presented in Table 5.16. It can be seen that as the period of non-smoking or reduced smoking increased, the difference in the prognosis of the three groups increased. It was not possible to continue the analysis after the 12-month interval, because the follow-up period was only four years.

Fourteen patients underwent repeat arterial surgery because of deteriorating symptoms. Nine of these were persistent smokers, and five were patients who stopped or reduced smoking after referral. Table 5.17 presents the intervals in months between these operations. Using a Mann-Whitney U test, the interval between the initial and repeat operations was significantly shorter in those patients who continued to smoke (U = 6, $p<0.05$).

(e) Blood pressure

Fourteen patients had a history of hypertension and had received treatment prior to referral for IC. There was no significant difference in the prognosis of those with and

FIGURE 5.5


THE EFFECT OF ELEVATED SYSTOLIC BLOOD PRESSURE IN PATIENTS WHO CONTINUED TO SMOKE AFTER REFERRAL
PROPORTION OF PATIENTS WITH NO ADVERSE EVENT (log scale)
1.00
0.75
0.50
0.25
0.10
Systolic B.P. <160 N =28
Systolic B.P. >160 N = 7
X_1^2=4.19, p=0.0406
0
12
24
36
48
DATE OF REFERRAL
TIME AFTER REFERRAL (months)

without a history of hypertension (corrected for age and sex, $X^2_1 = 0.65$, $p = 0.4219$).

The mean systolic pressure at referral was 146 mm Hg (range = 110 to 220, standard deviation = 24), and there was no significant effect of age on the mean level. The patients were divided using an arbitrary cut-off point of 160 mm Hg. There was no significant difference in the prognosis of those whose systolic pressure was greater than or equal to 160 mm Hg compared with patients whose SBP was below this level (corrected for age and sex, $X^2_1 = 0.01$, $p = 0.9740$). Other levels of SBP were also examined (140 mm, 180 mm), and no effect was found.

When the patients were divided according to their smoking habits after referral, an adverse effect of elevated systolic pressure became evident (Figure 5.5). Those patients who continued to smoke after referral and had an elevated systolic blood pressure ($\geq$160 mm Hg) had a significantly worse prognosis than normotensive smokers ($X^2_1 = 4.19$, $p = 0.0406$). This effect of SBP on prognosis was not found in those who stopped or reduced smoking possibly because of the small numbers of patients in these smoking categories. The age and sex distributions of the hyper- and normotensive patients within the smoking groups were similar. The overall effect of elevated SBP on prognosis, when corrected for smoking habits after referral and considering all the patients, was not statistically significant ($X^2_1 = 0.44$, $p = 0.5083$). Therefore, though an adverse effect of elevated SBP was evident within the group who continued to smoke, this result must be interpreted as inconclusive evidence of an interaction between smoking and SBP. It is likely that larger numbers of patients would be needed to examine the relationship between smoking habits, elevated SBP, and the prognosis of

patients with IC.

The mean diastolic pressure at referral was 90 mm Hg (range = 60 to 130, standard deviation 14). There was no significant increase in DBP with age, and when the patients were divided as described for systolic presure, there was no significant adverse effect of diastolic pressures greater than or equal to 90, 100, or 110 mm Hg despite the fact that systolic and diastolic pressures were strongly correlated ($r = 0.7525$, $p = 0.001$). When SBP was controlled, there was an adverse effect of diastolic pressure which was not statistically significant (for DBP$\geq$90, corrected for systolic pressure, $X^2_1 = 1.22$, $p = 0.2703$). Smoking after referral was also controlled for, and no significant effect of DBP on prognosis was found.

(f) Serum lipids

The mean fasting cholesterol concentration at referral was 6.3 mmol/l (range = 3.48 to 11.22, standard deviation = 1.38). There was no significant increase in serum cholesterol with age, and no significant effect of elevated cholesterol on prognosis, controlling for age and sex or smoking habits after referral. (Levels examined were 6.2, 6.7, and 7.7 mmol/l. For cholesterol $\geq$6.7 mmol/l, $X^2_1 = 0.53$, $p = 0.4665$, controlling for age and sex).

The mean fasting triglyceride concentration at referral was 1.68 mmol/l (range = 0.84 to 2.83, standard deviation = 0.55). As with cholesterol, there was no significant increase in triglyceride concentration with age, and no significant adverse effect of triglyceride on prognosis. (Levels examined were 1.70, 1.98 and 2.15 mmol/l. For triglyceride $\geq$2.15 mmol/l, $X^2_1 = 1.28$, $p = 0.2574$, controlling for age and sex).

(g) Blood glucose

The mean fasting glucose concentration at referral was 5.35

TABLE 5.20

THE PROPORTION OF PATIENTS WITH MORE THAN ONE RISK FACTOR* AT REFERRAL AND THE EFFECT ON DEATH AND AMPUTATION

No risk factors at referral	Patients No. (%)	Deaths No. (%)	Amputations No. (%)
None	4 (7)	1 (6)	0
One	14 (23)	4 (25)	1 (11)
Two	24 (40)	6 (38)	5 (56)
Three or more	18 (30)	5 (31)	3 (33)
Total	60(100)	16(100)	9(100)

* Risk factors were defined as:

Systolic BP	$\geq$ 160 mm Hg or Diastolic BP $\geq$ 90 mm Hg
Triglyceride	$\geq$ 2.15 mmol/l
Cholesterol	$\geq$ 6.7 mmol/l
Glucose	$\geq$ 5.56 mmol/l
Uric acid	$\geq$ 0.357 mmol/l
Smoking	$\geq$ 15 grams of tobacco/day throughout the follow-up period

TABLE 5.19

THE PROPORTION OF PATIENTS WITH RISK FACTORS AT FOLLOW-UP WHO KNEW OF THE ABNORMALITY AND WERE RECEIVING TREATMENT

	Factor present at follow-up No. patients (% of 43 pts)	Patient aware of factor No. (% of Column A)	Receiving treatment No. (% of Column A)
	Column A	Column B	Column C
SBP $\geq$ 160 or DBP $\geq$ 90 mm Hg	29 (67)	7 (24)	2 (7)
Cholesterol $\geq$ 6.7 or Triglyceride $\geq$ 2.15 mmol/l	17 (40)	3 (18)	2 (12)
Glucose $\geq$ 5.56 mmol/l	12 (28)	0	0

TABLE 5.18

THE PROPORTION OF PATIENTS WITH PERSISTENT RISK FACTORS AT FOLLOW-UP

Risk factor	Risk factor present at referral No. patients (% of 60 pts)	Patients with risk factor at referral alive at follow-up No. (% of Column A)	Surviving patients with risk factor present at follow-up No. (% of Column B)
	Column A	Column B	Column C
SBP≥160 mm Hg	22 (37)	14 (64)	13 (93)
DBP≥90 mm Hg	34 (57)	25 (74)	20 (80)
Cholesterol≥6.7 mmol/l	18 (30)	15 (83)	8 (53)
Triglyceride≥2.15 mmol/l	13 (22)	10 (77)	3 (30)
Glucose≥5.56 mmol/l	9 (15)	4 (44)	3 (75)

mmol/l (range = 4.17 to 7.78, standard deviation = 0.73). There were no known diabetics in this study, and no increase in mean glucose with age. The effect of elevated glucose on prognosis was examined in the same manner as described earlier, and there was no significant effect at levels of 5.00, 5.56 or 6.12 mmol/l (for glucose $\geq$5.56 mmol/l X^2_1 = 0.54, p = 0.4608, controlling for age and sex).

4. CORRELATION AND INTERACTION AMONG RISK FACTORS

There were few statistically significant correlations among the risk factors, and those which did occur were correlations between the same variables measured at referral and again at follow-up. Patients with elevated risk factors at referral were often found to have the same abnormalities at follow-up (Table 5.18). This was due, in part, to a lack of awareness on the part of the patient, and a lack of medical treatment (Table 5.19).

The proportion of patients with one, two or three or more risk factors at referral and the effect of multiple risk factors on death and amputation is summarized in Table 5.20. I have included elevation of glucose and cholesterol as risk factors in this table even though they were not identified as risk factors for IC in Chapter 4 of this thesis, because these variables have been shown in other studies to increase the degree of atherosclerosis found in patients with PVD (Vogelburg et al, 1975; Kingsbury, 1966). Death and amputation occurred more frequently in patients with two or more risk factors, but when relative risks were calculated, there was no significantly increased risk of death or amputation in patients with multiple risk factors. When other adverse events were include in a life table analysis, there was no evidence of a synergistic effect of risk factors on the prognosis (corrected for age and sex,

χ^2_1 = 0.17, p = 0.9819). Other combinations of risk factors (including that presented in Table 4.18) were examined and different levels were used as cut-off points, but no significantly increased risk of adverse events with increasing numbers of risk factors was demonstrated.

D. DISCUSSION

The patients in this study were a consecutive series, and since the Radcliffe Infirmary is the centre to which most claudicants living in the Oxford area are referred, it is reasonable to assume that this group was representative of patients with moderate to severe symptoms of intermittent claudication requiring medical treatment. The size of the patient group, and the relatively short period of follow-up in this study made it necessary to define events other than death as evidence of clinical deterioration in order to examine the effect of risk factors on prognosis. It was felt that the subjective reporting of symptoms was unlikely to be accurate (Sigaard-Anderson and Petersen, 1968), and therefore events which clearly indicated a change in the patient's condition were chosen and defined as adverse events. The life table produced by this technique, while not having death as a firm end-point, does indicate changes of clinical importance. Every effort was made to avoid bias, and the time intervals for the survival curves were determined by a physician who was "blind" with respect to the patients' risk factors.

During a four-year follow-up period, 16 of the 60 patients (27%) died, a rate approximately the same as that found in other series (Bloor, 1960; Schadt et al, 1961; Begg and Richards, 1962). The cause of death was myocardial infarction or congestive heart failure in six (38%) and stroke in three (19%)

patients, and only three patients died of causes unrelated to vascular disease. It is of interest that three patients died of ruptured aortic aneurysm and two died after operations for peripheral vascular disease. Thus 31 per cent of the deaths were attributable to peripheral vascular disease, a greater proportion than found in other studies (Bloor, 1960; Tillgren, 1965a).

The patients who died were, with one exception, more than 60 years of age at referral, and there was an adverse effect of increasing age on prognosis. This effect was not statistically significant, possibly because arterial surgery (an adverse event in this study) was not usually considered in elderly patients unless the symptoms were severe. Older people with additional health problems such as arthritis and angina may be less mobile, and therefore less likely to seek medical help for their claudication.

Tillgren (1965b) observed a higher mortality rate in men with IC compared with women, and attributed this to an increased incidence of myocardial infarction in men. In the Framingham study, the four-year survival of all male claudicants was 85.8 per cent compared with 91.5 per cent of the women with IC. When patients with evidence of coronary artery and cerebral vascular disease were removed, the four-year survival rates of men and women were 94.0 per cent and 92.4 per cent, respectively (Kannel and Shurtleff, 1971). The male patients in my study had a higher prevalence of coronary artery and cerebral vascular disease than the women at referral, and this may have accounted for the higher death rate. There was no significant difference between men and women in the mean values of risk factors, and the proportion of smokers who stopped or reduced was the same in

both sexes.

Tillgren (1965a) reported a higher amputation rate in the male claudicants in his series, but this has not been found in other large studies (Silbert and Zazeela, 1958; Bloor, 1960). There were only nine amputations in my series of patients, and all occurred in men. It is possible that the higher amputation rate in men was due to more severe PVD at the start of the study rather than a difference in the rate of deterioration after referral. There was no objective evidence for this, however, since the proportion of patients presenting with rest pain was greater in the women (38%) than the men (16%), and there was no significant difference in the walking distance or physical examination at referral. Because of the small number of women in this study, I feel that no firm conclusion can be drawn on the basis of this data concerning the relative amputation rates in the two sexes.

There was no significant difference in the life tables of the two sexes when all adverse events were considered. This was because clinical deterioration after referral occurred with equal frequency in men and women: three women developed rest pain, six had operations, and two had a myocardial infarction.

Eighteen patients had a history of myocardial infarction or angina prior to referral for PVD, and a total of 25 (including seven with a positive E.C.G.) had evidence of coronary artery disease. This disease was associated with an increased risk of mortality, since nine of the 16 patients who died (56%) came from this group. It is of interest that the prognosis of claudicants with coronary artery disease was not significantly worse than those without CHD. This was due, in part, to the definition of an adverse event in this study, since the majority

were non-fatal events related to PVD. The presence of angina limited the activity of patients, and may have reduced the frequency of requests for medical intervention. Of the six deaths due to myocardial infarction or congestive heart failure, three occurred in patients with no history of CHD. Similarly non-fatal myocardial infarction and onset of angina occurred with equal frequency in the two groups. The incidence of non-fatal myocardial ischaemia was similar to that found in other studies (Selvaag, 1956; Bloor, 1960). As discussed earlier, only two patients had myocardial infarction or angina defined as adverse events, so that the stipulation that only new ischaemic heart disease was an adverse event did not significantly bias the results.

Nine patients (15%) had a history of stroke prior to referral. Four of these also had evidence of coronary artery disease. Six of the nine patients (67%) died in the follow-up period (three of myocardial infarction, two of CVA, and one post-operatively) and one of the surviving patients had an amputation. Thus the prognosis of claudicants with cerebral vascular disease was significantly worse than those free of this complaint. The mortality rate of the patients with cerebral vascular disease was similar to that found in other series of stroke patients, and the presence of peripheral vascular disease did not add to the risk of death (Marquardsen, 1969; Matsumato, 1973). It is likely that the finding of cerebral and peripheral vascular disease in the same patient indicates severe diffuse arteriosclerosis with mortality due chiefly to coronary artery disease or recurrent stroke.

The only other risk factor which had a significant effect on the prognosis, independent of other risk factors, was the

smoking habit of patients after referral. Sixty-three per cent of the patients who stopped or reduced smoking completed the follow-up period without an adverse event compared with only 33 per cent of those who continued to smoke. As the period of abstinence from tobacco increased, the effect of stopping or reducing smoking became more apparent.

Other studies have demonstrated an improved life expectancy, amputation rate, or success of arterial surgery among claudicants who stopped smoking (Silbert and Zazeela, 1958; Jeurgens et al, 1960; Birckenstock et al, 1975; Robicseck et al, 1975). None of these studies examined the smoking history prior to referral, severity of arterial disease, or presence of other risk factors in those who stopped or continued to smoke, casting doubt on the conclusion that a change in smoking habits resulted in benefit to the patient. The patients in my study were assessed in a uniform manner, and the risk factors known to be of importance in the aetiology of atherosclerosis were measured. There was no apparent difference among the three smoking groups in the severity of PVD at referral or the prevalence of risk factors. Thus the improved prognosis of patients who stopped or reduced smoking can reasonably be attributed to the elimination or reduction of this risk factor. There was a small number of patients in this study. Nevertheless, the consistent and significant effect of smoking on prognosis is strong evidence to support the premise that stopping smoking, even after intermittent claudication is present, improves or at least prevents further deterioration of peripheral vascular disease. Further, continued smoking after the onset of IC significantly increases the likelihood of rest pain, reconstructive surgery, amputation, or death.

Some previous studies have found that elevated systolic or diastolic blood pressure had an adverse effect on the mortality or amputation rates of patients with IC (Spalding, 1956; Silbert and Zazeela, 1958; Begg and Richards, 1962). Others have found no effect of blood pressure on outcome (Selvaag, 1956; Jeurgens et al, 1960), and Taylor and Calo (1962) reported a lower amputation rate in hypertensive claudicants. None of these studies examined the effect of elevated blood pressure in those who continued to smoke compared with hypertensives who stopped smoking. The adverse effect of systolic pressure on prognosis in my study was not evident when age and sex were controlled, and became apparent when the patients were divided according to their smoking habits after referral: the effect of elevated SBP was significant only in those who continued to smoke. It is possible that the small group of hypertensive smokers differed from normotensive smokers in the severity of their PVD and prevalence of other cardiovascular diseases, though a careful review of their records provided no evidence for this. Another explanation is that elevated systolic pressure accentuated the damage to the arterial system caused by smoking, and worsened the prognosis. Since the effect of elevated SBP, corrected for smoking habits after referral, was not statistically significant when all the patients were considered, the observation that elevated SBP worsened the prognosis in patients who continued to smoke must be interpreted with caution. I feel that further investigation of larger numbers of patients would be necessary before a conclusion could be reached concerning the interaction of smoking and SBP and the consequences to the circulation.

Barndt et al (1977) demonstrated reversal of early femoral atherosclerosis in nine of 25 patients with hyperlipidaemia who

had been treated with lipid-lowering drugs and diet for 13 months. Only one of these patients had IC, however, and prospective studies have not demonstrated an adverse effect of cholesterol or triglyceride on the prognosis of patients with intermittent claudication (Jeurgens et al, 1960; Dormandy et al, 1973b). There was no significant effect of cholesterol or triglyceride on the prognosis of patients in my study, and no evidence of elevated serum lipids in those who died or had amputations. This observation is of some interest, since treatment of elevated lipids involves some considerable disruption of the patient's lifestyle, particularly when a stringent diet or drugs such as cholestyramine are required to achieve acceptable serum levels. The decision whether to treat an elevated level of cholesterol or triglyceride must take into account the possibility of co-existent coronary artery or cerebral vascular disease and the reduced risk of myocardial infarction or stroke which might result if the concentrations of serum lipids were reduced. Prospective studies have shown a protective effect of lowering serum lipids in the primary prevention of ischaemic heart disease, but studies of secondary prevention have had negative results (J. Royal College of Physicians, 1976). Nor is there evidence that cerebral vascular disease can be prevented in this way. Since many claudicants have symptoms of coronary or cerebral vascular disease when referred for IC, the chief causes of mortality in claudicants may not be affected by control of elevated serum lipids. While lipid control may benefit the individual, it is possible that efforts in this area may reduce patient compliance in reducing another more important risk factor, smoking.

The patients in this study had a mean fasting glucose which

was higher than found in other series of claudicants or in the general population (Leren and Haabrekke, 1971b; Bliss et al, 1972; Lewis et al, 1974). There were no known diabetics in this study, but nine patients (15%) had a fasting glucose of 100 mg/100 ml or more. Prospective studies have shown that diabetic patients with IC have a higher amputation and death rate than non-diabetic claudicants (Silbert and Zazeela, 1958; Schadt et al, 1961). This increase in the amputation rate of diabetics may be due to increased disease in distal arteries (Strandness et al, 1964; Vogelburg et al, 1975). Diabetics also show an increased morbidity and mortality from coronary and cerebral vascular disease (Ostrander et al, 1965; Garcia et al, 1974). Though there is evidence that the prevalence and severity of peripheral vascular disease increase with the level of glucose in non-diabetics (Kingsbury, 1966; Kannel and Shurtleff, 1971), no previous prospective study has shown that the prognosis of non-diabetic claudicants is affected by the glucose concentration and there was no evidence in this study that an elevated blood glucose was associated with mortality, amputation, or a worsening of prognosis.

Only cerebral vascular disease and continued smoking after referral had a significant adverse effect on prognosis, independent of other risk factors. Failure to demonstrate a synergistic effect of risk factors may, therefore, simply reflect the lack of influence these factors had on prognosis. It is possible that longer observation of a larger patient group would reveal significant interactions.

Very few of the patients with elevated lipids, glucose or blood pressure at follow-up had been told by their doctors of these abnormalities or were receiving treatment. This may simply

reflect a policy of benign neglect on the part of the medical profession, and in view of the findings of this study it is difficult to comment on the preferred medical treatment of claudicants. Certainly the patient must be encouraged and helped to stop smoking. The fact that two-thirds of the patients in this study continued smoking after referral represents a significant failure of long-term medical care and demonstrates the need for consistent support in order to break this very strong addiction. Hypertension should be treated, since the risks of stroke and congestive heart failure are reduced by blood pressure control, and elevated systolic pressure may have an adverse effect on the peripheral circulation of patients who refuse to stop smoking. There is no evidence that biochemical abnormalities affect the prognosis of PVD, and treatment may cause significant inconvenience to the patient. I would hesitate to advise therapeutic nihilism when glucose or lipid levels are very high, however, since treatment may avert catastrophies such as stroke and myocardial infarction in the individual patient.

E. SUMMARY

Continued smoking after referral significantly worsened the prognosis of patients with IC, as did cerebral vascular disease. Elevated systolic blood pressure had a significant adverse effect only in those who continued to smoke. Other risk factors such as serum lipids and blood glucose did not seem to affect prognosis, and there was no evidence of a synergistic effect of multiple risk factors on the outcome. Plasma fibrinogen was not measured at the initial assessment, and therefore its effects could not be examined.

The factor associated with the greatest risk of developing IC, smoking, and the one which should be easiest to remove (see

Discussion, Chapter 4), played a central role in determining the fate of people with PVD. Patients should be encouraged to stop smoking, since the majority who do will avoid reconstructive surgery, amputation and death for at least three years. Those who continue smoking may expect a deterioration of symptoms, and a greater likelihood of serious complications and death.

CHAPTER 6

A FOLLOW-UP STUDY OF 160 PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE

Chapter 6 A FOLLOW-UP STUDY OF 160 PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE

A. INTRODUCTION

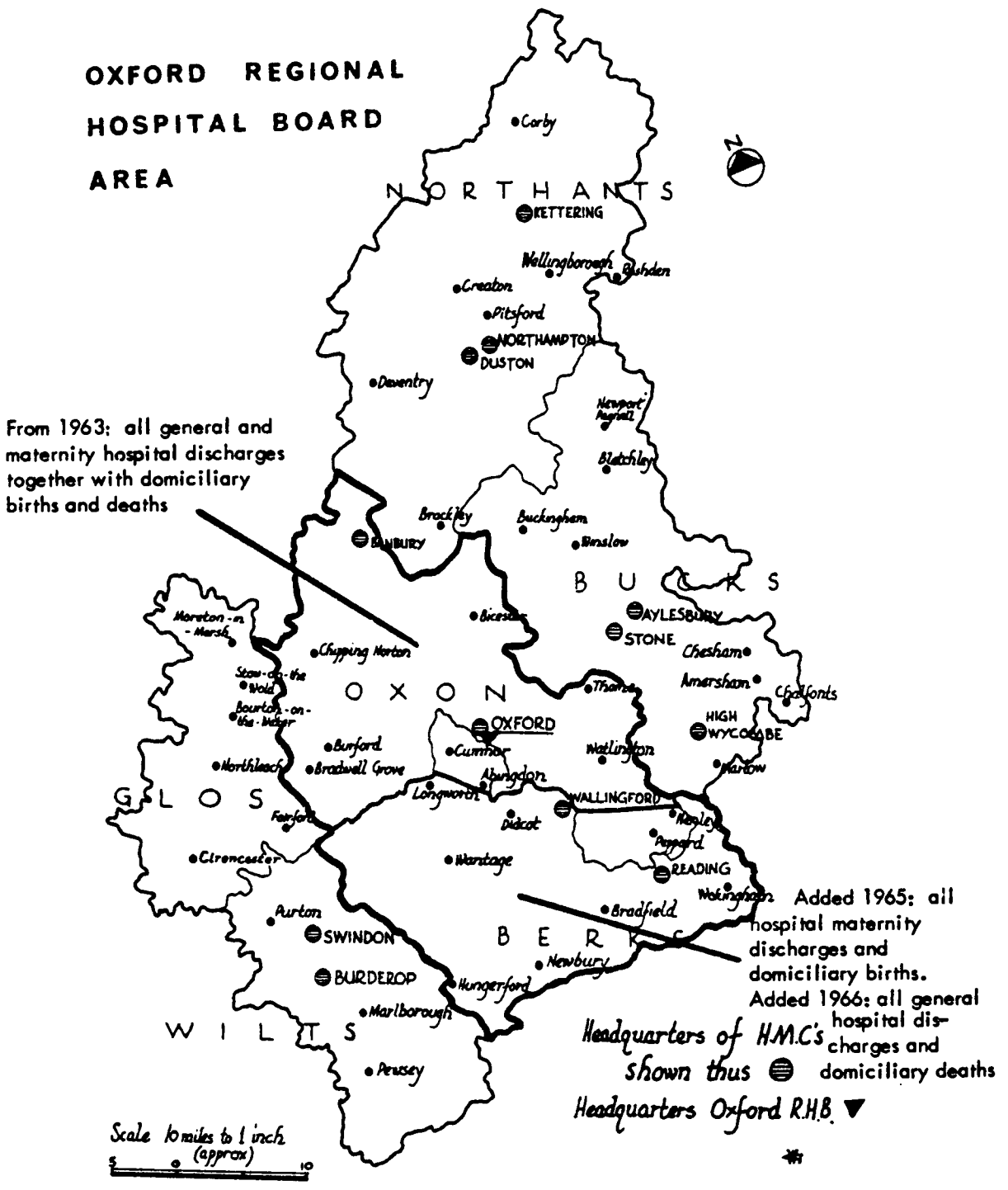
The study described in Chapter 5 provided information concerning the prognosis of 60 patients referred to hospital because of intermittent claudication (IC). Despite the short period of follow-up, it was possible to demonstrate a significant effect of certain risk factors such as smoking on prognosis. Other risk factors such as coronary artery disease did not seem to affect the outcome, possibly because there were too few patients, the period of follow-up was too short, or because non-fatal ischaemic episodes such as onset of rest pain were included as adverse events in the analysis. In order to provide further information about prognosis, using only death and amputation as end-points, it was decided to identify a larger number of patients admitted to hospital for peripheral vascular disease (PVD), and to determine their subsequent morbidity and mortality. Information provided by the Oxford Record Linkage Study (ORLS) made it possible to identify all patients discharged from hospitals in the Oxford area in 1965 and 1966 with a diagnosis of PVD. Data concerning subsequent hospital admissions, surgical procedures, and deaths during the period from January 1st, 1965 to December 31st, 1972 were also provided by the ORLS. The hospital notes of these patients were reviewed, and the effects of certain risk factors on prognosis were examined.

B. METHODS

1. IDENTIFICATION OF PATIENTS AND METHOD OF FOLLOW-UP

The ORLS, which began in 1963, is a system which records

FIGURE 6.1


OXFORD REGIONAL HOSPITAL BOARD AREA
From 1963: all general and maternity hospital discharges together with domiciliary births and deaths
Added 1965: all hospital maternity discharges and domiciliary births.
Added 1966: all general hospital discharges and domiciliary deaths
Headquarters of H.M.C's shown thus
Headquarters Oxford R.H.B.
Scale 10 miles to 1 inch (approx)
N O R T H A N T S
O X O N
B U C K S
B E R K S
G L O S
W I L T S
Corby
KETTERING
Wellingborough
Rushden
Creaton
Pitsford
NORTHAMPTON
DUSTON
Daventry
Newport Pagnell
Bletchley
Brackley
Buckingham
BANBURY
Winslow
AYLESBURY
STONE
Chesham
Amersham
Chalfonts
HIGH WYCOMBE
Marlow
Thame
Watlington
OXFORD
Cumnor
Abingdon
Burford
Bradwell Grove
Northleach
Longworth
WALLINGFORD
Didcot
Wantage
Moreton-in-Marsh
Chipping Norton
Stow-on-the-Wold
Bourton-on-the-Water
Fairford
Cirencester
Purton
SWINDON
BURDEROP
Marlborough
Pewsey
Hungerford
Newbury
Bradfield
Wokingham
READING
Pangbourne
Henley

information about every birth, death, hospital in-patient discharge, and obstetric delivery occurring in the Oxford area (average population 355,000 during the five-year period 1963 to 1967). In 1966 the system was expanded to include the Reading area, and Figure 6.1 shows the current area from which information is collected by the ORLS (Baldwin, 1972; Baldwin, 1973; Hobbs et al, 1976). The years 1965 and 1966 were chosen as the starting point of my study because this was the earliest time at which all general hospitals in the ORLS area were included in the system. The follow-up was stopped because ORLS data was incomplete after 1972. The length of follow-up varied from six to eight years, depending on the date of first admission for PVD.

Information collected by the ORLS concerning hospital discharges in 1965 and 1966 included the patient's name, sex, date of birth, date of admission, date of discharge, diagnosis at discharge (coded according to the 7th Revision of the International Classification of Diseases, 1955), surgical procedures (coded according to the Classification of Surgical Operations, 1956), and disposition after discharge (home, short-term convalescent hospital, long-term care). Subsequent admissions of a patient to the same hospital or to another hospital in the ORLS area were linked using identifiers such as surname, date of birth, and N.H.S. number. It was estimated that 95 per cent of all possible linkages were found in this way (Baldwin, 1973), and thus it was possible to determine morbidity (as measured by subsequent hospital admissions and surgical procedures) and mortality (microfilm of death certificates formed a part of the linked record) of patients admitted to hospital for PVD. It should be noted that deaths which occur outside of hospital are

also recorded by the ORLS.

A total of 493 patients were identified who had been discharged from hospital in 1965 or 1966 with the diagnoses shown in Appendix 6.1 or who had undergone the types of operations shown in Appendix 6.2. Theoretically all patients having an amputation or reconstructive operation because of PVD should have been found simply by using the diagnostic rubrics shown in Appendix 6.1. However, on the advice of people working for the ORLS a search was made through the operations index (which is maintained separately from the ORLS diagnostic index) using the codes shown in Appendix 6.2, since it was felt that some patients might be missed unless this was done. The hospital discharge summaries of these patients were examined using the microfilm records of the ORLS, and 230 patients were excluded because their reason for hospital admission or operation was not atherosclerotic vascular disease. Most of those excluded (208 patients) were identified initially because of amputations performed for a wide variety of causes including crush injuries (43 patients), onychogryphosis (46 patients), overlapping toes (32 patients), or congenital deformities (16 patients), or who had arterial surgery for diseases such as temporal arteritis (biopsy, 11 patients), arterial embolism (26 patients), or cerebral vascular disease which was coded incorrectly (28 patients). Twenty-two patients had been incorrectly coded as having PVD in the diagnostic index. Raynaud's disease (13 patients), thrombo-angiitis obliterans (seven patients), and chilblains (two patients) were the correct diagnoses in these patients.

Using the ORLS microfilm record, it was not possible to determine whether an admission in 1965 or 1966 was the first

TABLE 6.2

THE PROPORTION OF PATIENTS WHO SURVIVED FOR FIVE YEARS AFTER THE FIRST HOSPITAL ADMISSION FOR PVD COMPARED TO THE ESTIMATED FIVE-YEAR SURVIVAL OF THE GENERAL POPULATION OF ENGLAND AND WALES*

	Proportion of people surviving five years			
Age (yrs)	Men with PVD	Men in the general population	Women with PVD	Women in the general population
35-49	0.60	0.98	1.00	0.98
50-59	0.76	0.92	0.86	0.96
60-69	0.48	0.80	0.64	0.90
70-79	0.27	0.59	0.33	0.73
80-94**	0.14	0.44	0.20	0.59

* Rates for the general population of England and Wales were calculated from Table 12 (1968-1970) of the Annual Abstract of Statistics (1971), pp. 38

** Rates for the general population were provided only for those 80-85 years of age, so that the proportion surviving is an overestimate compared to the patients with PVD

TABLE 6.1

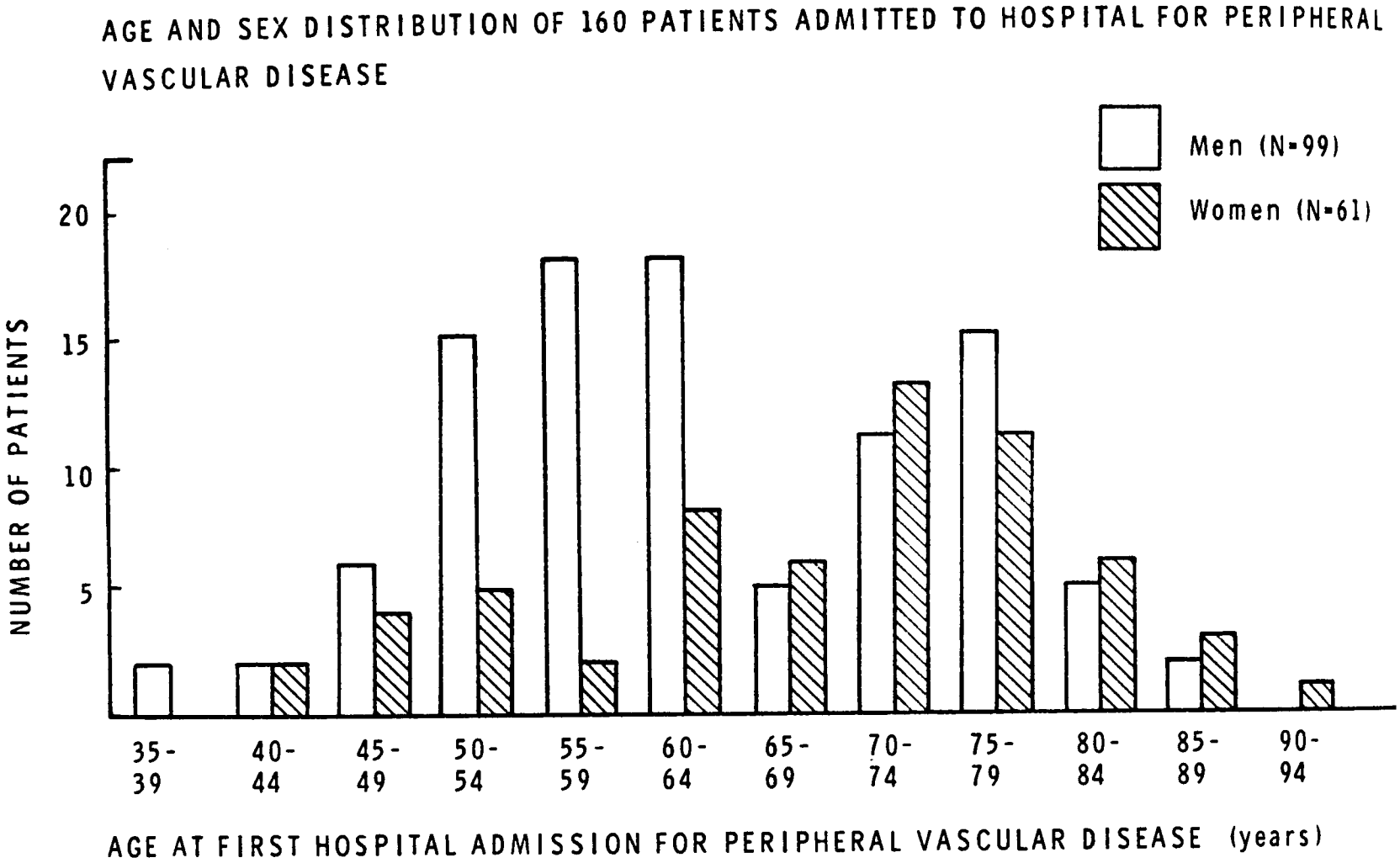
THE PRINCIPAL CAUSES OF DEATH OF 94 PATIENTS WITH PVD WHO DIED IN THE FOLLOW-UP PERIOD

Cause of death	ICD Code*	Men No. (%)	Women No. (%)	Total No. (%)
Pneumonia	480-486	12 (20.3)	9 (25.7)	21 (22.3)
Acute myocardial infarction	410	14 (23.7)	6 (17.1)	20 (21.3)
Congestive heart failure	427.0	4 (6.8)	5 (14.3)	9 (9.6)
Cerebral thrombosis	443.0	5 (8.5)	4 (11.4)	9 (9.6)
Pulmonary embolus	450	4 (6.8)	5 (14.3)	9 (9.6)
Ischaemic heart disease	412	5 (8.5)	0	5 (5.3)
Pulmonary oedema	429	2 (3.4)	1 (2.9)	3 (3.2)
Post-operative death**	796.9	2 (3.4)	1 (2.9)	3 (3.2)
Carcinoma of lung	162.1	2 (3.4)	1 (2.9)	3 (3.2)
Ruptured aortic aneurysm	441.9	1 (1.7)	1 (2.9)	2 (2.1)
Respiratory failure	796	1 (1.7)	1 (2.9)	2 (2.1)
Sudden death (cause unknown)	795	1 (1.7)	1 (2.9)	2 (2.1)
Trauma	N996	2 (3.4)	0	2 (2.1)
Coronary arterio-sclerosis	412	1 (1.7)	0	1 (1.1)
Peripheral vascular disease	443.9	1 (1.7)	0	1 (1.1)
Chronic bronchitis	491	1 (1.7)	0	1 (1.1)
Uraemia	792	1 (1.7)	0	1 (1.1)
Total		59 (100)	35 (100)	94 (100)

* ICD Codes are from the 8th Revision of the International Classification of Diseases (1965)

** The post-operative deaths occurred after surgical procedures for peripheral vascular disease

FIGURE 6.2


AGE AND SEX DISTRIBUTION OF 160 PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE
Men (N=99)
Women (N=61)
NUMBER OF PATIENTS
20
15
10
5
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90-94
AGE AT FIRST HOSPITAL ADMISSION FOR PERIPHERAL VASCULAR DISEASE (years)

hospital admission for PVD, or if an admission had occurred prior to 1965. To check on this, the hospital records of the remaining patients were examined (14 sets of notes could not be found), and 160 patients (99 men and 61 women) were identified whose first hospital admission for PVD was in 1965 or 1966. The mean age of the men was 63.6 years, and that of the women was 68.6 years. The age and sex distribution of the patients is shown in Figure 6.2.

2. STATISTICAL ANALYSES

When reviewing the hospital notes, information was obtained concerning such risk factors as diabetes, coronary artery disease, and hypertension. The effect of these factors on prognosis was then examined by the life table method described in Chapter 5 (Pike et al, 1976; Peto et al, 1977).

C. RESULTS

1. DEATHS IN THE FOLLOW-UP PERIOD

There were 94 deaths (59 men, 35 women) during the follow-up period. The principal causes of death recorded on the death certificates of these patients are summarized in Table 6.1, and all causes of death (including contributing causes) recorded are presented in Appendix 6.3.

All patients in this study were followed for at least five years, and the proportion of patients who survived for five years after their first hospital admission for PVD compared with the estimated proportion of people in the general population of England and Wales who would survive for five years, controlling for age and sex, is presented in Table 6.2. Except for the small group of women aged less than 50 years (six patients), there was a marked reduction in the survival of the patients with PVD compared with the general population. I have

TABLE 6.6

SURGICAL OPERATIONS FOR PVD PERFORMED DURING THE FOLLOW-UP PERIOD

Name of operation	No. operations in men	No. operations in women	Total No. operations
Amputations*			
1. Above knee	24	12	36
2. Through-knee	0	3	3
3. Below knee	2	2	4
4. Foot	3	6	9
5. Toe	11	8	19
Arterial reconstruction**			
1. Bypass procedure	53	21	74
2. Endarterectomy	29	14	43
3. Aneurysmectomy	4	0	4
Sympathectomy***	24	14	38

* Five men and two women had bilateral above-knee amputation Six of the thirty-six above-knee amputations were preceded by amputation of a toe or foot on the same leg.

** Three patients who had reconstructive surgery had subseque above knee amputation on the same side, and five had amputation of toes. Thirteen patients had more than one reconstructive operation.

*** Twenty-three patients who had sympathectomies had subseque amputations.

TABLE 6.5

PRINCIPAL DISCHARGE DIAGNOSES OF PATIENTS WITH PVD ADMITTED TO HOSPITAL DURING THE FOLLOW-UP PERIOD

Discharge diagnosis	Men No. Admissions	(%)	Women No. Admissions	(%)	Total No. Admissions	(%)
Peripheral vascular disease	131	(44.3)	69	(37.5)	200	(41.7)
Convalescent and limb-fitting	40	(13.5)	45	(24.5)	85	(17.7)
Diabetes mellitus	17	(5.7)	9	(4.9)	26	(5.4)
Gangrene	13	(4.4)	7	(3.8)	20	(4.2)
Cerebral thrombosis	11	(3.7)	6	(3.3)	17	(3.5)
Acute myocardial infarction	9	(3.0)	7	(3.8)	16	(3.3)
Ischaemic heart disease	11	(3.7)	4	(2.2)	15	(3.1)
Ischaemic rest pain (leg)	8	(2.7)	5	(2.7)	13	(2.7)
Pneumonia	5	(1.7)	5	(2.7)	10	(2.1)
Congestive heart failure	3	(1.0)	6	(3.3)	9	(1.9)
Carcinoma	9	(3.0)	0		9	(1.9)
Failure of reconstructive arterial surgery	8	(2.7)	0		8	(1.7)
Arteriosclerosis	4	(1.4)	3	(1.6)	7	(1.5)
Chronic bronchitis	7	(2.4)	0		7	(1.5)
Ischaemic skin ulcer	3	(1.0)	3	(1.6)	6	(1.3)
Aortic aneurysm	5	(1.7)	0		5	(1.0)
Deep vein thrombosis	1	(0.3)	4	(2.2)	5	(1.0)
Pulmonary embolism	2	(0.7)	2	(1.1)	4	(0.8)
Hypertension	1	(0.3)	3	(1.6)	4	(0.8)
Depression	0		3	(1.6)	3	(0.6)
Angina	2	(0.7)	0		2	(0.4)
Arterial embolism	0		2	(1.1)	2	(0.4)
Peptic ulcer	2	(0.7)	0		2	(0.4)
Transient ischaemic attacks	1	(0.3)	1	(0.5)	2	(0.4)
Hyperlipidaemia	1	(0.3)	0		1	(0.2)
Alcoholism	1	(0.3)	0		1	(0.2)
Constipation	1	(0.3)	0		1	(0.2)
Total	296	(100)	184	(100)	480	(100)

TABLE 6.4

NUMBER OF HOSPITAL ADMISSIONS OF PATIENTS WITH PVD DURING THE FOLLOW-UP PERIOD

Number of admissions	Men No. (%)	Women No. (%)	Total patients No. (%)	Total number of admissions
1	29 (29.3)	21 (34.4)	50 (31.3)	50
2	27 (27.3)	16 (26.2)	43 (26.9)	86
3	14 (14.1)	8 (13.1)	22 (13.8)	66
4	9 (9.1)	5 (8.2)	14 (8.8)	56
5	10 (10.1)	2 (3.3)	12 (7.5)	60
6	3 (3.0)	1 (1.6)	4 (2.5)	24
7	3 (3.0)	2 (3.3)	5 (3.1)	35
8	3 (3.0)	3 (4.9)	6 (3.8)	48
≥9	1 (1.0)	3 (4.9)	4 (2.5)	55
Total	99 (100)	61 (100)	160 (100)	480

TABLE 6.3

THE OBSERVED NUMBER OF DEATHS IN THE PATIENTS WITH PVD DURING A FIVE-YEAR FOLLOW-UP PERIOD COMPARED TO THE EXPECTED NUMBER OF DEATHS IN THE GENERAL POPULATION, CONTROLLING FOR AGE AND SEX

	Men			Women		
Age	No. at risk	observed deaths	expected deaths	No. at risk	observed deaths	expected deaths
35-49	10	4	0.20	6	0	0.12
50-59	33	8	2.64	7	1	0.28
60-69	23	12	4.60	14	5	1.40
70-79	26	19	10.66	24	16	6.48
80-94	7	6	3.92	10	8	4.10
Total	99	49	22.02*	61	30	12.38**

Significance levels of increased deaths in patient group

* $X^2_1 \simeq 49.0$, $p<0.0001$

** $X^2_1 \simeq 33.3$, $p<0.0001$

X^2 values were calculated according to the formula -

$$X^2_1 \simeq \sum \frac{(/O-E/-\frac{1}{2})^2}{N.p.(1-p)}$$

(Normal approximation to the binomial distribution, Diem and Lentner (1970), pp. 183)

O = observed deaths
E = expected deaths = No. at risk x probability of death
N = total number of patients
p = probability of death in normal people (from Table 6.5)

used the rates shown in Table 6.2 to calculate the expected number of deaths which would occur during a five-year follow-up in a general population with the age and sex distribution of the patients in this study (Table 6.3). The patients with PVD were more than twice as likely to die than people in the general population.

2. HOSPITAL ADMISSIONS AND DURATION OF STAY IN HOSPITAL

The 160 patients had a total of 480 hospital admissions (including the first admission for PVD) during the follow-up period (Table 6.4). The principal diagnoses at discharge are summarized in Table 6.5. The average duration of each hospitalization, excluding convalescent admissions, was 18 days (range three to 108), and if all admissions including those for convalescence and limb fitting are counted, there were a total of 11,190 patient-days in hospital during the follow-up period.

3. SURGICAL OPERATIONS

Table 6.6 summarizes the surgical procedures performed for PVD during the follow-up period, including those done at the first hospital admission. Twenty-eight men (28%) and 20 women (33%) had amputations of some kind, and 12 patients had amputation of a foot or more on both legs. Reconstructive operations were performed on 39 men (39%) and 14 women (23%), and subsequent amputations occurred in eight of these patients. Sympathectomy was performed in 38 patients, many of whom had severe PVD, and subsequent amputation occurred in more than one-half.

4. THE EFFECT OF CERTAIN RISK FACTORS ON THE DEATH AND AMPUTATION RATES

(a) Age and sex

Figure 6.3 shows the proportion of patients surviving after the first hospital admission for PVD, divided by age. A

FIGURE 6.5

THE EFFECT OF ISCHAEMIC HEART DISEASE ON THE SURVIVAL OF PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE

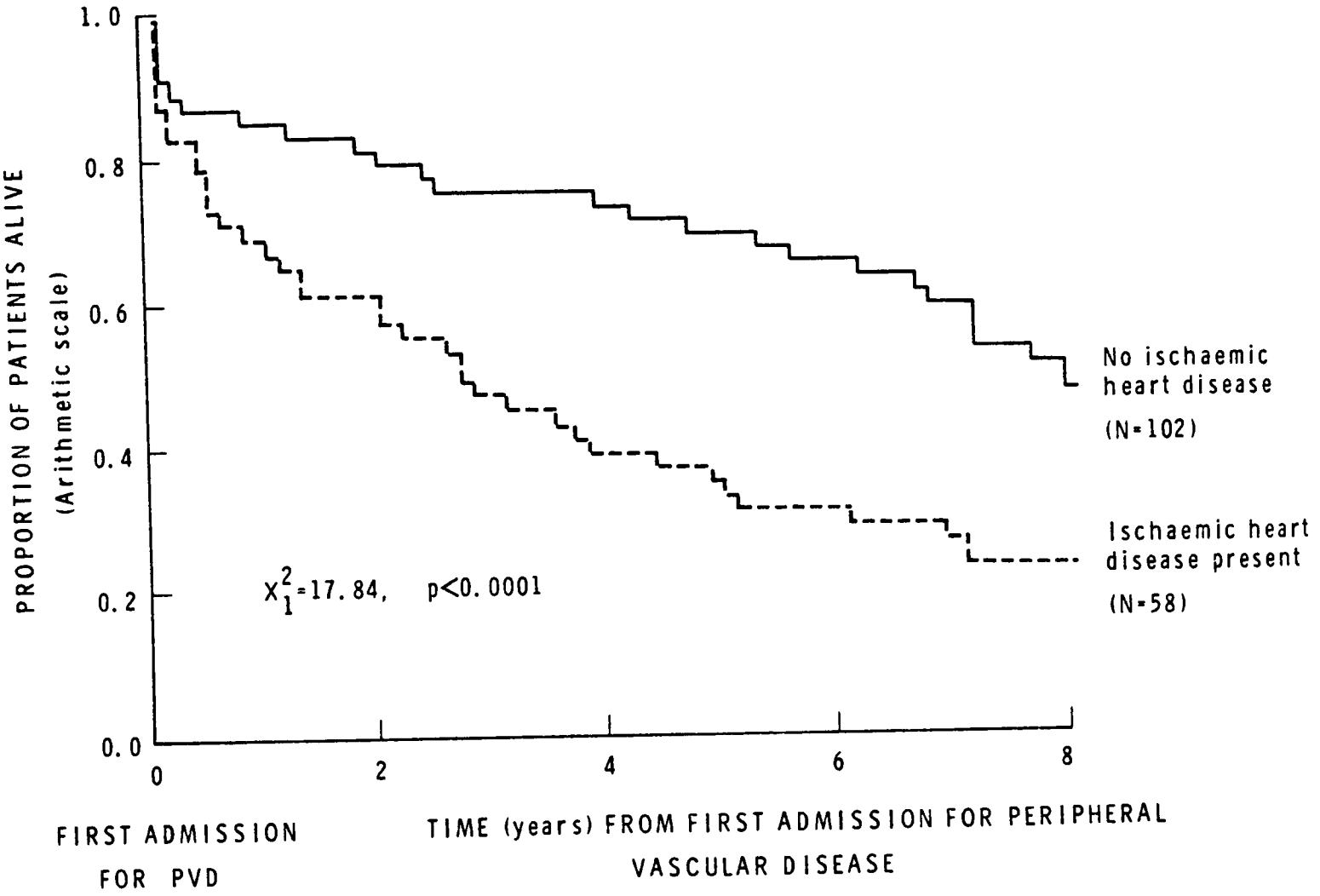


FIGURE 6.3

THE EFFECT OF AGE ON SURVIVAL OF PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE

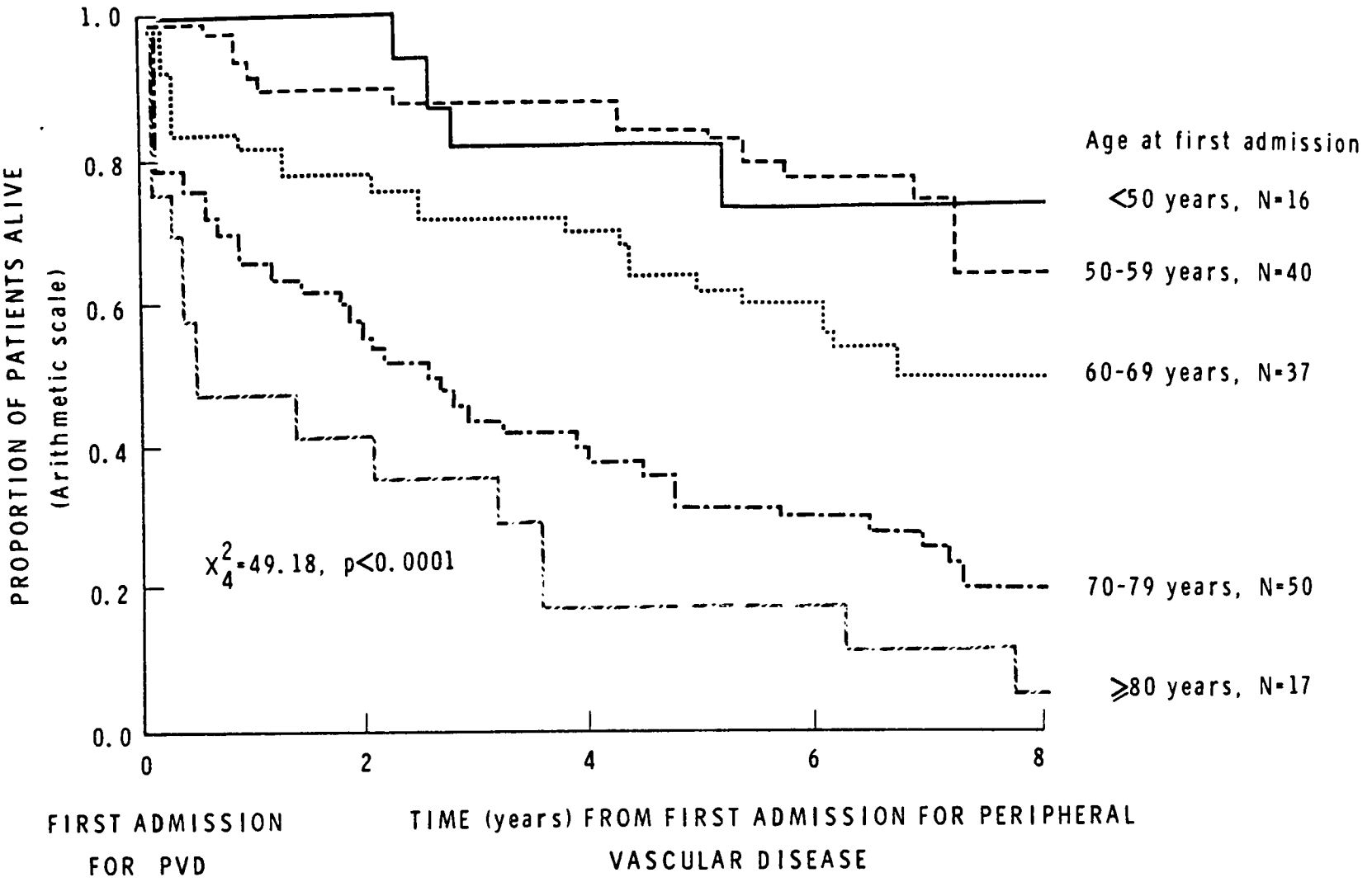
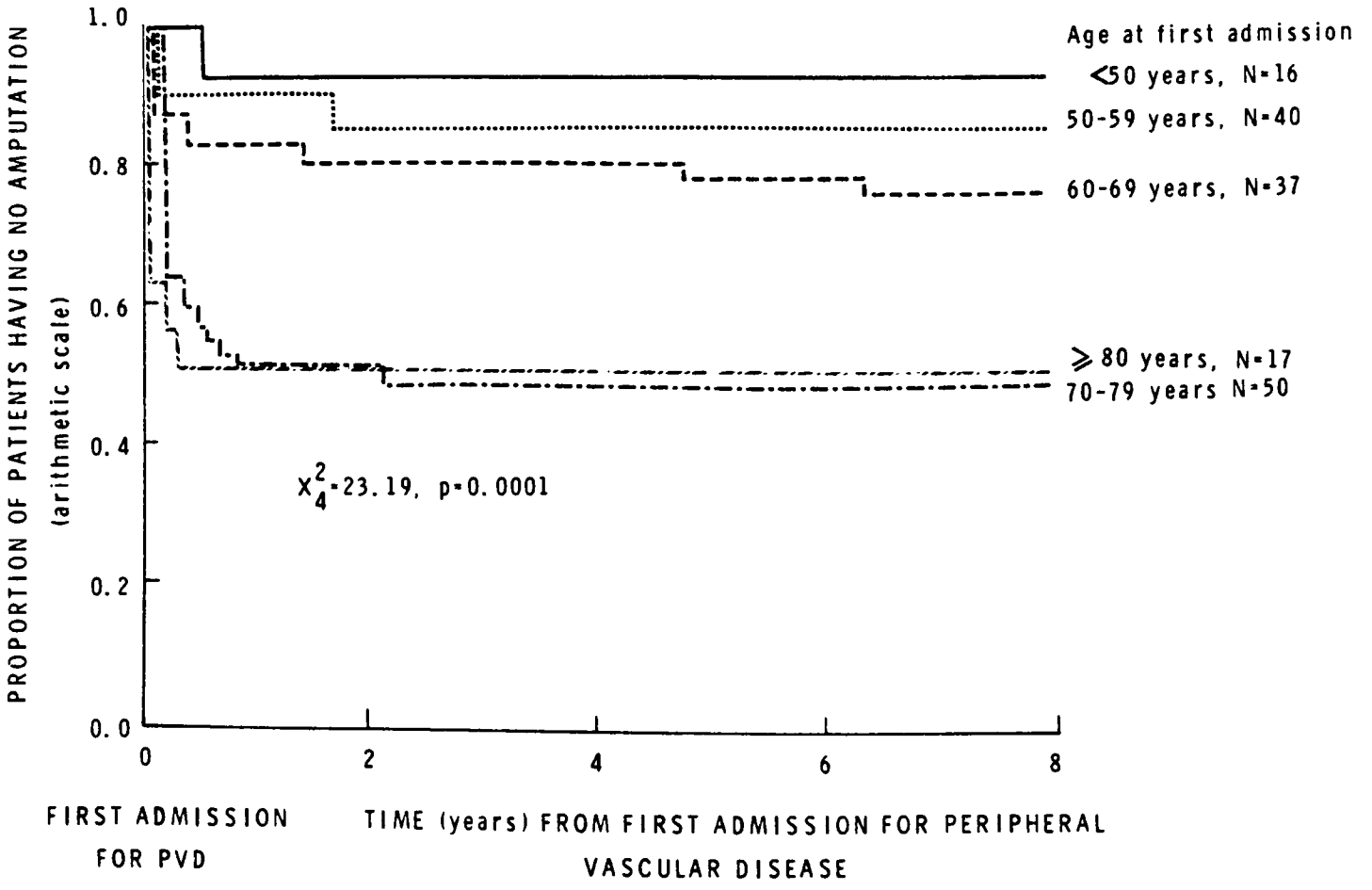


FIGURE 6.4

THE EFFECT OF AGE ON THE AMPUTATION RATE OF PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE



significantly higher proportion of older patients died during the follow-up period (corrected for sex, $X^2_4 = 52.42$, $p<0.0001$). The proportion of patients having an amputation, divided by age, is presented in Figure 6.4. The time intervals used to compute this life table were from the first admission for PVD to the first amputation, so that multiple amputations in the same patient do not appear. It can be seen that approximately one-half of those 70 years and older had amputations within the first year, and that the risk of amputation was significantly greater in the older patients (corrected for sex, $X^2_4 = 21.62$, $p = 0.0002$). Eleven of the 18 patients who had more than one amputation were 70 years or older.

A greater proportion of men than women died during the follow-up period, but, corrected for age, there was no significant difference in the survival of the two sexes ($X^2_1 = 3.03$, $p = 0.0818$). Nor was there a significant effect of sex on the amputation rate (corrected for age, $X^2_1 = 0.36$, $p = 0.5509$).

(b) Ischaemic heart disease

Fifty-eight patients (31 men, 27 women) had evidence of ischaemic heart disease (IHD) at the first hospital admission for PVD (criteria for diagnosing IHD were the same as discussed in Chapter 4). The death rate of patients with IHD was significantly higher than that of those without IHD (Figure 6.5). (Corrected for age and sex, $X^2_1 = 6.62$, $p = 0.0101$). The presence of IHD did not increase the amputation rate compared with claudicants free of IHD.

(c) Cerebral vascular disease

Thirty-five patients (22 men, 13 women) had a history of transient ischaemic attacks (a neurological disorder of vascular

FIGURE 6.8

THE EFFECT OF DIABETES ON THE AMPUTATION RATE OF PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE

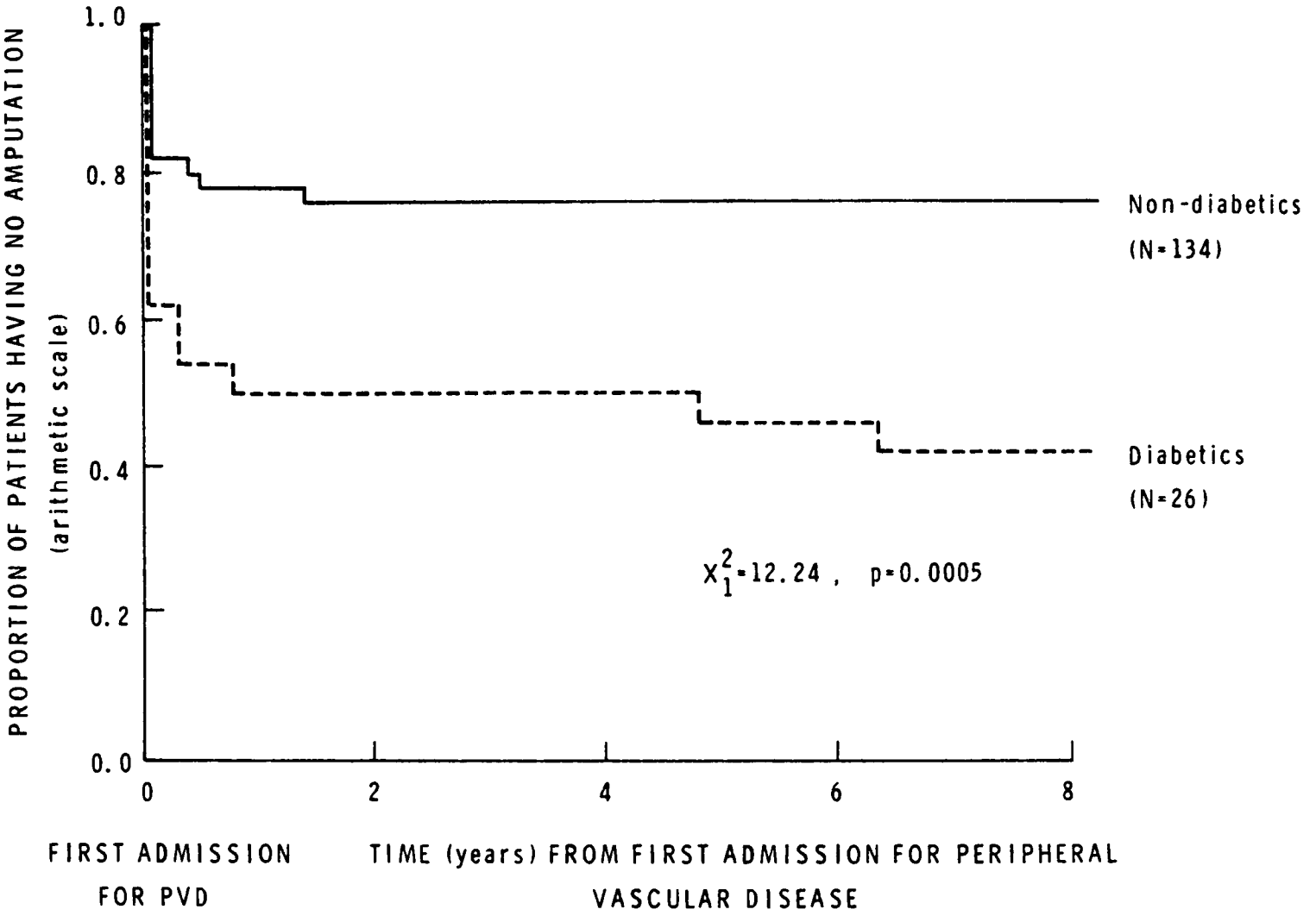


FIGURE 6.6

THE EFFECT OF CEREBRAL VASCULAR DISEASE ON THE SURVIVAL OF PATIENTS ADMITTED TO HOSPITAL FOR PERIPHERAL VASCULAR DISEASE

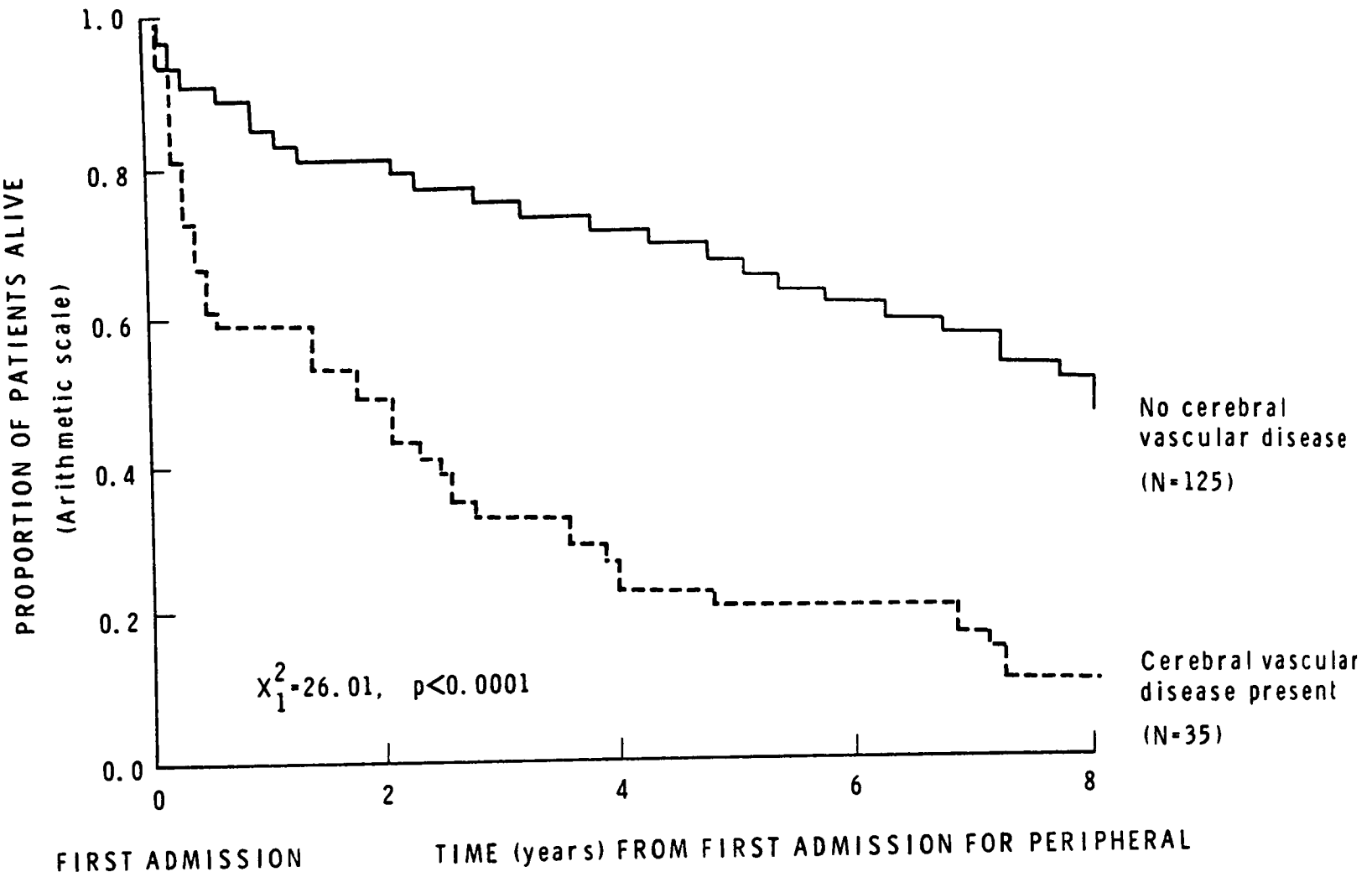
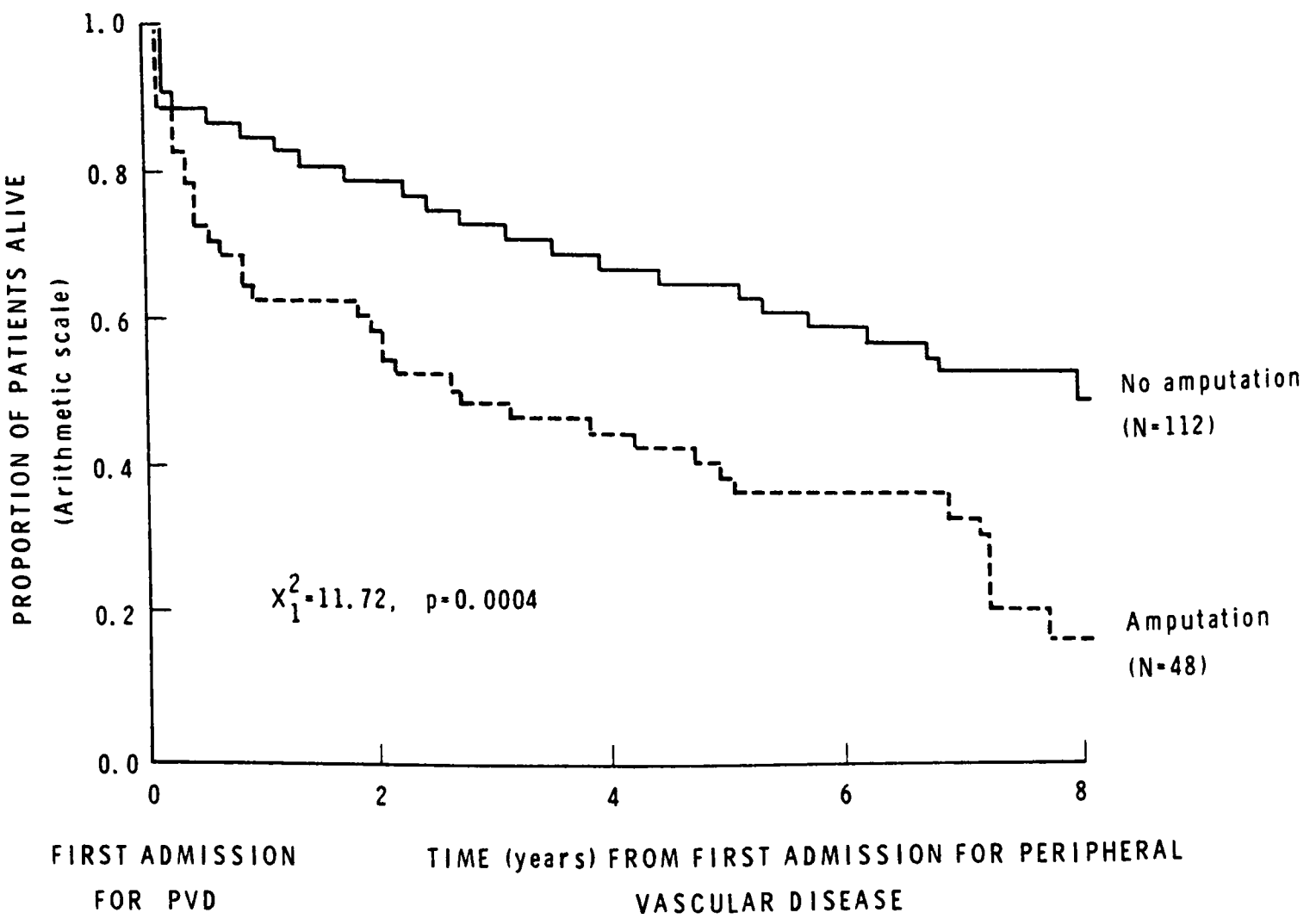


FIGURE 6.7

THE SURVIVAL OF PATIENTS ADMITTED TO HOSPITAL FOR PVD WHO HAVE AMPUTATION COMPARED TO THOSE WITHOUT AMPUTATION



origin lasting less than 24 hours, Dyken et al, 1977)) or stroke at first admission for PVD. The survival of these patients was significantly less than those with no history of cerebral vascular disease (Figure 6.6). (Corrected for age and sex, $X^2_1 = 14.53$, $p = 0.0001$). Patients with cerebral vascular disease did not have a higher amputation rate than those free of cerebral vascular disease.

(d) Amputation

Figure 6.7 shows the survival of the 48 patients who had an amputation compared with those who did not. A greater proportion of amputees died during the follow-up period, but when correction was made for age and sex, the difference between the two groups was not statistically significant ($X^2_1 = 2.40$, $p = 0.1211$).

(e) Diabetes

The diagnosis of diabetes was based on a history of previous treatment, since fasting glucose levels or the results of glucose tolerance tests were recorded infrequently in the hospital notes. Twenty-six patients (16 men, 10 women) had received treatment for diabetes at the time of the first hospital admission for PVD. There was no significant effect of diabetes on the death rate (corrected for age and sex, $X^2_1 = 0.02$, $p = 0.8800$), but diabetes was associated with an increased risk of amputation (Figure 6.8). (Corrected for age and sex, $X^2_1 = 10.07$, $p = 0.0015$).

(f) Blood pressure

Twenty patients(nine men, 11 women) had received treatment for hypertension, and blood pressure was recorded in the notes of 131 of the 160 patients (81%) at the first admission for PVD. The mean systolic pressure (SBP) was 168 mm Hg (range 120 to

320), and the mean diastolic pressure (DBP) was 96 mm Hg (range 70 to 130). The mean level was higher in the women (SBP 180, DBP 97) than the men (SBP 160, DBP 95), but the difference was not statistically significant. Patients with a history of hypertension did not have a higher death or amputation rate than patients without this history. Nor did elevated SBP (levels examined were 160, 180, 200 mm Hg) or DBP (levels examined were 90, 100, 110 mm Hg) have a significant effect on the death or amputation rates. It should be noted that these blood pressure measurements were simply taken from the notes and were therefore not recorded under standardized conditions.

(g) Smoking

Data on smoking habits at first admission were recorded in the notes of 117 of the 160 patients (73%). Of these, 152 (89%) were smokers or ex-smokers (defined as in Chapter 4). The date of stopping smoking in ex-smokers was usually not stated. The amount of tobacco smoked was recorded in 73 patients, and 46 (63%) smoked 15 or more cigarettes a day. The proportion of people who had smoked and the amount of tobacco smoked were similar in men and women.

Unfortunately, changes in smoking habits after the first admission were rarely recorded in the notes, and only 17 patients were said to have stopped (15) or reduced (two). I have examined the death and amputation rates of this small group of patients, and there was no significant improvement in prognosis compared with other smokers whose habits subsequent to admission were not recorded.

Fifteen patients had more than one amputation at different hospital admissions more than six months apart. The smoking habit at the second amputation was recorded in ten, and it is of

interest that eight patients were still smoking.

D. DISCUSSION

The principal causes of death in 47 of the 94 patients who died (50%) were attributed to coronary artery or cerebral vascular disease, and though pneumonia was the most common cause recorded, this was often the terminal complication of an illness initiated by an ischaemic event. This observation is in agreement with the studies described in Chapter 1 which found that most deaths in patients with PVD were due to atherosclerotic vascular disease in the coronary and cerebral circulations.

Peripheral vascular disease accounted for only six deaths (including three post-operative deaths), but was associated with significant morbidity. Forty-eight patients in this series (30%) had an amputation, many losing a leg above the knee. The amputation rate in this study was higher than that reported in other series of claudicants, possibly because of the advanced age of many of the patients when first admitted for PVD. Mathieson and Mune (1966) found that patients with PVD younger than 70 years of age usually presented to hospital with intermittent claudication, but those older than 70 were more than twice as likely to present with gangrene. The authors attributed this to decreased mobility in the elderly (and hence less opportunity to complain of IC), greater involvement of distal arteries, and a higher prevalence of diabetes mellitus.

The study described in Chapter 5 found that a greater proportion of men than women died during the follow-up. Higher mortality in men was also observed in this series of patients (though the difference in survival of the two sexes was not statistically significant), even though the women were an average of five years older. This was not due to an increased prevalence

of ischaemic heart disease or cerebrovascular disease at first hospital admission in the men, nor could it be explained on the basis of the other risk factors examined. It was of interest that cerebral thrombosis was the most common diagnosis listed as a primary or contributing cause of death in women, while myocardial infarction and ischaemic heart disease were recorded more frequently in men (see Appendix 6.3). This may indicate that the distribution of atherosclerotic lesions in women with PVD differs from that of men with PVD with a prediliction for coronary involvement in men. Since the incidence of coronary artery disease in the general population is greater than the incidence of atherothrombotic brain infarction (see Figure 1.1), and coronary artery disease occurs more frequently in men than women, it is likely that occult coronary atherosclerosis present at the first hospital admission accounted for the greater mortality in men. The study in Chapter 5 also found a higher amputation rate in men, though there were few women in the patient group. With the larger numbers in this study, no significant difference in the amputation rate of the two sexes was observed, a finding in agreement with other follow-up studies of patients with PVD (Silbert and Zazeela, 1958; Bloor, 1960).

The prevalence of ischaemic heart disease and cerebral vascular disease at the start of the follow-up period was higher than that found in other studies, though most series have reported evidence of generalized atherosclerosis in a significant proportion of patients (Selvaag, 1956; Spalding, 1956). Larger numbers and the longer period of follow-up resulted in the expected observation that patients with a history of ischaemic heart disease had a higher death rate than those without ischaemic heart disease, a finding not evident in the study

described in Chapter 5. Cerebral vascular disease (as in Chapter 5) was associated with a significantly increased mortality rate. There was no indication that patients with evidence of generalized atherosclerosis (i.e. ischaemic heart disease or cerebral vascular disease) had an increased risk of amputation compared with those with PVD only.

The increased amputation rate of diabetic patients has been found in other studies, and, as discussed in Chapter 1, may have been due to greater involvement of the distal arteries with poor development of collateral circulation and a decreased chance of successful reconstructive surgery. The effect of elevated serum lipids on prognosis could not be examined in this study because values were recorded in only a small proportion of the patients' notes. More complete data was available concerning blood pressure, and elevated levels of systolic and diastolic pressure were present in the majority of patients. An adverse effect of elevated blood pressure on the survival of claudicants has been shown in some studies (Spalding, 1956; Begg and Richards, 1962), but was not seen in this series. This may have been due to the very high prevalence of hypertension in the patient group which made it difficult to identify a significant number of normotensive people (only 34 patients had both systolic BP<160 and diastolic BP<90). Blood pressure was not measured under standardized conditions in this study so that there was undoubtedly considerable error in the values recorded. This may have masked a significant effect of blood pressure on prognosis.

One of the objectives of this study was to confirm the observation that patients with PVD who continue to smoke have a worse prognosis than those who stop or reduce (Chapter 5). The

data available in the hospital notes concerning smoking habits during the follow-up period were incomplete, however, perhaps indicating that the effect of smoking on the success of treatment was not appreciated in the mid-1960's (Robicsek et al, 1975; Birckenstock et al, 1975). As a result, I was unable to identify a significant number of patients who were smokers when first referred for PVD and who later stopped this habit. I would attribute the failure to demonstrate a significant effect of continued smoking on the death and amputation rates to the poor quality of the data. The study in Chapter 5, though containing fewer patients, had the advantage of complete data with a uniform assessment of all patients at the start of the follow-up period. Despite the small numbers, there was a significant improvement in prognosis after 12 months in those who stopped or reduced smoking, and the degree of improvement compared with those who continued smoking increased consistently as the period of abstinence from tobacco increased. For these reasons I feel that the conclusions reached in Chapter 5 concerning the effect of continued smoking on prognosis are valid and are in no way affected by the results of this second follow-up study.

The patients in this series were frequently re-admitted to hospital because of deterioration of their PVD or other closely-related problems such as coronary artery or cerebral vascular disease. Their rate of re-admission was higher than that of the general population (using re-admission rates for people admitted to major hospitals in the ORLS area for all causes), and the average duration of each acute admission (18 days) was twice as long as the average duration of admissions to general hospitals in the ORLS area for all causes (nine days for the year

1969) (Fedrick, 1977). The average cost per week of hospitalization per patient in the ORLS area, without considering the cost of any surgical or medical treatment, was approximately £54 in 1969 (Golding, 1977). (This figure has risen sharply in recent years to approximately £223 in 1976). Thus it can be appreciated that the patients with PVD consumed an inordinate proportion of the financial resources of the regional health authority.

Follow-up began with the first hospital admission for PVD, since the duration of symptoms prior to this admission was recorded in only some of the notes (and, when recorded, would likely have been subject to considerable error). However, symptoms undoubtedly existed for some time prior to this admission, and it is quite likely that most of this patient group (who had more severe disease than the patients identified in the postal survey, Chapter 4) would have consulted their general practitioners. Many were also followed as outpatients by hospital consultants for some time before admission. Thus even though death and amputation occurred frequently within the first year of follow-up, there would have been an opportunity to treat risk factors prior to the first hospital admission.

If one considers the observation that patients with IC who stop or reduce smoking when first referred to hospital have a better prognosis than patients who continue smoking (Chapter 5), one can postulate that if the patients in this series had been persuaded to give up smoking when they first consulted their doctor, at least some of the subsequent hospital admissions, deaths and amputations might have been avoided. In view of the frequent and protracted hospital admissions associated with PVD, the present high costs of medical care, and the inevitable loss

of productivity which would follow amputation, it can be argued that continued smoking not only places the individual patient with PVD at risk, but has significant adverse effects on the community as a whole.

E. SUMMARY

A group of 160 patients admitted to hospital for peripheral vascular disease in 1965 and 1966 were observed until the end of 1972. The morbidity and mortality associated with PVD were examined using information provided by a computer-based linked-record system. Peripheral vascular disease was associated with an increased risk of death compared with the general population. Within the patient group elderly people and those with a history of ischaemic heart disease and cerebral vascular disease at first admission had a higher mortality than patients free of these complaints. There was also considerable morbidity with frequent re-admission to hospital, reconstructive arterial surgery, and amputation. Factors associated with an increased risk of amputation were increasing age at first admission and a history of diabetes. Patient morbidity constituted a burden to the Health Service, and the possible consequences of continued smoking in these patients on medical resources were discussed.

SECTION 4

CHAPTER 7

A TRIAL OF CINNARIZINE IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

Chapter 7 A TRIAL OF CINNARIZINE IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

A. INTRODUCTION

The non-surgical treatment of peripheral vascular disease (PVD) has been reviewed in Chapter 1. None of these forms of therapy was shown to significantly improve the symptom of intermittent claudication (IC), and at the present time there is no drug available which has proven efficacy in the treatment of this disorder. Only three (7%) of 43 claudicants reviewed four years after referral were receiving medications to improve their claudication (Chapter 5), a fact which may reflect current medical opinion of the treatment available (Editorial, B.M.J., 1976d).

Reconstructive arterial surgery is the only form of therapy which, when successful, produces dramatic relief of symptoms. The decision to perform an operation is based on a number of criteria, some of which are discussed in Chapter 1. The attitude toward surgery varies in different centres, but even the most aggresive vascular surgeon has a large proportion of patients referred for whom no reconstructive operative procedure is suitable. Many of these people are seriously disabled and have severe pain. In addition to reducing factors such as smoking, which worsen prognosis, there is a continuing need to find a non-surgical form of treatment for a disease which afflicts approximately two per cent of adults.

A drug suitable for the treatment of intermittent claudication should have the following characteristics:

1. It should be effective orally with a duration of action long enough to permit a convenient dosage schedule.

2. It should be devoid of side effects at therapeutically effective dose levels, and should have no toxic interactions with other commonly used drugs.
3. Its mechanism of action should not result in general vasodilation, since this may reduce flow to the ischaemic limb.
4. It must result in significant symptomatic relief with improvement in objective measurements such as blood flow and exercise tolerance (i.e. symptom relief is not due simply to analgesia or a placebo effect).

During a review of the literature, I discovered reports of a drug named Cinnarizine which seemed to fulfil the first three criteria, and possibly the fourth. First used to treat vestibular disorders, Cinnarizine was found to increase post-ischaemic reactive hyperaemia in patients with PVD without causing changes in blood pressure or pulse rate (Schuermans et al, 1971; Ellis et al, 1975). This effect was evident within three days of starting the drug at doses of 75 to 150 mgm orally three times a day. The only significant side effect was drowsiness which usually stopped within a few days.

Experiments on animal preparations (rat aorta, rabbit mesenteric artery, perfused hind leg of the dog) have shown that Cinnarizine is a potent inhibitor of arterial smooth muscle cell contraction induced by several vasoactive substances including epinephrine, norepinephrine, angiotensin, potassium chloride, and 5-hydroxytryptamine (Godfraind, 1974; Godfraind and Kaba, 1969; Van Neuten and Janssen, 1972). The mechanism of action is believed to be a decrease in the influx of calcium ions across the depolarized membrane of stimulated smooth muscle cells, thus inhibiting the calcium-dependent contractile

proteins (Godfraind et al, 1973; Godfraind and Kaba, 1969).

Cinnarizine has been used in humans to treat crural ulcers due to diabetes, arteriosclerosis and varicose veins. Aussems and Muls (1970) added Cinnarizine or a placebo (double-blind) to the normal treatment of 44 patients, and found a significantly shorter healing time of the ulcers of patients treated with Cinnarizine. Similar conclusions were reached by Jacobs (1968) and Neto (1971) in two uncontrolled trials of 66 and 17 patients, respectively, who were suffering from ischaemic skin ulcers.

Forty-seven men aged 40 to 60 years with IC (walking distance 100 to 500 metres) were treated with Cinnarizine for a period of three months (Joos, 1968). Reported walking distance was the only measure of severity, and there was no change in this variable after treatment. A second group of 21 patients suffered from rest pain, and treatment with Cinnarizine was associated with a significant reduction in the amount of analgesics consumed and subjective improvement in 18 patients.

A randomized double-blind trial of Cinnarizine in the treatment of 18 claudicants was reported by Adriensen (1969). After eight weeks of treatment there was a striking improvement in the subjective symptoms of four of the nine patients treated with active drug compared with one patient on placebo who improved slightly. This improvement was associated with increased maximum blood flow to the leg (measured by ^{133}xenon clearance) which may have been partly attributable to a training effect of the exercise programme used to induce hyperaemia.

Schuermans et al (1971) studied the effect of Cinnarizine on 23 men aged 61 to 84 years who had evidence of PVD (muscle wasting, trophic changes, diminished pulses) without obstruction

of a major leg artery. Peripheral blood flow (I^{131}-tagged albumin clearance), vascular tone (digital plethysmography), and muscle capacity (ischaemic isotonic contraction after peroneal nerve stimulation) were measured at the start of the trial and after treatment with Cinnarizine for three months. Twelve patients were allocated at random to the treatment group, and 11 given a placebo (double-blind). At the end of the study there was a significant increase in the muscle capacity and reactive hyperaemia measured by plethysmography of the patients treated with Cinnarizine compared with the placebo group. There was also an increase in maximum flow to the leg in the treatment group which was not significant ($p=0.09$).

The patients studied by Schuermans et al had patent arteries, and details of symptoms such as IC and rest pain were not described. The results of this study cannot, therefore, be applied to patients with IC. Ellis et al (1975) examined the acute effect of Cinnarizine on the circulation of ten claudicants with angiographically-proven PVD. Patients were treated for seven days, and reactive hyperaemia after exercise was measured by mercury strain gauge plethysmography. At the end of the study there were significant increases in the post-exercise blood flow of all patients, and no evidence of a "steal" effect from the more diseased leg. Six of the 10 patients said their walking tolerance had improved.

Staessen (1977) treated 28 patients with PVD (16 with IC, 12 with rest pain) for four months in a double-blind trial of Cinnarizine compared with a placebo. Changes in patient symptoms were recorded with a questionnaire, and after four months there was a significant improvement ($p<0.05$) in those with IC treated with Cinnarizine compared with claudicants who received the

placebo, but no improvement in patients with rest pain. There were no objective measurements of blood flow or exercise tolerance.

The studies described above provided evidence that Cinnarizine may improve the subjective symptoms of claudicants. None of these recorded changes in the peripheral circulation after prolonged treatment with Cinnarizine using objective measurements such as the ankle systolic blood pressure or blood flow determined by plethysmography. In order to provide such data, it was decided to begin a trial of Cinnarizine in which subjective symptoms and objective measurements would be recorded and compared. A mercury strain gauge plethysmograph was used to measure blood flow, allowing comparison of this method and the Doppler ultrasound flow meter. It was decided initially to test the effect of four months treatment with Cinnarizine on the peripheral circulation of 20 claudicants. If there was any objective evidence of improved blood flow to the legs at the end of this period, a randomized double-blind trial of Cinnarizine compared with a placebo was planned.

B. METHODS

1. SUBJECTS

The patients in this study had been referred to the Radcliffe Infirmary, Oxford, because of intermittent claudication. All patients were considered initially for surgery, and were assigned to the drug trial if their symptoms had been stable for at least six months and if there was no immediate indication for arterial reconstruction. During a six-month recruitment period, 21 patients were considered eligible to start the trial, five of whom had had previous operations for PVD (more than six months before starting Cinnarizine). Two patients were rejected

from the study at the initial examination. One was found to have severe hypertension requiring urgent treatment with drugs which would alter blood flow to the legs, and the other patient suffered a pulmonary embolus before starting the drug and received long-term anticoagulant treatment. There was one diabetic treated with insulin, and two hypertensive patients whose medication was not altered during the trial. None of the other patients were taking medications on a regular basis.

In order to define the normal mean value and range of the blood flow variables measured in this study, control patients were selected who had been referred to the same group of surgeons for a variety of non-vascular diseases and who had no history of hypertension, hyperlipidaemia, diabetes, coronary artery or cerebral vascular disease. Strict matching for age was not done, since it has been shown that blood flow measurements are not significantly affected by age in normal people or patients with PVD (Myers, 1964; Sigaard-Andersen, 1965).

2. PATIENT ASSESSMENT AT THE START OF THE TRIAL

The technique used in the patient interview and physical examination was the same as described in Chapter 2. The stimulus used for the post-exercise ankle systolic pressure was 60 depressions of a foot treadle (resistance 6 kg.) in two minutes. A blood sample was drawn after a 12-hour fast, and a number of tests performed (Table 2.2). In addition to this, a mercury strain gauge plethysmograph was used to determine the resting blood flow and pattern of reactive hyperaemia following three minutes of arterial occlusion.

Cases and controls were told not to smoke, and drank only water on the morning of the interview. The examinations were performed in a warm room (24 to 28°C) and the legs were covered

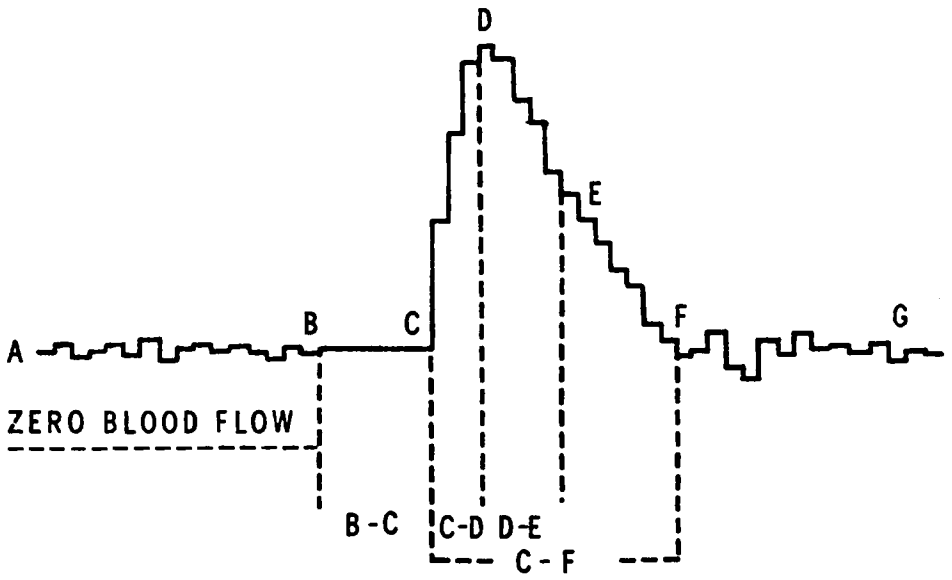
with a blanket. Skin temperature was recorded with a thermo-couple attached to the foot. The patient was supine in a comfortable bed, and the legs elevated slightly above the level of the heart to ensure venous drainage (Dahn, 1965). Blood pressure cuffs (20 cm wide) were placed around the thighs and connected to a two-channel compressed air system (venous occlusion pressure 40 mm Hg, arterial occlusion pressure 250 to 300 mm Hg). Ankle cuffs were not used, since it has been shown that the exclusion of foot blood flow has little effect on the hyperaemic response (Storen, 1967; Shepherd, 1950; Sigaard-Andersen, 1965). Silastic mercury strain gauges (internal diameter 0.30 mm, external diameter 0.64 mm) were applied to the calves at their greatest circumference. The location of the gauges (cm below patella) and circumference of the calf at that point were recorded so that conditions at follow-up examination could be standardized.

The plethysmograph was ECG-triggered, and, when recording blood flow, venous occlusion occurred for three heart beats with a recovery time of two heart beats. The compressed air systems had 100-litre reservoirs, allowing instantaneous (1.5 second) changes in pressure, and it was possible to begin recording flow within one heart beat after arterial occlusion. Thus there was no delay in measuring peak blood flow. Flow patterns for each leg (strain gauge signal and integrated arterial input) were produced on X-Y recorders.

Measurements did not begin until the patient's heart beat and skin temperature were stabilized. Resting blood flow was then recorded, and after at least two minutes at a constant level of flow the cuffs were inflated above arterial pressure for three minutes. At the end of this period the cuffs automatically

FIGURE 7.1

THE REACTIVE HYPERAEMIA PATTERN AFTER ARTERIAL OCCLUSION AND THE VARIABLES MEASURED



A	REST FLOW
B	ARTERIAL OCCLUSION BEGINS
C	ARTERIAL OCCLUSION ENDS
D	PEAK FLOW
E	½ (PEAK FLOW-REST FLOW)
F	END OF HYPERAEMIA
G	POST-STIMULUS FLOW
B-C	DURATION OF ARTERIAL OCCLUSION
C-D	TIME TO PEAK FLOW
D-E	TIME TO ½ (PEAK FLOW-REST FLOW)
C-F	DURATION OF HYPERAEMIA

deflated, the venous occlusion cycle started, and peak blood flow had been reached. The plethysmograph was calibrated each day and at the end of each measurement (the pen deflections produced by 0.1, 0.5, and 1.0 per cent lengthening of the gauges were recorded) to ensure a constant response. Blood flow was calculated according to the method described by Whitney (1953).

Figure 7.1 is a tracing of the plethysmograph record of a patient with mild IC (walking distance 500 yards). Variables measured included rest flow (A), peak flow (D), time to peak flow (C-D), and duration of hyperaemia (C-F). Patients with severe claudication often had peak flows much lower than shown in this example, with delayed onset and prolongation of hyperaemia.

After the patients had been examined they were instructed to take one tablet of Cinnarizine (75 mgm) three times a day. The pills were supplied in packets sufficient for one month, and the patients were told to bring their packets with them to the hospital when they came for follow-up. The pills were then counted to ensure that the patients had co-operated in taking the drug.

3. PATIENT FOLLOW-UP

The patients were asked to maintain a diary card of their symptoms (Appendix 7.1). Each was asked to record the number of times it was necessary to stop when walking a specific distance (e.g. from home to the bus stop) since subjective walking distance is an inaccurate index of severity (Sigaard-Andersen and Petersen, 1968). The mean number of stops was then calculated over a one-month period at the beginning and end of the trial and called the stop score. One month after starting Cinnarizine the patients were interviewed and examined, and the ankle systolic

FIGURE 7.2

CORRELATION BETWEEN THE RESTING ANKLE SYSTOLIC BLOOD PRESSURE RATIO AND THE PEAK BLOOD FLOW MEASURED BY MERCURY STRAIN GAUGE PLETHYSMOGRAPH

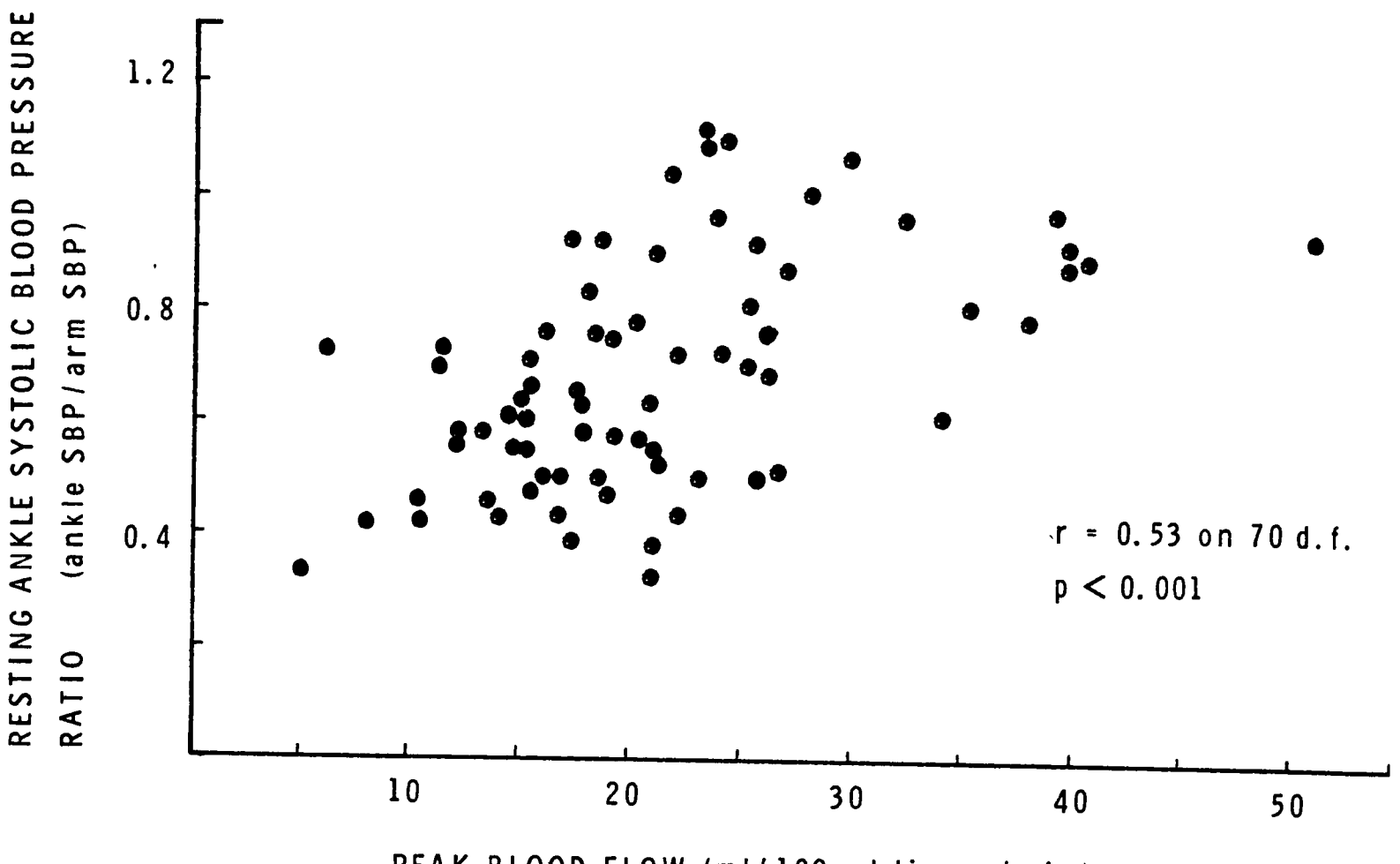


FIGURE 7.3

CORRELATION BETWEEN THE POST-EXERCISE ANKLE SYSTOLIC BLOOD PRESSURE RATIO AND THE PEAK BLOOD FLOW MEASURED BY MERCURY STRAIN GUAGE PLETHYSMOGRAPH

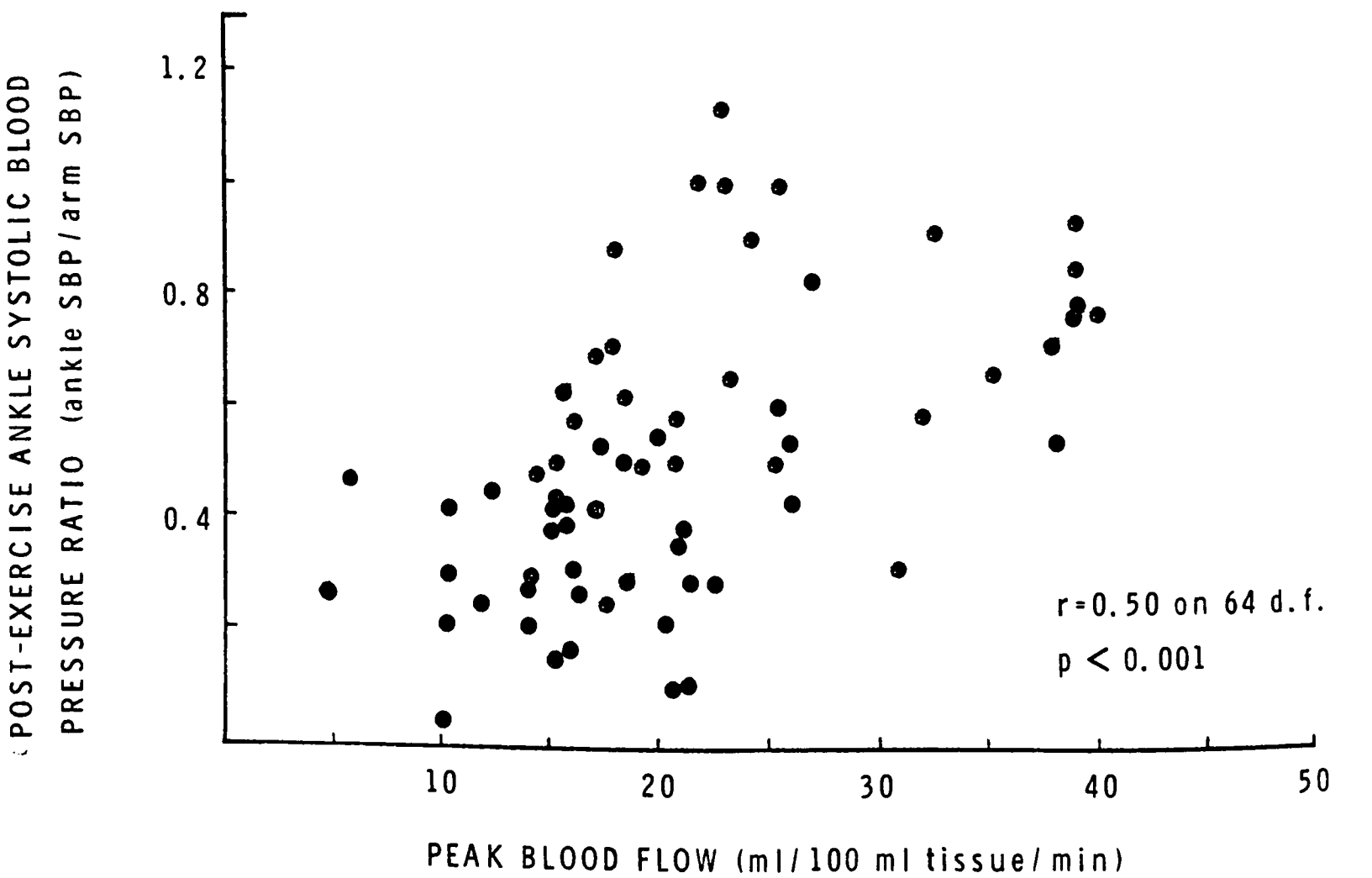


TABLE 7.1

WITHIN-PERSON CO-EFFICIENTS OF VARIATION OF VARIABLES MEASURED BY PLETHYSMOGRAPHY (24 OBSERVATIONS)

	Mean*	Co-efficient of variation (S.D./mean)
Rest flow (ml/100 ml tissue/min)	5.63	21%
Peak flow (ml/100 ml tissue/min)	26.51	8%
Ratio of peak flow/ rest flow	6.33	23%
Post-stimulus flow (ml/100 ml tissue/min)	5.83	14%
Time to peak flow (secs)	8.0	30%
T 1/2 (secs)	25.7	22%
Total time duration of hyperaemia (secs)	115.8	20%

* The means calculated were for 24 observations

pressure measured. At four months plethysmography was repeated to determine the effect of Cinnarizine on the peripheral circulation, and a fasting blood sample was drawn. Cinnarizine was then discontinued, and the patients were followed at monthly intervals (plethysmography was performed one month after the drug was stopped).

4. REPRODUCIBILITY OF THE PLETHYSMOGRAPH MEASUREMENTS AND CORRELATION OF BLOOD FLOW AND ANKLE SYSTOLIC PRESSURE TO PATIENT SYMPTOMS

Repeat observations were made on 24 cases and controls, and the coefficient of variation of the measurements was calculated (Table 7.1). Most of the variables were subject to a variation of approximately 20 per cent, and peak flow was the most reproducible measurement. There was no significant effect of age on blood flow when cases or controls were divided into ten-year age groups.

There was a significant positive correlation between the peak flow measured by plethysmography and the resting and post-exercise ankle systolic blood pressure ratios (Figures 7.2 and 7.3). In order to relate these variables to the severity of IC, correlation coefficients were calculated between the reported walking distance and stop score, and the Doppler and plethysmograph measurements (see Appendix 7.2). There was a significant positive correlation between reported walking distance and the post-exercise ankle systolic pressure ratio ($r = 0.51$ on 34 d.f., $p<0.01$) and between reported walking distance and peak flow measured by plethysmography ($r = 0.43$ on 34 d.f., $p<0.05$). There was also a significant negative correlation between the post-exercise ankle systolic pressure ratio and the stop score ($r = 0.42$, $p<0.05$). The only other flow variable that was significantly correlated with patient symptoms (walking distance)

TABLE 7.2

THE SMOKING HABITS* OF PATIENTS WITH IC AT THE START OF THE TRIAL

	Cases No. (%)
Non-smoker	1 (6)
Ex-smoker	3 (17)
Pipe and cigar smoker	1 (6)
Cigarette smoker -	
1-14/D	7 (39)
15-24/D	5 (28)
≥25/D	1 (6)
Total	18(100)

* The definition of smokers, ex-smokers and non-smokers is presented in Chapter 4

was the ratio of peak flow/rest flow ($r = 0.37$, $p<0.05$).

C. RESULTS

1. PATIENT INTERVIEWS AND EXAMINATIONS AT THE START OF THE TRIAL

One patient was withdrawn from the study after a month because of severe ischaemia requiring reconstructive surgery. The remaining 18 patients (16 men, two women) had a mean age of 58.0 years (range 47 to 67). Eleven had bilateral, and seven patients unilateral IC. All but two reported a gradual onset, and the average duration of symptoms was 24 months (range 12 to 84). No patient complained of rest pain, and the average reported walking distance was 400 yards (range 90 to 700). The patients' symptoms had been stable for at least six months before the start of the trial.

Three patients gave a history of myocardial infarction, and two of these suffered from angina. Five patients who had no history of coronary artery disease had electrocardiograms indicating ischaemia. Thus eight patients (44%) had evidence of ischaemic heart disease. One patient had suffered a stroke, and five had chronic bronchitis (criteria are discussed in Chapter 2). The smoking habits of the cases are presented in Table 7.2, and those of the controls used to establish the normal values for plethysmograph measurements are shown in Appendix 7.3.

Physical examination revealed that all patients had evidence of peripheral vascular disease (diminished or absent foot pulses, bruits, trophic changes) in at least one leg. None had skin ulcers or gangrene. No patients had had a sympathectomy, but five had undergone reconstructive arterial surgery.

As discussed earlier, none of the control patients had a history of peripheral vascular or coronary artery disease, and

TABLE 7.4

THE BLOOD FLOW MEASUREMENTS OF THE CONTROLS AND OF THE PATIENTS AT THE START OF THE TRIAL AND AFTER FOUR MONTHS TREATMENT

Variable $\bar{x} \pm$ S.E. (range)	Controls	Cases before Cinnarizine	Cases after four month treatment
Rest flow (ml/100 ml tissue/min) *	4.8 ± 0.5 (1.0 - 8.4)	6.5 ± 0.5 (1.0 - 15.6)	5.9 ± 0. (1.9 - 18
Peak flow (ml/100 ml tissue/min) **	34.8 ± 1.7 (18.9 - 60.5)	21.2 ± 1.5 (5.7 - 50.8)	21.1 ± 1 (5.0 - 39
Ratio of peak flow/rest flow **	9.3 ± 0.8 (2.7 - 20.0)	4.2 ± 0.6 (1.3 - 16.0)	4.7 ± 0 (1.5 - 17
Post occlusion flow (ml/100 ml tissue/min) *	4.8 ± 0.5 (0.9 - 13.2)	6.6 ± 0.5 (2.9 - 10.1)	6.2 ± 0 (2.8 - 18
Time to peak flow (secs) **	5.4 ± 0.2 (5.0 - 10.0)	14.7 ± 2.2 (5.0 - 60.0)	11.8 ± 2 (5.0 - 43
Time to ½ peak flow (secs) **	15.9 ± 1.4 (4.8 - 45.6)	35.6 ± 3.6 (7.2 - 78.0)	32.5 ± 3 (5.0 - 69
Total duration of hyperaemia (secs) **	114.1 ± 6.0 (31.2 - 159.0)	156.4 ± 8.3 (67.2 - 266.6)	153.2 ± 8 (91.2 - 248

Differences between controls and cases before treatment

* $p<0.02$

** $p<0.001$ Mann-Whitney U test (Siegel, 1956)

There were no significant differences between the paramet of cases measured before and after treatment. Wilcoxon matched-pairs signed ranks test (Siegel, 1956)

TABLE 7.3

THE RESULTS OF THE MEASUREMENTS* PERFORMED AT THE START OF THE TRIAL AND AFTER FOUR MONTHS OF TREATMENT WITH CINNARIZINE

Measurement $\bar{x} \pm$ S.E. (range)	Initial examination	Four month follow-up
Haemoglobin (gm/100 ml)	15.2 ± 0.31 (13.8 - 18.7)	14.5 ± 0.26 (12.7 - 16.3)
Haematocrit (%)	45.0 ± 0.9 (38.8 - 53.7)	42.8 ± 0.9 (35.3 - 48.0)
Blood glucose (mmol/l)	5.3 ± 0.9 (3.6 - 19.4)	5.5 ± 1.0 (3.8 - 19.7)
Serum cholesterol (mmol /l)	6.6 ± 0.4 (4.8 - 9.8)	6.8 ± 0.4 (5.1 - 9.7)
Serum triglyceride (mmol/l)	1.67± 0.22 (0.91- 2.27)	1.86± 0.13 (1.14- 2.57)
Plasma fibrinogen (mgm/100 ml)	244.9 ± 11.3 (183.0 - 328.0)	282.0 ± 20.2 (175.0 - 473.0)
Uric acid (mmol/l)	0.36± 0.02 (0.132- 0.466)	0.37± 0.03 (0.150- 0.611)
Systolic blood pressure (mm Hg)	151.1 ± 7.1 (120.0 - 230.0)	139.2 ± 5.0 (110.0 - 200.0)
Diastolic blood pressure (mm Hg)	85.8 ± 2.8 (80.0 - 110.0)	83.9 ± 2.8 (70.0 - 110.0)
Pulse rate (beats/min)	70.9 ± 2.2 (60.0 - 95.0)	71.2 ± 2.2 (55.0 - 85.0)
Resting ankle systolic blood pressure ratio (ankle SBP/arm SBP)	0.68± 0.04 (0.42- 1.12)	0.69± 0.03 (0.42- 1.06)
Post-exercise ankle systolic blood pressure ratio	0.48± 0.05 (0.05- 1.12)	0.54± 0.04 (0.21- 1.00)

* There were no statistically significant differences between any of these mean levels (paired t-test)

no evidence of these disorders was found when the patients were examined. The results of the measurements performed on the controls are presented in Appendix 7.4. All had normal ankle systolic pressure ratios at rest and after exercise (Yao et al, 1972). There was no significant difference between the controls and the patients with IC in the other variables measured.

2. THE EFFECT OF CINNARIZINE ON OBJECTIVE MEASUREMENTS

The mean levels and range of the measurements performed on the cases at the initial examination and after four months of treatment are presented in Table 7.3. Using a paired t-test, there was no significant difference between the two sets of results in any of the measurements (ankle systolic pressure ratios were also examined with the Wilcoxon matched-pairs signed-ranks test, Siegel, 1956).

Table 7.4 presents the blood flow measurements of the controls and of the patients at the start of the trial and after four months' treatment. The control patients had lower resting and post-occlusion flows and higher peak flows than the cases, and time to peak flow and duration of hyperaemia was significantly shorter in the controls (Mann-Whitney U test, Siegel, 1956). There was no significant change in any of the flow measurements in the patients with IC after four months' treatment with Cinnarizine (Wilcoxon matched-pairs signed-ranks test, Siegel, 1956).

3. CHANGES IN PATIENT SYMPTOMS AFTER TREATMENT WITH CINNARIZINE

Using the Wilcoxon matched-pairs signed-ranks test, there was a significant ($p<0.05$) improvement in the walking distance reported by the patients (11 said they could walk further), though there was only a modest increase in the mean walking

distance from 400 yards at the start of the trial to 450 yards after treatment. There was also a significant decrease in the stop score (Wilcoxon matched-pairs signed-ranks test, $p<0.01$) and the frequency and severity of muscle cramps (Sign test, $p<0.04$, Siegel, 1956). Cinnarizine had no effect on the complaint of cold extremities.

Six patients stopped smoking during the trial or reduced their daily consumption to fewer than ten cigarettes. It is of interest that all these patients reported an improvement in walking distance and stop score. Of the nine patients who did not change their smoking habit, only three said they were improved at the end of the study. There was no objective evidence of improved blood flow in those who stopped or reduced smoking when these patients were examined separately.

Cinnarizine was discontinued after four months, and the patients were seen one month later. Two patients stated that their walking tolerance had decreased after the tablets were withdrawn, and the remainder reported no change. There was no significant change in the Doppler or plethysmographic measurements compared with those made at the end of the trial.

4. SIDE EFFECTS

One patient developed an annular lichenoid skin rash after three months on Cinnarizine. A consultant dermatologist was not certain if the rash was due to the drug, and it persisted for some time after the trial. The most common side effect (eight patients) was mild drowsiness during the first few days which was not present at the one-month follow-up visit. There were no other serious side effects.

D. DISCUSSION

The patients who participated in this study co-operated fully in maintaining their diary cards and taking their tablets (pill counts at follow-up were consistently correct). The failure of Cinnarizine to significantly improve the blood flow to the legs cannot, therefore, be attributed to a lack of patient compliance. It is possible that reported improvement in walking tolerance may have been due to a redistribution of blood flow or improved utilization of oxygen by the leg muscles, variables not measurable by the techniques used in this study (Schuermans et al, 1971). These changes were quite small, however, and since this was not a randomized double-blind-trial, it is not correct to attribute improvement in subjective symptoms to treatment with Cinnarizine. When discussing the treatment with the patients, it was emphasized that this was an experimental trial, and that improvement might not occur. The patients were highly motivated, however, and it is possible that participation in the trial and the expectation of improvement may have accounted for changes in symptoms. Continued follow-up after the trial, with no active treatment, was sufficient to maintain the reported improvement of symptoms in most patients. The therapeutic measure most likely to result in increased walking tolerance was stopping or reducing smoking. In view of the failure of Cinnarizine to produce even slight improvement in the objective measurements of blood flow or ankle systolic pressure and the small improvement in subjective symptoms (which may simply have been a placebo effect), it was decided that further investigation of this drug in a double-blind trial was not indicated.

The mean values of blood flow obtained by the technique

used in this study were similar to those described by other workers who have examined the peripheral circulation by plethysmography (Whitney, 1953; Dahn, 1965; Hillestad, 1963v). Peak flow and the ratio of peak flow/rest flow were both significantly correlated with patient symptoms, and there were statistically significant differences between the cases and controls in all the flow variables.

The objective measurement most strongly correlated with patient symptoms was the ankle systolic pressure ratio taken after 60 depressions of the foot treadle. The Doppler flow meter was easy to use, and the examination took less than five minutes to complete. In contrast to this, a plethysmograph measurement lasted a minimum of 90 minutes (allowing for the patient's skin temperature to stabilize), and it required considerable experience to master the technique sufficiently to obtain reproducible tracings. The sudden inflation of the thigh cuff to arterial occlusion pressure was painful, and cases and controls were often reluctant to have repeat measurements. Because of the difficulties of plethysmography, and the fact that the ankle systolic pressure correlated more closely with patient symptoms, I believe that the Doppler flow meter was the better method of evaluating patients with PVD.

E. SUMMARY

Reports that Cinnarizine improved the symptoms of patients with peripheral vascular disease and increased blood flow to the legs without causing generalized vasodilation raised the possibility that this drug might be of use in the medical management of intermittent claudication. A preliminary investigation was carried out to evaluate the effect of the drug on objective measurements of the peripheral circulation. At the end of the

trial there was no evidence of improved blood flow to the legs, and only modest improvement in subjective symptoms which could be attributed to factors other than drug treatment. On the basis of these findings, it was decided that no further investigations were indicated.

The mercury strain gauge plethysmograph and the Doppler ultrasound flow probe were able to detect changes in the peripheral circulation of claudicants compared with normal controls, even when the symptoms of claudication were mild. The post-exercise ankle systolic ratio was the objective measurement which correlated most strongly with patient symptoms, and the Doppler flow meter was the preferred method of evaluating PVD.

REFERENCES

Abrams, M.E., Jarrett, R.J., Keen, H., Boyns, D.R. and Crossley, J.R. (1969). Brit. Med. J., 1, 599.

Abramson, D.I. (1967). Circulation in the Extremeties. Published by Academic Press Inc., New York.

Abu-Zeid, H. and Chapman, J. (1976). J. Chron. Dis., 29, 395.

Adar, R. and Salzman, E.W. (1975). New Engl. J. Med., 292, 348.

Addis, T. (1922). Arch. Intern. Med., 29, 539.

Adelson, E., Rheingold, J.J., Parker, O., Buenaventura, A. and Crosby, W.H. (1961). Blood, 17, 267.

Adriensen, H. (1969). Clin. Trials J. (London), 6, No. 3, 191.

Albert, R.E., Vanderlaan, M., Burns, F.J. and Nishizumi, M. (1977). Cancer Research (in Press).

Albrink, M.J., Meigs, J.W. and Man, E.B. (1961). Amer. J. Med., 31, 4.

Alpert, J., Larsen, O. and Lassen, N. (1969). Circulation, 39, 353.

Altschul, R. (1950). Selected studies on Arteriosclerosis. Published by Charles C. Thomas, Springfield, Illinois.

Anitschkow, N.N. (1913). Bietrl path. Anat., 36, 379.

Annual Abstract of Statistics No. 108 (1971). Central Statistical Office. A publication of the Government Statistical Service.

Armstrong, B.K., Mann, J.I., Adelstein, A.M. and Eskin, F. (1975). J. Chron. Dis., 28, 455.

Aronow, W.S., Stemmer, E.A. and Isbell, M.W. (1974). Circulation, 49.1, 415.

Aschoff, L. (1924). Lectures in Pathology. Published by Hoeber & Co., New York.

Ashley, F.W. and Kannel, W.B. (1974). J. Chron. Dis., 27, 103.

Astrup, P., Kjeldsen, K. and Wanstrup, J. (1967). J. Atheroscler. Res., 7, 343.

Astrup, T. (1958). Wein. Ztschr. f. inn. Med., 39, 373.

Astrup, T. (1959). In: Connective Tissue, Thrombosis, and Atherosclerosis. Edited by Page, I.H. Published by Academic Press, New York, pp. 223.

Auerbach, O., Hammond, E.C. and Garfinkel, L. (1965). New Engl. J. Med., 273, 775.

Aussems, J. and Muls, M. (1970). Clin. Trials J., 7, 274.

Baer, S. and Heine, W.I. (1949). J.A.M.A., 139, 733.

Baldwin, J.A. (1972). The Statistician, 21, No. 4, 325.

Baldwin, J.A. (1973). Proc. R. Soc. London, 184, 403.

Ballantyne, D. and Lawrie, T.D.V. (1973). Clin. chim. Acta, 47, 269.

Barndt, R., Blankenhorn, D.H. and Crawford, D.W. (1974). Atherosclerosis, 20, 253.

Barndt, R., Blankenhorn, D.H., Crawford, D.W. and Brooks, S.H. (1977). Annals Int. Med., 86, 139.

Baron, J. (1827). Life of Edward Jenner. Published by H. Colburn, London, pp. 39.

Begg, T.B. and Richards, R.L. (1962). Scot. Med. J., 7, 341.

Benaim, M.E. and Dewar, H.A. (1975). J. Int. Med. Res., 3, 423.

Benditt, E.P. and Benditt, J.M. (1973). Proc. Nat. Acad. Sci., U.S.A., 70, 1753.

Bengtsson, C. and Tibblin, E. (1974). Acta Med. Scan., 196, 93.

Bennett, A.E. and Ritchie, K. (1975). Questionnaires in Medicine. A Guide to their design and use. Published by Burgess & Son, Abingdon, Oxfordshire.

Berg, K., Borreson, A. and Dahlen, G. (1976). Lancet, 1, 499.

Berglund, G., Andersson, O. and Wilhelmsen, L. (1976). Brit. Med. J., 2, 554.

Bergmeyer, H.U. and Bernt, E. (1965). In: Methods of Enzymatic Analysis. Edited by H.U. Bergmeyer. Published by Academic Press, London.

Birckenstock, W.E., Louw, J.H., Terblanche, J., Immelman, E.J., Dent, D.M. and Baker, P.M. (1975). South African Med. J., 49, 1129.

Bjordal, R. (1970). Acta Chir. Scand., 136, 641.

Bliss, B.P., Kirk, C.J.C. and Newall, R.G. (1972). Angiology, 23, No. 2, 69.

Bloch, A., Dinsmore, R.F. and Lees, R.S. (1976). Lancet, 1, 928.

Bloor, K. (1960). Ann. Royal Coll. Surg. Eng., 28, 36.

Blumenthal, H.T. and Alex, M. (1975). Gerontologia, 21, No. 3, 1.

Bollinger, A., Barras, J.P. and Mahler, F. (1976). Circulation, 53, 506.

Bollinger, A., Schlumph, M., Butti, P. and Gruntzig, A. (1973). Scand. J. Clin. Lab. Invest., 31, Suppl. 128, 123.

Bothig, S., Metelitsa, V.I., Barth, W., Aleksandrov, A.A., Schneider, I., Ostrovskaya, T.P., Kokeiuna, E.V., Saposhnikov, I.I., Iliushina, I.P. and Gurevich, L.S. (1976). Cor Vasa, 18, No. 2, 104.

Bottiger, L.E. and Svedberg, C.A. (1967). Brit. Med. J., 2, 85.

Bouley, F. (1831). Red. d. Med. veterin. prat., 8, 517.

Boyd, A.M., Ratcliffe, A.H., Jepson, R.P. and James, G.W.H. (1949). J. Bone Joint Surg. 31-B, 325.

Brahme, F., Swedenborg, J. and Tibell, B. (1969). Acta Chir. Scand., 135, 679.

Breckenridge, A. (1966). Lancet, 1, 15.

Brest, A.N. and Gifford, R.W. (1971). (Editors). Cardiovascular Clinics, 3, No. 1. 'Peripheral Vascular Disease'. Published by F. A. Davis, Co., Philadelphia.

Brest, A.N. and Moyer, J.H. (1967). (Editors). Atherosclerotic Vascular Disease - a Hahnemann Symposium. Published by Butterworths, London.

Brittin, G.M. and Johnson, C.A. (1969). Am. J. Clin. Path., 52, No. 6, 679.

Brodie, B.C. (1846). Lectures Illustrative of Various Subjects in Pathology and Surgery. Published by Longman, London, pp.360.

Brodie, T.G. and Russell, A.E. (1905). J. Physiol., 32, 47.

Brown, D.F. and Daudiss, B.S. (1973). Circulation, 47, 558.

Browse, N.L., Gray, L., Jarrett, P.E.M. and Morland, M. (1977). Brit. Med. J., 1, 478.

Buck, R.C. (1962). Brit. J. Exp. Path., 43, 236.

Burns, A. (1809). Observations on some of the most frequent and important diseases of the heart. Published by Bryce & Co., Edinburgh.

Burton, A.E. (1976). Health Bulletin, 34, No. 2, 76.

Busco, J.S., Greenleaf, J.E., Kaye, R.L. and Averkin, E.G. (1970). Amer. J. Cardio., 25, 46.

Carew, T.E., Koschinsky, T., Hayes, S.B. and Steinberg, D. (1976). Lancet, 1, 1315.

Carlson, L.A. (1960). Acta Med. Scand., 167, 399.

Carlson, L.A. (1972). Lancet, 1, 865.

Carlson, L.A. and Lindstedt, S. (1968). Acta Med. Scand., Suppl. 493, 1.

Carlson, A.L. and Wahlberg, F. (1966). Acta Med. Scand., 180, 307.

Cartwright, A. and Ward, A.W.M. (1968). Brit. J. Prev. Soc. Med., 22, 199.

Chakrabarti, R., Fearnley, G.R. and Evans, J.E. (1968). Lancet, 2, 1007.

Chakrabarti, R. and Meade, T.W. (1975). Authors (letter) - Lancet, 1, 799.

Chamberlain, J., Housley, E. and MacPherson, A.I.S. (1975). Brit. J. Surg., 62, 64.

Charcot, J.M. (1859). Compt. rend. d. 1. Soc. d. Biol., 5, No. 2, 255.

Charcot, J.M. (1887). Le progres médical, 6, No. 2, 1.

Chien, S., Usami, S., Dellenbreck, R.J. and Gregersen, M. (1970). Amer. J. Physiol., 219, 136.

Classification of Occupations (1970). Office of Population Censuses and Surveys. Her Majesty's Stationery Office, London.

Classification of Surgical Operations (1956). General Register Office. Her Majesty's Stationery Office, London.

Classification of Surgical Operations, Second Revision (1969). Office of Population Censuses and Surveys. Somerset House, London.

Clowes, A.W. and Karnowsky, M.J. (1977). Nature, 265, No. 5595, 625.

Coffman, J.D. and Javett, S.L. (1963). Circulation, 28, 932.

Coffman, J.D. and Mannick, J.A. (1965). New Engl. J. Med., 273, No. 24, 1297.

Colt, J.D. (1971). Angiology, 22, No. 7, 375.

Commins, B.T. (1975). Ann. occup. Hyg., 18, 69.

Commins, B.T. and Lawther, B.J. (1965). Br. J. Indust. Med., 22, 139.

Connor, W.E. and Poole, J.C.F. (1961). Quart. J. Exp. Physiol., 46, 1.

Cooper, K.H., Pollock, M.L., Martin, R.P., White, S.R., Linnerud, A.C. and Jackson, A. (1976). J.A.M.A., 236, No. 2, 166.

Copley, A.L. (1955). In: Thrombosis and Embolism. Published by Schwabe, Basel, pp. 458.

Coronary Drug Project Research Group (1976). J. Chron. Dis., 29, 557.

Cramp, D.G. and Robertson, G. (1968). Analyt. Biochem., 25, 246.

Cramp, D.G., Tickner, T.R. and Wills, M.R. (1976). Lancet, 2, 176.

Cutajar, C., Brown, N. and Marston, A. (1971). Brit. J. Surg., 58, No. 7, 532.

Czochra-Lysanowicz, Z., Gorski, M. and Kedra, M. (1959). Ann. Univ. Curie-Sklodowska (Med), 14, 181.

Dahn, I. (1965). I - Acta Chir. Scand., 131, 42. II - Acta Chir. Scand., 131 , 61.

Dawber, T.R., Kannel, W.B., Revotskie, N., Stokes, J., Kagan, A. and Gordon, T. (1959). Amer. J. Publ. Health, 49, 1349.

Dianzani, M.U., Torrielli, M.V., Canuto, R.A., Garcea, R. and Feo, F. (1976). J. of Path., 118, 193.

Diem, K. and Lentner, C. (1970). (Editors). Documenta Geigy Scientific Tables - Seventh Edition. Published by J. R. Geigy S.A., Basle, Switzerland.

Dintenfass, L. (1968). Med. J. Australia, 1, 681.

Dintenfass, L., Julian, D.G. and Miller, G.E. (1966). Am. Heart J., 71, 587.

Doll, R. and Hill, A.B. (1964). Brit. Med. J., 1, 1399.

Doll, R. and Peto, R. (1976). Brit. Med. J., 2, 1525.

Dormandy, J.A. (1970). Ann. Royal Coll. Surgeons of Engl., 47, 211.

Dormandy, J.A., Goyle, K.B. and Reid, H.L. (1977). Lancet, 1, 625.

Dormandy, J.A., Gutteridge, J.M.C., Hoare, E. and Dormandy, T.L. (1974). Brit. Med. J., 4, 259.

Dormandy, J.A., Hoare, E., Colley, J., Arrowsmith, D.E. and Dormandy, T.L. (1973a). Brit. Med. J., 4, 580.

Dormandy, J.A., Hoare, E., Khattab, A.H., Arrowsmith, E.D. and Dormandy, T.L. (1973b). Brit. Med. J., 4, 581.

Dorn, H.F. (1959). Publ. Health Rep., 74, 581.

Doyle, J.T., Dawber, T.R., Kannel, W.B., Heslin, A.S. and Kahn, H.A. (1962). New Engl. J. Med., 266, 796.

Doyle, J.T., Dawber, T.R., Kannel, W.B., Kinch, S.H. and Kahn, H.A. (1974). J.A.M.A., 190, 886.

Dry, T.J. and Hines, E.A. (1941). Ann. Int. Med., 14, 1893.

Duguid, J.B. (1949). Lancet, 2, 925.

Durrington, P.N., Manning, A.P., Bolton, C.H. and Hartog, M. (1976). Lancet, 2, 394.

Dyken, M.L., Conneally, P.M., Haerer, A.F., Gotshall, R.A., Calanchini, P.R., Poskanzer, D.C., Price, T.R. and Swanson, P.D. (1977). J.A.M.A., 237, 882.

Eastcott, H.H.G. (1962). Lancet, 2, 1117.

Ebel, A. and Kuo, J. (1967). Arch. Phys. Med. and Rehab., 48, 611.

Editorial (1976a). Brit. Med. J., 1, 481.

Editorial (1976b). Brit. Med. J., 1, 542.

Editorial (1976c). Brit. Med. J., 1, 1105.

Editorial (1976d). Brit. Med. J., 1, 1165.

Editorial (1977a). Brit. Med. J., 2, 1.

Editorial (1977b). Brit. Med. J., 1, 1115.

Editorial (1975a). Lancet, 1, 501.

Editorial (1975b). Lancet, 2, 113.

Editorial (1975c). Lancet, 2, 398.

Editorial (1976a). Lancet, 1, 783.

Editorial (1976b). Lancet, 1, 1333.

Editorial (1976c). Lancet, 2, 409.

Editorial (1977). Lancet, 1, 127.

Eggstein, M. and Kreutz, F.H. (1966). Klinische Wochenschrift, 44, 262.

Ellis, F., Jagenau, A. and Loots, W. (1975). J. Int. Med. Res., 3, 93.

Elmfeldt, D., Vedin, A., Wilhelmsson, C., Tibblin, G. and Wilhelmsen, L. (1976). J. Chron. Dis., 29, 221.

Epstein, F.H., Francis, T., Hayner, N.S., Johnson, B.C., Kjelsberg, M.O., Napier, J.A., Ostrander, L.D., Payne, M.W. and Dodge, H.J. (1965). Amer. J. Epid., 81, 307.

Epstein, F.H., Ostrander, L.D., Johnson, B.C., Payne, M.W., Hayner, N.S., Keller, J.B. and Francis, T. (1965). Ann. Int. Med., 62, 1170.

Erb, W.H. (1898). Deutsch. med. f. Nenvenheilk, 13, 1.

Erdi, A., Kakkar, V.V., Thomas, D.P. and Lane, D.A. (1976). Lancet, 2, 342.

Eriksson, M. and Carlson, L.A. (1974). In: Atherosclerosis III. Edited by Schettler, G. and Weizel, A., Berlin, pp. 838.

Evans, J., Dunleavy, J., Sutcliffe, T. and Perry, J. (1975). The Oxford Medical Information System for Primary Care. A background paper for the Day Symposium on Information Systems in the Health and Social Services at Oxford, 27th June.

Farish, E., Shepherd, J., Lawrie, T.D.V. and Morgan, H.G. (1975). Clin. Chim. Act, 62, 97.

Fedrick, J. (1977). Personal communication.

Fisher, M., Duryee, A. and Wright, I. (1939). Amer. Heart J., 18, 425.

Fodor, J., Hejl, Z., Santrucek, M., Vavrik, M., Vrbova, D. and Weber, K. (1968). Cor Vasa, 10, 41.

Fowler, G., Butterfield, W.H.J. and Acheson, R.M. (1970). Guy's Hospital Reports, 119, 297.

Frederickson, D.S., Levy, R.I. and Lees, R.S. (1967). New Engl. J. Med., 276, 32.

Fyfe, T. and Quin, R.O. (1975). Brit. J. Surg., 61, 320.

Garcia, M.J., McNamara, P.M., Gordon, T. and Kannel, W.B. (1974). Diabetes, 23, 105.

Gardham, J.R.C. (1976). Brit. J. Hosp. Med., 16, 43.

Gero, S., Bihari-Varga, M. and Virag, S. (1973). In: Vascular and neurological changes in early diabetes. Edited by Camerini-Davalos, R.A. and Cole, H.S. Published by Academic Press, New York.

Gillespie, J.A. (1966). Angiology, 17, 280.

Gillum, R.F., Feinleib, M., Margolis, J.R., Fabsitz, R.R. and Brasch, R.C. (1976). J. Chron. Dis., 29, 289.

Godfraind, T. (1974). Brit. J. Pharm., 52, 120.

Godfraind, T. and Kaba, A. (1969). Brit. J. Pharm., 36, 549.

Godfraind, T., Kaba, A. and Rojas, R. (1973). Brit. J. Pharm., 49, 164.

Goldbourt, U. and Medalie, J.H. (1974). Brit. J. Prev. Soc. Med., 28, 116.

Goldbourt, U. and Medalie, J.H. (1977). Amer. J. Epid., 105, 75.

Goldbourt, U., Medalie, J.H. and Neufeld, H.N. (1975). J. Chron. Dis., 28, 217.

Goldenberg, S., Alex, M., Joshi, R.A. and Blumenthal, H.T. (1959). Diabetes, 8, 261.

Goldflam, S. (1895). Deutsch. med. Wochenschenschrift, 21, 587.

Golding, D. (1977). Personal communication.

Goldstein, J.L., Hazzard, W.R., Schrott, H.G., Bierman, E.L. and Molutsky, A.G. (1973). J. Clin. Invest., 52, 1533.

Gomes, J.A.C., Venkatachalapathy, D. and Haft, J.I. (1976). Amer. Heart J., 91, 425.

Gordon, T. and Kannel, W.B. (1971). J.A.M.A., 215, 1617.

Gordon, T. and Kannel, W.B. (1972). J.A.M.A., 221, 661.

Gordon, T., Sorlie, P. and Kannel, W.B. (1976). Int. J. Epid., 5, 327.

Gordon, T. and Thom, T. (1975). Prev. Med., 4, 115.

Gotto, A.M., Yeshurun, D. and De Bakey, M.E. (1976). J. Chron. Dis., 29, 677.

Goyle, K.B. and Dormandy, J.A. (1976). Lancet, 1, 1317.

Greenfield, A., Whitney, R. and Mowbray, J. (1963). Brit. Med. Bull., 19, 101.

Greenhalgh, R.M., Lewis, B., Rosengarten, D.S., Calnan, J.S., Mervart, I. and Martin, P. (1971). Lancet, 2, 947.

Gresham, G.A. (1976). Atherosclerosis, 23, 379.

Grun, J. (1972). Ann. N.Y. Acad. Sci., 203, 29.

Haeger, K. (1974). Amer. J. Clin. Nutr., 27, 1179.

Hall, A.P. (1965). Arthritis Rheum., 8, 846.

Hamilton, M., Pickering, G.W., Roberts, J.A.F. and Sowry, G.S.C. (1954). Clin. Sci., 13, 11.

Hamilton, M., Wilson, G., Armitage, P. and Boyde, J.T. (1953). Lancet, 2, 367.

Hammond, E.C. (1964). J. Nat. Cancer Inst., 32, 1161.

Hammond, E.C. (1966). Nat. Cancer Inst. Monograph, 19, 127.

Harrison, N. (1975). Ann. occup. Hyg., 18, 37.

Hartmann, G. (1976). Cardiology Today, 4, No. 3, 6.

Hewlett, A.W. and Van Zwaluenberg, J.G. (1909). Heart, 1, 87.

Higgins, M.W. and Kjelsberg, M. (1967). Amer. J. Epid., 86, 60.

Hillestad, L.K. I - (1962), Acta Med. Scand., 172, 301. II - (1962), Acta Med. Scand., 172, 307. III - (1962), Acta Med. Scand., 172, 573. IV - (1963), Acta Med. Scand., 173, 467. V - (1963), Acta Med. Scand., 174, 23. VI - (1963), Acta Med. Scand., 174, 671. VII - (1963), Acta Med. Scand., 174, 687.

Hobbs, M.S.T., Fairbairn, A.S., Acheson, E.D. and Baldwin, J.A. (1976). Brit. J. Prev. Soc. Med., 30, 141.

Hobson, W. and Pemberton, J. (1955). The health of the elderly at home. Published by Butterworth, London.

Holm, J., Dahllhof, A.G., Bjorntop, P. and Schersten, T. (1973). Scand. J. Clin. Lab. Invest. Suppl. 128, 31, 201.

Holman, R.L., McGill, H.C., Strong, J.P. and Geer, J.C. (1958). Amer. J. Path., 65, 66.

Hyman, C. and Winsor, T. (1959). Amer. J. Cardiol., 4, 566.

Imparato, A.M., Kim, G., Davidson, T. and Crowley, G.J. (1975). Surgery, 78, 795.

International Classification of Diseases (1955). Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Based on the Recommendations of the Seventh Revision Conference, Volumes I and II. World Health Organization, Geneva, 1957.

International Classification of Diseases (1965). Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Based on the Recommendations of the Eighth Revision Conference, Volumes I and II. World Health Organization, Geneva, 1967.

Jacobs, A. (1968). Ars Med., 23, 799.

Janzon, L. (1975). Acta Chir. Scand., 141, 596.

Jarrett, R.J. (1976). Brit. J. Hosp. Med., 16, 200.

Jarrett, R. and Keen, H. (1976). Lancet, 2, 1009.

Jepson, R.P. and Harris, J.D. (1969). Med. J. Australia, 2, 639.

Jeurgens, J.L., Barker, N.W. and Hines, E.A. (1960). Circulation, 21, 188.

Johnson, B.F. and Munro-Faure, A.D. (1976). Authors (letter) - Lancet, 1, 1019.

Jones, J.G. and Sinclair, A. (1975). Ann. occup. Hyg., 18, 15.

Joos, F. (1968). Folio St. Jan., 2, 176.

Journal of the Royal College of Physicians (1976), 10, No. 3, 12.

Kakkar, V.V. (1977). Medicine. The Monthly Add-On Series. No. 27, 1417.

Kaminski, D.L., Barner, H.B., Doughi, J.A., Kaiser, G.C. and Willman, V.L. (1972). Arch. Surg., 104, 527.

Kannel, W.B. (1964). Ann. int. Med., 60, 1103.

Kannel, W.B., Castelli, W.P., Gordon, T. and McNamara, P.M. (1971). Ann. int. Med., 74, 1.

Kannel, W.B., Castelli, W.B. and McNamara, P.M. (1968). Nat. Cancer Inst. Monogr., 28, 9.

Kannel, W.B. and Dawber, T.R. (1974). Brit. J. Hosp. Med., 2, 508.

Kannel, W.B., Gordon, T. and Schwartz, M.J. (1971). Amer. J. Cardiol., 27, 335.

Kannel, W.B. and Shurtleff, D. (1971). Cardiovascular Clinics, 3, No. 1, 37.

Kannel, W.B. and Shurtleff, D. (1973). Geriatrics, 8, 61.

Kannel, W.B., Skinner, J.J., Schwartz, M.J. and Shurtleff, D. (1970a). Circulation, 41, 875.

Kannel, W.B., Wolf, P.A., Verter, J. and McNamara, P.M. (1970b). J.A.M.A., 214, 301.

Kavanaugh, G.J., Svien, H.J., Holman, C.B. and Johnson, R.M. (1968). J.A.M.A., 206, 2477.

Keen, H. (1976). Postgraduate Med. J., 52, 445.

Keen, H., Rose, G.A., Pyke, D.A., Boyns, D.R., Chloverakis, C. and Mistry, S. (1965). Lancet, 2, 505.

Keen, H., Track, N.S. and Sowry, G.S.C. (1975). Diabète et Métabolisme, 1, 159.

Kerschbaum, A. and Bellett, S. (1964). J.A.M.A., 187, 132.

Kershbaum, A., Bellet, S., Caplan, R.F. and Feinberg, L.J. (1962). Amer. J. Cardiol., 10, 204.

Kershbaum, A., Bellet, S., Dickstein, E.R. and Feinberg, L.J. (1961). Circulation Research, 9, 631.

Kershbaum, A., Bellet, S., Jiminez, J. and Feinberg, L.J. (1966a). J.A.M.A., 195, 1095.

Kershbaum, A., Bellet, S. and Hirabayashi, M. (1966b). Clin. Res., 14, 350.

Kershbaum, A., Jiminez, J., Bellet, S. and Zanuttini, D. (1966c). J. Atheroscler. Res., 6, 524.

Kershbaum, A., Khorsandian, R., Caplan, R.F., Bellet, S. and Feinberg, L.J. (1963). Circulation, 28, 52.

Kesteloot, H., Vuytesteke, M. and Van Houte, O. (1976). J. Chron. Dis., 29, 301.

Kilpatrick, J.A. (1948). Brit. Heart J., 10, 48.

Kingsbury, K.J. (1966). Lancet, 2, 1374.

Kissin, M., Stein, J. and Adelman, R. (1950). Angiology, 1, 141.

Kjeldsen, K. (1969). Smoking and Atherosclerosis. Published by Munksgaard, Copenhagen.

Knowles, H.C. (1970). In - Diabetes Mellitus: Theory and Practice. Edited by Rifkin, H. Published by McGraw Hill, London.

Kremer, V.G.J., Neimczyk, H., Poeplau, W. and Nicolescu, R.F. (1973). Munch. med. Wochenschr., 115, 662.

Kronig, B. (1976). Cardiology Today, 4, No. 3.

Kunlin, J. (1949). Arch. Mal. Coeur., 42, 371.

Larsen, O.A. and Lassen, M.A. (1969). Angiologica, 6, 288.

Lee, P.N. (1976). Editor of Statistics of smoking in the United Kingdom. Tobacco Research Council: London. Published by R. MacLehose & Co., Glasgow.

Leren, P. (1968). Bull. N.Y.Acad.Med., 44, 1012.

Leren, P., Askevold, E.M., Foss, O.P., Froili, A., Grymyr, D., Helgeland, A., Hjermann, I., Holme, I., Lund-Larsen, P.G. and Norum, K.R. (1975). Acta Med. Scand., Suppl. 588, 1.

Leren, P. and Haabrekke, O. (1971a). Acta Med. Scand., 189, 495.

Leren, P. and Haabrekke, O. (1971b). Acta Med. Scand., 189, 511.

Lewis, B. (1974). Lancet, 1, 141.

Lewis, B., Chait, A., Oakley, C.M.O., Wootton, I.D.P., Krikler, D.M., Onitiri, A., Sigurdson, G. and February, A. (1974). Brit. Med. J., 3, 489.

Lewis, T. (1932). Arch. Int. Med., 49, 713.

Lewis, T., Pickering, G.W. and Rothschild, P. (1931). Wesley Carpenter Lecture, New York.

Lindbom, A. (1950). Acta Rad. Suppl. 80, 1.

Lithell, H., Hedstrand, H. and Karlsson, R. (1975). Acta Med. Scand., 197, 473.

Livingstone, P.D. and Jones, C. (1958). Lancet, 2, 602.

Lord, J.W. (1965). J.A.M.A., 191, 249.

Lupien, P., Moorjani, S. and Awad, J. (1976). Lancet, 1, 1261.

Mackereth, M. and Lennihan, R. (1970). Angiology, 21, 704.

Magibow, R.S., Magibow, S.J., Pollack, H., Bookman, J.J. and Osserman, K. (1953). Amer. J. Med., 15, 322.

Mann, J.I. (1977). Personal communication.

Mann, J.I. and Thorogood, M. (1975). Brit. Heart J., 37, 790.

Mantel, N. and Haenzel, W. (1959). J. Nat. Cancer Inst., 22, 719.

Marchand, F. (1904). Uber Arterioskterose. Verhandl. des Kongresses fur innere Med., 21, 23.

Marder, L., Becker, G.H., Maizel, B. and Necheles, H. (1952). Gastroenterology, 20, 43.

Marquardsen, J. (1969). The national history of acute cerebrovascular disease. Published by Munksgaard, Copenhagen.

Martin, G.M. and Sprague, C.A. (1973). Exp. Mol. Pathol., 18, 125.

Mason, S.G. and Goldsmith, H.L. (1969). Circulatory and respiratory mass transport. Edited by Wolstenholme, G.E.W. and Knight, J. Published by J. & A. Churchill, London, pp. 105.

Mathew, N.T., Davis, D., Meyer, J.S. and Chandar, K. (1975). J.A.M.A., 232, 262.

Mathieson, F.R. and Mune, O. (1966). Acta Chir. Scand., Suppl. 357, 78.

Matsumato, M., Whisnant, J.P., Kurland, T. and Okazaki, H. (1973). Stroke, 4, 20.

McDowall, R.J.S. (1956). The control of the circulation of the blood. Published by W. M. Dawson & Sons Ltd., London.

McGill, H.C., Geer, J.C. and Strong, J.P. (1963). In: Atherosclerosis and its origin. Edited by Sandler, M. and Bourne, G.H. Published by Academic Press Inc., New York, pp. 39.

McKusick, V.A., Harris, W.S., Otteson, O.E., Goodman, R.M., Shelley, W.M. and Bloodwell, R.D. (1962). J.A.M.A., 181, 5.

Meade, T.W., Chakrabati, R. and North, W.R.S. (1977). Brit. Med. J., 1, 837.

Meade, T.W. and Wald, N.J. (1977). Brit. J. Prev. Soc. Med., 31, 25.

Medalie, J.H. and Goldbourt, U. (1976). Ann. int. Med., 84, 526.

Medalie, J.H., Papier, C.M., Goldbourt, U. and Herman, J.B. (1975). Arch. int. Med., 135, 811.

Mendlowitz, M., Grossman, E.B. and Alpert, S. (1953). Amer. J. Med., 15, 316.

Merrill, E.W. (1969). Physiological Reviews, 49, 863.

Merrill, E.M. and Pelletier, G.A. (1967). J. Appl. Physiol., 23, 178.

Miettenen, O.S. (1970). Biometrics, 26, 75.

Mikkelson, W. (1965). Arthritis Rheum., 8, 853.

Miller, N.E., Forde, O.H., Thelle, D.S. and Nijos, O.D. (1977). Lancet, 1, 965.

Miller, N.E. and Miller, G.J. (1975). Authors (letter) - Lancet, 1, 1033.

Milne, J.S. and Williamson, J. (1972). Age and Ageing, 1, 146.

Moncada, S., Higgs, E.A. and Vane, J.R. (1977). Lancet, 1, 18.

Morrison, A.D., Clements, R.S. and Winegrad, A.I. (1970). In: Atherosclerosis: Proceedings of the Second International Symposium. Edited by Jones, R.J. Published by Springer-Verlag, Berlin, pp. 119.

Mustard, J.F. and Murphy, E.A. (1963). Brit. Med. J., 1, 846.

Myers, K. (1964). Angiology, 15, 293.

Myrhe, H.O. (1973). Scand. J. Clin. Lab. Invest., 31, Suppl. 128, 129.

National Heart and Lung Institute Task Force on Arteriosclerosis. DHEW Publication No. (NIH) 72-219. Vol. 2. Washington, D.C. Government Printing Office, 1971.

Nayman, J. (1974). Aus. N.Z.J. Surg., 44, 157.

Neto, E.S. (1971). A. Folha Medica, 63, 137.

Newland, C.A. and Waters, W.E. (1977). Int. J. Epid., 6, 65.

Newland, H. (1975). Medical Hypotheses, 1, 152.

Nie, N.H., Bent, D.H. and Hull, C.H. (1970). Statistical Package for the Social Sciences. Published by McGraw-Hill Book Company, London.

Nichols, A.B., Ravenscroft, C., Lamphiear, D.E. and Ostrander, L.D. (1976). J.A.M.A., 236, 1948.

O'Brien, J.R., Etherington, M.D. and Jamieson, S. (1976). Lancet, 1, 878.

Olefsky, J.M., Crapo, P. and Reaven, G.M. (1976). Amer. J. Clin. Nutr., 29, 535.

Oliver, M.F. and Boyd, G.S. (1959). Lancet, 2, 210.

Olson, R.E. (1973). Circulation, 48, 179.

Olsson, A.G. and Carlson, L.A. (1975). Acta Med. Scand., Suppl. 580, 5.

Olsson, A.G., Ekelund, L.G. and Carlson, L.A. (1975). Acta Med. Scand., 198, 55.

Ostrander, L.D., Francis, T., Hayner, N.S., Kjelsberg, M.O. and Epstein, F.H. (1965). Ann. int. Med., 62, 1188.

Ostrander, L.D. and Lamphiear, D.E. (1976). Circulation, 53, 152.

Owens, J.C. (1973). In: Complications in vascular surgery. Edited by Beebe, H.G. Published by J. B. Lippincott Co., Philadelphia and Toronto, pp. 201.

Page, I.H., Lewis, L.A. and Mornuddin, M. (1959). J.A.M.A., 171, 1500.

Parker, F. (1960). Amer. J. Path., 36, 19.

Parry, C.H. (1799). An inquiry into the symptoms and causes of the syncope anginosa, commonly called angina pectoris. Published by R. Cruttwell, London.

Patterson, D. and Slack, J. (1972). Lancet, 1, 393.

Petersen, F.B. (1967). Acta Chir. Scand., 133, 627.

Peto, R., Pike, M.C., Armitage, P., Breslow, N.E., Cox, D.R., Howard, S.V., Mantel, N., McPherson, K., Peto, J. and Smith, P.G. (1977). Brit. J. Cancer, 35, 1.

Petrie, J.C. (1976a). Brit. Med. J., 2, 289.

Petrie, J.C. (1976b). Brit. Med. J., 2, 359.

Pickering, G. (1976). Author (letter) - Lancet, 1, 1403.

Pike, M.C., Howard, S.V., Smith, P.G. and Casagrande, J. (1976). D.H.S.S. Cancer Epidemiology and Clinical Trials Unit, 9 Keble Road, Oxford. Survival Analysis Computer Programme (SURVC). March 22.

Pike, M.C. and Morrow, R.H. (1970). Brit. J. Prev. Soc. Med., 24, 42.

Poiseuille, J.L.M. (1846). Mem. Acad. Sci., Paris, 9, 443.

Pollack, A.V. and Jackson, D.W. (1970). Brit. J. Surg., 57, 344.

Poole, J.C.F. (1958). Brit. Med. Bull., 14, 253.

Postlethwaite, J.C. and Dormandy, J.A. (1975). Ann. of Surg., 181, 799.

Postlethwaite, J.C., Goyle, K.B., Dormandy, J.A. and Hynd, J.W. (1977). Brit. J. Surg., 64, 28.

Prentice, C.R.M. and McNicol, G.P. (1971). The Practitioner, 206, 331.

Rankin, H.W.S., Horn, D.B., Mackay, A.W. and Forgan, C.M. (1976). Health Bulletin, 34, 60.

Ratnoff, O.D. and Menzie, C. (1951). J. Clin. Lab. Sci., 37, 316.

Reece, B.L. (1974). Brit. J. Hosp. Med., 12, Equipment Supplement (November), 5.

Reid, D.D., Brett, G.Z., Hamilton, P.J.S., Jarrett, R.J., Keen, H. and Rose, G. (1974). Lancet, 1, 469.

Reid, H.A. and Chan, K.E. (1968). Lancet, 1, 485.

Reid, H.L., Dormandy, J.A., Reid, H.L., Barnes, A.J., Lock, P.J. and Dormandy, T.L. (1976). Lancet, 1, 666.

Robbins, S.L. (1967). Pathology. Published by W. B. Saunders Co., London.

Robicsek, F., Daugherty, H.K., Mullen, D.C., Masters, T.N., Narbay, D. and Sanger, P.W. (1975). J. Thor. and Cardio. Surg., 70, 107.

Rodger, J.C., Sheldon, C.D., Lerski, R.A. and Livingstone, W.R. (1976). Brit. Med. J., 1, 1125.

Rogers, P.H. and Sherry, S. (1976). Progr. in Cardio. Dis., 19, 235.

Rokitansky, C. (1852). A manual of pathological anatomy. Translated by Day, G.E. Sydenham Society, London, 4, 261-272.

Roos, J. (1957). Thromb. Drath. Haemorrh., 1, 471.

Rose, G.A. (1962). Bull. W.H.O., 27, 645.

Rose, G.A. and Blackburn, H. (1968). Cardiovascular Survey Methods. W.H.O., Monograph Series No. 56, Geneva.

Rose, G., Reid, D., Hamilton, P., McCartney, P., Keen, H. and Jarrett, R. (1977). Lancet, 1, 105.

Rosenblatt, G., Stokes, J. and Bassett, D.R. (1965). J. Clin. Lab. Med., 65, 202.

Ross, R. and Glomset, J.A. (1973). Science, 180, 1332.

Ross, R. and Glomset, J.A. (1976). New Engl. J. Med., 295, 369, 420.

Ross, R. and Harker, L. (1976). Science, 193, 1094.

Rossi, E. (1976). J. Chron. Dis., 29, 215.

Roth, G.M. and Shick, R.M. (1958). Circulation, 17, 443.

Royal College of General Practitioners (1963). Brit. Med. J., 2, 655.

Rushmer, R.F., Baker, D.W. and Stegall, H.F. (1966). J. Appl. Physiol., 21, 554.

Russell, M.A.H. (1976). Brit. Med. J., 1, 1430.

Ruys, J. and Hickie, J.B. (1976). Brit. Med. J., 2, 87.

Satomura, S. (1957). J. Acoust. Soc. Amer., 29, 1181.

Schadt, D.C., Hines, E.A., Jeurgens, J.L. and Barker, N.W. (1961). J.A.M.A., 175, 937.

Scharf, Y., Nahir, M., Plavnic, Y., Ben-Arieh, J., Lichtig, C. and Gellei, B. (1971). J.A.M.A., 215, 1323.

Schatz, I.J. (1971). Cardiovascular Clinics, 3, No. 1, 93.

Schmutzler, R. (1975). Thromb. Drath. Haemorrh., 34, 569.

Schoop, W. (1973). Scand. J. Clin. Lab. Invest., 31, Suppl. 128, 197.

Schuermans, V., Boermans, A., Geivers, H., Jagenau, A. and Brugmans, J. (1971). Arzneimittel-Forsc., 21, 1541.

Searcy, R.L. and Bergquist, C.M. (1962). Clin. Chim. Acta, 5, 192.

Selvaag, O. (1956). Acta Med. Scand., Suppl. 319, 59.

Sharp, C.L., Butterfield, W.J.H. and Keen, H. (1964). Proc. of the Royal Soc. of Med., 57, 193.

Sheldon, J.H. (1948). The Social Medicine of Old Age. Published by Geoffrey Cumberlege, Oxford University Press, London.

Shepherd, J.C. (1950). Clin. Sci., 9, 49.

Shepherd, J.C. (1963). Physiology of the Circulation in Human Limbs in Health and Diseases. Published by W. B. Saunders Co., Philadelphia.

Shorey, R.L., Sewell, B. and O'Brien, M. (1976). Amer. J. Clin. Nutr., 29, 512.

Shute, W.E., Shute, E.V. and Vogebang, A. (1947). Med. Res., 160, 21.

Siegel, S. (1956). Nonparametric statistics for the behavioural sciences. Published by McGraw-Hill Kogakusha Ltd., Japan.

Sigaard-Andersen, J. (1965). Acta Chir. Scand., 130, 190.

Sigaard-Andersen, J. and Petersen, F.B. (1968). Angiology, 19, 426.

Silbert, S. and Zazeela, H. (1958). J.A.M.A., 166, 1816.

Silver, R.A., Schuele, H.L., Stack, J.K., Conn, J. and Bergan, J.J. (1969). Arch. Surg., 98, 523.

Silverman, J.J. (1946). Amer. Heart J., 32, 82.

Simmons, H.T. (1936). Lancet, 1, 73.

Singer, A. and Robb, C. (1960). Brit. Med. J., 2, 633.

Skovborg, F., Nielsen, A., Schlichtkrull, J. and Ditzel, J. (1966). Lancet, 1, 129.

Skrede, S. and Kvarstein, B. (1975). Acta Chir. Scand., 141, 333.

Slack, J. (1969). Lancet, 2, 1380.

Sloan, J.M., MacKay, J.S. and Sheridan, B. (1971). Diabetologia, 7, 431.

Spalding, W.B. (1956). Canadian Med. Ass. J., 75, 105.

Staessen, A.J. (1977). VASA, 6, 59.

Stamler, J. (1970). Therapeutische Umschau/Revue Therapeutique, 27, 133.

Steele, J.M. (1952). Arteriosclerosis. From: Gowdry's Problems of Ageing. Edited by Lansing, A.I. Third edition, 1952, pp. 306. Published by The Williams & Wilkins Co., Baltimore.

Stehbens, W.E. (1975). Lancet, 1, 724.

Stephensen, N. (1973). Scand. J. Clin. Lab. Invest., 31, Suppl. 128, 219.

Storen, G. (1967). Scand. J. Clin. Lab. Invest., 20, 147.

Strandness, D.E. (1971). Cardiovascular Clinics, 3, No. 1, 54.

Strandness, D.E., Priest, R.E. and Gibbons, G.E. (1964). Diabetes, 13, 366.

Strandness, D.E., Schultz, R.D., Sumner, D.S. and Rushmer, R.F. (1967). Amer. J. of Surg., 113, 311.

Strandness, D.E. and Stahler, C. (1966). J.A.M.A., 196, 1.

Strong, J.P., McGill, H.C., Tehada, C. and Holman, R.L. (1958). Amer. J. Path., 34, 731.

Strong, J.P. and Richards, M.L. (1976). Atherosclerosis, 23, 451.

Strong, J.P., Wainwright, J. and McGill, H.C. (1959). Circulation, 20, 1118.

Sznajderman, M. and Oliver, M.F. (1963). Lancet, 1, 962.

Taylor, G.W. (1973). Peripheral Vascular Surgery. Edited by Birnstingl, M. Published by Heinemann, London, pp. 211.

Taylor, G.W. and Calo, A.R. (1962). Brit. Med. J., 1, 507.

Thieme, W.T., Strandness, D.E. and Bell, J.W. (1965). Northwest Med., 64, 264.

Thienes, C.H. (1960). Ann. N.Y. Acad. Sci., 90, 239.

Thomas, M. and Quick, C. (1976). Brit. Med. J., 1, 1531.

Thompson, D. (1976). Personal communication.

Thompson, J.E. (1974). New Engl. J. Med., 290, 950.

Thomsen, H.K. (1974). Atherosclerosis, 20, 233.

Tillgren, C. (1965a). Acta Med. Scand., 178, 103.

Tillgren, C. (1965b). Acta Med. Scand., 178, 121.

Tria, E. and Scanu, A.M. (1969). Structural and functional aspects of lipoproteins in living systems. Published by Academic Press, London.

Truswell, A.S. and Mann, J.I. (1972). Atherosclerosis, 16, 15.

Tse, R.L. (1971). Angiology, 22, 1.

Turner, R. and Ball, K. (1976). Authors (letter) - Brit. Med. J., 2, 365.

Turner, R.C. and Holman, R.R. (1976). Lancet, 1, 1272.

Turner, R.W.D. (1976). In: Nutrition in the Community. Edited by MacLaren, D.S. Published by John Wiley & Sons, London, pp. 227.

Van Neuten, J.M. and Janssen, P.A.J. (1972). European J. Pharm., 17, 103.

Verhaegen, H., Roels, V., Adriensen, H., Brugmans, J., De Cock, W., Dony, J., Jagenau, A. and Schuermans, V. (1974). Angiology, 25, 261.

Virchow, R. (1971). Cellular Pathology as based upon Physiological and Pathological Histology. Translated by Chance, F. Published by Dover Publications Inc., New York.

Vogelburg, K.H., Berchtold, P., Berger, H., Gries, F.A., Klinger, H., Kubler, W. and Stolze, T. (1975). Atherosclerosis, 22, 271.

Vyden, J.K., Thorner, J., Nagasawa, K., Takano, T., Groseth-Dittrich, M.F., Perlow, R. and Swan, H.J.C. (1975). Amer. Heart J., 90, 703.

Wald, N. (1976). Lancet, 1, 136.

Wald, N., Howard, S., Smith, P.G. and Bailey, A. (1975). Thorax, 30, 133.

Wald, N., Howard, S., Smith, P.G. and Kjeldsen, K. (1973). Brit. Med. J., 1, 761.

Wald, N., Idle, M., Smith, P.G. and Bailey, A. (1977). Lancet, 1, 110.

Wanstrup, J., Kjeldsen, K. and Astrup, P. (1969). Acta Path. Microb. Scand., 75, 353.

Wardle, E.N. and Trinder, P. (1976). Authors (letter) - Lancet, 2, 470.

Weaver, J.P.A., Evans, A. and Walder, D.N. (1969). Clin. Sci., 36, 1.

Webster, W.S., Clarkson, T.B. and Lofland, H.B. (1970). Exper. Mol. Pathol., 13, 36.

Weinrath, L.A. and Herzstein, J. (1946). J.A.M.A., 131, 205.

Wenzel, D.G., Turner, J.A. and Kissil, D. (1959). Circ. Res., 7, 256.

Wessler, S. (1971). Cardiovascular Clinics, 3, No. 1, pp. 2.

Westfall, T.C. and Watts, D.T. (1964). J. Appl. Physiol., 19, 40.

Westling, H. (1973). Scand. J. Clin. Lab. Invest., 31, Suppl. 128, 207.

Whelan, R.F. (1967). Control of the Peripheral Circulation in Man. Published by C. C. Thomas, Springfield, Illinois.

Whitney, R.J. (1953). J. Physiol., 121, 1.

Whyte, H.M. (1975). Lancet, 1, 906.

Widmer, L.K. (1963). Bibl. Cardiol., 13, 67.

Widmer, L.K., Greensher, A. and Kannel, W.B. (1964). Circulation, 30, 836.

Wilens, S.L. (1962). Science, 138, 975.

Williams, H.T.G., Fenna, D. and Macbeth, R.A. (1971). Surg. Gynec. Obstet., 132, 662.

Winocour, P.D., Turner, M.R., Taylor, T.G. and Munday, K.A. (1977). Authors (letter) - Lancet, 1, 959.

Wiseman, R. (1676). Several Cherurgical Treatises. Published by Norton and Macock, London.

Wolf, G.K. (1976). European J. Clin. Pharm., 9, 387.

Wolfe, U.G. and Beven, E. (1971). Cardiovascular Clinics, 3, No. 1, 66.

Wollenweber, J., Doenecke, P., Greten, H., Hild, R., Mobbe, F., Schmidt, F.H. and Wagner, E. (1971). Deutsche Medizinishe Woch., 96, 103.

Woodcock, J.P. (1976). Rep. Prog. Phys., 39, 65.

World Health Organization Tech. Rep. Ser. (1958), 143, 4.

Wright, I.S. (1976). J.A.M.A., 236, 261.

Wynder, E.L. and Hoffman, D. (1965). Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. Published by Academic Press Inc., London.

Yao, S.T. (1970). Brit. J. Surg., 57, 762.

Yao, S.T., Hobbs, J.T. and Irvine, W.T. (1972a). Surg., Gynec. Obstet., 134, 963.

Yao, S.T., Needham, T.N. and Gourmoos, C. (1972b). Surgery, 71, 4.

Zak, A. (1921). Wien. Archiv. f. inn. Med., II, 405.

Zetterquist, S. (1970). Scand. J. Clin. Lab. Invest., 25, 101.

Zetterquist, S., Bergvall, U., Linde, B. and Pernow, B. (1971). Scand. J. Clin. Lab. Invest., 28, 408.

APPENDIX 2.1

THE SOCIOECONOMIC GROUP DISTRIBUTION OF THE POPULATIONS SERVED BY THE DONNINGTON HEALTH CENTRE AND THE SONNING COMMON HEALTH CENTRE

SEG.	Description	Sonning Common		Donnington H.C.	
		No.	%	No.	%
1.	Employers & Managers large establish.	119	10.8	178	3.1
2.	Employers & Managers small establ.	127	11.5	343	6.0
3.	Professionals - self employed	21	1.9	43	0.8
4.	Professionals - employed	78	7.1	212	3.7
5.	Senior non-manual worker	140	12.7	360	6.2
6.	Junior non-manual worker	114	10.3	703	12.2
7.	Personal service workers	14	1.3	211	3.7
8.	Foremen and supervisors - manual	45	4.1	263	4.6
9.	Skilled manual workers	147	13.3	1573	27.3
10.	Semi-skilled manual workers	63	5.7	1181	20.5
11.	Unskilled manual workers	33	3.0	5	0.1
12.	Self-employed non-professional	99	9.0	293	5.1
13.	Farmers - employed	14	1.3	5	0.1
14.	Farmers - self-employed	15	1.4	4	0.1
15.	Agricultural workers	24	2.2	9	0.2
16.	Armed forces	7	0.6	38	0.7
17.	Miscellaneous	45	4.1	336	5.8
	TOTAL	1105	100	5757	100

Reference. Census 1971 Great Britain
Summary Tables (1% Sample)
Publ. London. Her Majesty's Stationery Office (1973)

APPENDIX 2.2

FIRST MAILING

Oxford University
Department of Social & Community Medicine

8 KEBLE ROAD, OXFORD, OX1 3QN
Telephone (0865) 511293/4

Dear Madam,

I am a doctor working in the Radcliffe Infirmary, and studying those diseases which cause painful walking. With the approval of your General Practitioner, I am sending you a brief questionnaire which is approved by the World Health Organisation, and which asks some questions about your legs. I would appreciate it very much if you could take the few minutes necessary to answer this questionnaire, and to return it to me in the reply-paid envelope. I can assure you that strict confidence will be maintained with respect to your answers.

In any survey of this type, it is most important to receive as many answers as possible, if the results are to be meaningful. Regardless of whether you have pain or not, I should be most grateful if you would complete the form and return it to me. Your co-operation will enable me to determine the size of the problem, and may identify a solution.

Thank you very much,

Yours sincerely,

W.G. Hughson, M.D.

APPENDIX 2.2 (cont'd.)

SONNING COMMON HEALTH CENTRE
WOOD LANE, SONNING COMMON
NR. READING, RG4 9SW

Dear Sir (or Madam)

We have agreed to participate in Dr Hughson's survey on painful walking in the hope that the knowledge gained may benefit those in the practice with this problem, and people living elsewhere as well. We would encourage you to answer the questionnaire even if you do not have pain when you walk. Only in this way can we estimate the size of the problem and focus attention where it is needed.

All your answers will be treated in the strictest confidence. We will appreciate your co-operation very much.

Yours sincerely

Dr P.M.R. Hemphill
Dr T.I. Stewart
Dr J.C. Hasler
Dr Helen McEwen

APPENDIX 2.2 (cont'd.)

Donnington Health Centre,

1 Henley Avenue,

Oxford.

Dear

We have arranged for our Canadian medical colleague to send you the enclosed simple question list. Before selecting your name, Dr. Hughson had to convince us that this was a proper and useful enquiry and we are satisfied.

Please, therefore, consider the enclosed papers and fill them in before returning them. Your co-operation may mean that we shall be able to serve our patients better because of the greater understanding we gain from this research.

Should you wish to discuss any points of difficulty relating to the questions, please contact Dr. Lawrence at the Health Centre.

Thank you for your kind help,

Yours sincerely,

DR. R.G. SEAVER

DR. D.H. RICHARDS

DR. P.A. LAWRENCE

DR. ALISON WAGER

APPENDIX 2.2(a)

SECOND MAILING

Oxford University
Department of Social & Community Medicine

8 KEBLE ROAD, OXFORD, OX1 3QN

Telephone (0865) 511293/4

In recent weeks I have been conducting a survey of people living in the Oxford area. The questionnaire in this survey is designed to identify those people who develop pain in their legs on walking. To date, I have not received your questionnaire. It is possible that the letter was lost in the post, and I am, therefore, sending you another questionnaire with a reply-paid envelope.

In any survey of this type it is most important to receive as many answers as possible, if the results are to be meaningful. Regardless of whether you have pain or not, I should be most grateful if you could find the time to answer the questions and return the form to me. Your co-operation will greatly assist my research, and may identify a solution to the problem.

Thank you very much,

Yours sincerely,

William Hughson

W.G. Hughson, M.D.

Sonning Common Health Centre,
Wood Lane,
Sonning Common,
Nr. Reading, RG4 9SW.

In recent weeks, Dr. Hughson has been conducting a survey on painful walking. We agreed to allow him to approach you in the hope that the knowledge gained might help people in the practice, and those living elsewhere as well.

Most people do not have pain when walking, and may simply answer "No" to the first question.

Those who find the questions difficult to answer may explain their problem in the "Comments" section at the end of the form. The first results of this survey have been quite helpful, but we cannot really assess the problem unless everyone returns the questionnaire, so we are asking everyone to do so. All answers will be treated in the strictest confidence, and we will appreciate your help very much.

Yours sincerely,

Dr. P.M.R. Hemphill

Dr. T.I. Stewart

Dr. J.C. Hasler

Dr. Helen McEwen

APPENDIX 2.2(b)

THIRD MAILING

Oxford University
Department of Social & Community Medicine

8 KEBLE ROAD, OXFORD, OX1 3QN
Telephone (0865) 511293/4

The Department of Social & Community Medicine has been conducting a survey of people in the Oxford area designed to identify those people who develop pain in their legs on walking. The results to date are very interesting, and it seems the problem affects many people. However, this survey is difficult to interpret unless the majority of people return our questionnaire.

I would ask you to take the few minutes necessary to answer the questions and return the form in the reply-paid envelope. Even if you have no pain, your response will be of great assistance. Your co-operation will enable us to plan an intelligent approach to treatment, and thus benefit many people.

Thank you very much,

Yours faithfully,

W.G. Hughson, M.D

APPENDIX 2.2(b) (cont'd.)

Donnington Health Centre,

1 Henley Avenue,

Oxford.

Dear

You are probably suffering from no symptoms and therefore ignored the two previous questionnaires which our colleague Dr. Hughson has sent to you. May I explain again that we only need you to write "No pain" on the front of the form and return it at no cost. Of course, if you have symptoms, we want to know about them.

We are rather embarrassed to discover that some of our patients have not even felt able to make this simple response and we would urge you to help us because of the benefits we are sure can accrue to this community.

Yours sincerely,

DR. R.G. SEAVER

DR. D.H. RICHARDS

DR. P.A. LAWRENCE

DR. ALISON WAGER

APPENDIX 2.2(c)

LETTER TO POSITIVES AND QUESTIONABLY POSITIVES

Donnington Health Centre,

1 Henley Avenue,

Oxford.

Dear

I would like to thank you for returning my questionnaire on painful walking. Your response has been very helpful, and I certainly appreciate your co-operation.

Your answer to the questionnaire indicates that you experience some discomfort while walking. With the consent of your General Practitioner, I have arranged to see patients in the Health Centre. I would like to discuss your problem further, and would be most grateful if you could telephone the Appointments Desk, Oxford 771313 (ask for Dr. Seaver's practice, extension 30) after 10.30 a.m. and make an appointment to see me.

I look forward to meeting you,

Yours sincerely,

William Hughson, M.D.

APPENDIX 2.2(d)

LETTER TO CONTROLS

OXFORD UNIVERSITY
DEPARTMENT OF SOCIAL & COMMUNITY MEDICINE

8 Keble Road, Oxford, OX1 3QN.
Tel: (0865) 511293/4

Dear

I would like to thank you very much for answering our questionnaire on painful walking. Even though you do not have this problem, your answer has been very helpful in enabling us to determine the size of the problem. It is our hope that the results of the survey will lead to a better understanding of the causes of the disease, and to successful treatment.

Those people who have given a positive response to the questionnaire are coming to the Radcliffe Infirmary for an interview and a brief examination. Our measurements are simple, neither painful nor inconvenient, and give quite an accurate account of the patient's circulation.

In order to understand a disease, it is necessary to know how those who are suffering differ from normal people. This requires us to interview people who are fortunate in having no complaints. We would be very grateful indeed if you would allow us to interview you. An appointment can be made at your convenience by phoning my secretary, Mrs. Diana Collinge, at Oxford 511293 or 511294.

Once again, thank you very much for your co-operation,

Yours sincerely,

W.G. Hughson, M.D.

APPENDIX 2.3 (see back pocket)

APPENDIX 2.4 (see back pocket)

APPENDIX 3.1

THE QUESTIONNAIRE RETURN RATE AND FOLLOW-UP IN THE ENTIRE POSTAL SURVEY POPULATION

Age (yrs)	No. men in population	No. questionn-aires returned (%)	No. in follow-up	Total male returns (%)	No. women in population	No. questionn-aires returned (%)	No. in follow-up	Total female returns (%)	Total No. persons	Total questionn-aires returned (%)	Total No. in follow-up	Total returns (%)
<45	19	13 (68.4)	0	13 (68.4)	2	2 (100)	0	2 (100)	21	15 (71.4)	0	15 (71.4)
45-49	437	369 (84.4)	13	382 (87.4)	26	26 (100)	0	26 (100)	463	395 (85.3)	13	408 (88.1)
50-54	433	364 (84.1)	24	388 (89.6)	449	388 (86.4)	15	403 (89.8)	882	752 (85.3)	39	791 (89.7)
55-59	277	240 (86.6)	12	252 (91.0)	368	319 (86.7)	13	332 (90.2)	645	559 (86.7)	25	584 (90.5)
60-64	292	248 (84.9)	8	256 (87.7)	376	332 (88.3)	10	342 (91.0)	668	580 (86.8)	18	598 (89.5)
65-69	277	248 (89.5)	11	259 (93.5)	342	313 (91.5)	6	319 (93.3)	619	561 (90.6)	17	578 (93.4)
70+	3	3 (100)	0	3 (100)	2	2 (100)	0	2 (100)	5	5 (100)	0	5 (100)
Total	1738	1485 (85.4)	68	1553 (89.4)	1565	1382 (88.3)	44	1426 (91.1)	3303	2867 (86.8)	112	2979 (90.2)

APPENDIX 3.2

THE EFFECT OF AGE ON THE CLASSIFICATION OF QUESTIONNAIRES

Classification	<45 yrs No. (%)	45-49 yrs No. (%)	50-54 yrs No. (%)	55-59 yrs No. (%)	60-64 yrs No. (%)	65-69 yrs No. (%)	70+ yrs No. (%)	Total No. (%)
Positive for IC	0	0	9 (1.1)	4 (0.7)	10 (1.7)	9 (1.6)	0	32 (1.1)
Negative for IC	12 (80.0)	363 (89.0)	699 (88.4)	515 (88.2)	521 (87.1)	491 (84.9)	5	2606 (87.5)
Questionably positive	0	6 (1.5)	7 (0.9)	6 (1.0)	13 (2.2)	22 (3.8)	0	54 (1.8)
Refusal	0	3 (0.7)	10 (1.3)	6 (1.0)	6 (1.0)	6 (1.0)	0	31 (1.0)
Dead or disabled	0	1 (0.2)	6 (0.8)	4 (0.7)	7 (1.2)	12 (2.1)	0	30 (1.0)
Emigrated	2 (13.3)	33 (8.1)	56 (7.1)	49 (8.4)	37 (6.2)	34 (5.9)	0	211 (7.1)
Questionnaire error	0	0	0	0	0	1 (0.2)	0	1 (0.03)
Missing data	0	2 (0.5)	4 (0.5)	0	4 (0.7)	3 (0.5)	0	13 (0.4)
Miscellaneous	1 (6.7)	0	0	0	0	0	0	1 (0.03)
Total	15 (100)	408 (100)	791 (100)	584 (100)	598 (100)	578 (100)	5 (100)	2979 (100)

APPENDIX 4.1

THE LEVELS USED WHEN CALCULATING STANDARDIZED RELATIVE RISK, CORRECTING FOR CONFOUNDING VARIABLES

Variable	Levels
1. Systolic blood pressure (mm Hg)	<140 140 to 159 160 to 199 ≥200
2. Diastolic blood pressure (mm Hg)	60 to 79 80 to 99 100 to 119 120 to 139
3. Serum cholesterol (mmol/l)	<5.16 5.16 to 6.17 6.18 to 7.20 7.21 to 8.23 ≥8.24
4. Serum triglyceride (mmol/l)	<1.70 1.71 to 2.36 2.37 to 3.04 ≥3.05
5. Blood glucose (mmol/l)	<5.56 5.57 to 7.73 ≥7.74
6. Serum uric acid (mmol/l)	<0.24 0.25 to 0.35 0.36 to 0.47 ≥0.48
7. Plasma fibrinogen (mgm/100 ml)	<240 240 to 299 ≥300
8. Quetelet's index (weight/height^2)	<2.00 2.00 to 2.49 2.50 to 2.99 ≥3.00
9. Smoking (grams of tobacco/day)	<1 1 to 14 ≥15

APPENDIX 4.2

THE LOCATION OF PAIN IN PATIENTS WITH IC

	Right leg	Left leg	Total
Calf only	23	28	51
Calf and foot	7 *	8	15
Calf and knee	1	1	2
Calf and thigh	11	6	17
Calf, foot and thigh	3	1	4
Calf, foot and buttock	2	3	5
No pain	7	7	14
Total	54	54	108

* One patient with severe pain in right calf and foot had a through-knee amputation and is included here.

APPENDIX 4.3

ARTERIOGRAPHIC FINDINGS AND OPERATIVE PROCEDURES IN PATIENTS WITH IC

Patient	Age	Arteriogram	Operation
Mr. S	66	Complete block L femoral artery	L femoral-popliteal vein bypass
Mr. B	51	Incomplete block R iliac artery	R iliac endarterectomy
Mr. C	51	Complete block R femoral artery	R femoral-popliteal vein bypass
Mr. W	64	Complete block R femoral artery with poor distal vessels	R femoral-popliteal bypass (failed) R through-knee amputation
Mr. B	65	Incomplete block L iliac a.	L aorto-iliac endarterectomy
Mr. H	61	Aortic aneurysm Complete block R iliac artery	Aortic aneurysmectomy Dacron Y bypass graft R iliac endarterectomy
Mrs. S	66	Short incomplete block R iliac a. Complete block L femoral a.	None
Mr. E	64	Diffuse disease in aorta and bilateral diffuse disease in iliac and femoral arteries	None

APPENDIX 4.4

PALPATION OF THE LEG PULSES OF CASES AND CONTROLS

		Normal No. (%)	Diminished No. (%)	Absent No. (%)	Total no. pulses	
Cases*	Femoral a.	72 (67)	33 (31)	3 (3)	108	
	Popliteal a.	40 (37)	54 (50)	13 (12)	107	1 patient with through-knee amputation
	Dorsalis pedis a.	14 (13)	53 (50)	40 (37)	107	
	Posterior tibial a.	14 (13)	57 (53)	36 (34)	107	
Controls**	Femoral a.	211 (98)	5 (2)	0	216	
	Popliteal a.	203 (94)	13 (6)	0	216	
	Dorsalis pedis a.	182 (84)	24 (11)	10 (5)	216	
	Posterior tibial a.	197 (91)	17 (8)	2 (1)	216	

* All cases had diminished or absent pulses in at least one leg

** Eighty-eight controls (81%) had normal pulses in both legs

APPENDIX 4.5

INSPECTION OF THE LEGS OF CASES AND CONTROLS

	Cases No. limbs (%)	Controls No. limbs (%)
Trophic changes	26 (24)	6 (3)
Ulceration	6 (6)	0
Gangrene	2 (2)	0

APPENDIX 4.6

THE RESTING ANKLE SYSTOLIC BLOOD PRESSURE RATIO (ANKLE SBP/BRACHIAL SBP) OF CASES AND CONTROLS

Age (yrs)		Cases		Controls	
		Right leg	Left leg	Right leg	Left leg
45-49	n	3	3	6	6
	$\bar{x} \pm$ S.E.	0.78 ± 0.09	0.90 ± 0.10	1.19 ± 0.03	1.22 ± 0.20
50-54	n	10	10	20	20
	$\bar{x} \pm$ S.E.	0.75 ± 0.08	0.76 ± 0.08	1.19 ± 0.02	1.19 ± 0.02
55-59	n	5	5	10	10
	$\bar{x} \pm$ S.E.	0.73 ± 0.06	0.71 ± 0.06	1.20 ± 0.04	1.24 ± 0.04
60-64	n	12	13	26	26
	$\bar{x} \pm$ S.E.	0.58 ± 0.06	0.68 ± 0.06	1.21 ± 0.03	1.20 ± 0.03
65-69	n	23	23	46	46
	$\bar{x} \pm$ S.E.	0.73 ± 0.05	0.75 ± 0.05	1.16 ± 0.02	1.15 ± 0.02
Total	n	53	54	108	108
	$\bar{x} \pm$ S.E.	0.70 ± 0.03	0.74 ± 0.03	1.18 ± 0.01	1.18 ± 0.01

APPENDIX 4.7

THE EXERCISE ANKLE SYSTOLIC BLOOD PRESSURE RATIO (ANKLE SBP/BRACHIAL SBP) OF CASES AND CONTROLS

Age (yrs)		Cases		Controls	
		Right leg	Left leg	Right leg	Left leg
45-49	n	3	3	3	3
	$\bar{x}$ ± S.E.	0.49 ± 0.12	0.79 ± 0.13	1.11 ± 0.02	1.09 ± 0.02
50-54	n	8	8	14	14
	$\bar{x}$ ± S.E.	0.48 ± 0.07	0.43 ± 0.05	1.15 ± 0.01	1.18 ± 0.02
55-59	n	4	4	8	8
	$\bar{x}$ ± S.E.	0.42 ± 0.05	0.53 ± 0.05	1.18 ± 0.06	1.24 ± 0.05
60-64	n	6	6	19	19
	$\bar{x}$ ± S.E.	0.30 ± 0.05	0.48 ± 0.07	1.15 ± 0.02	1.15 ± 0.02
65-69	n	15	15	32	32
	$\bar{x}$ ± S.E.	0.55 ± 0.06	0.56 ± 0.07	1.15 ± 0.02	1.14 ± 0.02
Total	n	36	36	76	76
	$\bar{x}$ ± S.E.	0.48 ± 0.03	0.53 ± 0.04	1.15 ± 0.01	1.16 ± 0.01

APPENDIX 4.8

THE MEAN SYSTOLIC BLOOD PRESSURE OF CASES AND CONTROLS DIVIDED BY AGE AND SEX

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x} \pm$ S.E.	160.0 ± 5.8	130.8 ± 5.5	-	-	160.0 ± 5.8	130.8 ± 5.5
50-54	n	10	20			10	20
	$\bar{x} \pm$ S.E.	157.0 ± 8.7	138.3 ± 4.6	-	-	157.0 ± 8.7	138.3 ± 4.6
55-59	n	3	6	2	4	5	10
	$\bar{x} \pm$ S.E.	183.3 ± 18.6	150.8 ± 7.6	180.0 ± 40.0	128.8 ± 4.3	182.0 ± 16.2	142.0 ± 5.9
60-64	n	10	20	3	6	13	26
	$\bar{x} \pm$ S.E.	172.0 ± 8.6	136.5 ± 4.1	153.3 ± 3.3	155.8 ± 10.5	167.7 ± 7.0	141.0 ± 4.2
65-69	n	17	34	6	12	23	46
	$\bar{x} \pm$ S.E.	165.0 ± 5.4	155.0 ± 4.3	155.8 ± 11.6	166.2 ± 6.0	162.6 ± 4.9	157.9 ± 3.6*
Total	n	43	86	11	22	54	108
	$\bar{x} \pm$ S.E.	165.7 ± 3.8	144.8 ± 2.5	159.5 ± 8.7	156.6 ± 5.2	164.4 ± 3.5	147.2 ± 2.3

* Comparison of the systolic pressure of controls 45-49 years of age to that of controls 65-69 years of age (t-test, $t = 4.12$, $p<0.001$)

APPENDIX 4.9

THE MEAN DIASTOLIC BLOOD PRESSURE OF CASES AND CONTROLS DIVIDED BY AGE AND SEX

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x}$ ± S.E.	90.0 ± 10.0	75.0 ± 4.1	-	-	90.0 ± 10.0	75.0 ± 4.1
50-54	n	10	20			10	20
	$\bar{x}$ ± S.E.	91.0 ± 4.3	82.8 ± 2.4	-	-	91.0 ± 4.3	82.8 ± 2.4
55-59	n	3	6	2	4	5	10
	$\bar{x}$ ± S.E.	93.3 ± 8.8	84.2 ± 2.4	92.5 ± 17.5	73.8 ± 2.4	93.0 ± 7.3	80.0 ± 2.4
60-64	n	10	20	3	6	13	26
	$\bar{x}$ ± S.E.	91.5 ± 3.3	79.8 ± 2.3	88.3 ± 4.4	85.0 ± 4.1	90.8 ± 2.6	81.0 ± 2.0
65-69	n	17	34	6	12	23	46
	$\bar{x}$ ± S.E.	85.0 ± 2.8	85.1 ± 2.0	88.3 ± 3.3	87.1 ± 3.0	84.6 ± 2.2	85.7 ± 1.7*
Total	n	43	86	11	22	54	108
	$\bar{x}$ ± S.E.	88.8 ± 1.9	82.6 ± 1.2	86.4 ± 3.3	84.1 ± 2.2	88.3 ± 1.6	82.9 ± 1.0

* Comparison of the diastolic pressure of controls 45-49 years of age to that of controls 65-69 years of age (t-test, $t = 2.41$, $p<0.02$)

APPENDIX 4.10

THE MEAN FASTING CHOLESTEROL CONCENTRATION (MMOL/L) OF CASES AND CONTROLS DIVIDED BY AGE AND SEX*

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x}$ ± S.E.	6.1 ± 0.4	5.1 ± 0.4	-	-	6.1 ± 0.4	5.1 ± 0.4
50-54	n	10	20			10	20
	$\bar{x}$ ± S.E.	6.1 ± 0.3	5.9 ± 0.2	-	-	6.1 ± 0.3	5.9 ± 0.2
55-59	n	2	4	2	4	4	8
	$\bar{x}$ ± S.E.	6.5 ± 0.7	5.3 ± 0.4	6.5 ± 0.8	6.3 ± 0.6	6.5 ± 0.5	5.8 ± 0.4
60-64	n	9	20	3	6	12	26
	$\bar{x}$ ± S.E.	6.1 ± 0.3	6.3 ± 0.3	7.3 ± 0.6	7.0 ± 0.3	6.4 ± 0.3	6.4 ± 0.2
65-69	n	15	29	6	12	21	41
	$\bar{x}$ ± S.E.	5.8 ± 0.2	6.2 ± 0.1	7.6 ± 0.6	7.0 ± 0.3	6.3 ± 0.3	6.5 ± 0.1*
Total	n	39	79	11	22	50	101
	$\bar{x}$ ± S.E.	6.0 ± 0.1	6.0 ± 0.1	7.3 ± 0.4	6.9 ± 0.2	6.3 ± 0.2	6.2 ± 0.1

* Comparison of the cholesterol concentration of controls 45-49 years of age compared with that of controls 65 to 69 years of age (t-test, $t = 3.40$, $p<0.005$)

APPENDIX 4.11

THE MEAN FASTING TRIGLYCERIDE CONCENTRATION (MMOL/L) OF CASES AND CONTROLS DIVIDED BY AGE AND SEX

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x} \pm$ S.E.	2.37 ± 0.38	1.63 ± 0.10	-	-	2.37 ± 0.38	1.63 ± 0.10
	n	10	20			10	20
50-54	$\bar{x} \pm$ S.E.	2.43 ± 0.16	2.10 ± 0.20	-	-	2.43 ± 0.16	2.10 ± 0.20
	n	2	4	2	4	4	8
55-59	$\bar{x} \pm$ S.E.	2.01 ± 0.20	1.74 ± 0.11	2.49 ± 0.17	1.82 ± 0.13	2.85 ± 0.20	1.78 ± 0.08
	n	9	20	3	6	12	26
60-64	$\bar{x} \pm$ S.E.	1.56 ± 0.18	1.91 ± 0.13	1.86 ± 0.58	1.79 ± 0.17	1.94 ± 0.18	1.88 ± 0.11
	n	15	29	6	12	21	41
65-69	$\bar{x} \pm$ S.E.	2.32 ± 0.58	2.04 ± 0.16	3.14 ± 0.87	1.80 ± 0.15	2.56 ± 0.42	1.97 ± 0.10*
	n	39	79	11	22	50	101
Total	$\bar{x} \pm$ S.E.	2.22 ± 0.23	1.98 ± 0.08	2.67 ± 0.50	1.78 ± 0.10	2.32 ± 0.19	1.92 ± 0.06

* Comparison of the triglyceride concentration of controls 45-49 years of age to that of controls 65 to 69 years of age (t-test, $t = 2.40$, $p<0.025$)

APPENDIX 4.12

THE MEAN FASTING BLOOD GLUCOSE CONCENTRATION (MMOL/L) OF CASES AND CONTROLS DIVIDED BY AGE AND SEX*

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x} \pm$ S.E.	5.2 ± 0.2	4.9 ± 0.3	-	-	5.2 ± 0.2	4.9 ± 0.3
50-54	n	10	20			10	20
	$\bar{x} \pm$ S.E.	5.2 ± 0.1	5.7 ± 0.6	-	-	5.2 ± 0.1	5.7 ± 0.6
55-59	n	3	6			5	10
	$\bar{x} \pm$ S.E.	5.6 ± 1.0	5.4 ± 0.3	4.4 ± 0.2	4.6 ± 0.1	5.1 ± 0.6	5.1 ± 0.2
60-64	n	10	20	3	6	13	26
	$\bar{x} \pm$ S.E.	5.3 ± 0.4	5.3 ± 0.2	5.3 ± 0.7	5.1 ± 0.2	5.3 ± 0.3	5.3 ± 0.1
65-69	n	17	34	6	12	23	46
	$\bar{x} \pm$ S.E.	6.1 ± 0.7	5.9 ± 0.4	5.8 ± 1.0	5.2 ± 0.3	6.0 ± 0.6	5.8 ± 0.3
Total	n	43	86	11	22	54	108
	$\bar{x} \pm$ S.E.	5.6 ± 0.3	5.6 ± 0.2	5.4 ± 0.6	5.1 ± 0.2	5.6 ± 0.3	5.5 ± 0.2

* There was no significant difference between the mean levels compared

APPENDIX 4.13

THE SMOKING HABIT OF CASES AND CONTROLS DIVIDED BY AGE AND SEX*

Age (yrs)		Smokers		Ex-smokers		Non-smokers		Total	
		Men No.(%)	Women No.(%)	Men No.(%)	Women No.(%)	Men No.(%)	Women No.(%)	Men No.(%)	Women No.(%)
45-49	No.Cases(%)	2(67)	-	1(33)	-	0	-	3(100)	-
	No.Controls(%)	3(50)	-	1(17)	-	2(33)	-	6(100)	-
50-54	No.Cases(%)	9(90)	-	1(10)	-	0	-	10(100)	-
	No.Controls(%)	10(50)	-	7(35)	-	3(15)	-	20(100)	-
55-59	No.Cases(%)	2(67)	1(50)	1(33)	0	0	1(50)	3(100)	2(100)
	No.Controls(%)	2(33)	2(50)	3(50)	2(50)	1(17)	0	6(100)	4(100)
60-64	No.Cases(%)	7(70)	2(67)	2(20)	0	1(10)	1(33)	10(100)	3(100)
	No.Controls(%)	8(40)	2(33)	8(40)	1(17)	4(20)	3(50)	20(100)	6(100)
65-69	No.Cases(%)	12(71)	2(33)	5(29)	3(50)	0	1(17)	17(100)	6(100)
	No.Controls(%)	10(29)	0	19(56)	0	5(15)	12(100)	34(100)	12(100)
Total	No.Cases(%)	32(74)	5(45)	10(23)	3(27)	1 (2)	3 (27)	43(100)	11(100)
	No.Controls(%)	33(38)	4(18)	38(44)	3(14)	15(17)	15 (68)	86(100)	22(100)

* The percentages ( ) are totalled within each age group. The sexes are considered separately.

APPENDIX 4.14

THE MEAN WEIGHT* (GMS/DAY) OF TOBACCO SMOKED BY CASES AND CONTROLS DIVIDED BY AGE AND SEX

Age (yrs)	Weight (grams)	Male cases	Male controls	Female cases	Female controls	All cases	All controls
	n	3	4			3	3
45-49	$\bar{x} \pm$ S.E.	16.3 ± 4.9	22.8 ± 4.2	-	-	16.3 ± 4.9	22.8 ± 4.2
	n	10	17			10	17
50-54	$\bar{x} \pm$ S.E.	14.6 ± 1.8	21.8 ± 3.5	-	-	14.6 ± 1.8	21.8 ± 3.5
	n	3	5	1	4	4	9
55-59	$\bar{x} \pm$ S.E.	20.0 ± 2.3	16.4 ± 5.0	20.0 ± 0	5.8 ± 2.5	20.0 ± 1.6	11.7 ± 3.4
	n	9	16	2	3	11	19
60-64	$\bar{x} \pm$ S.E.	22.3 ± 4.5	17.0 ± 2.8	16.0 ± 1.0	7.7 ± 2.2	21.2 ± 3.7	15.5 ± 2.5
	n	17	29	5	0	22	29
65-69	$\bar{x} \pm$ S.E.	18.9 ± 3.4	17.5 ± 2.0	19.0 ± 5.6	all non-smokers	19.0 ± 2.8	17.5 ± 2.0
	n	42	71	8	7	50	78
Total	$\bar{x} \pm$ S.E.	18.5 ± 1.8	18.6 ± 1.4	18.4 ± 3.4	6.6 ± 1.6	18.5 ± 1.6	17.5 ± 1.3

* 1 cigarette = 1 gram tobacco
1 small cigar = 2 grams tobacco
1 large cigar = 5 grams tobacco

APPENDIX 4.15

COHb LEVELS (PER CENT SATURATION OF Hb) OF CASES AND CONTROLS BY THE WEIGHT OF TOBACCO (GRAMS) SMOKED ON THE DAY OF THE EXAMINATION

Weight of tobacco (gms)		COHb (per cent saturation Hb) 0.-0.99	1.00-1.99	2.00-2.99	3.00-3.99	4.00-4.99	5.00-5.99	6.00-6.99	7.00-7.99	8.00-8.99	9.00-9.99	Total
1-4	No. cases (%)	6(29)	11(52)	3(14)	1 (5)							21
	No. controls (%)	3(43)	4(57)									7
5-9	No. cases (%)		3(30)	5(50)		1(10)	1(10)					10
	No. controls (%)		5(45)	4(36)	1 (9)						1(9)	11
10-14	No. cases (%)				1(100)							1
	No. controls (%)				1(100)							1
15-19	No. cases (%)											
	No. controls (%)			1(25)	1(25)		1(25)		1(25)			4
20-24	No. cases (%)											
	No. controls (%)											
25-29	No. cases (%)				1(100)							1
	No. controls (%)		1(100)									1
30-34	No. cases (%)											
	No. controls (%)					1(100)						1
Total	No. cases (%)	6(18)	14(42)	8(24)	3 (9)	1 (3)	1 (3)					33
	No. controls (%)	3(12)	10(40)	5(20)	3(12)	1 (4)	1 (4)		1 (4)		1(4)	25

APPENDIX 4.16

DEPTH OF INHALATION OF TOBACCO SMOKE REPORTED BY CASES AND CONTROLS WHO WERE SMOKERS OR EX-SMOKERS

	Cases No. (%)	Controls No. (%)
No inhalation	3 (6)	9 (12)
Slight inhalation	10 (20)	33 (42)
Moderate inhalation	28 (56)	26 (33)
Deep inhalation	9 (18)	10 (13)
Total	50 (100)	78 (100)

APPENDIX 4.17

THE EFFECT OF SMOKING HABIT ON CERTAIN RISK FACTORS FOR PERIPHERAL VASCULAR DISEASE

	Systolic BP n $\bar{x} \pm$ S.E.	Diastolic BP n $\bar{x} \pm$ S.E.	Cholesterol (mmol/l) n $\bar{x} \pm$ S.E.	Triglyceride (mmol/l) n $\bar{x} \pm$ S.E.	Glucose (mmol/l) n $\bar{x} \pm$ S.E.	Fibrinogen (mgm %) n $\bar{x} \pm$ S.E.	Quetelet's index (weight/height^2) n $\bar{x} \pm$ S.E.	Uric acid (mmol/l) n $\bar{x} \pm$ S.E.
Cases who smoke (37)	37 166.6 ± 4.1	37 89.0 ± 1.7	35 6.2 ± 0.2	35 2.35 ± 0.25	37 5.5 ± 0.3	34 259.7 ± 7.6	37 2.43 ± 0.05	35 0.363 ± 0.012
Controls who smoke (37)	37 139.5 ± 4.3	37 80.9 ± 1.8	34 6.0 ± 0.2	34 1.94 ± 0.09	37 5.3 ± 0.3	35 251.5 ± 12.6	37 2.30 ± 0.06	37 0.339 ± 0.012
Cases - (13) ex-smokers	13 161.9 ± 8.5	13 86.9 ± 4.6	11 6.5 ± 0.4	11 2.45 ± 0.59	13 5.7 ± 0.6	11 277.5 ± 13.8	13 2.48 ± 0.08	11 0.369 ± 0.030
Controls - (41) ex-smokers	41 149.6 ± 3.0	41 83.2 ± 1.6	39 6.1 ± 0.2	39 2.11 ± 0.14	41 5.8 ± 0.3	40 243.1 ± 8.4	41 2.51 ± 0.04	41 0.345 ± 0.012
Cases - (4) non-smokers	4 152.5 ± 4.8	4 86.3 ± 3.8	4 6.8 ± 0.5	4 1.66 ± 0.33	4 5.4 ± 0.8	3 266.3 ± 34.9	4 2.78 ± 0.43	4 0.387 ± 0.042
Controls - (30) non-smokers	30 153.5 ± 4.4	30 84.8 ± 2.0	28 6.6 ± 0.2	28 1.71 ± 0.09	30 5.4 ± 0.2	27 251.9 ± 8.0	30 2.64 ± 0.25	29 0.327 ± 0.018

APPENDIX 4.18

THE MEAN FIBRINOGEN CONCENTRATION (MGM %) OF CASES AND CONTROLS DIVIDED BY AGE AND SEX

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x} \pm$ S.E.	280.0 ± 9.5	251.2 ± 17.3	-	-	280.0 ± 9.5	251.2 ± 17.3
50-54	n	10	18			10	18
	$\bar{x} \pm$ S.E.	248.0 ± 10.2	243.4 ± 13.4	-	-	248.0 ± 10.2	243.4 ± 13.4
55-59	n	2	6	1	4	3	10
	$\bar{x} \pm$ S.E.	250.0 ± 16.0	217.8 ± 9.6	234.0 ± 0	218.2 ± 29.3	244.7 ± 10.7	218.0 ± 12.0
60-64	n	7	18	3	6	10	24
	$\bar{x} \pm$ S.E.	245.1 ± 11.8	241.8 ± 13.0	274.3 ± 35.9	223.5 ± 9.9	253.9 ± 13.1	237.2 ± 10.1
65-69	n	16	33	6	11	22	44
	$\bar{x} \pm$ S.E.	274.0 ± 14.0	264.4 ± 12.7	284.2 ± 20.6	257.8 ± 13.9	276.8 ± 11.4	262.8 ± 10.1
Total	n	38	81	10	21	48	102
	$\bar{x} \pm$ S.E.	261.1 ± 7.1	250.3 ± 6.9	276.2 ± 15.9	240.5 ± 9.9	264.2 ± 6.5	248.3 ± 5.8

APPENDIX 4.19

THE MEAN URIC ACID CONCENTRATION (MMOL/L) OF CASES AND CONTROLS

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x} \pm$ S.E.	0.476 ± 0.030	0.351 ± 0.018	-	-	0.476 ± 0.030	0.351 ± 0.018
50-54	n	10	20			10	20
	$\bar{x} \pm$ S.E.	0.345 ± 0.018	0.357 ± 0.018	-	-	0.345 ± 0.018	0.357 ± 0.018
55-59	n	3	6	2	4	5	10
	$\bar{x} \pm$ S.E.	0.321 ± 0.042	0.333 ± 0.036	0.244 ± 0.089	0.292 ± 0.036	0.286 ± 0.048	0.315 ± 0.024
60-64	n	10	20	3	6	13	26
	$\bar{x} \pm$ S.E.	0.381 ± 0.018	0.339 ± 0.018	0.363 ± 0.054	0.321 ± 0.024	0.381 ± 0.018	0.333 ± 0.012
65-69	n	17	34	6	12	23	46
	$\bar{x} \pm$ S.E.	0.369 ± 0.024	0.345 ± 0.018	0.387 ± 0.048	0.298 ± 0.024	0.375 ± 0.018	0.333 ± 0.012
Total	n	43	86	11	22	54	108
	$\bar{x} \pm$ S.E.	0.369 ± 0.012	0.345 ± 0.012	0.357 ± 0.036	0.303 ± 0.018	0.363 ± 0.012	0.339 ± 0.006

APPENDIX 4.20

THE QUETELET'S INDEX OF CASES AND CONTROLS DIVIDED BY AGE AND SEX

Age (yrs)		Male cases	Male controls	Female cases	Female controls	All cases	All controls
45-49	n	3	6			3	6
	$\bar{x} \pm$ S.E.	2.54 ± 0.08	2.36 ± 0.10	-	-	2.54 ± 0.08	2.36 ± 0.10
50-54	n	10	20			10	20
	$\bar{x} \pm$ S.E.	2.53 ± 0.05	2.42 ± 0.07	-	-	2.53 ± 0.05	2.42 ± 0.07
55-59	n	3	6	2	4	5	10
	$\bar{x} \pm$ S.E.	2.50 ± 0.15	2.46 ± 0.09	2.38 ± 0.43	2.34 ± 0.18	2.46 ± 0.16	2.42 ± 0.09
60-64	n	10	20	3	6	13	26
	$\bar{x} \pm$ S.E.	2.55 ± 0.16	2.32 ± 0.10	2.25 ± 0.18	2.19 ± 0.09	2.48 ± 0.13	2.29 ± 0.08
65-69	n	17	34	6	12	23	46
	$\bar{x} \pm$ S.E.	2.45 ± 0.10	2.48 ± 0.05	2.35 ± 0.13	3.03 ± 0.61	2.42 ± 0.08	2.62 ± 0.16
Total	n	43	86	11	22	54	108
	$\bar{x} \pm$ S.E.	2.50 ± 0.06	2.42 ± 0.03	2.33 ± 0.10	2.68 ± 0.34	2.47 ± 0.05	2.47 ± 0.07

APPENDIX 4.21

THE SOCIAL CLASS DISTRIBUTION OF CASES AND CONTROLS

Social class	Cases No. (%)	Controls No. (%)
I	3 (6)	10 (9)
II	10 (18)	26 (24)
III	30 (56)	46 (43)
IV	11 (20)	26 (24)
V	0	0
Total	54(100)	108(100)

APPENDIX 4.22

THE ALCOHOL CONSUMPTION OF CASES AND CONTROLS

	Cases $\bar{x} \pm$ S.E.	n	Controls $\bar{x} \pm$ S.E.	n
Beer (pints/week)	10.2 ± 2.1	34	6.9 ± 0.9	67
Spirits (oz./week)	8.1 ± 1.8	18	8.2 ± 1.3	37
Sherry, port, wine (glasses/week)	7.7 ± 2.4	11	5.3 ± 0.8	28
Non-drinkers	5 (9%)		13 (12%)	

APPENDIX 4.23

OBSTETRICAL AND GYNAECOLOGICAL HISTORY OF WOMEN WITH IC AND WOMEN CONTROLS

		Cases	Controls
Age at menarche (years)	$\bar{x} \pm$ S.E.	14.0 ± 0.3	13.6 ± 0.4
	(n)	(11)	(22)
	range	13-16	11-18
Parity	$\bar{x} \pm$ S.E.	1.6 ± 0.5	1.6 ± 0.3
	(n)	(11)	(22)
	range	0-6	0-6
Gravidity	$\bar{x} \pm$ S.E.	1.7 ± 0.4	1.9 ± 0.4
	(n)	(11)	(22)
	range	0-4	0-6
Age at first pregnancy	$\bar{x} \pm$ S.E.	23.5 ± 1.1	25.6 ± 1.2
	(n)	(8)	(16)
	range	20-28	19-35
Age at menopause (years)	$\bar{x} \pm$ S.E.	48.1 ± 1.0	50.2 ± 0.9
	(n)	(11)	(22)
	range	42-53	36-56

APPENDIX 4.24

CORRELATION COEFFICIENTS OF RISK FACTORS FOR INTERMITTENT CLAUDICATION IN CASES

		SBP	DBP	Chol.	Trigl.	Gluc.	Tobacco	COHb	Fibr.	Uric A.	Age	Quetelet's Index
Systolic blood pressure (SBP)	r		0.5672	-0.0169	-0.1192	-0.1896	-0.0062	0.1188	-0.1018	-0.1104	-0.0121	0.2050
	(n)		(54)	(50)	(50)	(54)	(50)	(33)	(48)	(50)	(54)	(54)
	signifi-cance		0.001	0.907	0.410	0.170	0.966	0.510	0.491	0.445	0.931	0.137
Diastolic blood pressure (DBP)		X	X	0.1238	0.1412	-0.1716	0.2011	-0.4105	-0.1257	0.1636	-0.2612	0.2227
				(50)	(50)	(54)	(50)	(33)	(48)	(50)	(54)	(54)
				0.392	0.328	0.215	0.161	0.018	0.394	0.256	0.056	0.106
Cholest-erol (Chol.)		X	X	X	0.1569	0.0292	0.0085	0.0180	0.1263	0.1563	-0.0051	0.0900
					(50)	(50)	(46)	(33)	(47)	(48)	(50)	(50)
					0.277	0.840	0.956	0.921	0.397	0.289	0.972	0.534
Trigly-ceride (Trigl.)		X	X	X	X	0.0793	-0.0412	0.1957	0.0512	0.2646	-0.2153	0.1570
						(50)	(46)	(33)	(47)	(48)	(50)	(50)
						0.584	0.786	0.275	0.732	0.069	0.133	0.276
Glucose (Gluc.)		X	X	X	X	X	-0.0997	0.1186	-0.0133	0.1411	0.0995	0.2940
							(50)	(33)	(48)	(50)	(54)	(54)
							0.491	0.511	0.929	0.328	0.474	0.031
Amount tobacco smoked (grams/D)		X	X	X	X	X	X	-0.1455	0.0576	-0.0485	0.0236	0.1412
								(33)	(45)	(46)	(50)	(50)
								0.419	0.707	0.749	0.871	0.328
Carboxy-haemo-globin (COHb)		X	X	X	X	X	X	X	0.0535	-0.4323	0.1164	0.2790
									(33)	(32)	(33)	(33)
									0.767	0.013	0.519	0.116
Fibrin-ogen (Fibr.)		X	X	X	X	X	X	X	X	0.4232	0.1622	0.0871
										(46)	(48)	(48)
										0.003	0.271	0.556
Uric Acid (Uric A.)		X	X	X	X	X	X	X	X	X	0.0814	0.0481
											(50)	(50)
											0.574	0.740
Age		X	X	X	X	X	X	X	X	X	X	-0.2200
												(54)
												0.110

APPENDIX 4.25

CORRELATION COEFFICIENTS OF RISK FACTORS FOR INTERMITTENT CLAUDICATION IN CONTROLS

		SBP	DBP	Chol.	Trigl.	Gluc.	Tobacco	COHb	Fibr.	Uric A.	Age	Quetelet's Index
Systolic blood pressure (SBP)	r (n) significance		0.7836 (108) 0.001	0.2151 (101) 0.031	-0.0618 (101) 0.539	0.1168 (108) 0.229	0.1999 (78) 0.079	0.1271 (25) 0.545	0.0071 (102) 0.944	0.0363 (107) 0.711	0.3747 (108) 0.001	0.2081 (108) 0.031
Diastolic blood pressure (DBP)	X	X		0.1252 (101) 0.212	-0.0722 (101) 0.473	0.0951 (108) 0.328	0.2125 (78) 0.062	0.3712 (25) 0.068	0.0216 (102) 0.829	0.0977 (107) 0.317	0.1892 (108) 0.050	0.1868 (108) 0.053
Cholesterol (Chol.)	X	X	X		0.0003 (101) 0.998	0.1132 (101) 0.260	-0.2470 (73) 0.035	-0.1529 (25) 0.466	-0.0061 (96) 0.953	-0.1713 (101) 0.087	0.3430 (101) 0.001	0.1100 (101) 0.273
Triglyceride (Trigl.)	X	X	X	X		0.0539 (101) 0.592	0.1203 (73) 0.311	0.0304 (25) 0.885	-0.2998 (96) 0.003	0.1218 (101) 0.225	0.0224 (101) 0.824	0.2495 (101) 0.012
Glucose (Gluc.)	X	X	X	X	X	0.1242 (78) 0.279	0.1668 (25) 0.426	0.0526 (102) 0.599	0.0217 (107) 0.825	0.1258 (108) 0.195	0.1983 (108) 0.040	
Amount tobacco smoked (grams/D)	X	X	X	X	X	X	0.6414 (25) 0.001	0.1300 (75) 0.266	-0.1084 (101) 0.281	0.1694 (102) 0.089	0.1100 (102) 0.271	
Carboxyhaemoglobin (COHb)	X	X	X	X	X	X	X	0.0526 (25) 0.803	-0.0759 (25) 0.719	-0.2530 (25) 0.222	-0.2254 (25) 0.279	
Fibrinogen (Fibr.)	X	X	X	X	X	X	X	X	-0.1084 (101) 0.281	0.1694 (102) 0.089	0.1100 (102) 0.271	
Uric Acid (Uric A.)	X	X	X	X	X	X	X	X	X	-0.0775 (107) 0.427	0.2481 (107) 0.010	
Age	X	X	X	X	X	X	X	X	X	X	0.1228 (108) 0.205	

APPENDIX 5.1

MEAN VALUES* OF CERTAIN RISK FACTORS AT REFERRAL: DEAD PATIENTS COMPARED TO SURVIVORS

	Dead (16) $\bar{x} \pm$ S.E.	Alive (44) $\bar{x} \pm$ S.E.
Systolic BP (mm Hg)	149.1 ± 5.6	145.3 ± 3.8
Diastolic BP (mm Hg)	92.8 ± 3.0	89.0 ± 2.3
Cholesterol (mmol/l)	5.69 ± 0.34	6.48 ± 0.20
Triglyceride (mmol/l)	1.47 ± 0.15	1.75 ± 0.08
Glucose (mmol/l)	5.66 ± 0.26	5.08 ± 0.14
Weight of tobacco smoked (grams/day)	16.6 ± 1.8	16.6 ± 2.4
Uric acid (mmol/l)	0.333 ± 0.024	0.339 ± 0.018
Quetelet's index (weight/height^2)	2.31 ± 0.07	2.26 ± 0.05

* There was no significant difference between any of these means at the 5% level

APPENDIX 5.2

MEAN VALUES* OF CERTAIN RISK FACTORS AT REFERRAL: AMPUTEES COMPARED TO THOSE WITHOUT AMPUTATION

	Amputees (9) $\bar{x} \pm$ S.E.	No amputations (51) $\bar{x} \pm$ S.E.
Systolic BP (mm Hg)	142.2 ± 9.1	147.1 ± 3.3
Diastolic BP (mm Hg)	83.9 ± 4.2	91.1 ± 2.0
Cholesterol (mmol/l)	6.28 ± 0.41	6.25 ± 0.20
Triglyceride (mmol/l)	1.69 ± 0.23	1.68 ± 0.08
Glucose (mmol/l)	5.56 ± 0.12	5.27 ± 0.21
Weight of tobacco smoked (grams/day)	19.2 ± 4.0	16.1 ± 2.0
Uric acid (mmol/l)	0.292 ± 0.042	0.351 ± 0.018
Quetelet's index (weight/height^2)	2.41 ± 0.16	2.25 ± 0.05

* There was no significant difference between any of these means at the 5% level

APPENDIX 5.3

THE AGE AND SEX DISTRIBUTION OF THE MEN WHO HAD AMPUTATIONS

Age (yrs) at referral	No. at risk	No. (%) with amputation
40-49	6	2(33)
50-59	12	3(25)
60-69	24	3(13)
70-79	5	1(20)
Total	47	9(19)

APPENDIX 5.4

THE MEAN VALUES* OF CERTAIN RISK FACTORS FOR IC, DIVIDED BY SEX

Variable (at referral)	Men (47) $\bar{x} \pm$ S.E.	Women (13) $\bar{x} \pm$ S.E.
Systolic BP (mm Hg)	142.4 ± 3.0	160.4 ± 8.7
Diastolic BP (mm Hg)	88.2 ± 1.9	96.5 ± 4.7
Cholesterol (mmol/l)	6.10 ± 0.18	6.83 ± 0.49
Triglyceride (mmol/l)	1.66 ± 0.09	1.75 ± 0.16
Blood glucose (mmol/l)	5.44 ± 0.19	5.10 ± 0.25
Weight of tobacco smoked (grams/day)	17.1 ± 2.1	14.8 ± 2.7
Uric acid (mmol/l)	0.345 ± 0.018	0.315 ± 0.024
Quetelet's index (weight/height^2)	2.27 ± 0.06	2.26 ± 0.10

* There was no significant difference between any of these means at the 5% level

APPENDIX 5.5

THE PREVALENCE OF SYMPTOMATIC CORONARY ARTERY AND CEREBRAL VASCULAR DISEASE AT REFERRAL, DIVIDED BY SEX

	Men (47) No. (%)	Women (13) No. (%)
Myocardial infarction	12(26)	2(15)
Angina	10(21)	2(15)
Stroke	8(17)	1 (8)

APPENDIX 5.6

THE PERIPHERAL PULSES OF THE PATIENTS WHO STOPPED, REDUCED, OR CONTINUED SMOKING

		Stopped smoking (11)	Reduced smoking (9)	Continued smoking (39)
		No. legs=22	No. legs=18	No. legs =78
		No. pulses(%)	No. pulses(%)	No. pulses(%)
Femoral pulse	Present	14 (64)	10 (56)	46 (59)
	Reduced	4 (18)	8 (44)	23 (32)
	Absent	4 (18)	0	7 (9)
Popliteal pulse	Present	6 (27)	9 (50)	26 (33)
	Reduced	3 (14)	4 (22)	21 (27)
	Absent	13 (59)	5 (28)	31 (40)
Dorsalis pedis pulse	Present	4 (18)	5 (28)	11 (14)
	Reduced	2 (9)	0	15 (19)
	Absent	16 (73)	13 (72)	52 (67)
Posterior tibial pulse	Present	5 (23)	8 (44)	18 (23)
	Reduced	4 (18)	2 (11)	15 (19)
	Absent	13 (59)	8 (44)	45 (58)

APPENDIX 6.1

RUBRICS OF THE 7TH REVISION OF THE INTERNATIONAL CLASSIFICATION OF DISEASES* (1955) USED TO IDENTIFY PATIENTS WITH PERIPHERAL VASCULAR DISEASE

DISEASES OF ARTERIES (450-456)

450. General arteriosclerosis

450.0. Without mention of gangrene

Arteriosclerosis, except cerebral and coronary

general
senile

Arteriosclerotic vascular disease

Atheroma of artery, except cerebral and coronary

Calcareous degeneration of artery

Degeneration or sclerosis:

aortic
arterial
arteriovascular
vascular

Endarteritis deformans or obliterans

Senile:

arteritis
endarteritis

450.1. With mention of gangrene as a consequence

Senile gangrene

451. Aortic aneurysm, non-syphilitic, and dissecting aneurysm

Aneurysm, abdominal (aorta)
Aortic aneurysm specified as non-syphilitic
Dilatation of aorta
Dissecting aneurysm of aorta
Hyaline necrosis of aorta
Rupture of aorta NOS

* Corresponding rubrics in the 8th Revision of the Classification of Diseases (1965) are 440-448

APPENDIX 6.1 (cont'd.)

453. Peripheral vascular disease

454. Arterial embolism and thrombosis

Embolism) of any artery except cerebral (332), coronary
Thrombosis) (420.1), pulmonary (465), and mesenteric (570.2)

Embolism (of):

NOS
aorta
septic (not puerperal)

455. Gangrene of unspecified cause

Gangrene, mortification, or phagedaena (dry, moist, or unqualified) of unspecified cause, not classifiable elsewhere

Gangrenous cellulitis or dermatitis

Spreading cutaneous gangrene

APPENDIX 6.2

RUBRICS OF THE CLASSIFICATION OF SURGICAL OPERATIONS (1956) USED TO IDENTIFY PATIENTS WITH PERIPHERAL VASCULAR DISEASE*

PERIPHERAL NERVE AND SYMPATHETIC SYSTEM (030-049)

040. Section of sympathetic nerve

Section of ganglionated chain

Splanchnicotomy

041. Ganglionectomy and sympathectomy

Ganglionectomy

Ganglio-sympathectomy

Ramisectomy

Resection of hypogastric plexus

Splanchnicectomy

Sympathectomy

042. Sympathicotripsy

043. Injection into sympathetic nerve or ganglion

Alcohol

Procaine

Phenol

049. Other operations on sympathetic system

Gangliorrhaphy

Ganglionostomy

Sympathectomy, periarterial

LOWER LIMB AMPUTATIONS AND DISARTICULATIONS (890-899)

890. Abdominopelvic amputation

Amputation:

abdominopelvic

hindquarter

* Corresponding rubrics in the Second Revision of the Classification of Surgical Operations (1969) are 036-039, 870-889

APPENDIX 6.2 (cont'd.)

891. Disarticulation at hip joint

Amputation of lower limb:

by disarticulation

Disarticulation at hip (joint)

892. Amputation, thigh

Amputation:

femur:

lower half
neck
supracondylar
transcondylar
with transposition of patella
upper half

lower limb:

by excision
NOS

thigh

893. Disarticulation at knee

Disarticulation at knee

894. Amputation, leg

Amputation:

below knee, site of election
Symes'

895. Amputation, foot

Amputation:

metatarsal
mid-tarsal
supramalleolar
with transposition of tuberosity of os calcis
through metatarsals
transtarsal

896. Amputation, toe

Amputation of toe

OPERATIONS ON ARTERIES (EXCEPT GREAT VESSELS OF THORAX) (900-909)

Note: This section excludes operations on great vessels in thorax (320-329)

900. Arteriotomy with exploration

Angiotomy

Arteriotomy

NOS
with exploration

901. Arteriotomy with embolectomy

Arteriotomy

with embolectomy

Embolectomy

Removal of embolus

902. Arterectomy

Angiectomy

Arterectomy

with ligation of ends
with restoration by anastomosis

903. Excision of aneurysm

Aneurysmectomy

Excision of aneurysm

904. Arteriorrhaphy

Angiorrhaphy

Arteriorrhaphy

Suture of artery

905. Aneurysmorrhaphy

Aneurysmorrhaphy

Endoaneurysmorrhaphy

obliterative
restorative

906. Arterioplasty

Anastomosis:

arterial
arteriovenous
of blood vessel NOS

Angioplasty

Angiostomy

Arterioplasty

Femoro-popliteal by-pass

907. Ligation of artery

Ligation:

artery
blood vessel NOS

908. Filipuncture

Electrocoagulation

Filipuncture

Wiring of aneurysm

909. Other operations on arteries

Angiography

Angiotripsy

Arteriography

Arteriostrophy

Catheterisation, arterial

Compression of blood vessels

Thrombo-endarterectomy

Excision of arteriovenous fistula

Fistulectomy, arteriovenous

Puncture, arterial

Stripping of blood vessel

Endarterectomy

APPENDIX 6.3

ALL CAUSES OF DEATH RECORDED ON THE DEATH CERTIFICATES OF 94 PATIENTS WITH PVD WHO DIED IN THE FOLLOW-UP PERIOD

Cause of death	ICD code*	Men (59) No. (% of deaths)	Women (35) No. (% of deaths)	Total (94) No. (% of deaths)
Acute myocardial infarction	410	20 (33.9)	8 (22.9)	28 (29.8)
Cerebral thrombosis	443	10 (16.9)	14 (40.0)	24 (25.5)
Pneumonia	480-486	13 (22.0)	11 (31.4)	24 (25.5)
Peripheral vascular disease	443.9	15 (25.4)	6 (17.1)	21 (22.3)
Ischaemic heart disease	412	15 (25.4)	3 (8.6)	18 (19.1)
Congestive heart failure	427.0	6 (10.2)	5 (14.3)	11 (11.7)
Arteriosclerosis	440	8 (13.6)	3 (8.6)	11 (11.7)
Diabetes mellitus	250	6 (10.2)	5 (14.3)	11 (11.7)
Coronary arterio-sclerosis	412	9 (15.3)	1 (2.9)	10 (10.6)
Post-operative death**	796.9	7 (11.9)	3 (8.6)	10 (10.6)
Pulmonary embolus	450	4 (6.0)	6 (17.1)	10 (10.6)
Hypertension	400-404	5 (8.5)	2 (5.7)	7 (7.4)
Gangrene	445	2 (3.4)	4 (11.4)	6 (6.4)
Chronic bronchitis	491	5 (8.5)	0	5 (5.3)
Ruptured aortic aneurysm	441.9	3 (5.1)	1 (2.9)	4 (4.3)
Aortic aneurysm	441.0	3 (5.1)	0	3 (3.2)
Pulmonary oedema	429	2 (3.4)	1 (2.9)	3 (3.2)
Carcinoma of lung	162.1	2 (3.4)	1 (2.9)	3 (3.2)
Respiratory failure	796	1 (1.7)	1 (2.9)	2 (2.1)
Sudden death (cause unknown)	795	1 (1.7)	1 (2.9)	2 (2.1)
Trauma	N996	2 (3.4)	0	2 (2.1)
Emphysema	492	1 (1.7)	0	1 (1.1)
Uraemia	792	1 (1.7)	0	1 (1.1)
Parkinson's disease	342	1 (1.7)	0	1 (1.1)
Hypothyroidism	244	0	1 (2.9)	1 (1.1)

* ICD Codes are from the 8th Revision of the International Classification of Diseases

** Eight of the ten post-operative deaths occurred after surgical procedures for peripheral vascular disease

APPENDIX 7.1 (see back pocket)

APPENDIX 7.2

CORRELATION COEFFICIENTS BETWEEN REPORTED EXERCISE TOLERANCE AND MEASUREMENTS MADE BY DOPPLER ULTRASOUND FLOW RECORDER OR PLETHYSMOGRAPHY

Variables correlated*	Correlation coefficient (34 degrees of freedom)	Significance
Post-exercise systolic BP ratio and walking distance	0.51	$p<0.01$
Post-exercise ankle systolic BP ratio and stop score**	-0.42	$p<0.05$
Peak blood flow and walking distance	0.43	$p<0.05$
Peak blood flow and stop score	-0.20	N.S.
Ratio of peak flow/ rest flow and walking distance	0.37	$p<0.05$
Ratio of peak flow/ rest flow and stop score	-0.11	N.S.
Resting ankle systolic BP ratio and walking distance	0.28	N.S.
Resting blood flow and walking distance	-0.03	N.S.
Time to peak flow and walking distance	-0.21	N.S.
Total duration of hyperaemia and walking distance	-0.01	N.S.

* The lower of the two values of ankle systolic pressure or blood flow (i.e. the more diseased leg) was used in calculating the correlation coefficient

** Stop score = the mean number of times it was necessary to stop (calculated over a one-month period) when walking a fixed distance

APPENDIX 7.3

THE SMOKING HABITS* OF PATIENTS FREE OF PVD WHO WERE USED TO ESTABLISH NORMAL VALUES FOR PLETHYSMOGRAPH MEASUREMENTS

	No. patients (%)
Non-smoker	3 (16)
Ex-smoker	9 (47)
Pipe and cigar smoker	2 (11)
Cigarette smoker -	
1-14/D	4 (21)
15-24/D	0
≥25/D	1 (5)
Total	19(100)

* The definition of smokers, ex-smokers and non-smokers is presented in Chapter 4

APPENDIX 7.4

THE RESULTS OF THE MEASUREMENTS PERFORMED ON THE CONTROL PATIENTS (19 MEN)

	Mean ± S.E.	Range
Age (yrs)	52.5 ± 3.1	26.0 - 68.0
Haemoglobin (gm/100 ml)	15.0 ± 0.4	12.1 - 16.7
Haematocrit (%)	44.1 ± 1.2	36.0 - 55.3
Blood glucose (mmol/l)	4.9 ± 0.1	4.0 - 5.3
Serum cholesterol (mmol/l)	5.6 ± 0.3	4.3 - 6.2
Serum triglyceride (mmol/l)	1.56 ± 0.18	0.81 - 2.02
Plasma fibrinogen (mgm/100 ml)	278.8 ± 17.6	173.0 - 374.0
Uric acid (mmol/l)	0.34 ± 0.001	0.28 - 0.43
Systolic blood pressure (mm Hg)	134.1 ± 5.1	110.0 - 185.0
Diastolic blood pressure (mm Hg)	77.1 ± 3.4	55.0 - 110.0
Pulse rate (beats/minute)	68.0 ± 2.0	60.0 - 85.0
Resting ankle systolic BP ratio (ankle SBP/arm SBP)	1.18 ± 0.02*	1.00 - 1.40
Post-exercise ankle systolic BP ratio	1.16 ± 0.02*	1.00 - 1.35

* Ankle systolic pressure ratios of controls were significantly greater ($p<0.001$) than those of patients with IC (Mann-Whitney U test, Siegel, 1956)

UNIVERSITY OF OXFORD

DEPARTMENT OF

SOCIAL & COMMUNITY MEDICINE

INTERMITTENT CLAUDICATION SURVEY

INSTRUCTIONS: Please write your name. date of birth, age and sex in the spaces provided.

NAME.....DATE OF BIRTH.....

SEX MALE / FEMALE AGE.....

In answering the questions, simply place an "X" in the box next to the correct answer. Please ignore the numbers and boxes that appear in the right-hand margin.

Please answer all the questions.

SAMPLE QUESTION:

Have you ever experienced dizziness?

Yes [X]

No [ ]

For official use

1–5 [ ][ ][ ][ ][ ]

6–11 [ ][ ][ ][ ][ ][ ]

12–13 [ ][ ]

14 [ ]

---

1 *Do you get pain in either leg on walking?*

Yes [ ]

No [ ]

15 [ ]

2 *Does this pain ever begin when you are standing still or sitting?*

Yes [ ]

No [ ]

16 [ ]

3 *In what part of your leg do you feel the pain?*

The pain occurs in my calf/calves only [ ] 17 [ ]

The pain occurs in my calf and in another part of my leg [ ] 18 [ ]

The pain is not in my calf but in another part of my leg [ ] 19 [ ]

4 *If the pain occurs in another part of your leg- other than the calf,please state the location in the space below* (e.g. buttock, hip, thigh, knee, foot, etc.)

LOCATION OF PAIN.....

20–21 [ ][ ]

5 *Do you get this pain if you walk uphill or hurry?*

Yes [ ]

No [ ] 22 [ ]

Don't know because I never walk uphill or hurry [ ]

6 *Do you get this pain if you walk at an ordinary pace on the level?*

Yes [ ]

No [ ] 23 [ ]

7 *Does this pain ever disappear while you are walking?*

Yes [ ]

No [ ] 24 [ ]

HAVE YOU ANSWERED ALL THE QUESTIONS?–PLEASE TURN OVER

For official use

8 *What do you do if you get this pain while you are walking?*

I stop or I slow down ☐

I carry on ☐ 26 ☐

9 *What happens to the pain if you stand still?*

The pain is relieved completely ☐ 27 ☐

The pain is partially relieved ☐ 28 ☐

The pain is unaffected by rest ☐ 29 ☐

10 *How many minutes does it take for the pain to stop after you are standing still?*

NUMBER OF MINUTES..... 30–31 ☐☐

11 *For how many years have you been troubled by this pain?*

NUMBER OF YEARS I HAVE HAD THIS PAIN..... 32–33 ☐☐

12 *Have you told your doctor of this complaint?*

Yes ☐ 34 ☐

No ☐

13 *Have you had any treatment for this complaint?*

Yes ☐ 35 ☐

No ☐

14 *If you have had treatment, please indicate the type of treatment in the spaces below*

TREATMENT..... 36–37 ☐☐

.....

15 *Are you still receiving treatment for this complaint?*

Yes ☐ 38 ☐

No ☐

PLEASE CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS

PLEASE PUT THE ANSWER SHEET IN THE REPLY-PAID ENVELOPE AND RETURN IT TO ME

THANK YOU VERY MUCH FOR YOUR CO-OPERATION

COMMENTS

1 *Are there any parts of this questionnaire which are confusing, misleading, or difficult to answer ? If so, please describe your problem in the space below*

2 *Do you have any suggestions as to how we may improve the questionnaire?*

SUGGESTIONS

THANK YOU FOR YOUR HELP

APPENDIX 2.4

Patient's Name .....

Sex .....

Address .....

.....

Telephone No. .....

D.O.B. .....

N.H.S. No. .....

Hospital No. .....

Occupation/Posture .....

.....

G.P./Consultant .....

Date of Interview .....

1-4 ☐☐☐☐

5 [1] Card No.

6-11 ☐☐☐☐☐☐

12 ☐ Sex

13 ☐

Height (cm) ..... 14-16 ☐☐☐

Present weight (kgm) ..... 17-19 ☐☐☐

Max. weight in past (kgm) ..... 20-22 ☐☐☐

MEDICAL HISTORY AND TREATMENT

D.V.T. 23 ☐

V.V. 24 ☐

Raynaud's 25 ☐

C.V.A. 26 ☐

T.I.A. 27 ☐

Migraine 28 ☐

Previous myocardial infarct 29 ☐

If yes, No. most recent 30 ☐

Time since last (MOS) 31-32 ☐☐

Hospital .....

Date .....

Angina? If yes, duration (MOS) 33 ☐

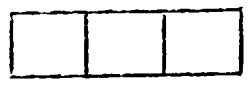
On severe exertion = 1

Walking = 2 34-35 ☐☐

At rest = 3

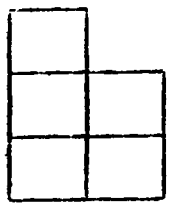
36 ☐

TREATMENT FOR HEART DISEASE

Diuretic = 1.....
Nitro/Vasodilator = 2 .....
Digoxin Prep = 4 .....
B Blocker = 8 .....
Antiarhythmic = 16 ..... 37-39 
Surgery = 32 .....
Diet = 64 .....
Other = 128 .....

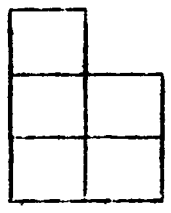
Hyperlipidaemia? Duration (yrs)

TREATMENT FOR HYPERLIPIDAEMIA

Diet = 1 40
Medication = 2 ..... 41-42 43-44 

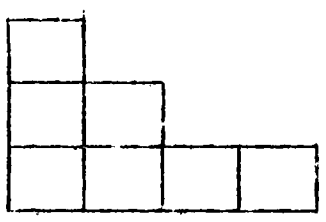
Diabetes? Duration (yrs)

TREATMENT FOR DIABETES

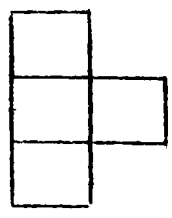
Diet = 1 45
Oral hypoglycemic = 2 46-47
Insulin = 4 ..... 48-49 
Other = 8 .....

Hypertension? Duration (yrs)

TREATMENT FOR HYPERTENSION

Diuretic = 1 50
Central action = 2 51-52
Ganglion Blocker = 4 ..... 53-56 
Post-gang adr. block = 8 .....
Rauwolfia alk = 16 .....
Methyldopa = 32 .....
Alpha adr. block = 64 .....
Beta adr. block = 128 .....
Vasodilator = 256 .....
Diet = 512 .....
Other = 1024 .....

Respiratory Disease? Duration (yrs)

Specify 57
..... 58-59
60 

TREATMENT FOR RESP. DISEASE

Antibiotic = 1 .....
Bronchodilator = 2 .....
Steroids = 4 ..... 61-62 
Other = 8 .....

Other drugs — Specify

Sympathomimetic	63	
Antithyroid	64	
Analgesics	65	
Antiinflammatory	66	
Antidepressants	67	
Tranquillizers	68	
Anticoagulants	69	
Others	70	

Other medical conditions

Cancer (specify)	71	
Diverticulitis	72	
Appendicitis	73	
Ulcerative colitis	74	
Haemorrhoids	75	
Stomach/Duodenal ulcer	76	
Cholecystectomy	77	
Others	78	

PREVIOUS TREATMENT FOR CLAUDICATION

.....	79-80	
.....		
.....		

BEGIN NEW CARD
REPEAT COLS 1-4

	1-4	
	5	2 Card No.

OBSTETRICS AND GYNAECOLOGY

Age at menarche	6-7	
Parity	8-9	
Gravidity	10-11	
Infertility	12	
Age at first pregnancy	13-14	
Menopause? Y = 1 N = 2	15	
Age at menopause	16-17	
Pre eclampsia?	18	

No = 1
Yes - Hospital < 1 week = 2
Yes - " >1 week = 3
Yes - Perinatal death = 4

Oral contraceptives? Y = 1 N = 2	19	
Specify	20	
Duration of use (yrs)	21-22	
Oestrogen replacement since menopause?	23	
Specify	24	
Duration of use (yrs)	25-26	

SMOKING HISTORY

Has pt. smoked today	27	☐
Did pt. smoke yesterday	28	☐
Is pt. a: smoker = 1, ex-smoker = 2, non-smoker = 3	29	☐
At what age did smoking begin	30-31	☐☐
Amounts		
Mfd. cigs. w. filter	32-33	☐☐ a day
Mfd. cigs. w.o. filter	34-35	☐☐ a day
Small cigars	36-37	☐☐ a day
Large cigars	38-39	☐☐ a week
Hand r. cigs. w. filter	40-41	☐☐ oz/wk
Hand r. cigs. w.o. filter	42-43	☐☐ oz/wk
Pipe tobacco	44-45	☐☐ oz/wk
Pipes	46-47	☐☐ a day
Which of above by weight was smoked in past five years (1-8)	48	☐
If an ex-smoker, age when quit	49-50	☐☐
If a current smoker, ever quit for 1 yr or more	51	☐
Total no. years non-smoker	52-53	☐☐
How long since resumed	54-55	☐☐
Brand		
Cigarettes	56-57	☐☐
Cigars	58-59	☐☐
Pipe tobacco	60-61	☐☐
Inhale		
A. Do not = 1 B. Slightly = 2 C. Moderately = 3 D. Deeply = 4	62	☐
Smoking today		
Cigarettes	63-64	☐☐
Cigars	65-66	☐☐
Pipes	67-68	☐☐
COHb time of blood test	69-72	☐☐☐☐
(i)	73-75	☐☐☐
(ii)	76-77	☐☐
(iii)	78-79	☐☐
Level	80	☐
BEGIN NEW CARD REPEAT COLS 1-4	1-4	☐☐☐☐
	5	☐ 3 Card No.

We would like to know at what times you smoke.

(a) Please indicate by a dash across the appropriate time scale each time you have smoked a cigarette, a cigar or a pipe so far today, thus —

Please do not indicate anything you have smoked after your blood test. Try to get the total number of dashes right even if you are not sure about the exact time at which you smoked, and check that the number of dashes in each column is equal to the total you have indicated.

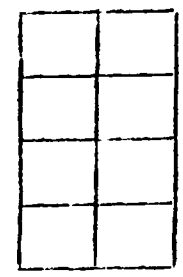
Cigarettes	Cigars	Pipes
Midnight (last night)	Midnight (last night)	Midnight (last night)
1 am.	1 am.	1 am.
2 am.	2 am.	2 am.
3 am.	3 am.	3 am.
4 am.	4 am.	4 am.
5 am.	5 am.	5 am.
6 am.	6 am.	6 am.
7 am.	7 am.	7 am.
8 am.	8 am.	8 am.
9 am.	9 am.	9 am.
10 am.	10 am.	10 am.
11 am.	11 am.	11 am.
12 noen	12 noon	12 noon
1 pm.	1 pm.	1 pm.
2 pm.	2 pm.	2 pm.
3 pm.	3 pm.	3 pm.
4 pm.	4 pm.	4 pm.
5 pm.	5 pm.	5 pm.
6 pm.	6 pm.	6 pm.
7 pm.	7 pm.	7 pm.
8 pm.	8 pm.	8 pm.
9 pm.	9 pm.	9 pm.
10 pm.	10 pm.	10 pm.
11 pm.	11 pm.	11 pm.
Midnight (tonight)	Midnight (tonight)	Midnight (tonight)

Total cigarettes, cigars and pipes smoked so far today

☐☐ 33-34	☐☐ 35-36	☐☐ 37-38

ALCOHOL CONSUMPTION

Beer (pints/wk) 6-7 8-9 10-11 12-13



Spirits (oz/wk)

Sherry, Port, Wine (glasses/wk)

Others (oz/wk)

CLAUDICATION

RIGHT LEFT

Present 14-15



Onset

Gradual = 1
Sudden = 2
Unknown = 3

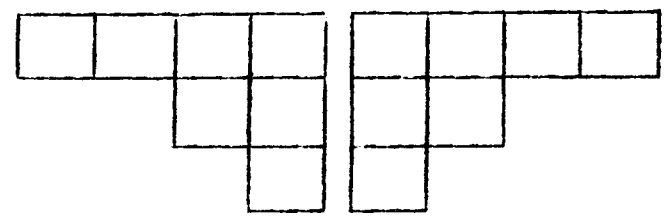
16-17



Distance at onset (m) 18-25

Time since onset (mos) 26-29

Stopped due this leg 30-31



Site

Back = 1
Buttock = 2
Hip = 4
Thigh = 8
Knee = 16
Ankle/foot = 32

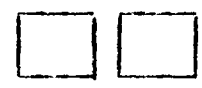
32-35



Progress in past year

Worse = 1
Better = 2
Unchanged = 3

36-37

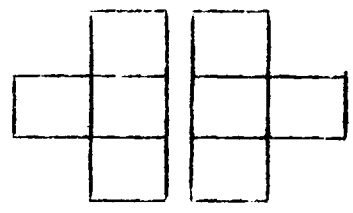


Rest pain

Present 38-39

Duration (mos) 40-43

Progress past year - W = 1, B = 2, U = 3 44-45



Sympathectomy

None = 1
Chemicals = 2
Surgical = 3

46-47



Time since (mos) 48-51



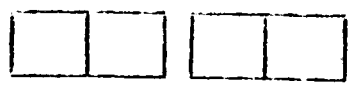
AMPUTATION

None = 1
Foot = 2
Below knee = 3
Through knee = 4
Above knee = 5

52-53



Time since (mos) 54-57



RECONSTRUCTIVE OPERATIONS

Endart = 1	Aorta	58
Vein bypass = 2	Iliac	59-60
Dacron bypass = 3	Sup. femor.	61-62
Embolectomy = 4	Prof. femor.	63-64
Aneurysmect = 5	Popliteal	65-66

Specify .....

.....

Time since last operation (mos) 67-70

MOST RECENT ARTERIOGRAM

Normal = 1	Aort. seg.	71-72
Short incomp BL=2	Iliac seg.	73-74
Long incomp BL=3	Prof. seg.	75-76
Comp BL and good collat=4	Fem. seg.	77-78
Comp block = 5	Pop. run-off	79-80

BEGIN NEW CARD
REPEAT COLS 1-4 1-4

4 Card No.

Time since last done (mos) 6-9

PHYSICAL EXAM

Pulses		Femoral	10-11
Normal = 1		Popliteal	12-13
Diminished = 2		Ant. Tib.	14-15
Absent = 3		Post. tib.	16-17
Ulcers	Y = 1	N = 2	18-19
Trophic changes	Y = 1	N = 2	20-21
Gangrene	Y = 1	N = 2	22-23

LABORATORY INVESTIGATIONS

Haematology -	Hb	24-26
	HcT	27-29
	WBC	30-32

Urine

(i) Protein 33

(ii) Sugar 34

Biochemistry

Ca.	35-37
Phos.	38-39
R. Sug.	40-42
UREA	43-44
URICA	45-46

T. Prot.	47-48	
Alb.	49-50	
T. Bili.	51-52	
Alk. P.	53-54	
LDH	55-57	
SGOT	58-59	
Fasting cholesterol	60-62	
Fasting triglycerides	63-65	
Fasting glucose	66-68	
Serum fibrinogen (mgm %)	69-71	

ECG

Not available = 1
Normal = 2
Definite ischaemia = 4
Infarct = 8
Questionable isch. = 16
Other = 32

72-73

PT. ASSESSMENT OF DISEASE

Limited by:

No limitation = 1
Angina = 2
Claudication = 4
Resp. disease = 8
Arthritis = 16
C.U.A. = 32
Other = 64

74-76

.....

Degree of limitation

Severe = 1
Moderate = 2
Mild = 4

77

78-79

80

BEGIN NEW CARD
REPEAT COLS 1-4

1-4

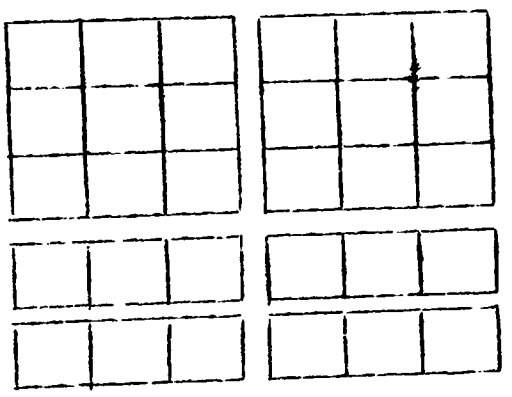
5 | 5 | Card No.

PRESSURES

		RIGHT	LEFT
Resting			
Syst.	Arm	6-11	
	Foot	12-17	
	Difference	18-29	
Diast.	Arm	24-29	
Ratio (ankle/arm)		30-35	

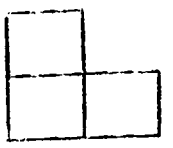
Exercise

Syst.	Arm	36-41
	Foot (min. press.)	42-47
	Difference	48-53
Diast.	Arm	54-59
Ratio (ankle/arm)		60-65



Blood pressure gradient

Is pt. able to exercise? Y=1 N=2 — 66

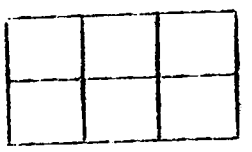


If not, why? — 67-68

Angina = 1
ECG = 2
Resp. dis. = 4
C.U.A. = 8
Arthritis = 16
Other = 32

Exercise rate

No. of steps — 69-71



Time (sec) — 72-74

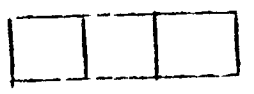
ECG

Not available = 1
Normal = 2
Definite isch. = 4
Infarct = 8
Questionable isch. = 16
Other = 32



75-76

Room temperature (^{o}C) — 77-79



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APPENDIX 7.1

CINNARIZINE PERIPHERAL STUDY

CNZ 102

RADCLIFFE INFIRMARY

PATIENT'S NAME .....

HOSPITAL NUMBER .....

DOCTOR'S NAME .....

DATE ISSUED .....

NEXT APPOINTMENT .....

TO THE PATIENT

Please remember to take one capsule three times a day and fill in the card every day. Please grade symptoms daily as:

Absent	0
Mild	1
Moderate	2
Severe	3

On each day (when possible) we ask you to take a regular walk and count the number of times you have to stop because of leg pain.

Activity to be assessed daily

.....

.....

.....

WEEK NO.....

DAY NO.	DAY & DATE	SYMPTOMS				NO. OF TIMES ASSESSED ACTIVITY STOPPED BECAUSE OF LEG PAIN
		REST PAIN DAY	REST PAIN NIGHT	COLD FEET	LEG CRAMPS OR DISCOMFORT	
TOTAL						

OTHER COMMENTS .....

.....

WEEK NO.....

DAY NO.	DAY & DATE	SYMPTOMS			NO.OF TIMES ASSESSED ACTIVITY STOPPED BECAUSE OF LEG PAIN
		REST PAIN	COLD FEET	LEG CRAMPS OR DISCOMFORT	
		DAY | NIGHT			
TOTAL					

OTHER COMMENTS .....

.....

WEEK NO.....

DAY NO.	DAY & DATE	SYMPTOMS				NO. OF TIMES ASSESSED ACTIVITY STOPPED BECAUSE OF LEG PAIN
		REST PAIN		COLD FEET	LEG CRAMPS OR DISCOMFORT	
		DAY	NIGHT			
TOTAL						

OTHER COMMENTS .....

.....

WEEK NO.....

DAY NO.	DAY NO.	DAY & DATE	SYMPTOMS			NO.OF TIN ASSESSED ACTIVITY STOPPED BECAUSE (LEG PAIN
			REST PAIN	COLD FEET	LEG CRAMPS OR DISCOMFORT	
			DAY | NIGHT			
TOTA	TOTAL					

OTHE OTHER COMMENTS .....

....

NOTES