

NOTHING IS PERMANENT EXCEPT CHANGE

(Heraclitus, 535 B.C.)

**AN INTER-RACIAL STUDY INTO THE PATTERN AND
PREVALENCE OF ATHEROSCLEROTIC PERIPHERAL
VASCULAR DISEASE IN THE UNIVERSITY-BASED
VASCULAR SURGICAL SERVICE IN DURBAN**

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DEDICATION

There are many among us, and some who are no longer with us, who have been part of my life, work and aspirations; who have loved, nurtured, taught, inspired and created in me a sublime sense of love and profound desire to understand and care, believe and appreciate, question the unexplained and explore the unknown; those who with assistance, advice, caution, criticism and even discipline have tempered my personality and philosophies, attitudes and attributes and perhaps my destiny - **my parents, family, friends, teachers, colleagues and patients.** This thesis is dedicated to every one of them, none of whom I would like to single out, every one of whom I am deeply indebted and grateful to.

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ABSTRACT

This study investigates the clinical and major risk factor profiles in Whites, Indians and Blacks with atherosclerotic peripheral vascular disease at the Vascular Service in Durban; and compares them to that for coronary artery disease in the same race groups.

The clinical profile for chronic peripheral vascular disease was established in a retrospective study of 2175 patients seen at the Vascular Service during 1981-1986. Atherosclerosis was confirmed in 1974 patients (92,3%) on the basis of clinical, doppler, angiographic and histological evidence. The disease predominantly affected the aorta and distal peripheral vessels. Extracranial cerebrovascular disease occurred less commonly in Blacks than in Whites and Indians. Occlusive disease was the most common pathological type in all race groups. Aneurysmal disease occurred mainly in the aorta with peripheral aneurysms being most common in Blacks. The disease manifested in Blacks at an earlier age and more aggressively than in Whites and Indians.

The risk factor profile for atherosclerotic peripheral vascular disease was established in a prospective study of 302 male patients consisting of 100 Whites, 97 Indians and 105 Blacks on the basis of historical, clinical and haematological data. The sample was randomly selected, and not strictly representative of the clinical pattern in the retrospective study. All patients were confirmed to have atherosclerosis on the basis of the previously mentioned criteria. Smoking was the single most common risk factor in all race groups. Hypertension occurred more commonly in Whites and Indians than in Blacks, while diabetes was commonest in Indians. Insulin resistance did not occur in Blacks, but was possibly present in Whites and Indians. Total cholesterol, LDL cholesterol and triglycerides were raised in Whites and Indians, but not in Blacks. HDL cholesterol was reduced in all 3 race groups.

These findings suggest that contrary to the established view, atherosclerotic peripheral vascular disease is an established entity in Blacks seen at the Vascular Service in Durban

without a concomitant increase in coronary and extracranial cerebrovascular disease. In Whites and Indians atherosclerosis occurred in all of the vascular beds. This could support the contention that in a socially developing society atherosclerosis affects the aorta and distal peripheral vessels before the coronary vascular bed. Since this occurs in the presence of normal levels of total cholesterol, LDL cholesterol and triglycerides, it does not support the contention that hypercholesterolaemic states are essential for atherosclerotic lesions to develop.

On this basis it is postulated that with social transition there is a differential atherosclerotic involvement of the vascular beds due to a differential vascular susceptibility. Smoking is an important socio-environmental risk factor, while at the biochemical level a reduced HDL cholesterol and not a raised total cholesterol, LDL cholesterol or triglyceride could trigger the 'lipid pathway' in atherogenesis. It is further postulated that the differential vascular susceptibility does not exist in a fully developed society once lipid aberrations include a raised total cholesterol, LDL cholesterol and triglycerides. Insulin resistance/hyperinsulinaemia may play a role in the evolution of the disease within the coronary vascular bed.

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LIST OF ABBREVIATIONS

AAA	:	Abdominal aortic aneurysm
AOI	:	Aorto-iliac
CV	:	Coefficient of variation
CVD	:	Cerebrovascular disease
ECG	:	Electrocardiogram
ECV	:	Extracranial cerebrovascular
FEM POP	:	Femoro-popliteal
HDL	:	High density lipoprotein
IHD	:	Ischemic heart disease
LDL	:	Low density lipoprotein
Lp(a)	:	Lipoprotein (a)
OD	:	Optical density
TIB PER	:	Tibio-peroneal
VLDL	:	Very low density lipoprotein

CHAPTER ONE

AIM OF THE STUDY

1. INTRODUCTION

"THE PROPER STUDY OF MANKIND IS MAN." (ALEXANDER POPE)

The geopolitical situation in South Africa presents a unique biological model to study atherosclerosis in a population which varies in its racial background and socio-economic development. The significance of such a study is perhaps best epitomised in the following statement:

"..... we cannot be complacent. Indian CHD mortality rates are still the highest in the world, rates for whites remain among the highest, coloured rates are considerable and black rates, although low, could be rising" (Seftel, 1994).

Cardiovascular diseases are the leading cause of premature death and disability in the developed world (Muntoni, 1995). Research has generally concentrated on the coronary and cerebral forms of the disease. Peripheral vascular disease has, however, received much less attention from epidemiologists (Balkau et al., 1994) and epidemiological information on peripheral vascular disease is considerably lacking (De Backer et al. 1979). Cardiovascular diseases, similarly, receive little or no attention in most African countries (Muna, 1993). Yet studies on ethnic differences in frequency of diseases can sometimes provide insights into etiological mechanisms and, hopefully, lead to interventions that decrease risk and frequency of the disease (Alter, 1994).

Based on this outlook and for reasons which will become more obvious in a **formulation and statement of the problem** this study investigates the inter-racial aspects of atherosclerotic peripheral vascular disease among patients seen at the Vascular Service in Durban. Its aim is to establish whether the disease is an emerging

entity in Black patients, to determine its relationship to coronary and cerebral atherosclerosis and to elucidate the relationship of risk factors to the patterns observed.

It is anticipated that the findings in this study will reflect the pattern of atherosclerosis in underdeveloped and developing societies with considerable implications for our understanding of the genesis of atherosclerosis, its etiological mechanisms and intervention strategies.

2. FORMULATION OF THE PROBLEM

Atherosclerosis is an extensively researched subject. Yet the disease remains enigmatic and continues to attract the attention of researchers. The following aspects of the disease serve as a background for the problem and purpose of this study.

- 2.1 Atherosclerosis is a chronic degenerative disease of the arterial wall which develops slowly and insidiously within individuals and in population groups as a whole.

The entire process from when the disease first establishes itself within the vasculature until clinical disease is evident can take years. It is only when these clinical effects become common clinical problems where previously they did not exist that atherosclerosis as a disease within a population group becomes noticeable and a cause for concern.

- 2.2 Atherosclerosis is currently considered to be the major cause of morbidity and mortality in most western and developed societies. Its involvement in developing societies, however, has not been clearly elucidated to any great extent and to date remains uncertain. The clinical impression though is that as social change occurs in developing societies, atherosclerotic lesions increase noticeably.

- 2.3 Although clinical disease usually manifests when fibrous plaques and complicated lesions occur, fatty streaks are also considered to be precursor lesions for atherosclerosis and are, therefore, part of the pathological process. Yet, interestingly, these potentially prototypic forms of atherosclerosis have been recorded in the literature as existing in individuals as early as infancy irrespective of race, gender, geographical location, socio-economic status and predisposition to atherosclerosis. There is no reasonable explanation for their quiescence from early infancy until consequential lesions develop, if they do. Their existence, furthermore, in those individuals or population groups who on the basis of genetic criteria, do not have a pre-disposition to atherosclerosis, still remains unexplained.
- 2.4 Even though race, age and gender are regarded as the genetic determinants of a predisposition to atherosclerosis, under certain conditions and circumstances, environmental factors have the capacity to override the genetic predisposition of individuals or population groups and establish new demographic profiles. There is, however, no definitive explanation of how this process takes place and this still remains a subject of great research interest.
- 2.5 Demographic patterns form an interesting aspect of atherosclerotic epidemiological research and are found to vary widely in both developed and developing population groups depending ultimately on the interplay between genetic and environmental factors, known and unknown. As a result of epidemiological work the following demographic patterns have been identified, but remain unexplained:-
- 2.5.1 that there are whole populations in underdeveloped countries and isolated communities in the West (e.g. the Portuguese, the Bulgarians and the Greeks) that are largely free from atherosclerosis (Stanton,1972; Walker,1975; Menotti and Giampaoli, 1986);
- 2.5.2 that there are different population groups living in a similar geographical environment (Blacks, Whites and Indians in South Africa) that have divergent patterns of atherosclerosis (Walker, 1987; Sempos et al.,1988); and

2.5.3 that there are different racial groups in different geographical locations (e.g. Blacks in South Africa, Japanese living in Japan and Chinese living in China) which have similar patterns of atherosclerotic disease. In all three instances atherosclerotic cerebrovascular disease occurs commonly while ischemic heart disease is considered rare.

- 2.6** Atherosclerosis is a dynamic process that is known to change in terms of person, place and time. The demographic patterns of atherosclerosis in any particular population group and geographical location are subject, therefore, to change with time. The socio-economic status prevalent in each particular instance appears to be intrinsically associated with the degree of atherosclerosis that would exist and as socio-economic conditions improve, the extent of atherosclerotic lesions seems to increase. Once again our knowledge with respect to the consistency of atherosclerosis and the manner of change is very limited. Yet vital clues to the aetiology, pathogenesis and treatment of atherosclerosis may exist in this potential field of research.
- 2.7** The appearance of atherosclerosis in a developing population hitherto unaffected by disease may not be a randomised process with the sudden appearance of, for example, coronary vessel involvement and ischemic heart disease. Instead atherosclerosis may evolve in a certain specific manner as if it had a natural history of development within the vasculature. There is little evidence or support for this view in the literature but if sufficiently substantiated could open a new, interesting and dynamic approach to the study of atherosclerosis.

While the above may be argued to be the case in a society in transition there is at this stage no indication of whether the same contention would hold in the translocation from a socially less developed society suddenly into one that is developed, for example the translocation of Japanese from Japan to Hawaii and the United States of America (Kato et al., 1973), or Indians from India to the United Kingdom, the West Indies and Fiji (Seedat et al., 1990).

2.8 The possibility of a sequential development of atherosclerotic lesions within a society in transition was originally promulgated by Walker (1975). He aptly summarised his observations as follows *"briefly in an African developing population, of disease consequent on an increasing severity and other promotive factors, the first to emerge is cerebrovascular disease. Among Negroes in Africa, in some large urban centres mortality rate for cerebrovascular disease, principally from cerebral haemorrhage, reaches out and then exceeds that of the White populations. Among Negroes in the United States, the proportion of total deaths due to cerebrovascular disease has risen to about 13%. Coronary heart disease, with a rise in prosperity, emerges much later than cerebrovascular disease; in sophisticated African Negro populations coronary heart disease still remains a negligible cause of death. Among Negroes in the United States, in some segments coronary heart disease mortality approaches that of Whites, among whom it causes 30% of all deaths. Peripheral vascular disease, virtually absent in populations living primitively increases in prevalence with a rise in privilege. As a clinical problem it emerges somewhat before coronary heart disease."*

Walker made these observations in African societies as they experienced a social transition. To date these views have no support in the literature, mainly because they have not attracted research interest.

2.9 It would seem that once there has been involvement of the coronary vascular bed the selectivity process responsible for the sequential evolution of atherosclerosis within the vasculature becomes extinct and atherosclerotic involvement of the different vascular beds becomes generalised and randomised, except possibly the extracranial cerebral vascular segment in Blacks, which according to evidence emerging from the United States of America suggests that involvement of these vessels is even further spared in spite of a level of sophistication among Blacks which equals that of Whites.

2.10 Of the different vascular beds it is coronary vascular involvement that has attracted the most research interest. In reviewing the literature it is apparent that current knowledge of the pathogenic mechanisms and risk factors involved in atherosclerosis has generally been derived from studies involving coronary heart disease. The

conclusions made from these studies have been extrapolated to apply to atherosclerosis in general within the various vascular beds both in individuals and in population groups as a whole, in developed and underdeveloped societies. The research interest attracted by coronary artery disease is mainly due to the alarmingly high mortality rates associated with this form of the disease as evidenced by arrhythmias, shock and sudden death. Research opportunities are also easily available on account of the ready availability of facilities and equipment which usually are easy to use, non invasive and carry a minimum of risk.

- 2.11 By contrast, the literature review indicates that peripheral vascular involvement with atherosclerosis has not attracted as much attention from researchers. The diaphragm, seemingly, is an impenetrable barrier between cardiac and peripheral vascular research. This lack of research interest could also be due to the lower mortality rates associated with peripheral vascular disease, even though it does cause a fair degree of morbidity. There are also fewer units specifically concerned with the extracerebral extracoronary circulation and investigative methods and equipment for the early detection of atherosclerotic lesions in this part of the vasculature have not been readily available. With the possible exception of the carotid duplex scanner and ultrasound flow probes, all other scientific techniques for the study of atherosclerotic lesions in the peripheral vasculature rely on arteriography which is expensive, invasive, carries a risk and is usually only done when surgery is considered as a form of treatment. Even when lesions are detected the problem is further compounded by a lack of accurate methods to quantitate the extent of the disease.

Directly and/or indirectly as a result of the problems discussed above our knowledge with respect to atherosclerotic peripheral vascular disease is largely dependent on autopsy studies and clinical impressions and is consequently lacking with respect to epidemiology, pathogenic mechanisms and biochemistry.

- 2.12 In view of the foregoing it would seem that if indeed there is an evolutionary basis for the development of atherosclerosis within the vasculature, even the possibility of its existence in a society in transition, then peripheral vascular atherosclerosis would

represent an early stage and coronary artery atherosclerosis a late stage of the process. If this does have any validity then our present understanding of the disease is largely derived from the end stage of the process which may reflect results and conclusions different from those at an earlier stage of the disease. This viewpoint is vindicated by increasing evidence that the risk factors for peripheral vascular disease may differ from those associated with coronary artery disease. There is therefore a great need to intensify our interest and study of atherosclerotic peripheral vascular disease.

3. **STATEMENT OF THE PROBLEM**

The established view is that atherosclerotic peripheral vascular disease in Blacks is rare. Little or no mention is made of the problem in the various text books dealing specifically with the practice of internal medicine, surgery and pathology in this population group (Robbs, 1985). There is no recent study in the literature to evaluate the status of atherosclerotic peripheral vascular disease among Blacks, Whites and Indians in South Africa. Based on the observations of Walker (1975), with social transition among Blacks the currently established view may no longer be valid and atherosclerotic peripheral vascular disease may be in the ascendancy in this race group, without a concomitant increase in coronary artery disease. By contrast the clinical pattern of coronary artery disease is well known for each of these race groups in South Africa and adequately covered in the medical literature.

There is also no study in the literature to evaluate the major risk factor profile in Whites, Indians and Blacks with atherosclerotic peripheral vascular disease in South Africa; and little is known about the relationship between risk factors and peripheral vessel atherosclerosis. By comparison, risk factors for coronary artery disease have been extensively investigated in each of these race groups locally. However, risk factors for coronary artery disease need not be the same for atherosclerotic peripheral vessel disease; nor do they need to have the same pathogenetic roles. This will be especially significant if the observations made by Walker (1975) do have validity and if they gain prominence in the medical literature.

4. PURPOSE OF THIS STUDY

In South Africa there are historically several racial groups differing from each other in descent, dietary habits, socio-economic status and predisposition to atherosclerotic disease. South Africa, since the late seventies and early eighties, is a society in transition and as a consequence of this the South African Black is at present undergoing a phase of rapid social change and improved socio-economic status.

South Africa and in particular the Vascular Service in Durban presents an ideal biological model to study atherosclerosis in a developing and changing society in contrast to a fully developed society of differing racial backgrounds.

The purpose of this study is therefore to carry out AN INTER-RACIAL STUDY INTO THE PATTERN AND PREVALENCE OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE IN THE UNIVERSITY-BASED VASCULAR SURGICAL SERVICE IN DURBAN in order to determine the following:-

- 4.1 What is the clinical profile of atherosclerotic peripheral vascular disease among White, Indian and Black patients seen at the Vascular Service in Durban?
- 4.2 What is the major risk factor profile in White, Indian and Black patients with atherosclerotic peripheral vascular disease seen at the Vascular Service in Durban?
- 4.3 How do the findings in 4.1 and 4.2 compare to the clinical and risk factor profiles for coronary artery disease in Whites, Indians and Blacks in South Africa? On this basis it is anticipated that:-
 - 4.3.1 the observations of Walker may be tested in socially developing and developed societies.

4.3.2 new clues to the pathogenetic role of lipids may be elucidated in socially developing and developed societies.

4.4 Can the clinical and major risk factor profiles for atherosclerosis be conceptualised in socially developing and developed societies on the basis of 4.1, 4.2 and 4.3?

It is believed that the findings in this study will significantly contribute to our understanding of the genesis and natural history of atherosclerosis, its etiological mechanisms in relation to the initiation and progression of the disease and intervention strategies, from a perspective which is unique in atherosclerotic research.

CHAPTER TWO

LITERATURE REVIEW

1. INTRODUCTION

"A PHYSICIAN CANNOT PRESCRIBE BY LETTER: HE MUST FEEL THE PULSE." (SENECA)

The pulse is a vital index of the integrity of the circulatory system. Therefore, a systematic evaluation of the arterial pulse in all four extremities and in the neck is an important part of any complete clinical examination. In general, palpation and comparison of the arterial pulses has a three fold value. Firstly, it provides information concerning the contractile status of the heart. Secondly, it elucidates aspects of cardiac rate and rhythm. Thirdly, it evaluates the integrity of the peripheral arterial blood supply and determines the localisation of any arterial lesions that may exist.

"Sphygmology", the science of the pulse, has an interesting heritage dating back to antiquity. Ancient Chinese physicians considered the palpation of the arterial pulses to be of paramount importance in medical diagnoses and believed that all diseases could be diagnosed from the pulse. About a century later, Herophilus of Alexandria classified the pulse, based on the four main qualities of size, frequency, force and rhythm. Rufus of Ephesus (second century A.D.) wrote a very enlightened treatise on the pulse and its changes associated with respiration, ageing and disease. Several of his teachings were incorporated by Claudius Galen (138 - 200 A.D.)

Claudius Galen stated that it required the whole life of a man to acquire a complete knowledge of the pulse. It is ironic that at present, when so much is known about the pulse and its underlying physiological mechanisms, the major dilemma concerning the pulse is its disappearance, the commonest cause of which in western populations is a

condition termed **ATHEROSCLEROSIS**. The view may now be held that it requires the whole life of a man to acquire a complete knowledge of why the pulse disappears.

What then is **ATHEROSCLEROSIS**?

2. **ATHEROSCLEROSIS**

Well-founded clinical data irrefutably indicate that the combined clinical sequelae of atherosclerosis today constitute the leading cause of death in industrialised countries (Altman and Ramos de Souza, 1985; Schoenfeld et al., 1985).

2.1 **HISTORICAL BACKGROUND**

Although a scourge of modern industrialised populations, atherosclerosis is an ancient disease that was detected in Egyptian mummies and described in Greek writings. The term atheroma (from the Greek athera, "grues") was revived by Albrecht von Haller (1755) to focus attention on the softening process which often accompanied the sclerosis and the aneurysms that had earlier been emphasised by da Vinci and then by Vesalius and other anatomists of the sixteenth and seventeenth centuries. For a time in the nineteenth century, it was believed that imbibition of substances from the blood (Virchow) or other events at the endothelial/blood interface caused atheromas (Rokitansky); but by the time the term atherosclerosis was coined (Marchand, 1904), the dominant concept was that the lesions were intimal softenings secondary to an increase in subintimal connective tissue due to irritative and mechanical forces. The present-day preoccupation with the aetiological importance of lipid infiltration began about 1910, with the demonstration of an increased amount of cholesterol in atheromas (Wardhaus, Aschoff) and the experimental production of atherosclerosis with the use of cholesterol (Ignatowski, Anitschkow, and others). Many of the present assumptions about the causes of atherosclerosis have been derived from epidemiological observations based on the occurrence of the complications of the disease. (Bierman, 1980).

2.2 DEFINITION

Current definitions of atherosclerosis tend to be expressed in terms of descriptive morphology and the basic pathological processes involved in the lesion because our knowledge of atherogenesis is still inchoate and the importance of the various mechanisms in the initiation and progression of atherosclerotic lesions is still largely unknown.

On this basis St Clair (1983) defined atherosclerosis as *"a pathological process of the large arteries in which there are focal accumulations of cells within the intima, lipids (both intra and extracellular), fibrous tissue, complex proteoglycans, minerals, blood and blood products. As the disease progresses, there is necrosis at the base of the lesion, medial damage, ulceration and thrombosis. Thrombosis is a frequent end-point resulting in occlusion of the artery and the onset of acute clinical events. The pathogenic mechanism(s) for the development of the atherosclerotic plaque are only now beginning to be understood and it is clear that they involve a complex interaction of the cells of the arterial wall with a variety of components in the blood including lipoproteins, platelets, other blood cells and a variety of chemical constituents. These interactions result in a complex series of biochemical changes within the arterial wall as the atherosclerotic plaque develops."*

However, the term atherosclerosis is often used not only to describe the arterial lesions of the disease, but also the secondary symptoms resulting from ischemia and necrosis in vital organs and thus atherosclerosis may be considered a pathological state or disease of the arterial wall, with both subclinical and clinical (or symptomatic phases).

What then are the clinical sequelae of atherosclerosis?

2.3 CLINICAL SEQUELAE

The clinical manifestations of atherosclerosis are as varied as the vessels affected and as the character and extent of the atheromatous change. The lesions themselves do not

cause symptoms and signs. They cause clinical disease as follows: by a narrowing of the vascular lumen causing ischemia, a sudden occlusion of the lumen, a superimposed thrombosis or haemorrhage into the atherosclerotic lesion to produce infarction, a site for thrombosis with subsequent embolism and a weakening of the wall of a vessel to form an aneurysm which may eventually rupture (Robbins, 1967).

Although no tissue or organ in the body may theoretically be regarded as immune to the risk of damage due to ischemia as a result of this process, symptomatic atherosclerotic disease is most often localised within the heart, brain and lower extremities, causing cerebrovascular disease, ischemic heart disease and peripheral vascular disease, making atherosclerosis the disease with the highest mortality and morbidity. It is also responsible for less common clinical syndromes involving the nervous system, the eyes, the gastro-intestinal tract and the kidneys (Robbins, 1967).

Atherosclerosis of the vessels to the brain clinically manifests as transient ischemic attacks and strokes; atherosclerosis of the coronary vessels as angina and myocardial infarctions; and atherosclerosis of the aorta and peripheral vessels as aneurysms, intermittent claudication, gangrene and ischemic ulcers.

2.4 LOCALISATION OF LESIONS

While atherosclerosis is an ubiquitous disease, it does afflict certain preferential sites within the vasculature. In the case of the extracerebral vessels, the most common sites of localisation of lesions are at the bifurcation of the common carotid artery, the internal carotid artery at the level of the carotid sinus and at the vertebro-basilar arterial junction. In the case of the intracerebral vessels, it primarily affects the main bifurcation of the middle cerebral artery, the posterior cerebral artery as it winds round the cerebral peduncle and the anterior cerebral artery as it moves upwards over the corpus callosum. Ordinarily it is rare for the intra-cerebral arteries to be affected beyond their first major branching (Solberg and Eggen, 1971; Bierman, 1980).

In the coronary vessels atherosclerotic lesions are most prominent in the main arteries, the highest incidence being a short distance from the ostia. Atherosclerosis is nearly always found in the epicardial (extramural) portion of the vessels while the intramural coronary arteries are spared (Solberg et al., 1985). Coronary atherosclerosis is usually diffuse and the degree to which the lumen is narrowed, varies. A single tiny plaque occluding an otherwise normal coronary artery is rare (Bierman, 1980).

The vessels to the lower extremities are also affected by atherosclerosis. The aorta, especially its abdominal portions, is involved earliest and most severely by atherosclerosis and is the bellwether of lesions elsewhere. In its abdominal portion, the aorta is usually most severely affected around its branches, and frequently at its bifurcation into the iliac arteries. Frazier et al. (1987) studied the extent of atherosclerosis in the aorta and showed that the supraceliac aorta was considerably less affected than the infra-renal aorta. In the lower limbs the incidence decreases peripherally as the musculoelastic vessels give way to large muscular arteries and these become smaller vessels, such as the plantar or digital vessels. Plaques and thromboses are particularly common in the femoral arteries, in Hunter's canal and in the popliteal artery just above the knee joint (Bierman, 1980).

The anterior and posterior tibial arteries are often both occluded but at different sites; the posterior where it rounds the internal malleolus and the anterior where it is superficial and becomes the dorsalis pedis artery. The peroneal artery which is well-embedded in the muscle often escapes even when the other major vessels are occluded and it may be the main blood supply to the extremity. Atherosclerosis involving the abdominal aorta causes less clinical problems than coronary or cerebral vessel involvement, except when the renal and mesenteric arteries are also affected or there is aneurysmal rupture (Bierman, 1980).

2.5 TYPES OF LESIONS

Focal lesions of atherosclerosis are characterised by three fundamental phenomena: proliferation of smooth muscle cells, deposition of intracellular and extracellular lipids, and accumulation of extracellular matrix components including collagen, elastic fibres and proteoglycans. The intima is the cell layer principally involved in atherosclerosis, although secondary changes are sometimes found in the media.

Three types of lesions are classically recognised, namely: the fatty streak, the fibrous plaque and the so-called complicated lesion (Ross and Glomset, 1976).

2.5.1 THE FATTY STREAK

The fatty streak is the fine gross appearance of any atherosclerosis. It is a yellowish, sessile lesion which causes little or no clinical symptoms. The age at which fatty streaks appear differs in different regions of the arterial tree, but they are present in the aorta of every child, regardless of race, gender and environment by 10 years of age (Ross and Glomset, 1976).

Two different types of lesions are classified as fatty streaks (Cresanta et al., 1986). One type occurs in childhood and adolescence and is found in all population groups studied. The lipid is mostly intracellular, but there is additional connective tissue and extracellular lipid (Cresanta et al., 1986) and covers 10% of the aortic intimal surface (Ross and Glomset, 1976). The second type, which is found in the adolescent and young adult population with a high prevalence of coronary heart disease (Cresanta et al., 1986) covers about 30% to 50% of the aortic intimal surface (Ross and Glomset, 1976). Much of the lipid is extracellular with a marked increase in extracellular connective tissue (Cresanta et al., 1986). This second type may progress to raised lesions, especially when present in the coronary vessels (Cresanta et al., 1986).

The yellow colour of these lesions is associated with the presence of lipid deposits found principally within the smooth muscle cells and in macrophages. Most of these

lipid deposits are in the form of cholesterol and cholesterol esters. The bulk of the cholesterol found within the fatty streak is probably absorbed from the plasma, but it is likely that the plasma lipids are hydrolysed and re-esterified once they have been taken up by the cells (Ross and Glomset, 1976).

2.5.2 THE FIBROUS PLAQUE

This is the most characteristic lesion of advancing atherosclerosis. It does not have the same ubiquitous distribution in the world's population that has been noted for fatty streaks (Ross and Glomset, 1976). It is grossly whitish in appearance and is elevated so that it protrudes into the lumen with subsequent narrowing of the artery. It consists principally of an accumulation of intimal, lipid-laden smooth muscle cells, the lipid being primarily cholesterol esters. These cells are also surrounded by lipid, collagen, elastic fibres and proteoglycans. Together the cells and the extracellular matrix components form a fibrous cap that covers the large, deeper deposit of the free extracellular lipid intermixed with cell debris (Ross and Glomset, 1976). The plaque may contain haemorrhage, thrombosis, ulcerations and calcification (Cresanta et al., 1986).

The view that fatty streaks become fibrous plaques is confusing and a matter of controversy (Ross and Glomset, 1976; Solberg and Strong, 1983; Cresanta et al., 1986). Since population studies have shown that fatty streaks appear earlier than fibrous plaque and in some cases in the same anatomical positions in the coronary and extracranial cerebral arteries, it has been suggested that they are the precursors of fibrous plaques (Ross and Glomset, 1976). In the aorta, however, fatty streaks appear in anatomical sites different from those at which fibrous plaques appear (Mitchell and Schwartz, 1965). The reasons for these differences have not been adequately explained.

A lesion generally accepted as the 'fore-runner' of the fibrous plaque is the 'fibro musculo elastic lesion' of the intima which consists of proliferated smooth muscle and connective tissue and which contains little or no lipid (Ross and Glomset, 1976).

2.5.3 THE COMPLICATED LESION

This is the third type of lesion, which appears to be a fibrous plaque that has become altered as a result of haemorrhage, calcification, cell necrosis and mural thrombosis. The distinctive characteristic of the complicated lesion is the presence of calcification. This type of lesion is often associated with occlusive disease (Ross and Glomset, 1976).

The occurrence of fibrous plaques and complicated lesions, unlike fatty streaks is influenced by race, age, gender and environmental factors (Walker, 1966).

2.6 PATHOGENESIS OF LESIONS

There are currently four major theories explaining the pathogenesis of atherosclerosis. They are not mutually exclusive, though the complex aetiology of atherosclerosis remains an enigma and is incompletely understood. The four theories are briefly reviewed.

2.6.1 INFILTRATION HYPOTHESIS

This is the oldest theory of atherogenesis. It postulates an alteration in the permeability of the endothelium with increased access of lipoproteins to the arterial wall, especially when the serum concentrations of certain lipoproteins are increased. Critics of this hypothesis point out its failure to explain the focal nature of atherosclerotic plaques, their preferential occurrence at selected vascular sites, and the presence of increased numbers of cells and increased quantities of collagen and glycosaminoglycans in the lesions. Despite these limitations, lipid infiltration is still considered to be an important event in the development of atherosclerosis (Schneider, et al., 1986).

2.6.2 INCRUSTATION THEORY

This concept was proposed by Duguid (1946), who postulated that the initial event in atherogenesis was thrombus formation. According to this theory, the cellular and

extracellular material in the atherosclerotic plaque are derived from activated vascular cells that migrate into the encrusted fibrin where they regenerate and synthesise extracellular matrix. Absence of definitive evidence that fibrous thrombi play a role in the initial phases of atherogenesis and failure to explain the accumulation of lipids in the lesions are major limitations of this theory (Schneider et al., 1986).

2.6.3 MONOCLONAL THEORY

This concept was proposed by Benditt (1977) and postulates that each lesion of atherosclerosis is derived from a single smooth muscle cell that serves as a progenitor for the remaining proliferative cells. Support for this theory comes from studies of two x-linked isoenzymes of glucose-6-phosphate dehydrogenase in a small group of women who possess both forms of the enzyme. It could be shown that in many, but not all atherosclerotic plaques, only one of the isoenzymes could be found whereas both were present in normal arterial tissue. A major weakness of this hypothesis is that it fails to explain the accumulation of lipids, the presence of monocytes and macrophages, and the preferential occurrence of plaques in specific anatomical locations. In addition, pathological proliferation of monoclonal smooth muscle cells has been difficult to confirm (Schneider et al., 1986).

2.6.4 RESPONSE TO TISSUE INJURY

This is currently the most popular theory of atherogenesis, although it dates back to the pioneering days of Virchow. The modern-day theory was initially based on the observation in experimental animals that denudation of a large area of the arterial endothelium is followed by intimal thickening with the accumulation of smooth muscle cells and extracellular matrix, very similar in appearance to an atherosclerotic plaque. Furthermore, intracellular and extracellular lipid accumulation could be observed if the injury was repetitive or if the animal was simultaneously fed with a cholesterol-rich diet. Later studies indicated that functional injury to the endothelium as well as the denudation can initiate the atherosclerotic process. This has led to a 'modified response to injury theory' that unifies many of the earlier hypotheses and is compatible with both

the cellular and chemical composition of the plaques as well as the fact that abnormalities in plasma lipids are clearly involved in the atherosclerotic process (Schneider et al., 1986).

As a working hypothesis, it is useful to regard atherosclerosis as a multifactorial disorder in which a variety of abnormalities can produce similar lesions of the arterial wall. Common to all is endothelial 'injury', which in turn results in a sequence of events that usually includes the migration and proliferation of smooth muscle cells, increased connective tissue formation and the appearance of lipid-containing foam cells and extracellular lipid in the arterial wall. The many factors that might indicate or accelerate this process make it difficult to isolate the contribution of any single factor (Schneider et al., 1986). Endothelial 'injury' may however, have different manifestations at different sites in different arteries (Ross and Glomset, 1976).

2.7 **EPIDEMIOLOGY**

From the foregoing it is evident that atherosclerosis is a disease occurring widely within the vasculature resulting in clinical effect/s which correlate with the site/s of pathology.

It has been shown that the clinical sequelae of atherosclerosis, - coronary heart disease, cerebrovascular disease and peripheral vascular disease - have striking demographic differences with respect to the prevalence and severity of atherosclerosis (Solberg and Strong, 1983). Atherosclerosis in the different vascular beds tends to vary from person to person, from time to time and from place to place. High prevalence and severity is found in most of the developed countries of the world with a relatively low prevalence and severity in most underdeveloped and developing countries of the world (Robbins, 1976).

Within the past two decades though, there have been marked but variable falls in mortality from coronary artery disease in many Western populations, but mainly in the United States of America and Australia (Walker et al., 1993). In South Africa

there is a spectral spread of the disease, being high in Whites, very high in Indians, lower in Coloureds and very low among Blacks (Walker et al., 1993). There is no data available on the current status of cerebrovascular disease and peripheral vascular disease in South Africa.

3. FACTORS INFLUENCING THE EPIDEMIOLOGICAL DISTRIBUTION OF ATHEROSCLEROTIC ARTERIAL DISEASE

Epidemiological observations have shown that there are certain naturally prevailing or inherent conditions which are nonmodifiable (Sherwin et al., 1986) and environmental factors which relate to the varying incidence of atherosclerotic arterial diseases. These are not, however, concerned with the more specific risk factors (smoking, hypertension, diabetes, hyperlipoproteinaemia, hyperinsulinaemia, hyperfibrinogenaemia, oestrogens, physical inactivity and obesity) which may be responsible for variations to the predisposition of populations to atherosclerosis (Kannel and Schatzkin, 1983).

3.1 AGE

Even though it is universally accepted that atherosclerosis is an age related disease, many studies have now established its presence in infancy and maintain that probable precursor forms of atherosclerosis are firmly established in most people by the age of 15 years, irrespective of race and gender (Ross and Glomset, 1976; Cresanta et al., 1986).

With an increase in age (especially after 40 years) these precursor forms of atherosclerosis selectively progress to established clinical disease (Tyagi et al. 1979). By the fifth decade and thereafter, atherosclerosis is responsible for the presence of coronary artery disease, cerebrovascular disease and aortic and peripheral vascular disease in susceptible individuals.

Atherosclerosis reflects an interaction among several age-related alterations of both structure and metabolism. While intrinsic ageing appears to play a role, particularly in relation to the biology of arterial wall cells, the selectivity and susceptibility to atherosclerosis is best considered as age-related, but profoundly influenced by both genetic and environmental factors, rather than by simply the inevitable consequence of intrinsic ageing (Bierman, 1978).

3.2 **GENDER**

The establishment of atherosclerosis as a distinct pathological entity with clinical repercussions up to the age of forty years does not occur uniformly between the genders. There is considerable evidence of a disparity and in general the disease tends to present clinically in males by the fourth decade and in females usually by the fifth decade, after which this disparity tends to diminish.

The reasons for this are unclear. The protective effect of oestrogens on the vasculature of females is a frequent hypothesis.

A further observation is that there is sometimes a definite female preponderance of the disease in the case of certain specific vessels under certain conditions. Several studies have established that atherosclerosis of the intracerebral vessels and the peripheral vessels of diabetic patients occurs more commonly in females (Coffman, 1979; Kannel and Schatzkin, 1983; Ruderman and Haudenschild, 1984). The reasons for these variations have not yet been elucidated.

3.3 **RACE**

The foregoing exposition on the association between atherosclerosis and the physical attributes of age and gender does not occur with equal specificity in people of different racial backgrounds (Solberg and Strong, 1983). There is now considerable epidemiological evidence indicating that people of different racial backgrounds living

in a similar environment differ in their natural predisposition to atherosclerotic vascular disease (Walker, 1987; Sempos et al., 1988).

The consensus is that atherosclerosis is uncommon in populations of Oriental and Negroid origin (Robbins, 1967). The prevalence of atherosclerosis is low in all the major vessels in people of Japanese origin living in Japan (Ishii et al., 1986; Benfante, 1992). In China, the Chinese appear to have a similar pattern (Bernhardt et al., 1986). The prevalence of atherosclerosis is also low in most Black African populations, including South Africa (Walker, 1966; Lee, 1971; Levy, 1971; Meyer, et al., 1971), and has been reported to be virtually non-existent in the Masai tribe of Kenya (Biss et al, 1971). Biss et al. (1971) found a remarkable paucity of atherosclerotic lesions in the major arteries and coronary vessels of the Masai with only occasional fatty streaks and fibrous plaques being noted. Likewise, cerebrovascular disease, peripheral vascular disease, angina pectoris and electrocardiographic evidence of ischemic heart disease are almost totally absent in the rural populations of New Guinea and the Solomon Islands. (Schneider et al., 1986).

On the contrary, people of European origin represent the vast majority of individuals afflicted by atherosclerosis which is established as the commonest cause of mortality and morbidity in these populations. The disease has an extremely high prevalence rate among Whites in the United States of America (accounting for more than half the deaths in middle aged Whites), in the United Kingdom, in the Scandinavian countries and in most other European countries (Robbins, 1967). The disease is also firmly established in the White population groups of Australia, New Zealand and South Africa. Exceptions to this are countries such as Portugal, Greece and Bulgaria where the prevalence of atherosclerosis is generally regarded as low. (Walker, 1975; Menotti and Giampaoli, 1986).

People of Indian origin living in India and indigenous Americans generally have a low prevalence of atherosclerosis.

3.4 ENVIRONMENT

Notwithstanding the prevalence of atherosclerosis as determined in terms of age, gender and racial criteria, geographical location has an independent and overriding influence on the predisposition to atherosclerosis. This contention is strongly supported in a number of epidemiological studies and is attributable to the interplay of many factors, most of which are thought to be environmental (Solberg and Strong, 1983).

Several studies have shown that people of a similar genetic and racial makeup, when raised in different geographical locations differ in their predisposition to atherosclerosis. In the case of Indians living in India several studies have shown a geographical variation. Subramaniam et al. (1967) produced evidence that atherosclerosis of the aorta of both genders and of the coronary arteries in males was more severe in Madras than had been reported from any other place in India. Similarly, Malhotra (1967) showed that atherosclerotic arterial disease was seven times more common in South India than in North India. It is also well established that Yemenite Jews (Asian and African Jews) have a lesser degree of atherosclerosis than do Ashkenazi Jews (Western Jews) and Israeli Jews (Walker, 1966).

These differences in prevalence, however, decrease when geographical differences are diminished. It has been shown that when Yemenite groups emigrate to Israel a marked increase in atherosclerotic lesions occurs to equate with that of Israeli Jews (Walker, 1966).

Conversely, it has been shown that different population groups (which in terms of racial criteria ought to have differences in the incidence of atherosclerosis), living together in the same geographical location sometimes present with similar atherosclerotic indices (Walker, 1966). In the United States of America several studies have produced evidence indicating that the incidence of atherosclerosis among local Blacks closely approaches that of Whites living in the same locality (Walker, 1966). Similarly, in South Africa it has been shown that Indian South Africans are as

susceptible to atherosclerosis as the local Whites. Indian South Africans are now sufficiently indigenous here for a valid comparison in this context to be made. The incidence of atherosclerotic cardiovascular disease in local Indians is strikingly higher than that of Indians living in India (Seedat et al., 1990).

When translocation occurs there is considerable evidence to suggest that the incidence of atherosclerotic arterial disease in the migrating population changes to approach and possibly equal that prevalent in the host country. It is well established that emigrant Indian populations to Fiji, Singapore, Trinidad and the United Kingdom have higher incidences of atherosclerotic vascular disease and specifically coronary artery disease than in India (Miller et al., 1984; Beckles et al., 1986; Seedat et al., 1990). In Japan the relative incidence of atherosclerosis is low. Ishii et al. (1986) made comparisons of atherosclerotic lesions in 25 to 44 year old men from Tokyo and New Orleans and showed more extensive involvement of raised lesions in the coronary vessels and abdominal aorta of Black and White men from New Orleans. Several studies, however, have shown that Japanese who migrate to Hawaii develop more ischemic heart disease than those who remain in Japan, and these trends are further exaggerated if they settle in the mainland United States (Malhotra, 1967).

Irrespective of geographical location there is a discernible difference with people living in rural environments. Studies emanating from the United States, India, Britain, and various other European countries have shown that people living in an urban environment have a greater tendency to develop occlusive vascular disease of the cerebral, coronary and peripheral vessels (Walker, 1966; Subramaniam and Kulangara, 1967). It has been shown that changes in the chemical composition of the aorta due to ageing in groups of Pedi Blacks in Pietersburg (a semi rural area), South Africa were less marked than those observed in the Black population living in Johannesburg's urban environment (Walker, 1966).

Thus environmental influences seem more important than race in determining the extent of atherosclerosis. Any genetic or racial factor is compounded by socio-economic differences between the races in any single geographical location promoting

the contention that environmental conditions predominantly determine the severity of atherosclerosis in any population.

4. ATHEROSCLEROTIC-ASSOCIATED RISK FACTORS

Although atherosclerosis is evidently affected by an interplay of age, gender, race and environmental factors, not all individuals and/or population groups are susceptible to atherosclerosis. Yet research has overwhelmingly shown that in the presence of certain conditions the predisposition to atherosclerosis is considerably increased. These conditions are commonly termed as 'risk factors', a concept which appeared in an early Framingham report (Kannel and Schatzkin, 1983).

Risk factors are a consequence of genetic and/or environmental influences and may or may not be in their own right, disease states. Nevertheless, when present, risk factors act as markers identifying those individuals most likely to develop atherosclerosis. In such instances corrective steps, when taken, play a vital role in preventing the deleterious clinical consequences of atherosclerosis. Essentially a risk factor must play a pathogenic role and the study of risk factors has yielded much of the current information on the pathogenic mechanisms involved in the aetiology of atherosclerosis, though our knowledge of the precise mechanisms is far from complete.

Risk factors are broadly categorised as major risk factors (hyperlipidaemia, diabetes, hypertension, hyperinsulinaemia, smoking, hyperfibrinogaemia and oestrogens) and minor risk factors (obesity, reduced physical activity and ECG abnormalities).

The major risk factors for atherosclerosis are almost always discussed and investigated in the context of coronary artery disease with little attention given to cerebrovascular and peripheral vascular disease. The following resumé of the literature provides an overview of the effects of the major risk factors in each of the major vascular beds, emphasising the disparity in research between these vascular beds. Risk factors for atherosclerotic lesions per se need not necessarily be identical

to those related to clinically overt coronary heart disease. Little is known about the relationship between risk factors and peripheral vessel atherosclerosis (Solberg and Strong, 1983).

4.1 HYPERLIPIDAEMIA

Overwhelming evidence involving clinical and epidemiological investigations, animal studies, metabolic studies, angiographic and pathological observations implicate lipoproteins in the pathogenesis of atherosclerosis. This is strongly supported by intervention studies inducing the regression of atherosclerosis (Kannel and Schatzkin, 1983; Schneider et al., 1986).

Plasma cholesterol is now established as an important risk factor with LDL cholesterol, the major cholesterol-carrying lipoprotein of blood playing a causal role in the process of atherogenesis (Kannel et al., 1979; Kannel, 1984; Berger, 1984). HDL cholesterol, the other major cholesterol-carrying lipoprotein of plasma and which physiologically functions in the removal of cholesterol from the tissues, is also strongly and independently related to atherogenesis, but the relationship is inverse (Miller, 1980; Berger, 1984; Altman and Ramos de Souza, 1985). Low levels of HDL cholesterol increase risk while high levels appear to be protective (Levy and Rifkind, 1980). The third lipoprotein fraction implicated in atherogenesis is serum triglycerides, but there appears to be no firm evidence on whether triglyceridaemia is an independent risk factor (Crique, 1986). The precise mechanisms by which hyperlipoproteinaemia causes atherogenesis are not completely understood and continue to attract research interest. There is also an ongoing search for new lipoproteins and lipoprotein subfractions that may be implicated in the 'lipid pathway' of atherogenesis (Altman and Ramos de Souza, 1985).

There is a linear relationship between the mean total blood cholesterol level and LDL cholesterol with the relative incidence of coronary heart disease amongst the world populations (Schneider et al, 1986). Important clinical studies which have established this relationship in western societies are the study of Fredrickson et al. (1967), the

Tromso Heart Study (1977), the Framingham Study (1971), and the study by Rhoades et al. (1976). By contrast individuals in rural China have the lowest mean blood cholesterol level (3,3 mmol/l), and the mean mortality rates due to coronary heart disease in the middle-aged individuals are approximately 5% of those in Great Britain (Galton, 1991). Similarly, studies in Japan in which the incidence of coronary heart disease is low (Menotti and Giampaoli, 1986; Galton, 1991) have shown that the level of cholesterol is less than 4.0 mmol/l (Durrington, 1991). In South Africa the high incidence of coronary heart disease among Whites and Indians is believed to be associated with high levels of total cholesterol and LDL cholesterol while the low incidence of coronary heart disease in Blacks is associated with normal levels of total cholesterol and LDL cholesterol.

The inverse relationship between HDL cholesterol and coronary heart disease has also been established in many population studies (Tyroler et al., 1980). In western societies the high incidence of coronary heart disease has been shown to be associated with a low HDL cholesterol level in studies by Barr et al. (1951), Nikkela (1953), the Co-operative Phenotyping Study (1977), the Framingham Study (1977) and in the Tromso Heart Study (1977). Protective levels of HDL cholesterol associated with a low incidence of coronary heart disease have also been reported in China (Bernhardt et al., 1986). In South African Blacks, HDL cholesterol levels are high (Walker and Walker, 1978; Steyn et al. 1991; Seedat et.al., 1992). In Whites and Indians, HDL cholesterol levels are low (Seedat et al., 1990; Seedat et al. 1994).

The relationship of triglycerides to coronary heart disease is not as well established. Various investigations, most notably the study by Goldstein et al. (1973) and the Stockholm Prospective Study (1972) have suggested that plasma triglycerides, independent of serum cholesterol may also be a risk factor for coronary heart disease (Schneider et al., 1986). Yet data from Framingham and elsewhere, have served to de-emphasise triglycerides as an independent risk factor (Kannel and Schatzkin, 1983) and it is regarded as a factor in coronary heart disease only when associated with a high cholesterol or with a low HDL cholesterol level (Carlson and Bottiger, 1972). Furthermore, in many parts of the world with a low incidence of ischemic heart

disease, the triglyceride levels are substantially higher than in areas with a high incidence of ischemic heart disease (Kannel and Schatzkin, 1983).

A review of the literature does not show any major studies that analyse the relationship of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides with atherosclerotic cerebrovascular disease. The role of hyperlipoproteinaemia in cerebral atherosclerosis is unclear and only weak and inconsistent relationships have been found. Epidemiological studies have failed to demonstrate a consistent relationship between plasma lipoprotein abnormalities and strokes in angiographically documented cerebral atherosclerosis (Randrup and Pakkenberg, 1967; Rossner et al., 1978; Murai et al., 1981). Positive findings are confined to those experiencing distinctively premature strokes, suggesting that lipoprotein abnormalities may be associated with atherosclerosis of the large cerebral arteries (Ford et al. 1985). Studies on patients with symptomatic angiographically proven carotid bifurcation disease have shown elevated triglycerides and elevated or normal total serum cholesterol concentrations compared to those in patients without vascular disease (Duncan et al., 1977; Terrence and Rao, 1983), suggestive of a positive non inverse association between carotid bifurcation atherosclerosis and plasma lipoprotein abnormalities (Ford et al., 1985). Other studies, on the contrary, suggest that the plasma lipid concentrations of total cholesterol and LDL cholesterol correlate inversely with the incidence of cerebral infarction (Kostner et al., 1983; Wolf et al., 1983).

The lipid connection with atherosclerotic peripheral vascular disease is also weak. It is generally believed that many patients under the age of 50 years with peripheral vascular disease have some form of hyperlipidaemia (Friedman, 1982), but there is a great deal of overlap and confusion about the precise types of hyperlipidaemia associated with peripheral vascular disease (Vogelberg et al., 1975; Crepaldi et al., 1977).

Attempts to clarify the hyperlipidaemia accompanying peripheral vascular disease according to the Fredrickson Scheme (1972) have been made, but the results differ

with respect to the relative frequency of different types of hyperlipidaemia. (Skrede and Kvarstein, 1975). Types IIa, IIb and IV dyslipoproteinaemia have been described to have a statistically greater prevalence of peripheral vascular disease (Pomrehn et al., 1986), but this is subject to differences of opinion regarding which is the more predominant type. Greenhalgh et al. (1975) found that Type IV was the most predominant lipoprotein abnormality while Leren and Haabrekke, (1971) found Type II to be 3 to 4 times more frequent than Type IV hyperlipidaemia. According to Rosen et al. (1973) attempts have been made to relate hyperlipidaemia types to the anatomical segment affected by atherosclerosis. Type II patients appear to have more proximal disease mainly in the pelvic distribution than in the more distal vascular segments of the lower limbs.

An analysis of case-controlled and cross-sectional studies on the association between lipids and peripheral vascular disease have also shown no consistent results (Pomrehn et al., 1986). Mean cholesterol and triglyceride levels were elevated in some, but not all studies in persons with peripheral vascular disease. In fact hyperlipoproteinaemia as currently defined is found in less than half of patients with peripheral vascular disease (Coffman, 1979).

Hypertriglyceridaemia has been considered to be an independent risk factor for specifically peripheral vascular disease by many researchers. (Sirtori et al., 1974; Skrede and Kvarstein, 1975). The suggestion has also been made that hypertriglyceridaemia tends to cause atherosclerotic changes at an earlier stage than hypercholesterolaemia and it is, therefore, likely that patients escape coronary artery disease while being susceptible to peripheral vascular disease (Greenhalgh et al., 1975). Bliss et al. (1972) compared young subjects with older subjects who were afflicted with peripheral vascular disease and found that hypercholesterolaemia was the more frequent abnormality, though this data also showed that triglycerides were twice as high as in patients who were controlled. The role of HDL cholesterol in peripheral vascular disease has also not been precisely understood, though a protective function is regarded as acceptable. Trayner et al. (1980) showed a relationship between low HDL cholesterol and atherosclerotic peripheral vascular disease and

attributed this to smoking, although Bradby et al. (1978) who also found a similar relationship, concluded that it was independent of smoking.

Lipoprotein abnormalities in peripheral vascular disease are even further compounded in diabetes in which there is a greater predisposition towards atherosclerosis of the peripheral vessels and which in its own right is associated with lipoprotein aberrations. Lipoprotein abnormalities, similarly, may be associated with enhanced platelet aggregation (Lane et al., 1986) contributing to thrombus formation (Mustara and Packham, 1975), particularly in the peripheral vessels.

The data now clearly demonstrates that a reduction of total serum cholesterol and LDL cholesterol levels reduced coronary heart disease mortality in men with elevated LDL cholesterol levels (Schoenfield et al., 1985). Intervention studies in which dietary and therapeutic controls of serum lipoprotein levels led to a regression of atherosclerotic lesions, resulting in a decrease in the rate of ischemic heart disease, have led Thomas et al. (1985) to conclude that a 2% reduction of coronary artery disease occurs for a 1% reduction in total cholesterol. Unfortunately there are no major intervention studies showing a similar trend in the case of atherosclerotic cerebrovascular disease and peripheral vessel disease and no consistent findings have been found in those studies that have attempted this (Coffman, 1979), though Zelis et al. (1970) indirectly produced evidence of regression after the treatment of hyperlipoproteinaemia.

In addition to the above lipoproteins, Lp(a) is emerging as an important risk factor for coronary heart disease (Austin and Hokanson, 1994). Lp(a) is an atherogenic lipoprotein resembling LDL cholesterol, but with the additional apo (a) (Maranhao et al., 1995).

Elevated plasma concentrations of Lp(a) are associated with the development of premature atherosclerosis in coronary artery disease (Valentine et al., 1994) in Caucasians (Austin and Hokanson, 1994; Moliterno et al., 1995; Maranhao et al., 1995), in Asians (Schreiner, 1994) and in the Japanese (Kario et al., 1994). This

seems not to be the case in Blacks as shown in observational studies (Austin and Hokanson, 1994). According to Maranhao et al., (1995) Black subjects with coronary artery disease had higher Lp(a) levels than Caucasians, but there was no significant difference between Black subjects with and without coronary artery disease. Similarly Moliterno et al., (1995) showed that Lp(a) levels were elevated among African-Americans. Early indications are that the plasma concentration of Lp(a) is not an independent risk factor for coronary artery disease in African-Americans (Schreiner, 1994; Moliterno et al., 1995), despite the markedly elevated levels of Lp(a) in Blacks. According to Maranhao et al., (1995) levels of Lp(a) were elevated to a greater extent among females with coronary artery disease than males with coronary artery disease.

Lp(a) levels are also believed to be elevated in cerebrovascular disease in Caucasians and Asians (Schreiner, 1994) and in cerebral infarction among the Japanese (Murai et al., 1986).

There is also little information on the association of Lp(a) and asymptomatic atherosclerosis in any age and gender group. In the ARIC study (1994) participants were measured for carotid atherosclerosis and Lp(a) levels. The results showed that for all race and gender groups, Lp(a) was higher among individuals with carotid atherosclerosis than for those without. From such data Lp(a) is considered to be a risk factor for preclinical atherosclerosis as well as for clinically overt cardiovascular disease (Schreiner, 1994).

Valentine et al. (1994) tested whether patients with premature peripheral vascular disease had elevated Lp(a) levels and what was its relative strength as a risk factor for premature peripheral vascular disease. The results suggest that Lp(a) levels in plasma are an independent discriminatory risk factor for premature peripheral vascular disease in White men.

Coronary artery disease is considered to be largely affected by behavioural and environmental factors and since genetic factors are firmly established as the determinants of plasma Lp(a) concentrations, Selby et al. (1994) looked into this and

found that unlike other lipoprotein risk factors for heart disease, Lp(a) had few behavioural and environmental correlates, at least among White women; nor did they explain the higher mean Lp(a) levels among Blacks compared to White women. Bovet et al. (1994) have advanced the hypothesis that genetic factors account for much of the variation of Lp(a) in Whites and Blacks.

4.2 DIABETES

As a disease entity diabetes occurs in both developed and underdeveloped populations and is prevalent in the Negroid, Caucasian and Oriental race groups (Ruderman and Haudenschild, 1984). Diabetes is a metabolic disorder which in its own right is a significant risk factor for atherosclerosis. Diabetics have a greater likelihood of developing atherosclerosis with the resultant complications of ischemic heart disease, cerebrovascular accidents and peripheral vascular disease than do non-diabetics (Ruderman and Haudenschild, 1984). In South African Blacks though, coronary heart disease and large vessel atheromatous disease are rare even in diabetes mellitus type II (Trowell, 1981). Similarly, Japanese diabetics, according to a nine year follow up in the WHO multiracial trial, tend to have low cardiovascular mortality rates when compared to diabetics of other nationalities, provided they remain in their own countries (Keen, 1991).

Diabetes can afflict an individual at any age, generally presenting as juvenile onset diabetes in the very young and as maturity onset diabetes from the teenage years onwards. Once the disease occurs, atherosclerotic complications tend to occur at an earlier age among diabetics than in non-diabetics (Garcia et al., 1974; Kannel and McGee, 1979) due to an acceleration of atherogenesis among diabetics.

In diabetics the atherosclerotic process may be influenced by the gender of the individual with diabetes, substantially eliminating the relative protection possessed by women (Ruderman et al., 1984; Schneider et al., 1986). Atherosclerosis among men with diabetes is twice as high as among non-diabetic men and for diabetic women the incidence is three times that of non-diabetic women cohorts (Kannel and Mc Gee,

1979). For each of the atherosclerotic cardiovascular diseases mortality and morbidity were higher for diabetic women than for diabetic men in the Framingham study. In a more extensive study conducted in Rancho Bernardo, California, it was shown that the relative risk of coronary heart disease was 3.3 times higher in diabetic women as opposed to 1.9 times in diabetic men (Durrington, 1991). In a more recent study among persons aged between 45 and 64 years, diabetes increased the ischemic heart disease rate by 9 to 10 times for women but by only 2 to 3 times for men. This observation was more pronounced for Black women than for White women (Blacks = 39%; Whites = 27%) than for men (Blacks = 19%; Whites = 14%) (Will and Casper, 1996). There appears, similarly, to be a relatively higher incidence of atherosclerotic cerebrovascular disease among women than in men as is the case in atherosclerotic peripheral vascular disease.

The reasons for this greater susceptibility of diabetic women to the cardiovascular sequelae of atherosclerosis is uncertain. Although differences in risk factors may not entirely account for this, a low HDL cholesterol level in the presence of diabetes may explain the higher coronary heart disease risk of women relative to men and in women the triad of obesity, diabetes and a low HDL cholesterol level may well be significant (Kannel and Schatzkin, 1983).

The other significant observation in diabetes is that atheroma seems to have characteristics different from non-diabetics, characteristics which influence both its nature and distribution. Atheroma appears to affect more peripheral sites in diabetics than in non-diabetics (Wissler, 1991), although atheroma in diabetes can occur throughout the different vascular beds and is associated with both strokes and coronary heart disease. Prospective population studies at Framingham and elsewhere confirm this comparison showing that the relative impact for diabetes is greatest for occlusive peripheral vascular disease (Kannel and McGee, 1979). Friedman (1982) showed that at least 15% to 20% of diabetic patients have atherosclerotic femoropopliteal disease and indicated that diabetes is the most commonly associated finding in patients with atherosclerotic peripheral vascular disease. Clinical evidence of peripheral arterial insufficiency occurs 11 times more frequently in diabetics than in

normal patients (Dry and Hines, 1941). An autopsy study found gangrene to be 40 times more common in diabetics than in non-diabetics over the age of 50 years (Friedman, 1982). Fuchs et al., (1985) showed that diabetes favours the femoro-popliteal and popliteal-tibial sites for occlusive disease to manifest. Aorto-iliac disease is associated with a somewhat lower incidence of diabetes (Friedman, 1982).

Once again the reasons for this observation are unknown considering that the arterial lesions in the cerebral, coronary and peripheral vessels are similar. One explanation probably relates to the different nature of the lesions. Furthermore, animal studies have shown that diabetic atheroma involves more smooth muscle proliferation and less lipid deposition than in non-diabetics. This could explain why muscular vessels such as the femoral arteries in diabetics are more likely to be affected by atheroma than the elastic arteries such as the aorta (Wissler, 1991). Increasing evidence suggests that high fibrinogen levels in diabetics may explain the more peripheral predisposition towards atherosclerosis (Vorster and Venter, 1994).

Diabetics tend to have higher levels of associated atherogenic risk factors such as obesity, hyperlipidaemia and hypertension than non-diabetics (Kannel and Schatzkin, 1983). However the excess risk of cardiovascular sequelae in diabetes cannot be entirely attributed to the excess of associated risk factors and diabetes may have an independent role in atherogenesis (Kannel and Schatzkin, 1983; Ruderman and Haudenschild, 1984).

Although diabetes is by definition a state of abnormal carbohydrate metabolism, defects in lipoprotein metabolism are a prominent feature of diabetes. More than 50% of diabetic men and women with proven atheroma also have hyperlipidaemia and diabetics with hyperlipidaemia are more likely to have atheroma than those with normal plasma lipids. The predominant dyslipoproteinaemia is a low level of HDL cholesterol and a hypertriglyceridaemia (about twice as frequent in men and about 4 times as frequent in females) and this is supported by studies on Indians with non insulin dependent diabetes in Durban (Jailal et al., 1985). Both these lipid aberrations constitute a major atherosclerotic risk in diabetics.

Diabetes is also associated with hypertension and the effect of diabetes in cerebral atherosclerosis appears to be greatest when diabetes is accompanied by hypertension.

4.3 HYPERTENSION

Like diabetes, hypertension is an important antecedent of atherosclerotic vascular disease and a vascular disorder in itself. It occurs commonly in developed and underdeveloped countries irrespective of the race group. Hypertensives have a greater likelihood to develop atherosclerosis than non-hypertensives. The incidence of atherosclerosis in the coronary, cerebral and peripheral vessels among hypertensives has, in the Framingham study, shown that hypertensive subjects had a sevenfold greater incidence of strokes, a fourfold increase in congestive cardiac failure, a threefold rise in coronary heart disease and a doubling of peripheral atherosclerosis when compared to normotensive individuals (Chobanian, 1983). A continuous exponential increase in risk is present over a whole range of blood pressures. Systolic as well as diastolic hypertension, borderline or mild hypertension, or mobile as well as fixed elevations of blood pressure, all can have deleterious effects especially on the cerebral circulation. Apart from the Framingham data it is unclear whether there is any prospective association between hypertension and peripheral vascular disease (Drury, 1989).

The International Atherosclerotic Project has perhaps provided the best evidence of the effect of hypertension on the extent and severity of arterial lesions (Robertson and Strong, 1968). The mean extent of fatty streaks and raised lesions in the coronary arteries and aortas of hypertensives was significantly greater than in controls, particularly in young individuals. Fibrous plaques and advanced lesions with calcification were, similarly, more frequently seen in hypertensives than normotensives. Increases in the extent and severity of atherosclerosis in a number of vascular beds including the coronary, cerebral, aortic and peripheral arteries of hypertensive patients have also been shown in several other post-mortem studies. (Chobanian, 1983; Solberg and Strong, 1983).

Hypertension also increases the predisposition of the major intracerebral arteries to atherosclerosis. Smaller intracerebral vessels may often be involved, often deep within the parenchyma of the brain, which can lead to strokes even in the absence of occlusive disease of the main cerebral arteries. Miliary aneurysms of the small penetrating cerebral arteries may occur, the so-called Charcot-Bouchard aneurysms. In addition, the small arteries of areas of the basal ganglia, thalamus and pons may show involvement with fat-filled intimal macrophages and deposition of fibrin. These changes appear to predispose to the development of infarcts which are common in long-standing hypertension. The relationship of these changes in small arteries to atherosclerosis is uncertain (Chobanian, 1983).

It has, however, been observed that in certain parts of Africa including the South African Blacks, where hypertension is prominent in endemic proportions and where intracerebral atherosclerosis is common, the incidence of coronary and peripheral atherosclerosis is uncommon (Seedat and Pillay, 1976; Trowell, 1981).

Similarly even though hypertension is common in Japan, atherosclerotic disease among the Japanese remains at a low incidence and the major complications of hypertension relate to congestive cardiac failure and cerebral haemorrhage (Hatano, 1975). The Japanese, however, also have low plasma lipoprotein concentrations and it would appear that a critical level of circulatory lipoproteins are required before the atherosclerotic process is affected by hypertension (Chobanian, 1983). According to Seftel (1978) in the absence of hypercholesterolaemia, hypertension may not be a significant atherogenic risk factor even in westernised populations. In western societies, however, such levels are probably the rule rather than the exception, and hypertension is regarded as a major factor promoting the cardiovascular complications associated with atherosclerosis (Chobanian, 1983).

The mechanisms by which hypertension cause atherosclerosis are vaguely understood. The clinical evidence, though, strongly suggests that it is the blood pressure itself rather than other associated haemodynamic abnormalities which is the major determinant of vascular changes in the arterial system. In the pulmonary circulation, which is normally protected from atherosclerosis, the disease rapidly develops typical

lesions if pulmonary hypertension is present (Heath et al., 1960). Similarly with arteriovenous fistulae and increased pressure in the nervous system, fibrous sclerosis of the affected veins may be observed (Moschowitz, 1950). The increased predisposition to the development of spontaneous atherosclerotic lesions, however, has not been demonstrated in hypertensive animals with the exception of the obese rat that has hyperlipidaemia, glucose intolerance and hyperinsulinaemia in addition to hypertension (Koletsky, 1973; Koletsky, 1975). Experiments into the role played by renin and angiotensin in atherogenesis have not been helpful (Chobanian, 1983). Similarly the role played by hypertension in intimal thickening and permeability, endothelial cell changes, medial changes, the role of sympathetic innervation and the response to arterial injury have left no definite insight into how hypertension promotes atherogenesis. (Chobanian, 1983).

There is, however, an abundance of evidence to demonstrate the importance of hypertension and other haemodynamic factors in enhancing the susceptibility to atherosclerosis and in the localisation of lesions.

It has also been found that although effective antihypertension therapy reduced the major complications of hypertension including congestive cardiac failure, cardiomegaly and both haemorrhagic and thrombotic strokes the information available suggests that it has little influence on the atherosclerotic process and on the incidence of coronary heart disease, unlike the success achieved with intervention studies in hyperlipidaemia (Chobanian, 1983). This has led Reaven to observe that concomitant abnormalities of insulin metabolism may be responsible for the failure of antihypertensive therapy to significantly reduce the risk of atherosclerosis in hypertensive patients leading to the view that hypertension and atherosclerosis may in some way be affected by hyperinsulinaemia (Reaven, 1991).

4.4 HYPERINSULINAEMIA

With the exception of LDL cholesterol, each of the other risk factors mentioned above, namely a reduced HDL cholesterol, an increased triglyceride, diabetes and

hypertension may be associated with high levels of insulin. The reason for this association is at this stage unclear, but since low HDL cholesterol levels, high triglyceride levels, diabetes and hypertension are all associated with atherosclerosis there is much speculation on whether increased insulin levels may be the modulator of macrovascular atherosclerotic disease playing a central role in its pathogenesis, either as an independent risk factor or in association with the abovementioned risk factors.

The possibility that hyperinsulinaemia may play an aetiological role in the development of atherosclerosis was reported by Stout (1979). This is supported in patients with established coronary, cerebral and peripheral arterial disease who have had elevated insulin responses to oral glucose compared with control subjects (Ruderman and Haudenschild, 1984; Schneider et al., 1986), though the emphasis is on studies associated with coronary rather than cerebral or peripheral vessel atherosclerosis. There is now increasing evidence that hyperinsulinaemia may have a direct causal effect on atherogenesis though the criteria for this has been difficult to meet. The evidence comes from clinical and population studies in both diabetic and non-diabetic cohorts. Furthermore, plausible *in vitro* data has been produced showing how insulin might have a direct effect on the vessel wall causing smooth muscle cell proliferation and the stimulation of lipid synthesis in the smooth muscle cell.

Multivariate analysis in three epidemiological studies in non-diabetic populations, namely the Helsinki (1979), Paris (1980) and Busselton (1979) studies, have demonstrated that hyperinsulinaemia is an independent predictor of coronary heart disease and cardiovascular disease in general. Other studies on Type II diabetic populations, one in females, have shown hyperinsulinaemia to be an independent risk factor by demonstrating a relationship between either fasting plasma insulin or insulin levels 2 hours after a glucose load and subsequent ischemic heart disease or ECG abnormality (Hillsen et al., 1984; Jarrett, 1988).

Despite criticisms of these studies other epidemiological work has shown that with hyperinsulinaemia the clinical end results of atherosclerosis in the form of

cardiovascular diseases increases. Patients with atherosclerotic diseases have a higher fasting insulin value and a higher total accumulated insulin value on oral glucose tolerance tests (Nagasaki et al., 1986).

The translocation of Japanese from Japan to the United States, similarly, resulted in higher levels of atherosclerotic disease. It has been shown that serum insulin levels prior to glucose administration are higher in Japanese American residents than in the Japanese resident in Hiroshima and that insulin reactivity following glucose administration was higher in the former (Nagasaki et al., 1986). In these studies no conclusion was made on whether the higher risk of atherosclerosis in Japanese Americans was independently due to these higher levels of insulin (Nagasaki et al., 1986). In South Africa insulin responses to glucose in Whites are almost twice as high as in Blacks (Schneider et al., 1986).

In examining the relationship of insulin levels with lipoproteins Stadler et al. (1981) have shown that there is a relation between depressed HDL cholesterol and an elevation of fasting insulin values, irrespective of obesity. They also showed that hyperinsulinaemia promotes hypertriglyceridaemia. It is generally accepted that the synthesis of VLDL in the liver is promoted by the activation of insulin and that serum triglyceride values are elevated by the increased conversion of lipids to fatty acids through the activity of acyl COA carboxylase (Nagasaki et al., 1986).

The relationship between insulin and diabetes has, similarly, been intensively investigated with special emphasis on the role that insulin may play in atherogenesis among diabetics. It has been shown that despite insulin secretion being depressed in insulin dependent diabetes mellitus, the administration of exogenous insulin results in an accompanying hyperinsulinaemia. On the other hand, the possibility that hyperinsulinaemia develops during the early stage of non-insulin dependent diabetes mellitus and the involvement of insulin resistibility in the development of diabetes mellitus has been investigated. The results of these studies show that many participants have hyperinsulinaemia in the early stage of diabetes mellitus (Nagasaki et al., 1986).

As far as the association between hypertension and serum insulin is concerned, it was reported by Modan et al. (1985), in their study on Israeli subjects of both genders between the ages of 35 to 75 years that both fasting and post-prandial insulin levels were significantly elevated in hypertensive subjects, independent of obesity, glucose intolerance, age and anti-hypertensive medication suggesting a relation between hyperinsulinaemia and hypertension.

The recognition of impaired tissue sensitivity with compensatory hyperinsulinaemia and its association with hypertension and lipid abnormalities has led Reaven to postulate the existence of the 'Reaven Syndrome' or 'Syndrome X' in which insulin resistance is considered to play the central role in the pathogenesis of cardiovascular atherosclerotic disease (Home, 1989).

Thus far the evidence is indicative of an association between hyperinsulinaemia and atherosclerosis with no absolute evidence that insulin is an independent risk factor for the disease. Although high insulin levels appear to be the problem, the actual primary defect is resistance to insulin. Serum insulin is known to rise when there is an increase to insulin resistibility in the peripheral tissues. The main causes of this are obesity, reduced physical activity and stress, all of which are considered to be associated with atherogenesis as major or minor risk factors.

Thus there appears to be increasing evidence that one way or the other insulin is implicated in the process of atherogenesis and in fact may be the modulator of the principal risk factors.

4.5 SMOKING

The association between cigarette smoking and atherosclerotic disease in the coronary, cerebral and peripheral vessels is well established on the basis of cohort and case-controlled epidemiological studies, clinical and pathological correlation, and laboratory findings (Juergens et al., 1960; Eastcott, 1962; Foder et al., 1968; Kannel and Shurtleff, 1973; Janzon, 1975).

Bogousslavsky et al. (1985) showed that smoking is strongly implicated together with hypertension and diabetes in the occlusion of the internal carotid artery. Many population samples have produced epidemiological data which consistently show that myocardial infarctions are related to smoking in terms of the number of cigarettes smoked per day. Strong and Richards (1976) in an autopsy study on Black and White men between the ages of 25-64 years found that atherosclerotic involvement of the aorta and coronaries was greatest in heavy smokers. Reed et al. (1987) showed that in a study on Japanese living in Hawaii, cigarette smoking was consistently associated with aortic atherosclerosis and inconsistently with coronary atherosclerosis. The association between smoking and atherosclerosis of the peripheral arteries is particularly strong. Gofin et al., (1987) showed smoking to be associated with intermittent claudication in Israeli subjects. Myers (1979) showed that continuous smoking worsened claudication, increased the risk of gangrene and decreased long-term patency rates in arterial reconstruction grafts and concluded that the effect of smoking was strongest for disease in arteries of the legs. Jonason and Bergström (1987) also showed the improvement of intermittent claudication and rest pain with the cessation of smoking in the subjects that were studied. Janzon (1975) and Cavallo-Perin et al. (1984) showed that peripheral vascular disease was higher in patients who smoked daily than in the general population.

Puchymayer (1984) found a relationship between the degree of atherosclerosis and the number of cigarettes smoked and with the age at which smoking was started, though the number of cigarettes is perhaps more important than the duration of the habit. Not surprisingly, the risk of myocardial infarction was halved with the cessation of smoking, with a further decline in risk over many years. Auerbach and Garfinkel (1980) showed a direct relationship between smoking habits and the extent of atherosclerotic lesions in 1416 autopsies. The extent of the lesions and an eight-fold increased incidence of aneurysms occurred more severely in the abdominal aorta than in the thoracic aorta and occurred in patients who smoked 1-2 packets of cigarettes per day.

A number of patho-physiological mechanisms explaining how smoking may accelerate the development of atherosclerotic disease and promote strokes, coronary attacks or intermittent claudication, rest pain, ischemic ulcers and gangrene have been proposed. The two major cigarette components, namely: nicotine and carbon monoxide, are toxins to the cardiovascular system. They evoke multiple adverse effects through cardiodynamic influences, haemostatic changes, vasculotoxic and inflammatory influences resulting in an acceleration of atherogenesis. Caro et al. (1987) found cigarette smoking to increase arterial wall stiffness and alter the pattern of arterial blood flow which is regarded as a contributory factor to the development of atherosclerosis. Toppling et al. (1977) looked at the relationship between smoking and lipoproteins. According to them the metabolism of VLDL and chylomicrons includes the extrahepatic hydrolysis of triglycerides by lipoprotein lipase. This results in cholesterol-rich 'remnants' which are further metabolised by the liver. There is experimental evidence that in patients with type III hyperlipoproteinaemia and smokers, hepatic-'remnant' metabolism may be depressed. In type III hyperlipoproteinaemia, the defect is inherited, while in smokers it occurs in response to raised concentrations of carboxyhaemoglobin. The striking clinical similarity between type III hyperlipoproteinaemic patients and smokers, namely a high incidence of peripheral vascular disease, may be due to a common cause: the accumulation of cholesterol-rich 'remnants' in the plasma. Garrison et al. (1979) and Criqui et al. (1980) reported an inverse association between smoking and HDL cholesterol in patients suggesting that a reduced HDL cholesterol associated with smoking predisposes to atherogenesis. Nicotine is believed to play a major role in platelet adhesiveness (Kannel and Schatzkin, 1983). Oberai et al. (1984) suggested that platelets in smokers are more adhesive to the vessel wall and it is believed that a platelet-derived growth factor, released in the vessel wall, may promote the proliferation of connective tissue. Kannel et al. (1987) have produced data which provides another mechanism by which cigarette smoking results in atherogenesis. At the 10th biennial examination of the Framingham study it was shown that although smoking and fibrinogen are both independent risk factors for atherocardi vascular disease, smoking resulted in an increase in fibrinogen according to the amount of smoking in each gender. In a 10 year follow up the risk increased progressively in

relation to antecedent fibrinogen levels. Carboxyhaemoglobin is also considered to play a role in atherogenesis by virtue of injury to the arterial intima. Smoking may also promote the underlying atherosclerotic process by inducing chronic hypoxia of the endothelium.

Smoking is perhaps more forceful as a risk factor in an already compromised arterial circulation. Epidemiological findings are consistent with this contention showing an association between smoking and a risk of strokes, myocardial infarction and peripheral vessel occlusion, independent of the levels of other cardiovascular risk factors (Kannel and Schatzkin, 1983). Additional support for this contention is provided by the observation that, in some parts of the world, where the arterial circulation remains uncompromised, the effect of heavy smoking is not associated with high levels of cardiovascular mortality and morbidity (Kannel and Schatzkin, 1983). The deleterious effects of smoking are, however, more prominent in the company of other predisposing risk factors.

In one study the benefits due to a cessation of cigarette smoking, did not extend beyond the age of 65 years, for heart attacks (Gordon et al., 1974). This is especially interesting because the impact for cigarette smoking is greater for occlusive peripheral arterial disease which usually occurs in a more advanced age. In any event, whereas the benefits of cessation on myocardial infarction rates could not be shown beyond the age of 65 years, mortality from coronary heart disease and death rates in general have distinctly benefited by cessation of smoking, even in advanced age. Cigarette smoking is therefore an avoidable major contributor to atherosclerosis.

It is also interesting to note than even though smoking is a habit practised virtually throughout the world; and as much as it is regarded as a risk factor for atherosclerosis, smoking is also very prevalent in countries in which the level of atherosclerosis causing peripheral arterial disease and ischemic heart disease is low, like in China and Japan, but in which strokes occur commonly (Bernhardt et.al., 1986; Galton, 1991).

4.6 HYPERFIBRINOGENAEMIA

Fibrinogen is a blood glycoprotein which plays a role in blood clotting, platelet and erythrocyte aggregation, the maintenance of blood viscosity and wound healing. In recent years hyperfibrinogenaemia, an excess of fibrinogen has emerged as a major independent risk factor for atherosclerosis (Naito et al, 1994; Vorster and Venter, 1994).

The evidence for this has come from a number of epidemiological, clinical and experimental studies (Vorster and Venter, 1994). Of these, the most notable are six prospective epidemiological trials, namely the Göteborg Study (1984) in Sweden, the Leigh Study (1985) in the United Kingdom, the Northwick Park Hewitt Study (1986) also in the United Kingdom, the Framingham Study (1987) in the United States of America, the Caerphilly and Spieldwell Collaborative Heart Disease Study (1991) in Wales and the Prospective Cardiovascular Münster Study (1987) in Germany.

The majority of studies have attempted to show a causal relationship between hyperfibrinogenaemia and coronary heart disease. Not much work had been done to confirm its relationship with strokes and peripheral vascular disease. Folsom (1992) indicated that increased fibrinogen levels may be associated with carotid atherosclerosis at an early asymptomatic stage in the Atherosclerosis Risk In Communities (ARIC) Study in the United States of America. Hughson et al (1978) found levels of fibrinogen to be higher among patients with intermittent claudication than in controls, suggesting that there is an association with atherosclerosis of the peripheral vessels.

The mechanisms through which hyperfibrinogenaemia causes atherosclerosis are as yet unestablished, but many hypotheses have been advanced. Briefly it has been suggested that fibrinogen and/or fibrin when in contact with the arterial wall, could initiate atherosclerosis by causing endothelial cell disorganisation and a "break-down" of the endothelial barrier with an increased impermeability to plasma proteins and lipoproteins. Fibrinogen could also initiate or stimulate smooth muscle cell

proliferation, provide an absorptive surface for HDL cholesterol accumulation, stimulate and support platelet and erythrocyte aggregation and enhance leukocyte adhesiveness and aggregation. Atherosclerotic plaques are known to contain fibrin (ogen). The fibrinogen peptides or degradation products enhance chemotaxis of inflammatory cells and cause vasoconstriction and cell proliferation. These effects essentially contribute to atherosclerosis while fibrinogen's role in blood viscosity, platelet aggregation and blood coagulation contribute to thrombus formation (Vorster and Venter, 1994).

Plasma fibrinogen levels reflect the balance between production and removal of fibrinogen from the circulation. While genetics may play a role in determining fibrinogen concentrations, there is strong support for the view that plasma levels are also influenced by lifestyle and environmental factors. Smoking probably has the most elevating effect on fibrinogen and this has been demonstrated in the Framingham Study (Kannel et al., 1987). Other factors include job strain or stress and blood oestrogen concentration. The effect of exercise on plasma fibrinogen levels is unclear, but it is believed that exercise stimulates the release of various plasminogen activators resulting in increased fibrinolysis and reduced fibrinogen (Vorster and Venter, 1994). Significantly Essien (1976) considered the probability of an enhanced fibrinolysis in Nigerians as the reason for a low prevalence of atherosclerosis among Nigerians.

It is, however, not clear if ethnicity or race influence fibrinogen levels (Vorster and Venter, 1994). The ARIC Study (1992) reported higher levels for United States Blacks than Whites, while lower levels were found in the Japanese than in White Americans (Iso et al., 1989). Venter et al. (1992) could not demonstrate a racial effect among South African populations.

Several abnormal physiological and disease states are associated with elevated plasma fibrinogen levels. These include diabetes, obesity, hypertension, renal disease, increased platelet aggregability, high LDL and low HDL levels, hypertriglyceridaemia

and hyperinsulinaemia (Wilkins and Back, 1978; Vorster and Venter, 1994). Each of these conditions, in their own right are known to influence the atherosclerotic process.

4.7 OESTROGENS

In the industrialised countries circulatory disease is a major cause of death in women accounting for nearly half the number of deaths. Its incidence increases with age, particularly after the menopause. In the United States of America, 42,5% of deaths among women over the age of 50 years are due to cardiovascular disease (Wren, 1992). Younger women, on the other hand, have a substantially lower risk of circulatory disease than do men, but the risk continues to rise with age until it approaches that of men (Wren, 1992). The female cardiovascular system therefore appears to be protected against atherosclerosis. Protection is thought to be mediated by endogenous oestrogens which women produce up to the age of menopause (Wren, 1992).

Women who had bilateral oophorectomy and/or hysterectomy before the menopausal years were found to have evidence of cardiovascular disease at an earlier age than was expected. This, however, was reversed when these women were subsequently given oestrogen replacement therapy (Burch et al., 1974; Bain et al., 1981). Similarly studies have been carried out in which oestrogens were replaced beyond the menopausal years, the relevant studies indicating a 45% decrease in the risk of cardiovascular disease (Wren, 1992). Evidence from animal and autopsy studies indicates that exogenous oestrogens inhibit the development of atherosclerotic coronary lesions (Pick et al., 1952; Burch et al., 1974). This is supported by coronary angiographic studies, case-controlled studies and prospective cohort studies, where lower levels of coronary artery occlusion are seen in women treated with exogenous oestrogen than in untreated women (Gruchow et al., 1988, Sullivan et al., 1988; Mcfarland et al., 1989). Clinical evidence also shows that oestrogens administered to women result in a lower incidence of atherosclerosis and myocardial infarction (Wren, 1992).

Additional evidence on the beneficial effects of oestrogens comes from studies in patients with other risk factors, such as smoking, hypertension, diabetes and hyperlipidaemia; in whom the administration of oestrogens reduced the degree of cardiovascular diseases to a greater degree than could be expected had they not been on oestrogen replacement therapy. (Wren, 1992).

There is no evidence in the literature to suggest that these observations are affected by race, socio-economic status and geographical location.

The benefits of oestrogens on cardioprotection have been explained on the basis of oestrogen-mediated changes in total cholesterol, HDL cholesterol and LDL cholesterol. (Bush et al., 1987; Wren, 1992). However, even though oestrogens have a positive effect on blood lipids in women, lipids are not responsible for all the protective effects. Oestrogens are considered to have a direct positive effect on the vessel wall by the inhibition of atheromatous plaque formation. The protection is mediated by a complex mechanism involving vessel intima, macrophages, platelets and arterial musculature. Consistent with this hypothesis is the fact that oestrogens reduce the formation of thromboxane. There is a reduced smooth muscle cell proliferation and an associated decreased uptake of cholesterol. Other direct effects on the blood vessel wall (at the level of the arterial intima) have been demonstrated, including alterations in collagen and elastin formation, as well as changes in prostacyclin production. Prostacyclin synthetase activity results in arterial vasodilatation and an improved pulsatile index. The increased vasodilatation results in an improved blood flow, reduced size for thrombosis and reduced risk of change due to atherosclerosis (Wren, 1992). Austin and Moss (1984) on the other hand proposed that the reduced severity of lesions in females may not be due to the presence of smaller numbers of precursor lesions, but rather to the slower progression of these lesions in the female patient.

These effects of oestrogens are likely to affect all arteries in the body, rather than the coronary vasculature only, where much of the research has been concentrated. There

is a paucity of research specifically directed towards cerebrovascular disease and less still towards peripheral vascular disease.

COMMENT

It is evident from the foregoing that the many factors which initiate or accelerate atherogenesis make it difficult to isolate the contribution of any risk factor. Risk factors may, indeed, not individually or collectively be causative, accelerative or synergistic, though there is the constant search for the single factor which may be the prime modulator for the process. There is also no unanimity of opinion on how risk factors pathogenetically affect the different vascular beds to cause atherosclerosis.

5. THE EMERGENCE OF ATHEROSCLEROTIC ARTERIAL DISEASE IN DEVELOPING POPULATIONS

If risk factors can play such a significant role in atherogenesis, much can be learnt about how they initiate the process by an intensive study of how atherosclerotic arterial disease emerges in developing populations hitherto unaffected by the disease. Yet little is known about the natural history of atherosclerosis in such instances. It is, therefore, hoped that a thorough understanding of the natural history of atherosclerotic arterial disease could add a new dimension to the vast knowledge already accumulated from the study of risk factors. In the section which follows the literature is reviewed to establish the pattern of emergence of atherosclerotic disease in developing populations.

5.1 CEREBROVASCULAR DISEASE

The cerebrovascular bed is the first major arterial bed to be afflicted by clinically significant atherosclerotic arterial lesions (Walker, 1975). This is especially evident in the developing Black populations of Africa and South Africa where according to Reef and Isaacson (1962) the South African Black, *"while being prone to the cerebral*

complications of atheroma, manifest a remarkable freedom from complications elsewhere in the body". Joubert et al. (1990), similarly, concluded "that in Black stroke patients the extracranial carotid arteries, the coronary vessels and the peripheral limb vessels are relatively less involved by atherosclerosis than is generally reported in White stroke patients".

As long as countries in Africa remain underdeveloped, atherosclerosis of the cerebral vessels remains rare. During the period 1957 to 1969 of the 581 necropsies undertaken in Khartoum, Sudan, atherosclerotic cerebrovascular disease was the cause of death in only 4 patients (Walker, 1975). Similarly in Uganda death from this cause was extremely rare in the 1940's and a review of 269 consecutive neurological admissions did not show evidence of cerebrovascular disease (Trowell, 1981).

With a rise in sophistication, however, atherosclerotic cerebrovascular disease emerged before atherosclerotic involvement of the coronary and peripheral vasculature. A second review of 700 consecutive neurological admissions to the Mulago Hospital in Uganda 12 years after the first review reported that 11% of patients had hypertensive cerebrovascular disease; and a third review of 600 neurological admissions after a lapse of another 14 years reported that 34% had hypertensive (not necessarily atherosclerotic) cerebrovascular disease (Trowell, 1981). The South African Black on the other hand has been exposed to western influences for a longer period and to a greater extent than his counterpart in the rest of Africa. (Trowell, 1981). It is therefore to be expected that atherosclerotic cerebrovascular disease in the South African Black would be more prevalent than in other parts of Africa. This was shown to be so in a study carried out in Johannesburg in 1960 with cerebrovascular disease having a distinctive presence and being slightly higher for Blacks than for Whites, though hypertension which is extremely common among Blacks could have accounted for deaths due to cerebral haemorrhage (Walker, 1975). Similar results have been shown in several American studies (Alter, 1994). An investigation into cerebrovascular disease in Evan's County, Georgia, has shown that the age specific prevalence rate of strokes was higher in Blacks than in Whites, the rate being almost 3 times greater in Blacks than in White women (Heyman et al.,

1971). In 1960 - 1961 patients with cerebrovascular disease in an American study accounted for 11% and 13% of total deaths for Whites and Blacks respectively (Walker, 1975). Generally though, no racial difference exists in atherosclerosis of the cerebral vessels (Meyer et al., 1971).

As western influence among Blacks increases atherosclerotic cerebrovascular disease in Blacks starts to resemble more closely the level of disease among Whites, though depending on the degree of these influences, Blacks from different geographical locations have a varied incidence of cerebrovascular disease (Resch et al., 1967). Up to a point it would seem that this similarity is confined to the cerebral vessels and is unaccompanied by similar changes in the coronary and peripheral vasculature, although this is by no means permanent as will be seen in the following sections.

The majority of Blacks, interestingly, tend to have occlusive disease of the intracranial cerebral vessels (Joubert et al., 1990). This is true of both South African and American Blacks. Whites on the other hand seem to have a greater involvement of the extracranial cerebral vessels (Caplan et al., 1986). This is true of Whites generally, including White South Africans, though there are no definitive studies outlining the distribution of atheroma in the neck vessels of local Whites. Similarly, in the case of the South African Indians there are also no definite studies outlining the distribution of atheroma in the neck vessels.

This differential distribution of atherosclerosis in the cerebral vessels of Blacks and Whites has been extensively reviewed by Gorelick et al., (1984) and Caplan et al., (1986). Angiographic and autopsy studies all confirm that Blacks are more prone to intracranial atherosclerosis while Whites have more extracranial disease. Studies on the distribution of occlusive sites by cerebral angiography in a racially mixed population of patients with symptomatic cerebrovascular disease showed that diffuse vascular tortuosity and dilatation of the intracerebral vessels were more frequent in Blacks, while large atherosclerotic plaques in the proximal cerebral vessels were more common in Whites. In the Joint Study of Extracranial Arterial Occlusion (1972) surgically accessible extracranial disease was more common in White patients (91%)

than in Black patients (9%). In a group of patients with angiographically documented non-embolic occlusion of the internal cerebral artery and the middle cerebral artery there was a preponderance of Blacks in the group with intracranial disease. Gorelick et al (1984) compared clinical and angiographic features of 26 Whites and 45 Black patients and showed that Whites had more severe occlusive disease of the internal carotid artery system and Blacks had more severe disease of the middle cerebral artery stem and the supraclinoid internal carotid artery system. These differences could not be explained by racial differences in the prevalence of hypertension, diabetes, hypercholesterolaemia and ischemic heart disease. An autopsy study carried out on Blacks and Whites in New Orleans showed that in the 65 - 69 year age group, 43% of Blacks had raised atherosclerotic intracranial lesions compared to only 8% among Whites (Caplan et al., 1986). In a study carried out on South African Blacks it was shown that the middle cerebral artery was more affected than any other intracranial vessels (Reef and Isaacson, 1962). They also showed that atherosclerotic disease of the extracranial carotid vessels in Blacks was rare. They examined 32 vessels and of these only 3 vessels showed ulcerated and calcified plaques. In 7 vessels there were no lesions at all. The atherosclerotic index, which expressed the severity of atherosclerosis in a scale ranging from 0 to 100 was below 1 in 25 vessels. The majority of vessels (19 or 60%) showed less than 5% of their surface area affected by the disease. The most severely affected vessels showed an atherosclerotic index of only 5. Similar results have been reported among Zimbabwean Blacks by Levy (1971). He reported that of a European population of 300,000 atherosclerotic plaques occurred in only 34 cases. By contrast, in 3 internal carotid arteries that were explored in Africans, disease was not on account of atherosclerosis. Levy (1971) concluded that *"it seems to us from post mortem studies that when atheroma does invade the cerebral vessels, those of the vertebro-basilar system are more involved than the carotid tree"*.

Since studies on Blacks in America have yielded similar results, it would seem that in Blacks, even in cases of increased privilege similar to that of Whites, there is no concomitant rise of atherosclerosis in the extracranial cerebral vessels (Caplan et al., 1986; Joubert et al., 1990).

The Japanese like Blacks have been shown to have a predisposition to occlusive lesions of the middle cerebral artery and a low prevalence of occlusive extracranial internal carotid artery disease (Caplan et al., 1986; Nagao et al., 1994). Similar results have been shown among the Chinese, with disease being common in the middle cerebral artery and rare in the carotid arteries (Caplan et al., 1986, Leung et al., 1993).

5.2 CORONARY VASCULAR DISEASE

With a rise in sophistication atherosclerotic lesions of clinical significance in the coronary vessels are slower at becoming manifest. All available evidence suggests that coronary artery disease is the last major cardiovascular atherosclerotic disease to emerge (Walker, 1975; Trowell, 1981).

In many parts of Africa atherosclerotic coronary vessel disease in Blacks does not occur. It has been stated that "*the Nigerian arteries are as smooth as velvet.....*" and that coronary artery disease is virtually non-existent even in the bustling capital of Lagos (Walker, 1975). Ogunnowo (1986) concluded that coronary occlusive disease among Nigerians occurred in the elderly, affluent and hypertensive patients exposed to western diets and habits (Trowell, 1981). The emergence of coronary heart disease in East Africans has been clearly documented. First, there was the stage of reputed absence. Second, there was the evidence of coronary heart disease made by the pathologist. Third, was the clinical report of coronary heart disease in a Ugandan judge. Ojiambo (1968) reported the first clinical case in Kenya; and Nhonoli (1968) the first case in Tanzania (Trowell, 1981). Between the periods 1968-1970 only 10 patients with coronary heart disease were seen at the teaching hospital in Accra, which has a population of 350,000 (Walker, 1975). This indicates that the disease is rare in all East Africans. The disease, though emerging, is rare in the South African Black population (Seftel, 1978; Trowell, 1981; Reddy et al., 1982). Reliable ischemic heart disease mortality data are, however, not available for the Black population of South Africa (Steyn et al., 1991). Among country dwellers the disease is virtually non-existent (Walker, 1975; Walker and Walker, 1978). In Johannesburg in 1977 there were 14 deaths from coronary artery disease at Baragwanath Hospital. This

favourable situation persists despite the presence of many of the established risk factors, some to a major degree (e.g. hypertension) in a significant proportion of the urban community. In a White population of similar size, age and gender as that of Blacks in Soweto, calculations suggest that 1500-1750 episodes of coronary heart disease or sudden death are expected annually (Walker 1975). Thus in South African Blacks the death rate is only 1-2% of that of South African Whites of similar age and gender (Trowell, 1981). According to Bertrand (1995) coronary heart disease is still rare representing only 6% of all cardiovascular diseases in Black Africans.

This situation contrasts with Blacks in the United States and with Whites and Indians in South Africa with both groups having a high incidence (Seedat et al., 1990) as well as with Whites the world over. In Evans County, in studies made on cardiovascular disease, it was reported that White males had an age-adjusted prevalence rate almost 3 times higher than that for Black males, although no ethnic differences were found for females (Walker, 1975).

Walker (1975) has expressed the opinion that South African Blacks will, in time, undoubtedly experience increases in the occurrence of coronary heart disease. It is, however, unwarranted to assume that as an increase in prosperity and rise in privilege occurs, mortality from coronary heart disease in South African Blacks will eventually and inevitably reach that of United States Blacks. Not only do South African Blacks differ ethnically and genetically, but even in any White population exposed to equally high socio-economic circumstances, there are widely different mortality rates from coronary heart disease. While the mortality from coronary heart disease appears to have reached a plateau in the United States and some European countries, it is still rising elsewhere (Walker, 1987). In yet other countries coronary heart disease still remains low and unchanged, as in Greece (Aravanis and Corcondilas, 1972; Walker, 1987).

5.3 PERIPHERAL VASCULAR DISEASE

There is a paucity of epidemiological information on the natural history and emergence of atherosclerotic peripheral vascular disease, in comparison to that available for cerebrovascular disease and coronary artery disease (Walker, 1975). This situation exists even though it has been claimed that in England chronic ischemia due to peripheral vascular disease is one of the commonest conditions seen in clinical practice. In fact much of the information available on the epidemiology of peripheral vascular disease arises from clinical and cohort studies and not from population-based studies, which are lacking (Kannel et al., 1970; De Backer et al., 1979).

Peripheral vascular disease has not been accorded the same intensity of investigation and study as cerebrovascular disease and coronary artery disease, perhaps because it does not have as marked an affect on mortality as the latter two diseases. The major concern with peripheral vascular disease lies in the morbidity it causes due to chronic limb ischemia. The health hazard of peripheral vascular disease lies principally in its association with an increased mortality from cerebrovascular disease and coronary heart disease.

Because of the lack of population-based studies, the current status of atherosclerotic peripheral vascular disease in many communities remains unestablished and it is not known whether the prevalence of the disease in these same communities is increasing, steady or decreasing. In addition the status of peripheral vascular disease in relation to cerebrovascular disease and coronary heart disease in many situations also remains unestablished (Friedman et al., 1973). Furthermore, as a direct result of the lack of epidemiological information, other aspects of peripheral vascular disease, namely, the pathology, the natural history (which needs to be better defined), the associated risk factors and the biochemistry are also lacking in comparison to that available for cerebrovascular disease and especially coronary heart disease.

Nevertheless, in western populations several studies have been carried out investigating peripheral vascular disease, though they have not been comprehensive.

In the Framingham Study, the annual average incidence rates of peripheral vascular disease for White men and women aged 55-64 years were 53 and 18 per 10 000 respectively (Kannel et al., 1970). In England, in a hospital population of the same age, in patients not admitted for vascular disease, the corresponding prevalence rates of peripheral vascular disease for men and women were reported to be 16% and 17% respectively (Ludbrook et al., 1962). In a study carried out on a middle aged population sample in Jerusalem it was shown that the prevalence of peripheral vascular disease, as determined by symptoms of intermittent claudication, was 1.3% in men and 1.8% in women and absent pedal pulses were found in 1.1% of the men and 2% of the women (Gofin et al., 1987). In an earlier study undertaken in Israel it was shown that the rate of peripheral vascular disease among immigrant Jews from North Africa was about one fifth of that of Jewish immigrants from Eastern Europe (Walker, 1975). In Greece in an investigation into peripheral vascular disease among rural populations, the occurrence of the disease was described as extremely low (Aravanis and Corcondilas, 1972).

In African populations the general consensus is that atherosclerotic peripheral vascular disease involving the aorta-iliac and distal peripheral segments is rare. Little or no mention is made of the problem in the various text books dealing specifically with the practice of internal medicine, surgery and pathology in this population group and what discussion there is focuses on idiopathic aortitis (Robbs, 1985). Grobbelaar (1974) reported on 70 Black patients who presented at his hospital with peripheral arterial disease. Of these 46% suffered from 'arteritis' which causes occlusion of the small vessels of the extremities by progressive transmural fibrosis; and 28% suffered from arterial disease of miscellaneous aetiology including idiopathic aortitis.

According to Friedman (1982) occlusive disease of the terminal aorta and the common iliac artery is one of the earliest atherosclerotic lesions and is regarded as the bellwether of lesions elsewhere. The mean age of patients presenting with isolated aorta-iliac occlusion was 49 years in one American series and this is representative of the age of presentation in other studies (Friedman et al., 1964).

Meyer et al. (1971) showed that the aortic lesions made their appearance in Whites in the second decade and that in Blacks in Pretoria the aortic indices were very low in all cases until the third decade. In Blacks, lesions developed with increasing age but at a slower rate. In Whites the development of lesions occurred in a similar way but more dramatically. Gender differences between White males and females only occurred after the fourth decade. No such differences occurred in Blacks. In this respect these findings are similar to those found in most European and American studies.

Higginson and Pepler (1954) studied the aortas of Blacks in a series of 523 post mortems on Black patients at Baragwanath Hospital in Johannesburg and did not find in the aortas examined a degree of atherosclerosis comparable to that in Whites.

Reef and Isaacson (1962) reported that in Blacks the aorta was affected more frequently and more severely than any other vessels. 25% of the aortas examined had less than 5% of their surface area affected by lesions and only 16% had more than 50% of their surface affected. The mean atherosclerotic index was 6, a figure indicating relatively slight involvement. The iliac arteries showed a similar pattern to the aorta and were also heavily afflicted. The highest atherosclerotic index recorded was 16.

By comparison with Black populations elsewhere in Africa, studies concluded in the Department of Pathology at the University of Zimbabwe showed that the atherosclerotic indices of the aortas of Zimbabwean Blacks are similar to those of the Blacks in South Africa (Levy, 1971). Likewise Biss et al. (1971) carried out necropsy studies on 7 Masai over 40 years of age and found that *"All aortas, even those from men over 60 years old showed a paucity of atherosclerosis. Only rare, small fatty streaks like those seen in teenage children in the UNITED STATES OF AMERICA were noted"*. In Blacks the disease is mainly of the occlusive variety which is common in Whites, but there is little in the literature concerning aneurysmal disease of the aorta.

According to Friedman (1982) femoro-popliteal and tibio-peroneal disease tends to develop later than aorta-iliac disease, and symptoms do not appear before the seventh decade. Tibial artery disease rises sharply after the age of 60 years and a significant proportion of the elderly commonly have some degree of occlusive disease.

In Britain distal occlusive disease is often regarded as a common cause of ischemia to the lower limbs (Walker, 1975). In South African Blacks, however, the clinical evidence is that disease of the distal vessels is rare. Very little mention is made of this problem in Blacks and what little is said emphasises this viewpoint (Robbs, 1985; Madiba and Robbs, 1990).

Though there are no statistics relating to the incidence and prevalence of peripheral vascular disease in any of the population groups in South Africa, particularly in the Blacks, the view that the disease is rare is derived from clinical impressions and the examination of hospital records, which is of necessity, selected. This view is epitomised by Alexander Walker who in a chapter on South African Blacks (Trowell, 1981) states quite categorically that peripheral vascular disease, virtually unknown in rural areas, remains rare in cities, even in smokers. Reef and Isaacson (1962) also reinforce this viewpoint in the following statement: *"ischemic atherosclerotic disease of the limbs is also unusual. It seems therefore, that the Bantu, while being prone to cerebral complications of atheroma, manifest a remarkable freedom from complications of atheroma elsewhere in the body"*.

Peripheral vascular disease is also rare in Zimbabwean Blacks. Levy (1971) stated that at the Harare Hospital, *"throughout the 12 years that I have been on the staff, there has not been a single case of amputation of the lower limbs for atherosclerotic gangrene apart from the occasional case associated with diabetes mellitus. In America there are approximately four occlusions of the leg vessels to every two coronary occlusions and to every one cerebral occlusion"*.

Robbs (1985) reviewed the common causes of ischemic disease of the aorta and peripheral vessels in Whites seen at the Vascular Unit in Durban and found that by

contrast to the situation in Blacks, atherosclerosis was extremely common and occurred as the commonest cause in 95% of patients seen.

In the developing countries such as China, there are no exact data on the morbidity of peripheral vascular disease, but the common opinion of many Chinese physicians is that the disease is very low (Bernhardt et al., 1986). He also concluded that the incidence of coronary heart disease and peripheral vascular disease in China is much lower while the mortality from strokes is higher than in western countries.

CHAPTER THREE

METHODOLOGY

1. INTRODUCTION

'BY DOUBTING WE COME TO QUESTION AND BY SEEKING WE COME UPON TRUTH.'
(ABELARD)

Durban has a cosmopolitan population consisting of Blacks, Whites and Indians, which is representative of the major population groups in South Africa:

The Vascular Service of the Department of Surgery in the Faculty of Medicine at the University of Natal in Durban is a single highly organised and specialised service which treats patients presenting with specifically vascular problems in the extracranial extracoronary circulation. At the time that this study was carried out, the service operated at three hospitals in Durban, namely Addington Hospital (for specifically White patients), King Edward VIII Hospital (for specifically Black and Indian patients), and RK Khan Hospital (for specifically Indian patients). The present study was carried out on Black, White and Indian patients seen at each of these three hospitals. These patients drained from the greater Durban metropolis, from throughout the province of Kwa Zulu Natal and as far south as the Transkei.

The Vascular Service provided at each of the hospitals mentioned above is directly linked to the Vascular Research Laboratory which is also under the auspices of the University of Natal's Department of Surgery. The Vascular Service and the Vascular Research Laboratory were established in the early eighties and though the main purpose was to treat patients attending each of the clinics at the three hospitals, all information relating to every patient treated at the service is scrupulously collected and recorded in the Vascular Research Laboratory. The information recorded is available for research study.

The Vascular Service and the Vascular Research Laboratory therefore provide a unique opportunity to study atherosclerosis within the extracranial extracoronary vasculature in a racially mixed society at different stages of social transition.

2. **EXPERIMENTAL DESIGN**

In order to address the general purposes of this study, there are two parts. The first part is a retrospective study which investigates the causes of peripheral vascular disease among Black, White and Indian patients seen at the Vascular Service in Durban and seeks to establish whether atherosclerotic peripheral vascular disease is an established entity among the Black patients seen at the Vascular Service and what is the distribution of peripheral vascular disease in Blacks, Whites and Indians.

The second part is a prospective study also carried out on Black, White and Indian patients seen at the Vascular Service and seeks to establish whether any markers can be identified to support the findings made in the retrospective study of part one.

3. **STUDY SAMPLE**

Every patient included in the sample of both the retrospective and prospective studies had first attended the Vascular Service's outpatient clinics at one of the hospitals and had been admitted to the vascular wards for elective evaluation and management. In certain instances where patients presented as emergencies, admission was via the casualty department.

3.1 **RETROSPECTIVE STUDY**

The retrospective study sample included all patients seen at the Vascular Service for the period 1981 to 1986. In all, the records of 2175 patients were reviewed inclusive of both male and female patients.

3.2 PROSPECTIVE STUDY

The prospective study sample consisted of patients seen at the Vascular Service during the period 1984 to 1986. Although it was intended to include in this study a total of 300 patients, 100 from each of the race groups under study, 302 patients were finally included of which 105 were Blacks, 97 were Indians and 100 were Whites. Females were not included in the study.

This is by no means a representative sample of Black, White and Indian patients who have peripheral vascular disease in Durban. It is believed that a number of patients, mainly Whites, but to some extent Indians too, affording private medical care would probably have attended private hospital centres. On the other hand those that did not seek private care among Whites and Indians, but who found it necessary to seek treatment would in all probability have been admitted to the Vascular Service. Similarly it is possible that the majority of Black patients who sought treatment at the provincial hospitals throughout Kwa Zulu Natal and as far as the Transkei (as opposed to those who did not seek treatment) would ultimately have been referred to the Vascular Service, while others who sought treatment may have attended directly without a referral. Therefore, the sample would ideally represent Black, White and Indian patients from throughout Kwa Zulu Natal and as far south as the Transkei who sought treatment for peripheral vascular disease at a provincial hospital and would not include patients treated at a private medical facility.

Subjects included in the study were randomly selected from patients who were presented for surgery at the Vascular Meeting held in the Vascular Laboratory on Friday afternoons. Randomisation took place by including the first three male patients, one from each race group, per week, into the sample. The approval of the patients to act as subjects was secured.

Each patient included in the study was confirmed to have atherosclerosis on the basis of clinical findings, doppler and duplex studies, angiographic studies and on

macroscopic and microscopic examination of lesions. Any patient who on the basis of these findings did not have atherosclerosis was not included in the sample.

4. **COLLATION OF DATA**

4.1 **RETROSPECTIVE STUDY**

Every elective patient admitted to the Vascular Service was evaluated according to a strict investigative protocol, and every patient admitted as an emergency was similarly evaluated on transfer to the vascular wards once the relevant emergency procedure had been completed and the patient stabilised. Upon discharge from the vascular ward a proforma (refer appendix 1) was completed by the Registrar in charge of the patient, recording patient details in respect of name, age, gender, race, presenting complaint, clinical findings, blood pressure, peripheral pulses, results of doppler tests and angiograms, blood results, diagnoses and surgical treatment and management. The patient details as recorded on these proformas were ultimately captured and stored on computer at the Vascular Research Laboratory.

In this study the patient records for the relevant period were retrieved from the computer and analysed for race, age, gender, anatomical and pathological distribution of peripheral vascular disease.

4.2 **PROSPECTIVE STUDY**

As in the retrospective study, each patient admitted to the prospective study was evaluated according to an investigative protocol.

4.2.1 **QUESTIONNAIRE**

The protocol commenced with the completion of a questionnaire by the writer for each patient admitted to the study (refer Appendix 2). The questionnaire was designed

to establish the patient's personal details and details relating to biological, ethnic and socio-economic data. An overview of the patient's dietary pattern was established. The patient's smoking and alcohol consumption habits of the past and present were also determined. These included details of duration, frequency, type and severity. A medical history of cerebrovascular accidents, ischemic heart disease (angina and myocardial infarction), hypertension, diabetes, gout and other medical or surgical illnesses of significance suffered by the patients, their siblings, their parents and grandparents was also elicited. A detailed history of all medication taken by the patient was also obtained. In patients with a history of cerebrovascular accidents, ischemic heart disease, hypertension and diabetes, the drug history was used to corroborate a history of the condition.

4.2.2 CLINICAL EXAMINATION

The writer then conducted a full clinical examination of each patient included in the study. Salient features of the clinical examination included a record of the blood pressure, the presence or absence of pulses and bruits (where significant) in the neck and extremities, namely the carotid, brachial, radial, abdominal aortic, femoral, popliteal, anterior and posterior tibial and dorsalis pedis pulses. The presence or absence of any aneurysms in any of the major arteries was also recorded. Height and weight was only measured in those patients who were mobile and only when the measurement of these parameters caused no inconvenience to the patient on account of symptomatology. These measurements were taken in light clothing and without shoes.

4.2.3 LABORATORY INVESTIGATIONS

The clinical examination was followed by a series of special investigations. Firstly venous blood samples were taken by the writer, drawn from the antecubital vein into appropriate evacuated glass tubes (vacutainers) for the determination of the patient's haematological status, the electrolyte and renal status and the level of uric acid. Blood samples for glucose levels, cholesterol levels (total cholesterol, LDL cholesterol and

HDL cholesterol), triglyceride levels and insulin levels were taken only after a 14 hour fast.

Secondly, a twelve lead resting ECG was taken by the writer on each patient. The resting ECG met with specifications as laid down by the American Heart Association.

Thirdly, blood flow to the lower limbs and/or carotid vessels (depending on the clinical indications) was assessed using bi-directional doppler ultrasonography. In the latter part of this study the carotid duplex scan was used with increasing popularity to determine carotid artery disease. Both doppler ultrasonography and carotid duplex scans were performed by the same operator. Ultrasound studies were performed to determine the site and size of aneurysms whenever they manifested.

Fourthly, arteriography using contrast dye was performed on all patients included in this study to establish the pattern of disease in the relevant arterial segment/s and to provide confirmation of atherosclerosis. Arteriography was part of the routine work up of the patient. Standard techniques involved the transfemoral retrograde passage of a catheter into the aorta or, if the femoral vessels were occluded, a translumbar puncture of the aorta. This, however, had the disadvantage of requiring femoral or regional anaesthesia. In the case of arteriography to the neck vessels the arch-angiogram was the standard procedure used.

Arteriography was complemented by the use of digital subtraction angiography (DSA), in which computer enhanced images were built up and all unwanted images (e.g. bones) are progressively subtracted from the picture after the injections of small amounts of contrast medium.

Upon completion of all investigations the clinical findings and test results were presented at a weekly meeting of vascular surgeons. At this meeting a decision was made with regard to the provisional diagnosis, the site of pathology, the possible cause and the form of treatment. All patients included in this study were subjected to the appropriate form of surgery. Prior to surgery each patient was assessed according

to the Goldman scale by a registrar/consultant because of the possible anaesthetic risks as determined by their associated illnesses and/or physical condition.

Patients then underwent the relevant operative procedure/s. At surgery, the provisional diagnosis was confirmed by macroscopic examination of the lesions. These findings were recorded in detail on the patient's operative charts. Histology was considered the final diagnostic arbiter. Specimens were consequently taken for histological examinations and the confirmation of atherosclerosis.

The writer, under the supervisor's guidance, assisted in a sufficient number of the respective procedures to be familiar with the techniques and procedures used in ultrasonography, arteriography and surgery.

Upon discharge all patient information was recorded on a proforma and captured on computer.

5. LABORATORY TESTS - PRINCIPLES AND METHODS

5.1 BLOOD ASSAYS

Blood collected in vacutainers was allowed to clot at room temperature, and after centrifuging at 3000 rpm for 15 minutes in a standard laboratory centrifuge, the serum was frozen at -20 deg C to be later assayed using the following principles and methods. In all instances the equipment was regularly calibrated and internal quality control tests done. These assays were performed by the writer with the assistance of technicians in the Department of Chemical Pathology, Faculty of Medicine, University of Natal, Durban.

The inter and intra assay coefficients of variation are shown in appendix 3.

5.1.1 TOTAL SERUM CHOLESTEROL

The total cholesterol in serum was quantitatively determined using an enzymatic cholesterol reagent kit. The total serum cholesterol concentration was read on the Beckman CX5.

Beckman controls Dimension 2 (normal) and Dimension 3 (elevated) were used in each assay.

5.1.2 SERUM TRIGLYCERIDES

The triglycerides in serum were quantitatively determined by using an enzymatic triglyceride reagent kit. The serum triglyceride concentration was read on the Beckman CX5.

Beckman controls Dimension 2 (normal) and Dimension 3 (elevated) were used in each assay.

5.1.3 SERUM HDL CHOLESTEROL

The principle of HDL cholesterol determination is based on the quantitative separation of HDL cholesterol from the lipoproteins with the aid of a suitable precipitant and the measurement of HDL cholesterol in the supernatant. The supernatant was formed by a polyanion precipitation method using sodium phosphotungstate and magnesium chloride. The HDL cholesterol concentration in the supernatant was quantitated using an enzymatic HDL cholesterol reagent kit (Boehringer Mannheim). The absorbance was read on a Beckman 42 Spectrophotometer from which the serum HDL cholesterol concentration was calculated using a dilution factor according to the following formula:

$$\text{HDL} = \text{O.D.} \times 3,35.$$

Controls (Boehringer Mannheim) were incorporated in each assay.

5.1.4 SERUM LDL CHOLESTEROL

The cholesterol in the supernatant was quantitatively determined by using an enzymatic cholesterol reagent kit (Boehringer Mannheim). The supernatant was formed by a precipitation method using polyvinylsulphate from which the absorbance was measured using a Beckman 42 spectrophotometer.

If the triglyceride concentration exceeded 4.5 mmol/l complete precipitation was not achieved and the specimens were reported as unsuitable for LDL cholesterol.

Controls (Boehringer Mannheim) were incorporated in each assay.

5.1.5 THE RATIO OF TOTAL CHOLESTEROL TO HDL CHOLESTEROL

The ratio of total cholesterol in serum to HDL cholesterol in serum was calculated by using the measurements of the respective parameters for the assays previously described.

5.1.6 URIC ACID LEVELS

The uric acid in serum was quantitatively determined using enzymatic uric acid reagent kits. The serum uric acid concentration was read on the Beckman CX5.

Beckman controls Dimension 2 (normal) and Dimension 3 (elevated) were incorporated in each assay.

5.1.7 PLASMA GLUCOSE

Glucose in plasma was quantitatively determined using the enzymatic glucose reagent kit. The plasma glucose was read on the Beckman CX5.

Beckman controls Dimension 2 (normal) and Dimension 3 (elevated) were incorporated in each assay.

5.1.8 SERUM INSULIN

The determination of serum insulin was performed by radioimmunoassay using the Phadebas insulin test. This was based on a double antibody solid phase technique. Specific antibodies to insulin were covalently bound to sephadex particles in the solid phase. The concentration of insulin in an unknown sample was evaluated by its capacity to compete with a fixed amount of labelled insulin of known concentration for the binding sites on the insulin antibodies. After incubation, the particles were sedimented by centrifugation, washed and the radioactivity bound to the sephadex particles were measured on a gamma counter. The amount of radioactivity was inversely proportional to the amount of insulin present in the sample.

Biorad controls were used.

5.2 BI-DIRECTIONAL DOPPLER ULTRA-SONOGRAPHY

This technique works on the principle that the transcutaneous passage of ultrasound waves through the artery detects the velocity of moving blood cells which is amplified into audible sound and is graphically recorded as a wave configuration. Standard information obtained included systolic blood pressure measurements and the ratio of lower limb (popliteal, peroneal, posterior tibial and anterior tibial) to brachial blood pressures (pressure index). Blood pressure variations between individuals made absolute pressure measurements of limited value. Use of the leg-to-brachial pressure ratio in which the patient's own blood pressure acted as a standard rendered the results more meaningful as an absolute number. In normal circumstances, the pressure recorded in the leg is higher than in the arm so that the ratio is greater than one. Any reduction in the ratio is indicative of circulatory compromise. This information confirmed the presence of arterial insufficiency and provided a readily available baseline upon which to quantify the efficiency of treatment.

In claudicants the degree of circulatory compromise was quantified by measuring pressures and pressure indices before and after standard physical exercise. Standard exercise was provided by a treadmill at a standard speed and inclination for a standard period of time. In the Vascular Research Laboratory patients were exercised at 3km/hr at a 10 degree inclination for one minute or until claudication forced the patient to stop walking. Study of the basic shape of the velocity wave-form, especially in the femoral arteries, provided a non-invasive way of deciding whether significant flow reduction was present in the intra-abdominal vasculature and in the femoral arteries.

The doppler ultrasonography technique was also used to determine flow in the carotid arteries working on the same principle. In the case of these vessels evidence of turbulence and reverse flow were regarded as indicative of carotid artery disease.

5.3 HISTOLOGICAL STUDIES

Atherosclerosis was confirmed on all patients included in this study by histology. Samples were taken, under the writer's supervision, from sites of lesions during the relevant operative procedures.

At surgery a macroscopic examination of the lesion was done. Thereafter specimens were taken and placed in ice for delivery to the Department of Pathology. In this laboratory specimens were fixed in 10% buffered formalin for a period of 6 - 12 hours. Samples were then selected for processing and routinely immersed in various concentrations of alcohol and xylene solutions. They were then embedded in paraffin wax. Thereafter 4 micron sections were cut and placed on glass slides to be routinely stained in haemotoxylin and eosin. They were then cover-slipped and inspected under light microscopy. These procedures were performed by the writer with the assistance of staff of the Department of Pathology, Faculty of Medicine, University of Natal, Durban. The interpretation of slides was done with the assistance of a pathologist from the department.

6. CRITERIA FOR DATA EVALUATION

The data collated in this study showed much individual variation and for the purposes of analysis, was evaluated according to definitive criteria as set out below.

6.1. ENVIRONMENTAL INFLUENCES (LOCALITY)

All information relating to environment was processed to establish whether patients came from a strictly rural or urban environment, or whether in fact there had been only periods of exposure to urbanisation (as a consequence of migratory labour practices) and what was the duration to such exposure, (either more or less than 10 years). Since many Blacks were referred from rural hospitals, a distinction needed to be made between those who were strictly urban, strictly rural and those who though rural based, had experienced urbanisation for a period sufficiently long to have been influenced by it. 10 years was considered reasonable and arbitrarily used as a designation, based on the study by Vlaicu et al. (1976).

6.2 EDUCATION STANDARDS

All information was processed to establish whether a patient had no formal schooling, a primary school education, a secondary school education or a tertiary education.

6.3 OCCUPATION

A patient was considered to have a sedentary occupation if he had a job for at least 8 hours per working day which did not demand any physical activity. If the patient's job required him to perform on the basis of physical activity, then this was considered to be a manual occupation.

6.4 SMOKING PATTERN

A patient was considered as a previous smoker if he had stopped smoking for at least a year. A patient was considered a mild smoker if he smoked less than 5 cigarettes per day, irrespective of the length of time he smoked. A moderate smoker was one who smoked 5 - 20 cigarettes a day for a period of less than 15 years. Anything above that was considered as excessive smoking.

There are no established criteria for the determination of smoking patterns. Most studies consider subjects as either smokers or nonsmokers. Since smoking is a major risk factor for atherogenesis and as this study investigates an emergent phase of the disease, it was decided to stratify the smoking habits of patients to determine what preliminary evidence may emerge between races with different levels of the disease. The classification was arbitrarily determined .

Further analysis of the pattern of smoking depended on the specific answers volunteered by patients with respect to type, number of cigarettes smoked and the period of the smoking habit.

6.5 DRINKING PATTERN

A patient was considered a previous drinker if he had stopped drinking for at least a year and a mild drinker if he drank the equivalent of 2 tots at a time, either on a daily basis, on weekends or occasionally, irrespective of the period of drinking. A heavy drinker was one who consumed alcohol excessively (the equivalent of 4 tots and over) at any sitting, either on a daily basis or weekends. Anything between these 2 extremes was regarded as moderate. Further analysis of the pattern of drinking depended on the specific answers volunteered by patients with respect to type, consumption and period of drinking.

The criteria to establish drinking patterns is variable. Objectively is usually a difficulty and estimates are questionable. It was decided to stratify the data and the classification was arbitrarily determined.

6.6 DIAGNOSIS OF CEREBROVASCULAR DISEASE

A patient was considered to have had a cerebrovascular accident on the basis of a history and/or clinical evidence of a stroke.

6.7 DIAGNOSIS OF ISCHEMIC HEART DISEASE

Patients were considered to have ischemic heart disease on the basis of a history of angina and/or myocardial infarction, corroborated by the use of anti-ischemic medication and/or ECG evidence of ischemia. Any patient with evidence of ischemia on resting ECG without a history or without treatment for ischemia was included in the list of patients having ischemic heart disease. ECG evidence of ischemia included deep Q waves, large ST segment depression, left ventricular hypertrophy and large T waves.

6.8. DIAGNOSIS OF HYPERTENSION

A patient was considered to be hypertensive on the basis of a history of hypertension corroborated by a history of treatment for the condition. If a patient without a history of hypertension and medication for the condition had a persistently elevated blood pressure of greater than 140/100 in the ward then the patient was considered to be hypertensive for the purposes of this study. On this basis patients would fall into the moderate to severely hypertensive category and not into the mildly hypertensive category. There is no clear evidence that cardiovascular mortality is affected in mild hypertension.

6.9 DIAGNOSIS OF DIABETES

A patient was considered as diabetic on the basis of a history of diabetes corroborated by a history of dietary control and/or treatment with oral hypoglycaemic agents or injections of insulin. If a patient without a history of diabetes and treatment with hypoglycaemic agents or insulin had a fasting blood glucose level of greater than 7,8 mmol/l or a random blood glucose level of greater than 11,1 mmol/l, then for the purposes of this study the patient was considered as diabetic.

6.10 DIAGNOSIS OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

The diagnosis attributed to each patient in the study was one which indicated the level of atherosclerotic vascular involvement in the extracranial extracoronary circulation as determined on clinical, ultrasonic doppler and angiographic findings with confirmation at surgery on the basis of macroscopic and microscopic information. Where occlusive atherosclerotic peripheral vascular disease occurred in the aorto-iliac, femoro-popliteal and tibio-peroneal segments these were accordingly separated in the analysis of the anatomical distribution.

Due to the poor quality of data obtained on the dietary history, this was excluded from further analysis.

7. ASSUMPTIONS

It was assumed that the information pertaining to the influence of urbanisation, the alcohol and smoking patterns of patients, their levels of education, their work history and their past medical and drug history was reliably reported.

8. LIMITATIONS

- 8.1** While this study aims to establish the emergence of atherosclerosis in the peripheral vascular beds of Blacks seen at the Vascular Service in Durban it is not possible to establish the extent to which the disease exists in the Black population as a whole.
- 8.2** It is not possible to make a true comparison of the extent of the disease between Blacks, Whites and Indians since not all patients with the disease would have presented at the Vascular Service.
- 8.3** It is not possible to definitively state with the information available and in the absence of specialised tests that atherosclerosis was limited to the level of vascular involvement described and that other parts of the vascular tree had not been afflicted by atherosclerosis.
- 8.4** The sample size may have a limiting effect on the identification of any significant patterns associated with the emergence of peripheral vascular disease in Blacks and/or any significant differences that may exist between race groups and/or specifically with different anatomical segments.
- 8.5** The length of time covered in this study may have a limiting effect on the identification of any significant patterns associated with the emergence of atherosclerotic peripheral vascular disease in Blacks and its relative importance with respect to the emergence of atherosclerotic extracranial cerebral and coronary vessel disease as may be found in other race groups. If this study had been a cohort with a community element and different ages had been studied more information could have been yielded with respect to the natural history of atherosclerosis.
- 8.6** It was anticipated at the very outset of the study that the determination of control groups would be a serious problem. It is for this reason that no firm decisions were made on control studies in the protocol.

The determination of an ideal control group is crucial if it is to have significant benefit in a study of this nature. The purpose of this is to establish an objective standard against which to compare the study group. This is essential if the effect of variables between the study and control groups are to be established, for the correct deductions and interpretations to be made.

It, therefore, follows that if there is an error in the selection of controls, this would have a negative effect on the deductions and interpretations that may follow and consequently on the outcome of the study.

In this study an attempt was made to establish control groups on Whites, Indians and Blacks. This included 10 Whites, 8 Indians and 20 Blacks and the results have been summarised in Annexure 3. Due to these small numbers no statistical analyses were performed and they were not used in this study.

Control studies were abandoned for the following reasons: Firstly, a control group should be a representative sample of the population from which the cases were recruited. This could not be done. Many of the patients came from rural-based hospitals.

The ideal control of these patients should have included control groups from rural-based hospitals; alternatively to use patients from rural-based hospitals present in the local hospital wards. This was not possible because patients were either very unwell and unable to undergo tests not related to their condition or they did not stay in hospital long enough for tests to be done. In the case of White patients most subjects were between the ages of 60 and 80 years. To get control groups belonging to this age range who were normal and in whom there was no vascular disease was also a great difficulty.

Secondly, atherosclerosis is a chronic disease that emerges insidiously in people. The study was not restricted to atherosclerosis in any one part of the vasculature, but looked at the whole vascular tree. Therefore, unambiguous evidence of the absence of

atherosclerosis within the vasculature was essential if the control groups were to provide meaningful deductions and interpretations. The importance of this was illustrated in the case of a subject included in the original control group who is known to have later manifested with ischemic heart disease and who subsequently underwent coronary bypass surgery.

Thirdly, in the view of the above it was essential to confirm that the control groups were free of atherosclerosis. Clinical studies alone were inadequate and not definitive enough. Invasive studies in the form of atheriography were impractical. This implies that ultrasonic doppler studies and / or carotid duplex scans would have to be done on all patients in the control group for objective evidence of normal vessels. In terms of costs, time, personnel and facilities these studies could not be justified, even on the hospital or vascular service budget.

Fourthly, given the time and nature of the tests needed, which also required subjects to fast prior to blood tests, patient co-operation was a difficulty.

Fifthly, if control groups were selected from normal people outside the hospital environment, there was the problem of differences in socio-economic status between the two groups, which also would have detracted from an ideal control group.

For these reasons, it was firmly believed that the control group would have been seriously flawed and subject to severe criticism in the final analysis. The value of the results in the study group would have been adversely affected by a poorly selected control group.

The decision was, therefore, made to let the results of the study group, particularly those of a socio-environmental nature be descriptive and be independently analysed; and those of a biochemical nature to be analysed in accordance with normally accepted reference values.

In the final analysis it was accepted that no definitive conclusions could be made on the findings in this study and all observations, interpretations and postulates would be limited by this.

9. **STATISTICAL METHODS**

Descriptive statistics consisting of means and standard deviations for continuous data and frequencies and percentages for categorical data were calculated for all variables. Descriptive results were stratified according to race, gender and age.

For comparison of categorical data the Chi-square test was applied. Students' unpaired t-tests were used to compare two groups (e.g. smokers v non-smokers) in respect of continuous data (lipid results), while Analysis of Variance was used to compare more than two groups (e.g. comparison of the 3 race categories).

A significance level of 0.05 was used for all statistical tests, unless where otherwise stated.

Multivariate Analysis of Variance was applied to the lipid results to determine which of the factors (smoking, diabetes, hypertension, occupation or race) were significantly associated with the outcome.

CHAPTER FOUR

RESULTS

'HOW LUCKY I AM. WHENEVER I MAKE A MISTAKE PEOPLE ARE SURE TO DISCOVER IT.'
(CONFUCIUS)

The results of this study are presented in two sections. The first section reflects the results of the retrospective study and sets out the epidemiological aspects of chronic peripheral vascular disease as seen at the Vascular Service in Durban.

The second section reflects the results of the prospective study and sets out the socio-economic, clinical and biochemical aspects of the study.

1. RESULTS OF THE RETROSPECTIVE STUDY

Results of this study are set out hereunder.

1.1 CAUSES OF PERIPHERAL VASCULAR DISEASE IN DURBAN (1981 - 1986)

Table 1 presents the data relating to the causes of peripheral vascular disease as seen at the Vascular Research Laboratory in Durban for the period 1981 - 1986.

TABLE 1 CAUSES OF PERIPHERAL VASCULAR DISEASE IN DURBAN (1981 - 1986)

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Atherosclerosis	871	96,9	363	90,5	740	84,6	1974	92,3
Large vessel arteritis	5	0,5	5	1,3	83	9,5	93	4,3
Distal Vessel Occlusive disease	23	2,6	33	8,2	52	5,9	83	3,4
TOTAL	899	100	401	100	875	100	2175	100

STATISTICS

$$x^2 = 121,45$$

Significant at 0,001 level

Meaning: Cause is related to race.

Significance: Atherosclerosis appears to be significantly higher in all race groups. Whites show significantly higher atherosclerosis. Blacks show significantly higher large vessel arteritis and distal vessel occlusive disease. Whites show the lowest distal vessel occlusive disease.

1.2 PATHOLOGICAL DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE BETWEEN RACES IN DURBAN (1981-1986)

Table 2 focuses on those patients in Table 1 who presented with atherosclerotic peripheral vascular disease and illustrates the pathological distribution in the form of aneurysmal disease and occlusive disease.

TABLE 2 PATHOLOGICAL DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE IN DURBAN (1981 - 1986)

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Aneurysmal	270	31,0	23	6,3	107	14,5	400	20,3
Occlusive Disease	601	69,0	340	93,7	633	85,5	1574	79,7
TOTAL	871	100,0	363	100,0	740	100,0	1974	100,0

STATISTICS

$$\chi^2 = 121,15$$

Significant at 0,001 level

Meaning: Type of pathology is dependent upon race.

Significance: All race groups have significantly more occlusive disease. Whites have significantly more aneurysms than expected compared to Blacks and Indians. Indians have significantly higher occlusive disease.

1.3 ANATOMICAL DISTRIBUTION OF ATHEROSCLEROTIC ANEURYSMAL DISEASE BETWEEN RACES IN DURBAN (1981 - 1986)

Table 3 presents the data relating to the anatomical distribution of aneurysmal disease as seen in Table 2 between the aortic and peripheral segments.

TABLE 3 ANATOMICAL DISTRIBUTION OF ANEURYSMAL DISEASE IN DURBAN (1981 - 1986)

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Aortic Segment	250	92,6	16	69,6	54	50,5	320	80,0
Peripheral Segment	20	7,4	7	30,4	53	49,5	80	20,0
TOTAL	270	100,0	23	100,0	107	100,0	400	100,0

STATISTICS $\chi^2 = 86,7$
Significant at 0,001 level

Significance: Aortic segment aneurysms are highest among Whites. There are significantly fewer peripheral segment aneurysms among Whites and Indians. There are significantly more peripheral segment aneurysms in Blacks and fewer aortic segment aneurysms in Blacks than in Whites and Indians.

1.4 ANATOMICAL DISTRIBUTION OF ATHEROSCLEROTIC OCCLUSIVE DISEASE BETWEEN RACES IN DURBAN (1981 - 1986)

Table 4 presents data relating to the anatomical distribution of occlusive disease in the extracranial, aorta-iliac, femoro-popliteal and tibio-peroneal segments between races.

TABLE 4: ANATOMICAL DISTRIBUTION OF ATHEROSCLEROTIC OCCLUSIVE DISEASE IN DURBAN (1981 - 1986)

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Extracranial	141	21,1	77	21,0	22	3,3	240	14,1
Aorto-iliac	269	40,3	128	35,0	287	43,0	684	40,2
Femoro-popliteal	187	28,0	177	48,4	280	41,9	584	34,3
Tibio-peroneal	71	10,6	44	12,0	80	12,0	195	11,5
TOTAL	668	100,0	366	100,0	669	100,0	1703	100,0

STATISTICS $\chi^2 = 40,70$
Significant at 0,001 level

Meaning: There is a difference in the distribution of occlusive disease between segments among Whites, Indians and Blacks.

Significance: There is significantly higher extracranial cerebrovascular segment disease among Whites. There is significantly higher aorto-iliac and femoro-popliteal segment disease in Blacks.

The overall anatomical distribution of occlusive disease may be summarised as follows:

In Whites the disease is commonest in the aorto-iliac segment (40,3%) reducing to 28% in the femoro-popliteal segment and 21,1% in the extracranial cerebrovascular segment. In Blacks the disease is commonest in the aorto-iliac segment (43%) and femoro-popliteal segment (41,9%). Thus reduces to 12% in the tibio-peroneal segment and is uncommon in the extracranial cerebrovascular segment (3,3%). In Indians the disease is commonest in the femoro-popliteal segment (48,4%). This reduces to 35% in the aorto-iliac segment, 21% in the extracranial cerebrovascular segment and 12% in the tibio-peroneal segment.

1.5 GENDER DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE BETWEEN RACES IN DURBAN (1984-1986)

Table 5 presents data relating to the distribution of atherosclerotic peripheral vascular disease in each gender and between the races on 1268 patients seen during the period 1984 - 1986.

TABLE 5 GENDER DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE BETWEEN RACES IN DURBAN (1984-1986)

Race	Female		Male		Total	
	No.	%	No.	%	No.	Ratio
						F
Whites	152	34,9	283	65,1	435	1 : 1,9
Indians	45	17,8	208	82,2	253	1 : 4,6
Blacks	103	17,8	477	82,2	580	1 : 4,6
TOTAL	300		968		1268	

Table 5 illustrates that there is a male preponderance of the disease in all race groups. In Indians and Blacks the ratio is 1 : 4,6 while in Whites the ratio between male and females is 1 : 1,9.

The male preponderance of the disease exists in both aneurysmal and occlusive disease and in the different vascular segments.

1.6 **AGE DISTRIBUTION AT PRESENTATION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE BETWEEN RACES IN DURBAN (1984 - 1986)**

Table 6 presents the data relating to the distribution of atherosclerotic peripheral vascular disease between races according to age on 1268 patients seen for the period 1984 - 1986.

TABLE 6 AGE DISTRIBUTION AT PRESENTATION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE BETWEEN RACES IN DURBAN (1984 - 1986)

AGE DISTRIBUTIONS	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
20 - 29 years	1	0,2	1	0,4	12	2,1	14	
30 - 39 years	4	0,9	9	3,6	49	8,5	62	
40 - 49 years	21	4,8	46	18,2	115	19,8	182	
50 - 59 years	45	10,3	91	36,0	170	29,3	306	
60 - 69 years	165	37,9	76	30,0	159	27,4	400	
70 - 79 years	161	37,0	26	10,3	56	9,7	243	
80 - 89 years	35	8,1	3	1,2	15	2,6	53	
>90 years	3	0,7	1	0,4	4	0,7	8	
TOTAL	435	100	253	100	580	100	1268	

The results show that the majority of patients present between ages of 50 years and 79 years. Presentation can be between 30 years and 49 years and it is the Black patient and to a lesser extent the Indian patient who present this early. Presentation can also be between 80 years and 89 years and it is the White patient who presents this late. In Blacks the mean age of presentation is $55,28 \pm 12,54$ years. In Indians the mean age of presentation is $57,52 \pm 10,65$ years and in Whites the mean age of presentation is $67,60 \pm 10,11$ years.

2. RESULTS OF THE PROSPECTIVE STUDY

Data derived from the questionnaire and from the blood investigations were processed and statistically analysed. It was decided not to include female subjects on account of their small numbers. The sample size was therefore restricted to 302 male patients consisting of 100 Whites, 97 Indians and 105 Blacks. Information relating to the marital status and the dietary history was also excluded from further analysis.

Results of this study are set out hereunder.

2.1 AGE DISTRIBUTION AT PRESENTATION OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 7 presents the age distribution at presentation of White, Indian and Black patients.

TABLE 7 AGE DISTRIBUTION AT PRESENTATION OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Age	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
20 - 29 years	0	0,0	0	0,0	1	1,0	1	0,3
30 - 39 years	1	1,0	1	1,0	4	3,8	6	2,0
40 - 49 years	7	7,0	15	15,5	26	24,8	48	15,9
50 - 59 years	13	13,0	40	41,2	39	37,1	92	30,4
60 - 69 years	49	49,0	33	34,0	25	23,8	107	35,4
70 - 79 years	29	29,0	8	8,3	8	7,6	45	14,9
80 - 89 years	1	1,0	0	1,0	2	1,9	3	1,0
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

Black patients presented between the ages of 21 and 89 years. White patients presented between the ages of 39 and 89 years and Indian patients between the ages of 31 and 80 years.

The majority of Black patients were between the ages of 41 and 70 years (24,8%, 37,1% and 23,8% in the fourth, fifth and sixth decades respectively). The majority of White patients were between 51 and 80 years (13%, 49% and 29% in the fifth, sixth and seventh decades respectively). Indian patients mainly presented between 41 and 80 years (15,5%, 41,2% and 34% in the fourth, fifth and sixth decades respectively). The peak age of presentation for the total sample was between the fifth and sixth decades (30,4% and 35,4% respectively). In general Black patients had an earlier age of presentation than either Indian or White patients.

2.2 ANATOMICAL DISTRIBUTION OF PERIPHERAL VASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS

Table 8 presents the data relating to the distribution of atherosclerotic peripheral vascular disease between races.

TABLE 8 ANATOMICAL DISTRIBUTION OF PERIPHERAL VASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Extra cranial	31	31,0	25	25,8	2	1,9	58	19,2
Abdominal Aortic Aneurysm	18	18,0	7	7,2	9	8,6	34	11,3
Aorta-iliac	31	31,0	4,0	41,2	55	52,4	126	41,7
Femoro-popliteal	20	20,0	25	25,8	39	37,2	84	27,8
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

Extracranial cerebrovascular is distributed mainly among the White and Indian patients seen. The disease is extremely rare in Black patients with only 2 patients being seen. Aorta iliac and femoro-popliteal disease was most commonly seen in Black and Indian patients while in White patients the aorta was affected to a lesser extent. Abdominal aortic aneurysms also occurred in Indian and Black patients but to a lesser extent than in Whites.

Therefore, in the sample of White patients selected, the disease is distributed throughout the vasculature in the extracranial cerebrovascular, aorta-iliac, and femoro-popliteal segments. The distribution in Indian patients is very similar. In Blacks the aorta-iliac and femoro-popliteal segments were mainly affected with extracranial cerebrovascular disease being uncommon. In all patients the disease is mainly occlusive.

There were no patients with tibio-peroneal disease in the sample.

2.3 ASSOCIATED ATHEROSCLEROTIC CEREBRAL AND CORONARY VASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Tables 9 and 10 illustrate the associated relationship of cerebrovascular disease and ischemic heart disease with patients who have chronic peripheral vascular disease.

TABLE 9 ASSOCIATED ATHEROSCLEROTIC CEREBROVASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Cerebro Vascular Disease: Nil	78	78,0	84	86,6	101	96,2	263	87,1
Cerebro Vascular Disease: Present	22	22,0	13	13,4	4	3,8	39	12,9
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

TABLE 10 ASSOCIATED ATHEROSCLEROTIC CORONARY VASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Ischemic Heart Disease: Nil	54	54,0	73	75,3	102	97,1	229	75,8
Ischemic Heart Disease: Present	46	46,0	24	24,7	3	2,9	73	24,2
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

Cerebrovascular disease occurred in 12,9% of the total sample. 22% of these patients were Whites, 13,4% were Indians and 3,8% were Blacks.

Ischemic heart disease occurred in 24,2% of the total sample. Of this Whites had the commonest association occurring in 46% of cases. In Indians 24,7% of patients had ischemic heart disease while in Blacks the disease was rare occurring in 2,9% of patients.

2.4 CLINICAL PRESENTATION OF PERIPHERAL VASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS

Table 11 illustrates the clinical presentation of White, Indian and Black patients presenting with chronic peripheral vascular disease.

TABLE 11 CLINICAL PRESENTATION OF PERIPHERAL VASCULAR DISEASE IN WHITE, INDIAN AND BLACK PATIENTS

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Foot Ulcers	5	5,0	8	8,3	50	47,6	63	20,9
Foot Gangrene	6	6,0	9	9,3	34	32,3	49	16,2
Claudication	34	34,0	52	53,6	16	15,2	102	33,8
Rest Pain	10	10,0	4	4,1	2	1,9	16	5,3
Impotence	2	2,0	1	1,0	1	1,0	4	1,3
Abdominal Mass	13	13,0	2	2,1	0	0,0	15	5,0
Abdominal Pain	3	3,0	3	3,1	1	1,0	7	2,3
TIA	27	27,0	18	18,6	1	1,0	46	15,2
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

The results indicate that foot ulcers and foot gangrene were the commonest forms of presentation in Black patients. Claudication was the commonest symptom in White and Indian patients. The other symptoms of abdominal pain, abdominal mass and transient ischemic attacks occurred in relation to the site of pathology in those White, Indian and Black patients who presented with these symptoms.

2.5 INFLUENCE OF URBANISATION ON WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 12 presents the degree of urbanisation of White, Indian and Black patients with peripheral vascular disease.

TABLE 12 INFLUENCE OF URBANISATION ON WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Rural	2	2,0	1	1,0	13	12,4	16	5,3
Urban <10 years	0	0,0	0	0,0	29	27,6	29	9,6
Urban >10 years	0	0,0	0	0,0	37	35,2	37	12,3
Urban	98	98,0	96	99,0	26	24,8	220	72,9
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

Table 12 illustrates the degree of urbanisation in White, Indian and Black patients. 12,4% of Blacks gave a history suggestive of no urban environmental influences. All the remaining Black patients were exposed to some degree of urbanisation, 24,8% being totally urban, 35,2% having spent more than 10 years in an urban environment and 27,6% less than 10 years.

Almost all the White and Indian patients included in the sample had been exposed to long periods of urbanisation.

2.6 EDUCATION STANDARDS OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE.

Table 13 illustrates the educational standards of White, Indian and Black patients presenting with chronic peripheral vascular disease.

TABLE 13 EDUCATION STANDARDS OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Nil	0	0,0	5	5,2	45	42,9	50	16,6
Till Std 3	0	0,0	10	10,3	31	29,5	41	13,4
Std 4 - 6	11	11,0	66	68,0	21	20,0	98	32,6
Std 6 - 10	77	77,0	14	14,4	7	6,7	98	32,6
Tech	6	6,0	1	1,0	0	0,0	7	2,3
University	6	6,0	1	1,0	1	1,0	8	2,7
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

Table 13 illustrates the levels of education of White, Indian and Black patients with peripheral vascular disease. The majority of Black patients had either no formal education (42,9%) or did not exceed standard 6. Only 6,7% had studied between the standard 6 and 10 levels and only 1 patient had been to university. In Indian patients 5,2% had no formal schooling, 10,3% had up to a level of standard 3 education, 68,0% up to the standard 6 level and 14,4% up to the standard 10 level. One Indian patient had attended a technical college and another had a university education. Whites on the other hand all had a formal education. 11% had reached the standard 6 level, 77% the standard 10 level while 12% had each gone to technikon, college and university.

2.7 WORK STATUS OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 14 illustrates the work status of White, Indian and Black patients with peripheral vascular disease with the purpose of differentiating between sedentary and manual workers.

TABLE 14 DISTRIBUTION OF WORK STATUS OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Sedentary Workers	55	55,0	49	50,5	11	10,5	115	38,1
Manual Workers	45	45,0	48	49,5	94	89,5	187	61,9
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

Interestingly 89,5% of Black patients seen were physically active and only 10,5% had a sedentary-type occupation. Whites and Indians on the other hand appear to be equally distributed between sedentary and manual type occupations.

2.8 DRINKING PATTERN IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 15 presents the drinking history of White, Indian and Black patients with peripheral vascular disease.

TABLE 15 DRINKING PATTERN IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Never Drank	9	9,0	19	19,6	13	12,4	41	13,6
Previously Drank	20	20,0	27	27,8	21	20,0	68	22,5
1 - 10 years	4	4,0	7	7,2	9	8,6	20	6,6
11 - 20 years	17	17,0	13	13,4	16	15,2	46	15,2
21 - 30 years	26	26,0	18	18,6	26	24,8	70	23,2
31 - 40 years	12	12,0	9	9,3	15	14,3	36	11,9
Over	12	12,0	4	4,1	5	4,8	21	7,0
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

13,6% of patients never drank. Of this 9% were Whites, 19,6% Indians and 12,4% Blacks. 22,5% of patients volunteered a history of having stopped more than 5 years previously. Of these 20% were Whites, 27,8% Indians and 20% Blacks. Among the current drinkers, 6,6% had been drinking for up to 10 years. 15,2% up to 20 years, 23,2% up to 30 years, 11,9% up to 40 years and 7% had been drinking for over 40 years.

Table 16 illustrates the alcohol preference of White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 16 ALCOHOL PREFERENCE OF WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Never Drank	10	10,6	19	19,6	14	13,6	43	14,6
Beer	25	26,6	0,	0,0	2	1,9	27	9,2
Spirits	33	35,1	64	66,0	8	7,8	105	35,7
Wine	3	3,2	1	1,0	0	0,0	4	1,4
Zulu Beer	0	0,0	0	0,0	34	33,0	34	11,6
Beer and Spirits	2,3	24,5	13	13,4	8	7,8	44	15,0
Spirits and Zulu Beer	0	0,0	0	0,0	28	27,2	28	9,5
Beer and Zulu Beer	0	0,0	0	0,0	5	4,9	5	1,7
Beer, Spirits and Zulu Beer	0	0,0	0	0,0	4	3,9	4	1,4
TOTAL	94	100,0	97	100,0	103	100,0	294	100,0

Wine was the least preferred, whilst spirits was the drink of choice consumed by 35,7% of patients, of whom 66% were Indians, 35,1% Whites and 7,8% Blacks. Beer was preferred by White patients while beer and spirits were taken by 24,5% of White patients, 13,4% of Indian patients and 7,8% of Black patients. Zulu beer was taken by only 33% of Blacks and was not consumed at all by White and Indian patients. Zulu beer was taken in association with spirits

in 27,2% of Black patients, with beer in 4,9% of these patients and with beer and spirits in 3,9% of patients.

Table 17 illustrates the severity of drinking in White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 17 SEVERITY OF DRINKING IN WHITE, INDIAN AND BLACK PATIENTS WITH ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE.

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Zero	10	10,6	19	19,6	14	13,6	43	14,6
Mild	34	36,2	16	16,5	15	14,6	65	22,1
Moderate	46	48,9	36	37,1	55	53,4	137	46,6
Severe	4	4,3	26	26,8	19	18,5	49	16,7
TOTAL	94	100,0	97	100,0	103	100,0	294	100,0

22,1% of patients described themselves as mild drinkers (36,2% Whites, 16,5% Indians and 14,6% Blacks). 46,6% of patients were considered to be moderate drinkers (48,9% Whites, 37,1% Indians, 53,4% Blacks). 16,7% of patients were heavy drinkers (4,3% Whites, 26,8% Indians and 18,5% Blacks).

2.9 SMOKING PATTERNS OF WHITE, INDIAN AND BLACK PATIENTS WITH ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Table 18 presents the history of smoking in White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 18 HISTORY OF SMOKING HABITS IN WHITE, INDIAN AND BLACK PATIENTS WITH ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Never Smoked	6	6,0	7	7,2	6	5,7	19	6,3
Smoked	94	94,0	90	92,8	99	94,3	283	93,7
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

The majority of patients were smokers (93,7%). Only 6,3% of patients were non-smokers. In both smokers and non-smokers there was an equality of distribution between races.

Table 19 illustrates the smoking preference of White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 19 SMOKING PREFERENCE IN WHITE, INDIAN AND BLACK PATIENTS WITH ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Never Smoked	6	6,4	5	5,2	5	4,8	16	5,4
Cigarettes	73	72,7	90	92,8	32	30,8	193	65,4
Tobacco	9	9,6	0	0,0	18	17,3	27	9,2
Snuff	0	0,0	2	2,0	1	1,0	3	1,0
Cigarettes and Tobacco	6	6,4	0	0,0	48	46,1	56	19,0
TOTAL	100	100,0	97	100,0	104	100,0	295	100,0

Cigarettes were the commonest form of smoking in all race groups accounting for 65,4% of patients. Tobacco only (self rolled cigarettes) was smoked by 9,6% of Whites and 17,3% of Blacks. Cigarettes and tobacco was smoked by 46,1% of Blacks and 6,4% of Whites.

Table 20 illustrates the severity of smoking among White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 20: EXTENT OF SMOKING HABITS IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Never	6	6,4	7	7,2	6	5,8	19	6,4
Mild	5	5,3	28	28,9	56	53,9	89	30,2
Moderate	40	42,6	39	40,2	33	31,7	112	38,0
Severe	43	45,7	23	23,7	9	8,7	75	25,4
TOTAL	94	100,0	97	100,0	104	100,0	295	100,0

A total of 30,2% of patients considered themselves to be mild smokers. 37,9% were moderate and 25,4% were heavy smokers. Blacks were mainly mild and moderate smokers, Indians were mainly moderate smokers and Whites were mainly moderate and severe smokers.

2.10 ASSOCIATED HYPERTENSION AND DIABETES IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 21 illustrates the association of hypertension and diabetes in White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 21: ASSOCIATED HYPERTENSION IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Hypertension: Nil	49	49,0	50	51,6	89	84,8	188	62,3
Hypertension: Present	51	51,0	47	48,4	16	15,2	114	37,7
TOTAL	100	100,0	97	100,0	105	100,0	302	100,0

TABLE 22: ASSOCIATED DIABETES IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	White		Indian		Black		Total	
	No.	%	No.	%	No.	%	No.	%
Absent	88	88,0	62	63,9	94	89,5	244	80,8
Present	12	12,0	35	36,1	11	10,5	58	19,2
TOTAL	100	100,0	97	100,0	104	100,0	295	100,0

Tables 21 and 22 illustrate the association of hypertension and diabetes in White, Indian and Black patients with peripheral vascular disease. Hypertension was commonest in White patients occurring in 51% of cases, 48,5% of Indians and 15,2% of Blacks. Diabetes occurred even less commonly in Whites, Indians and Blacks (12%, 36,1% and 10,5% respectively). Indians, however, had diabetes to a greater extent than either Whites or Blacks.

2.11 URATE, FASTING GLUCOSE AND FASTING INSULIN LEVELS IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 23 presents the levels of urates, fasting glucose and fasting insulin in White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 23: URATES, FASTING GLUCOSE AND FASTING INSULIN LEVELS IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE (UNITS = MMOL/L)

	White		Indian		Black		Total	
	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	n
Urates	0,41 \pm 0,13	21	0,37 \pm 0,12	47	0,31 \pm 0,08	56	0,35 \pm 0,12	124
Fasting Glucose	5,79 \pm 2,78	78	8,01 \pm 5,08	85	4,39 \pm 1,22	84	6,08 \pm 3,75	247
Fasting Insulin	7,73 \pm 5,05	44	12,06 \pm 10,63	44	7,60 \pm 5,53	44	9,18 \pm 7,67	143
FIGM	6,68 \pm 1,69		9,38 \pm 2,18		6,50 \pm 1,69		7,34 \pm 1,88	

FIGM = Fasting Insulin Geometric Mean

Note: Log transformations were applied to fasting insulin to normalise the distributions, hence geometric means were reported.

Urates for Black and Indian patients fall well within the normal range while the levels for White patients are on the upper level for normal at $0,41 \pm 0,13$, but Blacks differed significantly from Whites and Indians (overall $F = 8,02$, $p = 0,0005$).

The fasting glucose levels for the total sample are also within the normal range and so are the levels for White and Black patients. Indian patients, however, have a fasting glucose level of $8,01 \pm 5,08$ which exceeds the normal range. All three race groups differed significantly from each other ($F = 23,81$, $p < 0,0001$).

Similarly the fasting insulin levels for the total sample and for White and Black patients fall within the normal range. The fasting insulin levels in Indian patients exceeded normal ($12,06 \pm 10,63$) and was significantly higher than that for Whites and Blacks (overall $F = 6,85$, $p < 0,0014$).

2.12 LIPOPROTEIN LEVELS IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Table 24 presents the lipoprotein levels in White, Indian and Black patients with atherosclerotic peripheral vascular disease.

TABLE 24 : FASTING LIPOPROTEIN LEVELS IN WHITE, INDIAN AND BLACK PATIENTS WITH PERIPHERAL VASCULAR DISEASE (UNITS = MMOL/L)

	White		Indian		Black		Total	
	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	n
Triglycerides	$2,39 \pm 1,44$	73	$2,36 \pm 1,66$	71	$1,37 \pm 0,75$	82	$2,02 \pm 1,40$	226
Cholesterol	$5,99 \pm 1,46$	79	$6,02 \pm 1,60$	72	$4,25 \pm 1,12$	82	$5,39 \pm 1,63$	233
LDLc	$4,07 \pm 1,68$	41	$4,03 \pm 1,30$	48	$2,74 \pm 1,06$	62	$3,52 \pm 1,47$	151
HDLc	$0,89 \pm 0,33$	44	$0,85 \pm 0,26$	51	$0,92 \pm 0,34$	67	$0,89 \pm 0,32$	162
Tc:HDLc	$7,32 \pm 2,43$	42	$7,55 \pm 2,47$	50	$5,24 \pm 2,29$	66	$6,53 \pm 2,61$	158

LDLc = LDL Cholesterol; HDLc = HDL Cholesterol; Tc:HDLc = Total Cholesterol:HDL Cholesterol

The fasting triglyceride levels for the total sample exceeds the normal range and is $2,02 \pm 1,40$. Whites and Indians mainly contribute to this with their triglyceride levels being $2,39 \pm 1,44$ and $2,36 \pm 1,66$ respectively. The triglyceride levels of Black patients is significantly lower at $1,37 \pm 0,75$. Blacks differed significantly from Whites and Indians ($F = 14,97$, $p <$

0,0001) The total cholesterol value for the total sample is at the upper limit of the normal range ($5,39 \pm 1,63$). However, by comparison the levels for Whites and Indians ($5,99 \pm 1,46$ and $6,02 \pm 1,60$ respectively) are higher than that for Black patients ($4,25 \pm 1,12$). Blacks differed significantly from Whites and Indians. There were no differences between Whites and Indians ($F = 41,76$, $p \leq 0,0001$). Similarly the LDL cholesterol level for the total sample is within the normal range ($3,52 \pm 1,47$). By comparison the levels for Whites and Indians ($4,07 \pm 1,68$ and $4,03 \pm 1,30$) are higher than that for Blacks ($2,74 \pm 1,06$). Blacks, however, differed significantly from Whites and Indians ($F = 17,41$, $p < 0,0001$). HDL cholesterol levels range from $0,89 \pm 0,33$ (Whites) to $0,92 \pm 0,34$ (Blacks) which falls to the lower limits of normal. Indians had a level of $0,85 \pm 0,26$ while the level for the total sample was $0,89 \pm 0,32$. There was no significant difference between races ($F = 0,71$). Total cholesterol: HDL cholesterol was the lowest in Blacks ($5,24 \pm 2,29$) while in Whites and Indians it was higher at $7,32 \pm 2,43$ and $7,55 \pm 2,47$ respectively. It was $6,53 \pm 2,61$ for the total sample. Blacks differed significantly from Whites and Indians ($F = 16,59$, $p < 0,0001$).

2.13 RELATIONSHIP BETWEEN LIPOPROTEIN LEVELS AND ASSOCIATED CONDITIONS IN PATIENTS WITH ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Table 25 is an analysis of covariance used to describe the relationship between lipoproteins and the following independent variables of race, occupation, smoking, hypertension and diabetes. Age was used as a covariate in the model.

TABLE 25 RELATIONSHIP BETWEEN LIPOPROTEINS AND INDEPENDENT VARIABLES IN PATIENTS WITH ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Independent Variables	TOTAL CHOLESTEROL		TRIGLYCERIDE		LDLc		HDLc		Te/HDLc	
	F-Value	P-Value	F-Value	P-Value	F-Value	P-Value	F-Value	P-Value	F-Value	P-Value
Race	5,71	0,0039	3,23	0,0414	5,54	0,0049	0,08	0,9208	3,85	0,0237
Occupation	0,06	0,8051	0,62	0,4305	0,00	0,9514	0,71	0,4004	1,70	0,1940
Smoking	1,80	0,1807	1,76	0,1862	1,33	0,2516	0,35	0,5536	0,16	0,6868
Hypertension	1,01	0,3170	1,37	0,2430	0,49	0,4832	1,34	0,2485	1,03	0,3109
Diabetes	1,05	0,3071	6,86	0,0095	1,21	0,2742	3,11	0,0800	0,69	0,4069
Age	0,49	0,8160	1,57	0,1565	0,58	0,7471	0,75	0,6134	1,46	0,1956
Race x Age	0,61	0,7881	1,57	0,1270	1,03	0,4173	0,51	0,8448	0,40	0,9177

Race was the only significant factor associated with total cholesterol ($p = 0,0039$), LDL cholesterol ($p = 0,0049$) and Total cholesterol: HDL cholesterol ($p = 0,0237$). Triglycerides were significantly associated with race ($p = 0,0414$) and with diabetes ($p = 0,0095$). The race x age interaction was not significant.

3. GRAPHIC ILLUSTRATIONS OF ASPECTS OF THE RETROSPECTIVE AND PROSPECTIVE STUDIES

Selected results from the tables above in both the retrospective and prospective studies can, however, be more easily interpreted if represented graphically as figures 1, 2 and 3.

Figures 1 and 2 express graphically the data on the pattern and prevalence of atherosclerotic vascular disease in White, Indian and Black patients included in the retrospective and prospective studies. The data has already been described in detail in association with the relevant tables. Figure 1 using race as the independent variable shows the distribution of atherosclerosis for each race group in the different vascular segments and vascular beds. Figure 2 using vascular segment/vascular bed as the independent variable and using the same data shows the distribution of atherosclerosis in the different vascular segments/vascular beds for each race group. These graphic illustrations show that the prospective study sample is not strictly representative of the retrospective study sample.

Figure 3 graphically expresses data on the distribution of lipoproteins in each race group in the prospective study. The data has already been described in detail in relation to the relevant table. Figure 3 does, however, show that the total cholesterol, LDL cholesterol, triglycerides and total cholesterol: HDL cholesterol are reduced in Blacks compared to Whites and Indians, while HDL cholesterol is uniformly low in all 3 race groups.

4. HISTOLOGY FINDINGS IN THE RETROSPECTIVE AND PROSPECTIVE STUDIES

Histology studies have confirmed atherosclerosis in both the retrospective and prospective studies. Typically there was intimal thickening with fibrolipid degeneration, usually accompanied by cholesterol clefts and foam cells. Scattered among the debris were macrophages consisting of monocytes. This debris consisted of haemorrhagic areas with haemosideria. Foci of calcification were evident and in some cases organizing thrombotic lesions were also present. The extent to which these thrombi occluded the vessels varied.

The above description was made for both occlusive and aneurysmal disease, except that they were more pronounced in aneurysms. In the case of aneurysms the media was usually totally destroyed and associated with fibrotic and granular tissue.

These findings were similar in all the race groups and in the different anatomical segments.

FIG.: 1 VASCULAR DISTRIBUTION OF ATHEROSCLEROSIS IN THE DIFFERENT RACE GROUPS IN THE RETROSPECTIVE AND PROSPECTIVE STUDIES

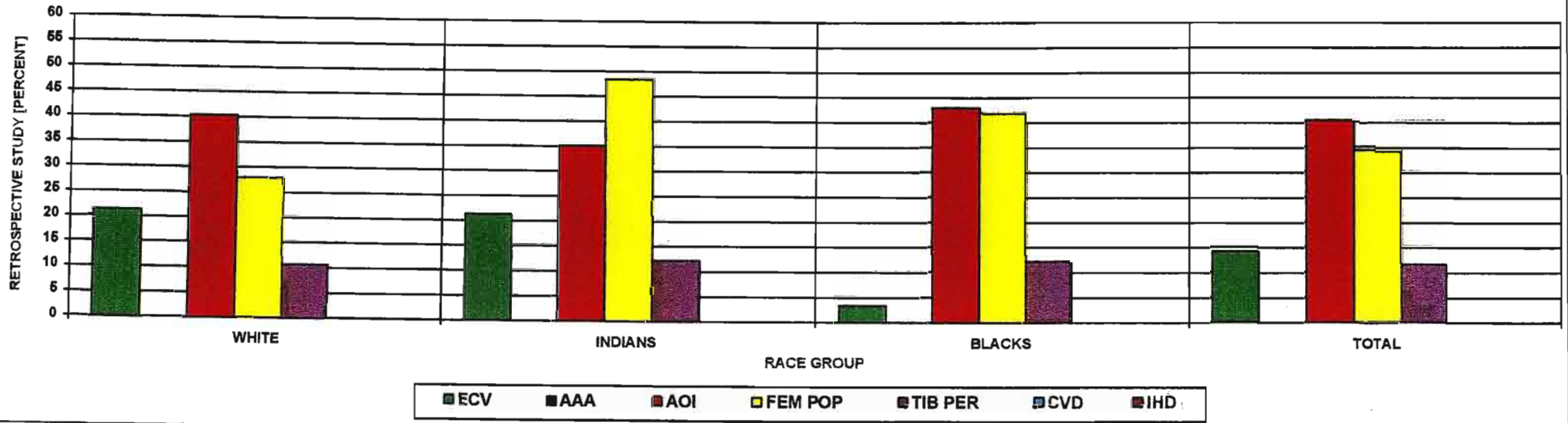


FIG.: 1 VASCULAR DISTRIBUTION OF ATHEROSCLEROSIS IN THE DIFFERENT RACE GROUPS IN THE RETROSPECTIVE AND PROSPECTIVE STUDIES

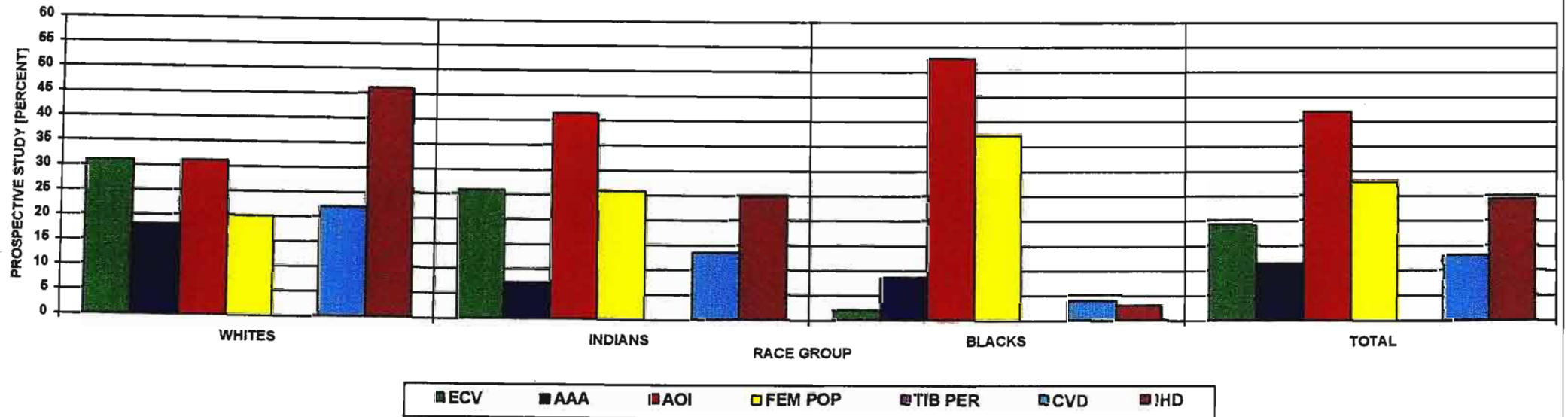


FIG. 2 INTER-RACIAL DISTRIBUTION OF ATHEROSCLEROSIS IN THE DIFFERENT PERIPHERAL VASCULAR SEGMENTS AND VASCULAR BEDS IN THE RETROSPECTIVE AND PROSPECTIVE STUDIES

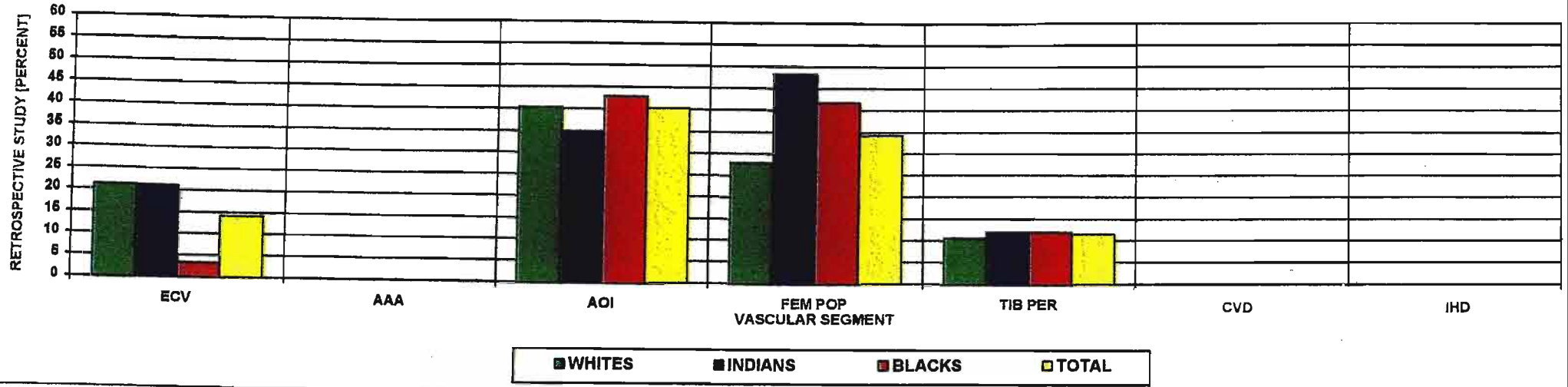


FIG. 2 INTER-RACIAL DISTRIBUTION OF ATHEROSCLEROSIS IN THE DIFFERENT PERIPHERAL VASCULAR SEGMENTS AND VASCULAR BEDS IN THE RETROSPECTIVE AND PROSPECTIVE STUDIES

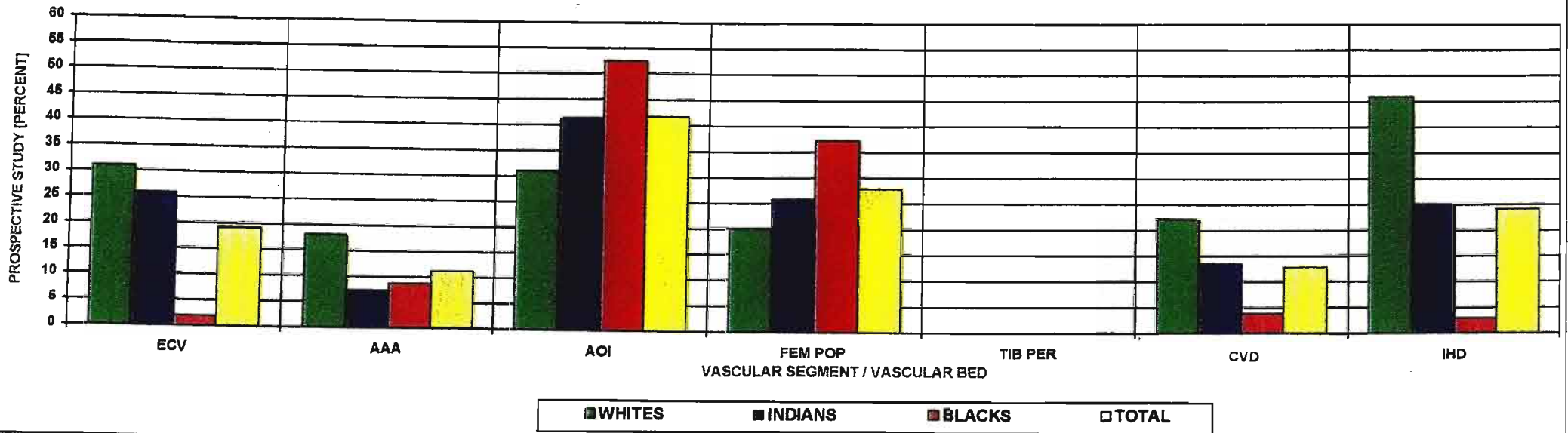
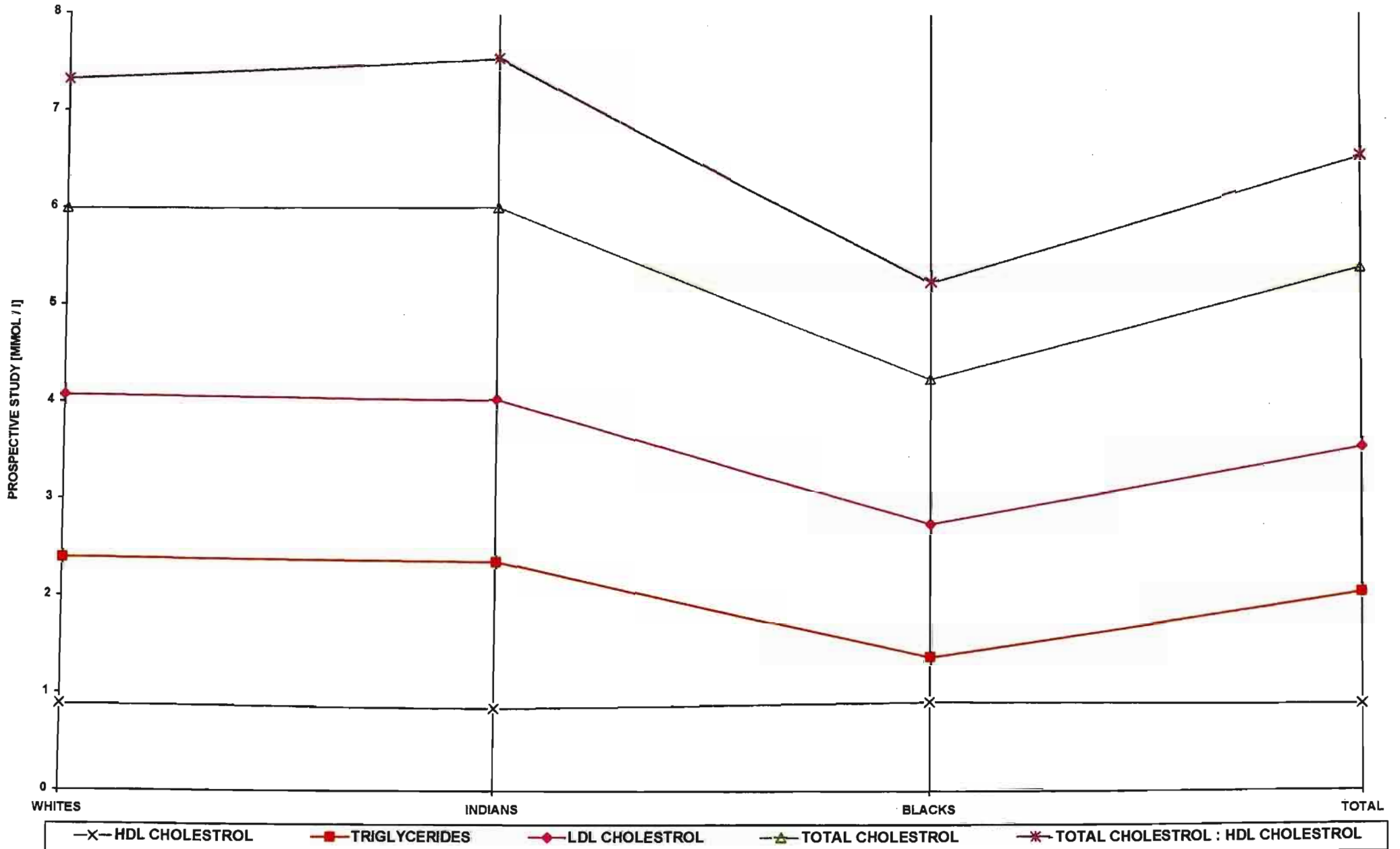


FIG.: 3 INTER-RACIAL DISTRIBUTION OF LIPOPROTEINS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE IN THE PROSPECTIVE STUDY



CHAPTER FIVE

DISCUSSION

1. INTRODUCTION

'WHAT PASSES FOR KNOWLEDGE IS OFTEN NO MORE THAN WELL-ORGANISED IGNORANCE.' (ANON)

Even though current scientific knowledge of cardiovascular atherosclerosis has developed to new heights at the biochemical and molecular level there is still much to be understood about the natural history and development of atherosclerosis in man. Due to the insidious nature of the disease and the difficulty in detecting its presence in the early stages, little is known about the conditions under which its development within the vasculature, both individually and in population groups as a whole, is triggered, established and controlled.

The development of atherosclerosis in man is an extremely complex and polyfunctional process which is not easily understood even at the present time. The unique geopolitical situation that existed in South Africa together with the current social changes taking place have provided a biological model which forms the basis of this study. The results raise interesting possibilities with major implications for our understanding of the genesis of atherosclerosis in man even at the biochemical and molecular levels.

2. LIMITATIONS IN THE STUDY

This is not a true epidemiological study and in this respect does have various limitations. Consequently the deductions and interpretations that can be made must not be over emphasised.

Firstly, the samples in this study may not be equally representative of the number of patients with chronic peripheral vascular disease in the various population groups. It is therefore not possible on the data obtained on both the retrospective and prospective studies to make meaningful conclusions on the prevalence or incidence of the disease in the various population groups in Durban, in Kwa Zulu Natal or in South Africa. While the Vascular Service treats patients referred from provincial hospitals throughout Kwa Zulu Natal there are also many patients with the disease who would have attended private medical centres in Durban and Pietermaritzburg.

It is believed that by comparison, and because of socio-economic reasons not many patients would have attended these centres, the only exceptions being those able to afford private medical care, on medical/insurance plans and who were younger and economically active. The majority of these would have been White and to some extent Indians as well.

Other patients not to have attended the Vascular Service would have been those who did not have medical treatment for chronic peripheral vascular disease on account of socio-economic reasons, transportation difficulties, access to medical facilities, incorrect diagnoses and non referrals. The majority of these would have been Black.

Nevertheless, in spite of the foregoing it is believed that the samples in both the retrospective and prospective studies are sufficiently representative of the number of patients seen at the Vascular Service in Durban and as they represent a selected group of patients referred from different hospitals throughout Natal for problems specifically related to chronic peripheral vascular disease, the results are sufficiently significant for valid deductions and interpretations to be made as a basis for further study.

Secondly, an aspect of this study which may be controversial is the absence of categorical evidence in the form of definitive studies to exclude atherosclerotic involvement of the cerebral and coronary vascular beds, particularly in Black patients under study. Such an exercise would have been impractical, extremely expensive, carry a considerable risk and was simply not warranted. This is a clinical study.

Therefore, clinical evidence of the presence or absence of atherosclerosis in the cerebral and coronary vascular beds was regarded as acceptable. In this respect the consensus in the medical literature regarding the involvement of these vascular beds in Blacks, Whites and Indians in South Africa was strongly relied upon.

Thirdly females were not included in the prospective study because of their small numbers. Females are known to significantly differ from males in their behavioural, social, occupational, physical and biochemical characteristics. Their exclusion would, therefore, have an effect on the results obtained in the study. The results in this study, together with the discussion and conclusions account for this omission.

Finally, this study has been limited by the lack of control studies for the occupational, social and biochemical risk factors. The reasons for this have been detailed in the chapter on methodology. This imposes strong limitations on the interpretations of results obtained in this study.

Where no established reference values and norms exist against which to compare the findings in this study, this will be stated and the interpretations that are advanced must be treated with caution. In the case of the biochemical results, normal reference values are used for analysis. It is against these values that the results obtained in this study are interpreted. It is acknowledged that these interpretations could have been enhanced if this study had established its own controls. This must not, however, diminish the observations and interpretations that have been advanced in this study.

Indeed, apart from these limitations the results in this study do provide plausible answers to the questions raised in establishing the problem and purpose of this study and are now discussed in detail.

3. CAUSES OF CHRONIC PERIPHERAL VASCULAR DISEASE IN DURBAN

The results in this study confirm that chronic peripheral vascular disease is an established problem among White, Indian and Black patients seen at the Vascular

Service in Durban during the period 1981 - 1986. The results also confirm the clinical impression that during this period Blacks have presented with symptoms suggestive of chronic peripheral vascular disease. Further analysis of the results has established that the major pathology associated with the emergence of chronic peripheral vascular disease in Blacks seen at the Vascular Service is atherosclerosis. This has been conclusively demonstrated on the basis of clinical, angiographic, surgical and histological evidence. Atherosclerosis involving the peripheral vasculature has not been previously identified as a major cause of pathology in Blacks both locally in Durban and generally in South Africa. The established view is that the disease is rare and *'little or no mention is made of the problem in the various text books dealing specifically with the practice of internal medicine, surgery and pathology in this population group'* (Robbs 1985). This viewpoint is also substantiated in various studies by Higginson and Pepler (1954), Reef and Isaacson (1962), and Meyer et al. (1971) and also appears to be the case in Black populations elsewhere in Africa as indicated by Levy (1971) in his study on Zimbabwean Blacks and by Biss et al. (1971) in his study on the Masai.

It must be emphasised that histology on light microscopy was consistent with a diagnosis of atherosclerosis and was the final arbiter of the presence of atherosclerosis in Blacks. Differences in the anatomical distribution of peripheral vascular disease could not be explained on the basis of histological variations. This is important because Gorelick et al. (1984) suggested that racial differences in anatomical distribution may be because lesions arise from a disorder that differs from atherosclerosis. The significance of this will become evident later in the study.

What little there is in the literature focuses on 'idiopathic aortitis', which was previously considered to represent the predominant cause of chronic peripheral vascular disease in Blacks (Robbs, 1985). The condition affects the small vessels of the extremities which become occluded by progressive transmural fibrosis thought to be due to delayed hypersensitivity reactions as a result of tuberculous infections (Grobbeelaar, 1974). Other known causes of chronic peripheral vascular disease in Blacks include a group of mixed pathologies such as collagen vascular disease,

cryoglobulinaemia, sickle cell anaemia and Primary Raynaud's disease (Robbs, 1985), all of which do not represent a significant cause of disease in Blacks, Whites and Indians in this study.

Based on these results it would be reasonable to conclude that atherosclerosis in the aorta and the peripheral vessels in Blacks is on the ascendancy and can now be regarded as an established entity, contradicting the hitherto accepted view that atherosclerotic peripheral vascular disease in Blacks in South Africa is rare.

The results also indicate that atherosclerosis was the predominant pathology in White and Indian patients seen at the Vascular Service during this period making atherosclerosis the predominant cause of chronic peripheral vascular disease in all of South Africa's major race groups. These results support the findings of Robbs (1985) who found atherosclerosis to be the major cause of peripheral vascular disease in Whites. Other causes of chronic peripheral vascular disease in Whites were thrombo-angitis obliterans, Takayashu's disease or aortic aortitis and fibromuscular dysplasia involving the iliac vessels (Robbs, 1985).

4. ANATOMICAL DISTRIBUTION OF EXTRACRANIAL EXTRACORONARY ATHEROSCLEROSIS

The results obtained in this study further demonstrate interesting differences in the anatomical distribution of atherosclerotic vascular disease in Blacks with Whites and Indians. In specifically the extracerebral extracoronary circulation this study has shown that atherosclerosis is literally creeping down the lower limbs of Blacks seen at the Vascular Service and that the disease is distributed in the aorta-iliac, femoro-popliteal and tibio-peroneal segments. In Indians and Whites atherosclerotic lesions appear to be similarly distributed. In Indians, however, involvement of the tibio-peroneal segment slightly exceeds that in Blacks and Whites. The only other condition in which there is a predilection for the more distal tibio-peroneal segment is in diabetes. Diabetes is known to be extremely prevalent in the Indian population of Natal (Omar et al., 1985). It is not possible on the basis of the evidence in this study

to associate the greater involvement of the tibio-peroneal segment in Indians to diabetes.

It is to be expected that the emergence of atherosclerotic lesions in the aorta and distal peripheral segments in Blacks would be accompanied by a concomitant rise in lesions within the extracranial cerebrovascular bed. Judging from the paucity of clinical disease as manifested by transient ischemic attacks, amaurosis fugax, slurring of the speech and the presence of carotid bruits this is not the case. By comparison Whites and Indians show a greater prevalence of extracranial cerebral atherosclerosis than do Blacks. The sparing of the extracranial cerebral vessels in Blacks is well described in the literature. Angiographic and autopsy studies as well as the Joint Study of Extracranial Arterial Occlusions all confirm that American Blacks are more prone to intracranial atherosclerosis while Whites have extracranial disease (Gorelick et al. 1984; Caplan et al. 1986). Local studies on South African Blacks by Reef and Isaacson (1962) and more recently by Joubert et al. (1990) also show that in Blacks there is a sparing of the extracranial cerebral vessels from atherosclerosis while intracranial atherosclerosis is an established entity. Similar results have been reported by Levy et al. (1971) on Zimbabwean Blacks. Interestingly the Japanese and the Chinese like Blacks have a predisposition to disease of the intracranial arteries and a lower prevalence of extracranial cerebral vessel disease (Caplan et al., 1986; Leung et al., 1993; Nagao et al., 1994).

Joubert et al. (1990), however, suggested that the sparing of these vessels may be lost as environmental factors associated with a rise in affluence contribute to a change in the pattern of arterial disease in Blacks. This view is not supported by the findings in this study. It has also been shown that in American Blacks the neck vessels remain unaffected by atherosclerotic lesions even after Blacks reach a level of affluence similar to that of Whites and start to experience ischemic heart disease suggestive of coronary vessel involvement with atherosclerosis. This suggests that atherosclerosis of the extracranial cerebral vessels, if it does occur, would only take place after coronary vessel involvement. Race was found to be the only significant factor

predicting the location of occlusive vascular disease in the extracranial cerebral vessels (Gorelick et al. 1984; Caplan et al. 1986).

5. PATHOLOGICAL DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

There are generally two types of pathological lesions associated with atherosclerosis, namely: occlusive and aneurysmal lesions. The results in this study show that these two types of lesions do not occur with equal uniformity between races in the various anatomical segments. The more predominant type of lesion is the occlusive type in each of the race groups and in all the anatomical segments. By contrast aneurysmal disease occurs far less commonly, but to a greater extent in Whites than in Blacks and least in Indians. There is no adequate explanation for this predisposition towards occlusive disease instead of aneurysmal disease in all race groups and in all anatomical segments.

Further analysis specifically of patients with aneurysmal disease reveals another interesting observation related to the distribution of aneurysms between races. In Whites the majority of aneurysms affected the abdominal aorta and occurred only minimally in the more distal peripheral segments. In Blacks this distribution is reversed with distal segment aneurysms occurring almost as frequently as aortic aneurysms. In Indians the pattern resembles that in Whites, but the disease did not occur as commonly. Once again there is no adequate explanation for this peculiar distribution of aneurysms between the vascular segments in the different races.

In fact the whole question of how and under what circumstances do either occlusive or aneurysmal disease form is unresolved in the literature and is an area for research.

6. **AGE DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE**

Atherosclerosis is regarded as an age-related disease which selectively progresses to establish clinical disease in susceptible individuals. Clinical disease occurs earlier in Blacks than in Whites, appearing by the early fifth decade in Blacks, in the late fifth decade in Indians and in the late sixth decade in Whites. These patterns of age distribution may not be a true epidemiological finding, but is representative of patients who presented at the Vascular Service during the period 1984 - 1986.

The early onset of atherosclerotic lesions in Blacks is unlikely to be the result of simply the ageing process, but could be consequent to a promotive factor or factors, especially since it was previously not observed to exist in any significant extent. The age at which atherosclerosis of the peripheral vessels occurs in Blacks in this study is equivalent to the age at which ischemic heart disease is high in Whites and Indians, usually between the fourth and sixth decade. Interestingly, however, it would seem from the results in this study that atherosclerotic peripheral vascular disease occurs at a later age than ischemic heart disease in Whites and possibly in Indians as well. The later presentation in Whites may be a reflection of longevity.

Age does, however, seem to influence the pathological type of lesion. Occlusive disease tends to present earlier than aneurysmal disease in all race groups.

7. **GENDER DISTRIBUTION OF ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE**

The results have shown a male preponderance of atherosclerotic vascular lesions in the extracranial extracoronary circulation in all three race groups and at all ages. This is supported in the literature. The only exception in which there is a female preponderance of the disease is in diabetes, but this exception was not investigated in this study.

Part of the reason for a reduced susceptibility to atherosclerosis among females is related to the vascular protection imparted by oestrogens (Wren, 1992). Oestrogens are known to protect the vasculature against the development of atherosclerotic lesions. The protection is believed to be mediated by a complex mechanism involving vessel intima, macrophages, platelets, arterial musculature and lipophoretic patterns. This protective effect is lost in the postmenopausal years and the rate of atherosclerotic lesions dramatically increases.

8. **RACE DISTRIBUTION OF ISCHEMIC HEART DISEASE**

Ischemic heart disease and consequently coronary atherosclerosis have always been clinically viewed as being rare in the Black population in South Africa. This is supported in a number of studies by Walker (1975). Seftel (1978) has suggested that the disease, though rare, is emerging in the South African Black population. According to Steyn et al. (1991) reliable ischemic heart disease mortality data are not available for the Black population of South Africa. Seedat et al. (1992) have reported in a study carried out on Blacks in Durban during the same period as the present study that the disease is rare. In fact the findings in the present study support the findings of Seedat et al. (1992) to an extent, demonstrating that in Blacks with peripheral vascular disease seen at the Vascular Service there is no strong association with ischemic heart disease. In White and Indian patients included in this study the association between atherosclerotic peripheral vascular disease and ischemic heart disease is greater. In general ischemic heart disease in both Whites and Indians in South Africa is regarded as extremely common.

9. **EMERGENCE PATTERNS OF ATHEROSCLEROTIC VASCULAR DISEASE**

It is therefore reasonable to conclude that atherosclerosis occurs in all the major vascular beds in South African Whites and Indians. In Blacks, however, atherosclerosis has now evolved from its predominantly intracerebral location to afflict the aorta and distal peripheral vessels, but not the extracranial cerebral vessels.

Coronary vessel involvement in Blacks has always been considered as rare and is still uncommon, though there are expectations of an increase (Seftel, 1993).

The emergence of atherosclerotic peripheral vascular disease in Blacks as demonstrated in the present study without a concomitant rise in ischemic heart disease and extracranial cerebral vascular disease raises the following questions: Firstly, is this a casual observation of no significance? Secondly, is it possible that the coronary and extracranial cerebral vessels do have atherosclerotic lesions which have been undetected because of the absence of tests to do so and consequently the observations in this study are erroneous? The third question brings into focus the limited scope of our knowledge regarding atherosclerosis in underdeveloped and developing populations and whether the emergence of atherosclerosis within the vasculature in a developing population does have an evolutionary pattern?

Such a possibility does exist. Walker (1975) made the observation that in a developing African population atherosclerosis first emerged in the intracerebral vascular bed. Peripheral vascular disease, virtually absent in populations living primitively, increased in prevalence with a rise in privilege and that as a clinical problem it emerged somewhat before coronary heart disease.

The findings in this study can be interpreted to support the concept of an evolutionary pattern of development for atherosclerotic lesions within the vasculature in a developing population. This provides vital information on the natural history of atherosclerosis. There is no doubt that this view will be controversial, but nevertheless cannot be ignored, given the tenable evidence of an evolutionary change, as described in this study. Although Walker (1975) first published his observations almost 25 years ago it has not attracted much scientific interest. The reasons for this are unknown, but could be attributable to a number of factors, mainly the efforts to understand atherosclerosis at the clinical endpoint of ischemic heart disease in developed western societies.

The literature reveals another interesting aspect of atherosclerosis and this is related to similarities that exist between the Oriental populations of China and Japan and the Negroid populations of Africa. Firstly, like in developing African populations, atherosclerotic cerebral disease occurs more commonly in the Chinese and Japanese population groups than does either coronary artery disease and peripheral vascular disease, and secondly, hypertension is extremely common in each of these three population groups.

However, as industrialisation has taken place in Japan many studies have produced evidence of a rise in coronary heart disease which appears to be accompanied by an elevation in blood lipids (Yutani et al., 1987). There are no studies emerging from Japan which deny or confirm the existence of atherosclerotic peripheral vascular disease as a clinical problem before the manifestation of ischemic heart disease, but recent studies by Nagao et al. (1994) suggest that severe atherosclerotic disease of the extracranial internal carotid arteries may now be on the ascendency among the Japanese. There is now every reason to believe that China will undergo some degree of social change. It will be interesting, to establish whether the views expressed in this discussion will be replicated among the Chinese.

One must at this stage also question whether a similar pattern of emergence did not take place in the South African White and Indian populations and among inhabitants of other developed countries, as their dynamics changed and before ischemic heart disease became prevalent.

Alternatively, it is possible that the evolutionary emergence of atherosclerosis as speculated in this study may be unique to the Black populations of Africa and may not occur in other race groups.

Many studies have examined the emergence of ischemic heart disease in population groups that translocated from their native countries to their adopted countries. Examples of such population groups have included Japanese who translocated from Japan to the United States (Kato et al., 1973) and Indians who translocated from India

to the United Kingdom, the West Indies and Fiji (Seedat et al., 1990). It needs to be questioned whether in these population groups atherosclerotic peripheral vascular disease had not emerged as a clinical problem before the apparent presence of coronary artery disease. If the observations on the natural history of atherosclerosis as enunciated above are not merely random and are in fact meaningful, then it is possible that this same sequence of events may have manifested themselves in all or most instances. If the peripheral vascular disease phase had been short-circuited, then the reason for this too, would need to be researched.

10. **THE NATURAL HISTORY OF ATHEROSCLEROSIS AND RISK FACTORS**

The preceding discussion strongly supports the concept of a natural history for atherosclerosis. The entire process from when the disease first establishes itself within the vasculature until clinical disease becomes evident can take years. It is only when these clinical effects become common clinical problems where previously they did not exist that atherosclerosis as a disease within a population group becomes noticeable and a cause for concern. The focus, however, has generally been on ischemic heart disease and consequently warnings by Rossouw et al. (1988), Seedat et al. (1992) and Seftel (1994), may well lose their significance if the presence of peripheral vascular disease is ignored and not recognised to indicate the presence of atherosclerosis in a developing society.

Much of our current knowledge regarding the pathogenic mechanisms of atherosclerosis has been derived from the study of risk factors associated with coronary artery disease and extrapolated to apply for atherosclerosis in general, both individually and in population groups as a whole. If coronary artery disease is the end stage of a disease process that could have started years before in the peripheral vasculature then this study may be of significance in assessing the relative importance of the known risk factors in different race groups with differing manifestations of the disease living in the same geographical location.

11. **THE INFLUENCE OF URBANISATION ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE**

There is now adequate evidence to suggest that whatever the genetic predisposition of an individual or population group to atherosclerosis as imparted by race, age and gender, environmental conditions may over-ride or interrelate with these and exacerbate the development of atherosclerotic lesions. Studies emanating from the United States, India, Britain and various other European countries have shown that irrespective of geographical location, people living in an urban environment have a greater tendency to develop atherosclerotic vascular disease. Similarly, it has been shown that differences in prevalence of atherosclerotic disease diminished when geographical differences were reduced as among Yemenite groups that migrated from Africa to Israel resulting in a marked increase in atherosclerotic disease which equalled that of Israeli Jews. In the United States several studies have shown that the prevalence of atherosclerosis among Blacks closely approaches that of Whites living in the same locality (Walker, 1966).

In South Africa, it has been shown that changes in the chemical composition of the aorta associated with ageing in groups of Pedi Blacks in Pietersberg (a semi-rural area) were less marked than those observed in the Black population living in Johannesburg's urban environment (Walker, 1966). This suggests that even in the same race group the process of urbanisation predisposes to atherosclerotic lesions.

In the present study it was shown that only a total of 5,3% of patients lived in a predominantly rural environment of whom almost all were Blacks. The rest of the Black patients had been exposed to urban influences for periods sufficiently long enough to have had a major impact on their lifestyles. This process of urbanisation may diminish the differences in risk factors between Whites, Indians and Blacks providing an equal opportunity for all to develop atherosclerosis. Urbanisation in itself does not mean that atherosclerosis will develop. Certain specific influences related to work status, social habits, disease states and dietary patterns with resultant biochemical aberrations are believed to be the factors which make individuals and

population groups susceptible to atherosclerosis. Intensive research needs to be undertaken to identify precisely what are these factors and what is their mechanism of action.

It is hoped that since this study has been carried out at a time when atherosclerosis is emerging in urbanised Blacks, the factor or factors responsible for initiating the process may be more closely identifiable.

Conversely the results also suggest that a lack of urbanisation does not prevent the development of atherosclerosis in the peripheral vessels, though this occurred in a minority of patients. Further research into this too may provide meaningful results.

These interpretations are made based on the profiles identified between Black, White, and Indian patients included in the study. Any definitive conclusions made from these interpretations must be based on the study of well-defined control groups.

12. THE INFLUENCE OF PHYSICAL ACTIVITY ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Many populations with a low incidence of atherosclerotic vascular disease have a high level of physical activity and conversely a greater predisposition to atherosclerosis exists among more sedentary individuals. Evidence for this comes from a number of autopsy studies correlating physical activity levels with the extent of coronary atherosclerosis in Westchester County, New York (Spain and Bradess, 1960), Britain (Morris and Crawford, 1958), Israel (Mitrani et al., 1970) and Finland (Rissanen, 1976). Morris et al. (1953) demonstrated that the mortality rate of sedentary bus drivers was substantially higher than that of bus conductors who by comparison had high levels of daily physical activity. Similarly British postal workers engaged in more active and physically demanding jobs had significantly lower coronary heart disease rates than sedentary clerks and supervisors. Retrospective studies in United States postal workers, railwaymen and North Dakota farmers and non-farmers have confirmed these observations (Schneider et al., 1986).

In this study work status was used as criterion to demonstrate the level of physical activity. Work status however, may not reliably evaluate the physical activity of a patient, but is, nevertheless, acceptable. In Black patients the majority were manual workers, while in White and Indian patients at least 50% were sedentary workers. These results would suggest that it is possible to develop atherosclerotic peripheral vascular disease in manual occupations which would presumably have a high level of physical activity. It further suggests that the beneficial effects imparted by a high level of physical activity may in some way be over-ridden to predispose the patient to atherosclerosis. Alternatively the effect of a reduced physical activity may be more pronounced in coronary atherosclerosis than in peripheral atherosclerosis. The relative increase in manual workers among Whites may in part be due to the socio-economic status of Whites attending the vascular service.

13. THE INFLUENCE OF ALCOHOL ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Alcohol is not considered to be a major risk factor but does represent one of the life style changes that would be likely to take place in a population undergoing social transition. This may be reflected in changes in type of alcohol consumed and/or in the drinking habits as reflected by the quality and/or duration of the habit.

The role of alcohol in cardiovascular atherosclerosis is controversial and undetermined. Generally it is believed that the effect of alcohol may be beneficial in terms of the quantity taken and the type. Population studies have shown that HDL levels are increased by alcohol consumption in a dose-response manner. This association has been repeatedly postulated as the explanation for the frequently observed protective effect against coronary artery disease in moderate alcohol consumption which is represented by two or fewer drinks per day (Moore and Pearson, 1986). However, it has been observed that beyond this level of consumption the risk of cardiovascular mortality increases (Criqui, 1986). Similarly it has been shown that alcoholic beverages consisting of high levels of brewers yeast (such as the traditional alcoholic beverages of Blacks) and red wine tend to have a beneficial effect

on the cardiovascular system (Rutolo and Hennessy, 1983; Smith et al., 1988). This may not be the case with beers and spirits.

An analysis of the alcohol drinking pattern in this study shows that 13,6% of patients denied any history of alcohol ingestion while 22,5% had stopped drinking more than 5 years previously. Of the drinkers the majority appeared to be moderate drinkers for a period of 20 - 40 years whilst severe drinking was most evident in Indians. There are, however, great differences in the alcohol preference of Blacks with that of Whites and Indians. In Blacks the drinks of choice was Zulu beer alone or Zulu beer in combination with beer and/or spirits. In Indians, the choice drink was spirits and in Whites it was beer.

An interesting observation is that 27,2% of Blacks take a combination of Zulu beer and spirits. This may well reflect a changing pattern in the drinking habits of Blacks. However, the relevance of this observation and the relationship between alcohol and atherosclerotic peripheral vascular disease can best be determined on studies specifically designed to elaborate on these views.

14. THE INFLUENCE OF SMOKING ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Smoking is a social habit which is regarded as a major risk factor for atherosclerosis. The association between smoking in the cerebral, internal carotid artery, coronary, aortic and peripheral vessels is well established on the basis of cohort and case-controlled epidemiological studies and in clinical and pathological correlations and laboratory findings. There are, however, differences of opinion about which vascular bed is most seriously affected by smoking (Reed et al. 1987), and the association between smoking and the peripheral vascular beds is particularly strong (Myer, 1979; Cavallo-Perin et al., 1984; Gofin et al. 1987; Jonason and Bergström, 1987). According to Seedat et al. (1992), smoking does not greatly affect coronary risk in people with a low serum cholesterol level but does contribute to the risk of cerebral vascular disease, though its effect on coronary risk cannot be ignored.

There is a direct relationship between smoking habits and the extent of atherosclerotic lesions (Auerbech and Garfinkel, 1980) and therefore the severity of smoking as a function of the number of cigarettes smoked and the duration of the habit is important.

In the present study a total of 6,3% of patients had never smoked. The rest of the patients in all race groups were moderate to heavy smokers for a period of twenty to forty years although 53,9% of Blacks were mild smokers. Although tobacco was smoked by a total of 9,2% of patients the majority of patients in all race groups smoked cigarettes.

These observations suggest that patients with atherosclerotic peripheral vascular disease, irrespective of race group are usually smokers. Whether this association is significant cannot be determined in the present study, in the absence of well defined controlled studies. These observations are however, in keeping with the association commonly found between smoking and atherosclerotic peripheral vascular disease as suggested in literature. Therefore, smoking, though not conclusively demonstrated in this study, may well play an important role in triggering the atherogenic process at the socio-environmental level.

The deleterious effects of smoking are more pronounced in the company of other predisposing risk factors. However, in the present study associated risk factors are more common in Whites and Indians, than in Blacks, once again suggesting that in the absence of other known risk factors smoking in its own right is sufficient to be seen as a marker for the disease.

There are a number of patho-physiological mechanisms to explain how smoking may accelerate atherosclerosis. Of significance is its effect on fibrinogen (Kannel et al., 1987) and its effects on lipo-proteins (Toppling et al., 1977; Garrison et al., 1979; Criqui et al., 1980). With respect to the latter, smoking has a significant effect on HDL levels independently of other risk factors and this observation may be of importance in the present study.

15. **THE INFLUENCE OF HYPERTENSION ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE**

Hypertension is in itself a vascular disorder, but since hypertensives have a greater propensity to atherosclerosis than non-hypertensives, it is regarded as an important antecedent of atherosclerotic disease.

Hypertension, however, is not specifically associated with a rise in privilege and manifests itself in people of all races irrespective of gender and environment. It occurs in both rural and urban environments and is common in the developed societies of Europe and the United States. It is equally common in the underdeveloped societies of China, Japan and Africa. In South Africa hypertension is a serious health problem and an estimated 7 million South Africans are affected by the disease. This includes all race groups, but the largest subgroup consists of the Black population.

The results in this study show no definitive association between hypertension and peripheral vascular disease. Only 37,7% of patients with peripheral vascular disease had hypertension. Of these 48,5% were Indians, 51% were Whites and 15,4% were Blacks. These results do not reflect the high incidence of hypertension in the general South African population particularly in South African Blacks and suggest that hypertension does not have a prominent influence on the emergence of atherosclerosis in the peripheral vessels. These findings will need to be confirmed in a controlled study.

If substantiated, this is not surprising because it is a well accepted fact that the main association between hypertension and atherosclerosis is in relation to the intracranial vessels with its major impact in the form of strokes either on the basis of atherosclerosis and haemorrhage. This has also been confirmed in studies from China and Japan, where the association between hypertension and strokes is high (Hatano, 1975; Bernhardt et al., 1986). In the Framingham Study it was shown that hypertensive subjects developed a sevenfold greater incidence of strokes, a threefold rise in coronary heart disease and only a doubling of peripheral vascular

atherosclerosis when compared to normotensive subjects. Similarly, in African populations, including South African Blacks, hypertension is most strongly associated with intracranial atherosclerosis and uncommonly associated with the incidence of coronary and peripheral atherosclerosis (Seedat and Pillay, 1976; Trowell, 1981).

However, it has been shown among the Japanese that when hypertension is accompanied by an increase in plasma lipoprotein levels above a certain critical level, the effect of hypertension seems to extend probably indirectly beyond the intracranial vascular bed to cause coronary atherosclerosis (Chobanian, 1983). According to Seftel (1978) in the absence of hypercholesterolaemia, hypertension is not a significant risk factor for atherosclerosis even in western populations, although in western societies this is the rule rather than the exception.

In the International Atherosclerosis Project lesions in the aorta occurred in association with hypertension (Robertson and Strong, 1968). Since 51% of Whites and 48,5% of Indians in this study had hypertension and an almost equal percentage respectively had aortic aneurysms it is possible that hypertension may play a role in aortic aneurysmal disease. Similarly its association with extracranial cerebrovascular disease in Whites and Indians cannot be excluded. These observations and interpretations will need to be tested in proper case controlled studies if they are to provide any insight into the aetiological mechanisms of aneurysms.

According to recent evidence hypertension may be an insulin resistant state. Insulin resistant states are accompanied by decreased HDL levels and a hypertriglyceridaemia and when present are believed to play a role in atherogenesis (Ferranini et al., 1987; Reaven, 1988).

16. THE INFLUENCE OF DIABETES ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Hypertension is strongly associated with diabetes, another major risk factor for atherosclerosis. Diabetes in its own right, is a metabolic disorder which like hypertension occurs in both developed and underdeveloped societies irrespective of race, age, gender and environment. There is, however, strong evidence to suggest that diabetic women are more predisposed to atherosclerosis even in the premenopausal years (Schneider et al., 1986; Ruderman et.al., 1984; Durrington, 1991). In the present study the effect of gender remains undetermined because females had not been included in the prospective study.

However, unlike hypertension, diabetics have a tendency to develop atherosclerosis in all the major vascular beds and are associated with cerebrovascular accidents, ischemic heart disease and peripheral vascular disease to a greater extent than non-diabetics (Ruderman et.al., 1984).

In this study diabetes occurred most commonly in Indian patients, (the high glucose levels were probably due to individual patients who were uncontrolled) and this perhaps reflects the high prevalence of diabetes in the general Indian population in Durban. On the contrary there is a low prevalence of diabetes in the sample of Black patients, even though there is believed to be an increase in the prevalence of diabetes among local Blacks (Omar et al., 1985; Walker and Walker, 1994). These results, however, provide no strong association between diabetes and peripheral vascular disease in each of the population groups including Whites, but will need to be confirmed in case controlled studies.

However, even though the prevalence of diabetes is low in this study, there are several interesting associations between diabetics in general and atherosclerotic peripheral vascular disease in Blacks in this study. Firstly, although diabetes can occur at any age, atherosclerotic complications tend to occur at an earlier age among diabetics than in non-diabetics (Garcia et.al., 1974; Kannel et.al., 1979). Similarly, peripheral

vascular disease in Blacks manifests at an earlier age than in Whites or Indians. Secondly, in both diabetics and in Blacks with peripheral vascular disease, clinical presentation is aggressive in the form of ulcers, sepsis and gangrene. Thirdly, in diabetics atheroma appears to affect the more peripheral vessels with femoro-popliteal and tibio-peroneal disease being common (Wissler, 1991; Friedman, 1982). This is similar to the findings in Blacks and Indians in this study. In diabetes this is explained on the basis that diabetic atheroma involves more smooth muscle proliferation and less lipid deposition than in non-diabetics. This would explain why muscular arteries such as the femoral arteries in diabetics are more likely to be affected by atheroma than the elastic arteries such as the aorta (Wissler, 1991). Insulin is believed to play an important role in smooth muscle proliferation and diabetes, like hypertension is associated with insulin resistance (Schreiner et al., 1986). However, based on the lipid and insulin results to follow it is unlikely that insulin resistance occurred in Blacks with peripheral vascular disease in this study, but this will need to be validated in case- controlled studies.

Besides insulin resistance, another prominent feature of diabetes relates to defects in lipoprotein metabolism. The predominant dyslipoproteinaemia in diabetes is a low HDL cholesterol and a hypertriglyceridaemia. Jailal et al., (1985) produced evidence of this in a study on Indians in Durban.

17. **THE INFLUENCE OF HYPERLIPOPROTEINAEMIA AND INSULIN RESISTANCE ON ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE**

Hyperlipoproteinaemias are closely associated with atherogenesis and though it is generally accepted that increases in total cholesterol, LDL cholesterol and triglycerides with a decreased HDL cholesterol are atherogenic there is no uniformity of opinion on their precise effects in the different vascular beds.

A good linear relationship generally exists between total cholesterol and LDL cholesterol and the relative incidence of coronary heart disease based on evidence by

Fredrickson et al. (1967), the Tromso Heart Study (1977), the Framingham Study (1971) and the study by Rhoades et al. (1976). Conversely populations with a low incidence of coronary mortality have low total cholesterol and LDL cholesterol levels such as in Japan and China. An inverse relationship, similarly, exists between HDL cholesterol and coronary heart disease as demonstrated by Barr et al. (1951), Nikkela (1953), the Co-operative Phenotyping Study (1977), the Framingham Study (1977) and the Tromso Heart Study (1977).

In South Africa the high incidence of coronary heart disease among Whites and Indians is accompanied by a linear relationship with total cholesterol and LDL cholesterol and an inverse relationship with HDL cholesterol. In the South African Black population the incidence of coronary heart disease is low, accompanied by a total cholesterol, LDL cholesterol, and triglyceride levels within the normal range and HDL cholesterol levels which are high and which are believed to be cardioprotective. Protective levels of HDL cholesterol are also associated with a low incidence of coronary heart disease in China (Bernhardt et al. 1986).

The relationship of triglycerides to coronary heart disease is not as well-established. Various studies by Goldstein et al. (1973) and the Stockholm Prospective Study (1972) have suggested that plasma triglycerides independent of serum cholesterol may be a risk factor for coronary heart disease (Schneider et al., 1986) but evidence from Framingham and elsewhere have de-emphasised triglycerides as an independent risk factor for coronary heart disease, except when associated with a high cholesterol or with a low HDL cholesterol (Carlson and Bottiger, 1972).

These relationships are not as well defined with respect to atherosclerosis in the cerebral, extracranial, aortic and peripheral vascular beds, suggesting that they may not be pathogenetically affected by lipoproteins in the same way. Only weak and inconsistent relationships have been found between hyperlipoproteinaemias and atherosclerotic cerebrovascular disease and positive findings are confined to patients with extracranial cerebrovascular involvement (Ford et.al., 1985). Similarly, the lipid connection with atherosclerotic peripheral vascular disease is weak. Analyses of case-

controlled and cross-section studies have shown no consistent results on the association between lipids and peripheral vascular disease (Pomrehn et al., 1986), though it is believed that most patients under the age of 40 years could have some form of hyperlipidaemia. Serum cholesterol is elevated in some studies, but not in all (Coffman, 1979). Triglycerides appear to be more independently associated with peripheral vascular disease than cholesterol. It has also been suggested that triglycerides tend to cause atherosclerotic peripheral vascular disease at an earlier stage than hypercholesterolaemia which is mainly associated with coronary heart disease (Greenhalgh et al., 1975). It is therefore likely that patients escape coronary heart disease while being susceptible to peripheral vascular disease (Greenhalgh et al., 1975; Bliss et al., 1972), on the basis of a hypertriglyceridaemia. The role of HDL cholesterol has not been extensively evaluated in peripheral vascular disease and cerebrovascular disease, though some studies have found an association between peripheral vascular disease and reduced levels of HDL cholesterol (Bradby et al., 1978; Trayner et al., 1980).

The results in this study show that in White and Indian patients, total cholesterol and LDL cholesterol levels were raised while in Black patients total cholesterol and LDL cholesterol levels were normal. HDL cholesterol was similar in all three race groups. In White and Indian patients HDL cholesterol levels were below normal and in Black patients the mean HDL cholesterol level was 0.92 ± 0.34 mmol/l, which is significantly lower than that expected for healthy Blacks (Walker and Walker, 1978; Rossouw et al., 1988; Jooste et al., 1990; Steyn et al., 1991; Seedat et al., 1992; Oelofse et al., 1996).

These results suggest that atherosclerotic peripheral vascular disease can occur with normal levels of total cholesterol and LDL cholesterol and this has been specifically demonstrated in the sample of Black patients included in this study who on clinical evidence are largely devoid of cerebrovascular and coronary artery disease. This is unlike the sample of White and Indian patients in whom there is a greater association of cerebrovascular and coronary artery disease and which may be related to the apparently higher levels of total cholesterol and LDL cholesterol in these patients.

The only explanation for the presence of atherosclerotic peripheral vascular disease from a point of view of lipid aberrations particularly in the sample of Black patients would, therefore, be on the basis of a reduced HDL cholesterol. This would suggest that HDL cholesterol reductions may play a crucial role in the development of atherosclerotic lesions in the peripheral vascular bed particularly in developing populations.

In the present study triglyceride levels were elevated in White and Indian patients but remained within normal limits in Black patients. These findings in White and Indian patients would accord with the view that triglycerides are an independent risk factor for peripheral vascular disease and could explain the presence of the disease in these patients. However, the findings in Blacks would not support the association between peripheral vascular disease and hypertriglyceridaemia as triglyceride levels are within normal limits in the sample of Black patients.

Hypertriglyceridaemia is regarded as a marker of insulin resistance (Seedat, 1994). Insulin resistance is increasingly considered as a precipitating factor for atherogenesis. However, in this study no tolerance tests were done to establish the insulinaemic and glycaemic response in the sample of patients, but insulin levels obtained were within normal limits, though significantly lower for Black and White patients than for Indian patients. Based on these results together with the diminished presence of hypertension and diabetes in Blacks it would be reasonable to conclude that Black patients with peripheral vascular disease do not have insulin resistance, though it is possible that insulin resistance may occur in White and Indian patients.

In a similar study by Keenan and Robbs (1985) it was shown that Black patients had a normal total cholesterol and LDL cholesterol level, a low HDL cholesterol level and an increased triglyceride level. Interestingly their findings are similar to the lipid aberrations commonly associated with non-insulin dependent diabetes mellitus, the implications of which need further evaluation. The results obtained in the present study are not entirely similar to the findings of Keenan and Robbs (1985).

18. SIGNIFICANCE OF REDUCED SERUM HDL CHOLESTEROL

Reductions in serum HDL cholesterol though present in White and Indian patients stand out as the single most important lipid aberration in Black patients with atherosclerotic peripheral vascular disease. This finding is of special significance with regard to the role of HDL cholesterol in normal physiological pathways and in the initiation of the 'lipid pathway' in atherogenesis. The following observations are consequently made:-

- 18.1 In the absence of a raised total cholesterol, raised LDL cholesterol, hypertriglyceridaemia and presumably in the absence of an insulin resistant state, it is possible that reductions in HDL cholesterol may play an important role in precipitating atherogenesis individually and in developing population groups as a whole.
- 18.2 In developing populations the process is initiated in the aorta and the distal peripheral vessels suggesting that the reductions in HDL cholesterol preferentially cause disease at these sites before involvement of the coronary and extracranial cerebrovascular beds. This is contradictory to the generally accepted view that HDL cholesterol physiologically acts to remove LDL cholesterol from the peripheral cells preventing atherosclerosis in the coronary vascular bed. This could mean that physiological levels of HDL cholesterol are not only "cardioprotective" but "vasculoprotective". It is therefore plausible to suggest that HDL cholesterol may be implicated in maintaining the integrity of the vascular cell membrane. Doubts about the negative relation between HDL cholesterol and the incidence of ischemic heart disease have previously been raised by Keys (1980) and supported by the findings of Knuiman and West (1981) who showed low HDL cholesterol in men of Africa, Asia and Surinan associated with a low death rate from ischemic heart disease (Altman and Ramos de Souza, 1985). Similarly Keenan and Robbs (1985) showed a reduced HDL cholesterol in Black patients who had an absence of ischemic heart disease, but in whom peripheral vessel atherosclerosis occurred.

- 18.3 In the presence of normal total cholesterol, LDL cholesterol and triglyceride levels together with normal or low total cholesterol/HDL cholesterol, atherogenesis due to reduced HDL cholesterol may not be adequately explained by the reverse cholesterol transport hypothesis and other biochemical pathways must be reconsidered.
- 18.4. The reduction of HDL cholesterol in the absence of other lipid aberrations provides us with a biological model which could impact on our understanding of HDL cholesterol and the mechanisms by which it acts physiologically and pathologically. Steinberg (1987) stated *'ways and means of testing the 'low HDL hypothesis' in animal models need to be found. If a low HDL level per se is as significant as it seems to be in determining the rate of progression of atherosclerosis, surely it should be possible to devise an animal model that will demonstrate its critical role. The difficulty is that most of the things one does to alter HDL levels alter lipoprotein metabolism in other ways at the same time, and it is difficult to design the appropriate single-variable study. Either through use of drugs that specifically influence HDL biosynthesis and secretion or through the use of genetic variants, one needs to find appropriate studies to demonstrate that HDL levels are per se related to the atherogenic process. The possibility remains that the low HDL level is simply a "marker" for some other metabolic process that may be more proximately related to atherogenesis.....'* In demonstrating a reduced HDL cholesterol per se in Black patients with peripheral vascular disease as in the present study the role of HDL cholesterol can be further investigated in vivo as suggested by Steinberg.

19. CAUSES OF REDUCED SERUM HDL CHOLESTEROL

The next problem is whether the reduced HDL cholesterol can be explained on the basis of lifestyle changes associated with the social transition of Blacks. In this study smoking was extremely common in all patients with atherosclerotic peripheral vascular disease irrespective of race. Keenan and Robbs (1985) though have questioned the importance of smoking in peripheral vascular disease in the absence of coronary heart disease, but according to Seedat et al., (1990) smoking does not greatly affect coronary risk in people with a low serum cholesterol level. Smoking is also

known to have an effect on lipoproteins and in particular HDL cholesterol. (Garrison et al., 1979). Crique et.al. (1980) have shown that there is an inverse nicotine/HDL correlation independent of the effects of age, hormone use in women, obesity, alcohol use and regular exercise. Similarly, thiocyanate and HDL changes, independent of changes in plasma triglycerides, alcohol use and degree of obesity are known to occur (Hulley et.al. 1977). In the present study multivariate analysis showed no association between HDL cholesterol and smoking, which is surprising given the high incidence of smoking and the reduced HDL cholesterol in patients of all races in this study, but importantly does suggest the possibility of other relationships, particularly in a developing society. This is supported by Bradby et al. (1978) who also found the association between atherosclerosis peripheral vascular disease and reduced HDL cholesterol to be independent of smoking.

But smoking is known to have a multiplicity of effects and may cause platelet adhesiveness, prostaglandin synthesis, monocytosis and fibrinogenaemia. All of these are believed to play a role in the atherogenic process. The cumulative effect of these together with the networking of their respective biochemical pathways of which the 'lipid hypothesis' is an integral part, is the development and evolution of atherosclerotic lesions. On the basis of the findings in this study it may be that HDL cholesterol reductions initiate the 'lipid pathway' and though smoking could play a major role, this is not clear. The causes of a reduced HDL cholesterol will need to be intensively investigated in patients with atherosclerotic peripheral vascular disease, particularly the Black patients in order to establish a link with lifestyle changes in a society undergoing social transition.

The importance of the 'lipid pathway' in atherogenesis is perhaps best illustrated by the regression of atherosclerotic lesions with the correction of lipid imbalances and therefore cannot be discounted.

20. SIGNIFICANCE AND CAUSES OF A DIFFERENTIAL VASCULAR SUSCEPTIBILITY TO ATHEROSCLEROSIS

Much work still needs to be done to confirm the phenomenon of an evolution of atherosclerosis within the vasculature as a population undergoes social transition. If such an entity can be confirmed conclusively, research in the field of atherosclerosis will also evolve towards new possibilities. It is not possible in this study to give definite answers for this observation but it is further postulated that the evolutionary pattern as discussed may be based on a differential vascular susceptibility to atherosclerosis. Speculation is made on the following possibilities, inter alia:

- 20.1** Are there differences in rates of ageing in the different vascular beds?
- 20.2** Are there differences in the chemical composition of the different vascular beds?
- 20.3** Does a reduction in HDL cholesterol set in motion a series of biochemical effects causing hypertriglyceridemia and raised LDL cholesterol and total cholesterol to sequentially affect different vascular beds?
- 20.4** Do these different vascular beds have different lipid receptors that would explain the findings?

The implications are considerable and it is hoped that the real contribution of this study would be to understand atherosclerosis from a new perspective and provide a better understanding of the natural history of atherosclerosis which would in turn give new insights into the disease at the biochemical and molecular level and its relationship to our lifestyle. The aetiological mechanisms and biochemical pathways of the most recently established risk factors such as fibrinogenaemia, homocysteinuria and lipoprotein(a) may be better served from such a perspective.

CHAPTER SIX

CONCLUSIONS

'IF ALL THE CENTURIES OF TIME, BECAME ONE MOMENT.'

(BAJRUNG SINGH)

In using the geopolitical situation in South Africa as a biological model to understand atherogenesis in socially developing and developed societies the following **conclusions** are made:

1. that atherosclerotic peripheral vascular disease involving the aorta and distal vessels is an established entity among Blacks seen at the Vascular Service in Durban during the period 1981 - 1986 and that the disease occurs without a concomitant increase in coronary artery disease and extracranial cerebrovascular disease. By contrast the disease is well distributed in all the major vascular beds in Whites and Indians. These findings may be interpreted to be the first substantial evidence in support of the observations made by Alexander RP Walker more than 25 years ago;
2. that at a biochemical level the clinical profile described above for Blacks is not accompanied by increases in total cholesterol, LDL cholesterol and triglycerides. This contrasts with the raised total cholesterol, LDL cholesterol and triglycerides present in Whites and Indians. Reductions in HDL cholesterol occurred in all 3 race groups. These findings are made in the absence of control groups and rely on established reference values, but illustrate the need to re-examine the pathogenetic role of the 'lipid pathway' in societies at different stages of transition and in relation to the accompanying profile of atherosclerotic vascular disease; and
3. that the biochemical changes, subject to confirmation in controlled studies appear to be related to socio-environmental factors associated with life-style changes which override and/or interrelate with the existing genetic predisposition to atherosclerosis based on race, age and gender to cause disease. Smoking is considered as an

important risk factor for atherosclerotic peripheral vascular disease. Its association with lipid aberrations to explain the link between smoking and atherogenesis is not clear in this study, although the literature is strongly in support of such an association.

On the basis of the findings in this study the following **postulates** are accordingly advanced to conceptualise the clinical and major risk factor profiles for atherosclerosis in societies at different stages of social transition:

1. that with social transition as among Blacks the differential involvement of the vascular beds is based on a differential vascular susceptibility to atherosclerosis. Smoking is an important social risk factor which could trigger this process while at the biochemical level a reduced HDL cholesterol and not a raised total cholesterol, LDL cholesterol or triglycerides may be the lipid aberration which triggers the 'lipid pathway' in atherogenesis; and
2. that a differential vascular susceptibility does not exist in a fully developed society once lipid aberrations include a reduced HDL cholesterol accompanied by a raised total cholesterol, LDL cholesterol and/or triglycerides, probably secondary to the reduced HDL cholesterol. It is also possible that insulin resistance/hyperinsulinaemia may play a role in causing atherosclerosis to evolve in the coronary vascular bed.

It is therefore **recommended** that the trends demonstrated in the present study and the postulates that have accordingly arisen be investigated in longitudinal, cross-sectional and case-controlled studies for further evaluation and definitive conclusions to be made.

In the **final analysis** this study strongly suggests that the genesis and natural history of atherosclerosis within the different vascular beds in different populations is due to an interplay of both genetic and socio-environmental factors. The susceptibility of the arterial wall in any individual or population group to atherosclerosis is dependent on a genetically determined response according to race, age and gender to the type, intensity and duration of socio-environmental factors. It is probably this balance which ultimately determines whether fatty streaks are physiology or pathology.

***'IF ALL THE VISIONS EVER SEEN,
WERE CONTAINED IN ONE PICTURE'***

(Bajrung Singh)

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VASCULAR SUMMARY SHEET

FIRST ADMISSION	<input type="checkbox"/>
CONTINUATION	<input type="checkbox"/>
REPEAT ADMISSION	<input type="checkbox"/>

NAME:

IP No. RACE: AGE: SEX:

OP No. SURGEON:

ADMISSION: DISCHARGE: DIED:

REFERRING DOCTOR: ADDRESS:

A. DIAGNOSIS

Trauma (a) Stab Blunt MVA Assault Gunshot Shotgun High vel missile

Other

(b) Artery injured

(c) Pathology: Spasm Thrombosis False aneurysm AVF

Transection

Aneurysm (a) Ruptured

Symptomatic

Dissecting

False

(b) Site(s)

(c) Cause - atherosclerotic Other

Acute arterial occlusion (a) Site

(b) Cause: embolus Source Thrombosis

Chronic arterial occlusion (a) Site

(b) Cause

Small vessel disease (a) Embolism

(b) Collagen vasc disease

(c) Diabetes

(d) Other

Thoracic outlet syndrome (a) Cervical rib

(b) Other (specify)

Congenital malformation

Veno-occlusive disease Acute upper segment thrombosis

Acute lower segment thrombosis

Chronic

F. INVESTIGATIONS

Hb..... PCV..... Platelets..... WCC.....
 ESR..... PI..... PTT..... CREAT.....
 Creat:Cl..... Chol..... Trig.....
 Na..... K..... Cl..... Urea.....
 Bl/gluc..... WR..... Vital:Cap.....
 PO₂..... ECG:Normal Abnormal CXR:Normal Abnormal
 Ultrasound:..... Pus swab:.....
 Cat Scan:.....
 Angiogram: Type..... Number:.....
 Date.....

G. NON-INVASIVE INVESTIGATIONS

Doppler pressures	Pre-op	Post-op
Pop	Rt Lt	Rt Lt
PT	Rt Lt	Rt Lt
PP	Rt Lt	Rt Lt
DP	Rt Lt	Rt Lt

Wave forms (femoral) Lt Normal Abnormal
 Rt

H. TREATMENT

Conservative.....
 Operative Date Graft(size/material)
 1.
 2.
 3.

1. POST-OPERATIVE COURSE

Early (less than 2/52) Uneventful Other.....
 Graft occlusion
 Haemorrhage
 Sepsis : wound
 : graft
 : other
 Systemic complications.....
 Died (cause)

late.....

PERIPHERAL VASCULAR DISEASE PROFILE

Experiment/Control I.P.No..... O.P.No..... Name..... Age.....Yrs

Original Residence.....(...../yrs) Present Residence.....(...../yrs) Marital status: Single/Married/Divorced/Widow/er

Alcohol Yes/No/Previously (for.....mth/yrs) Type..... Quantity.....day/week

Smoking: Yes/No/Previously (for.....mths/yrs) cigarettes/tobacco/pipe <5/day 5-10 20-30 +30 < 5oz/day 5-10 10-20 20-30

Vegetables Yes/No/Only (.....dys/wk) Pap. +/- Rice..... Greens..... Mushroom..... Other.....

Meat Yes/No/Only (.....dys/wk) Mutton..... Pork..... Beef..... Chicken..... Fish..... Shellfish..... Other.....

Fruits: Yes/No/Only (.....dys/wk) Type..... Sugar in tea/coffee/other.....(.....teaspoons/cup) eggs...../wk

Education: Nil < Std 6 Std 6-10 Tech. University

Occupation: Not employed for.....yr/mth < 20yr of age..... 20-30yrs..... 30-40yrs..... 40-50yrs..... 50..... retired at.....age.....

Previous Dx (*where app) CVA Angina Myo.Infarct Hypert. diabetes Past PVD Past aneurysm NonatheromDx(Name Dx)

Father

Mother

Brother

Sister

Grandfather

Grandmother

Drugs Oral contraceptives Yes/No Type..... Taken for.....yrs

Antihypertensives Yes/No Type..... Taken for.....yrs

Hypoglycaemics Yes/No Type..... Taken for.....yrs

Others Yes/No Type..... Taken for.....yrs

Presentation: Ulcers(-/-) Rest pain () Impotence() Claudic.() Gang.() Mass()puls/nonpuls. TIA() (° () Sens()Rigd()

Rt hand/arm

Lt hand/arm

Rt foot/L.L.

Lt foot/L.L.

Ht.....cm Wt.....kg BP.....(resting 2 } hour) CXR Normal/Abn (Pathology.....)

ECG (N) ischaemic changes (+/-) L.V.Hypertrophy() R.V.Hypertrophy() Hypertensive changes() Myocardial Inf. pres./rec() Other.....

Pulses(technical) Carotid Brachial Radial Aorta abd. Femoral Popliteal Dorsalis pedis Tibio-peroneal (Add ✓ if bruits present)

(R)

(L)

Dopplers

(R)

(L)

Angiogram: Date..... Type..... No..... Normal/segments dx/diffuse dx Aorta(+/-) Aorto-iliac(+/-) Iliac(/) IF(/) F/A

F/P (/) Popliteal (/) Tibio/peroneal (/) Carotids (/) Other (/) Aneurysm (/) Site.....

Histology reports: Atherosclerotic disease (+/-) Comments.....

Vascular Sx Dates 1..... 2..... 3..... 4..... X/over..... Bypass..... Embolect. B/KA.....(R/L) AKA.....(R/L) Other.....

Blood results

FBC rbcs..... Hb..... wbcs..... platelets..... ESR..... MCHC..... MCV.....

Lipogram profil (Fasting) Cholesterol..... Tryglycerides..... LDL..... HDL.....

Serum protein electrophoresis

TFT

Creatinine

Urates

Urea/Electrolytes NA..... K+..... Cl⁻.....

Glucose Fasting..... 1 hr..... 2hr.....

Insulin Fasting..... 1 hr..... 2hr.....

PI

PTI

Fibrinogen

Creatinine clearance

Trace elements Zn..... FE..... MG..... Chromium..... Cu.....

Urinalysis Normal/abnormal Path.findings..... Nephrotic syndrome +/-

APPENDIX 3

	<i>CV% Inter assay</i>	<i>CV% Intra assay</i>
Cholestrol	1,3	0,7
Triglycerides	1,4	0,97
HDL Cholestrol	2,2	1,4
Insulin	3,0	4,6
Glucose	0,6	1,2
Uric Acid	1,7	0,65

APPENDIX 4**TABLE ILLUSTRATING LEVELS OF BIOCHEMICAL TESTS ON A LIMITED NUMBER OF WHITE, INDIAN AND BLACK CONTROLS**

	White		Indian		Black	
	Mean	n	Mean	n	Mean	n
Urates	0,41	9	,47	7	,31	18
Fasting glucose	5,10	9	5,60	8	5,20	19
Fasting insulin	8,00	10	15,20	8	7,80	15
Fasting triglycerides	1,20	10	2,90	8	1,10	19
Fasting Cholestrol	6,20	10	5,90	8	4,60	19
Fasting LDL	4,50	10	4,30	8	2,40	20
Fasting HDL	1,30	10	0,97	8	1,30	20
Tc:HDLc	4,80	10	6,10	8	3,50	19