UNIVERSITY OF LONDON

THE PREVALENCE OF DIABETIC FOOT DISEASE

M D THESIS

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ABSTRACT

THE PREVALENCE OF DIABETIC FOOT DISEASE

During a surveillance programme all the known diabetics (1150) were identified from a general population of 97,034 representing all patients registered with 10 general practices. A control group of 751 non-diabetic subjects were also drawn from the same general population. A single observer reviewed 1077 (93.6%) of the diabetics and 480 (69%) of the controls. Peripheral vascular disease was detected using doppler ankle/brachial pressure index in 20.6% (95% CI 18.2-23.0) of diabetics and 9.6% (95% CI 7.0-11.2) of controls. There was no significant difference between the prevalence in non-insulin dependent and insulin dependent diabetics after adjusting for age. The prevalence in either type of diabetes was however significantly greater than in controls. Multiple logistic regression analysis revealed that age, cerebrovascular disease, coronary artery disease, mean systolic blood pressure, blood glucose, proteinuria and serum cholesterol were significantly and independently associated with the presence of peripheral vascular disease in diabetics. Body mass index was inversely associated. For controls only age and smoking were found to be significant variables. Neuropathy determined by clinical evaluation and sensory vibration thresholds was found in 16.8% (95% CI 14.6-19.0) of diabetics and 2.9% (95% CI 1.4-4.3) of controls ($p<0.001$). There was however no significant difference between insulin dependent and non-insulin dependent diabetics after accounting for age. Alcohol intake, age, height, HbA1, foot deformity and the presence of any retinopathy were significantly associated with neuropathy in diabetics and only male sex, age and foot deformity in controls. Past or present foot ulceration occurred in 7.4% (95% CI 5.8-9.0) of diabetics and 2.5% (95% CI 1.1-3.9) of controls ($p<0.001$). Amputation was found in 1.4% (95% CI 0.7-2.1) of diabetics but in no controls. Using logistic regression analysis ulceration was significantly associated with duration of diabetes, foot deformity, absent light touch, impaired pain perception, an absent dorsalis pedis pulse and the presence of any retinopathy. For controls only absent light touch was significant. Using a stepwise multiple regression only age and duration of diabetes were significantly associated with the presence of amputation.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
df	degrees of freedom
GP	General Practitioner
HDL	High Density Lipoprotein
IDDM	Insulin Dependent Diabetes Mellitus
IDDs	Insulin Dependent Diabetics
LDL	Low Density Lipoprotein
mmol	millimoles
NIDDM	Non-insulin Dependent Diabetes Mellitus
NIDDs	Non-insulin Dependent Diabetics
OHA	Oral Hypoglycaemic Agent
OR	Odds Ratio
SD	Standard Deviation
T4	Thyroxine
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
VLDL	Very Low Density Lipoprotein
WHO	World Health Organisation

ACKNOWLEDGEMENTS

This project would not have been possible without the virtually unique "shared care" system of diabetic patient management that exists in Poole. I am, therefore, indebted to all the general practitioners and their staff who co-operated in the survey. Above all I wish to thank Dr Ron Hill who from the inception of this project has offered enormous amounts of help, advice and encouragement. Further thanks must also go to Dr Wendy Gatling whose practical experience in the nephropathy survey proved invaluable throughout the project. I would also like to mention the hard work and assistance of Olive Foley, my research nurse. Further thanks must also go to the Poole Hospital Biochemistry Department for the analysis of all blood samples and the Medical Physics Department for their help in the measurement of autonomic function tests and the provision of office space. Throughout the project I have put enormous strain on the library staff at Poole who have never failed to find the most elusive of references. Jackie Wicks also deserves a special mention for all her help in typing and, above all, her patience! Professor Jarrett, my adviser, has not only given valuable advice throughout the survey but has also managed to teach me to write English! I am also indebted to Mark Mullee for his help in the statistical analysis of the results.

Finally, the list of acknowledgements would not be complete without a special thank you to my wife Judy who has tirelessly read through all my work on several occasions and has given me every encouragement and support.

INTRODUCTION

Diabetic complications are still a major cause of morbidity and mortality despite advances in the management of the metabolic consequences of the syndrome. As a result of a propensity to distal polyneuropathy and peripheral vascular insufficiency the diabetic is prone to ulceration and gangrene of the lower extremities. The latter is one of the most distressing of diabetic complications inevitably culminating in amputation.

West (1978) noting the marked variation in susceptibility to gangrene amongst the populations of diabetics, suggested that epidemiology should play a prominent role in elucidation and prevention. However because of methodological differences and lack of studies in representative diabetic populations West concluded "the present status of data in this field is an epidemiologist's nightmare!" Even today, although we know that diabetics are greatly at risk of amputation compared to their non-diabetic counterparts (Most and Sinnock 1983, Waugh 1988) we still do not know the precise prevalence and relative impact of risk factors for amputation and ulceration. Furthermore we do not know the optimal preventive strategies for peripheral neuropathy and peripheral vascular disease.

Studies investigating diabetic foot disease and its risk factors are difficult to perform. Firstly, they need to be population based to avoid sampling bias. Secondly, there will be a background of foot disease in the non-diabetic population making it difficult to define the additional effects of diabetes. Thirdly, particularly with regard to neuropathy, the effects of aging make it difficult to define normal from abnormal in any particular age category. Fourthly, many of the observations in diabetic foot disease are subjective and therefore open to inter-observer error. To circumvent these problems there ideally should be only one observer and a comparison group of age and sex matched non-diabetics drawn from the same general population.

Even allowing for these difficulties the paucity of information is surprising. Connor (1987) estimated the cost of a major amputation to be £8,544 per patient. Using Waugh's (1988) data on the relative risk of becoming an amputee and assuming that the

prevalence of diabetes in the UK is of the order of 1%, then this amounts to a spending of approximately £50,000,000 by the Health Service on amputations alone. This of course merely covers one aspect of diabetic foot disease. Ulceration and treatment for peripheral vascular disease will also require hospitalisation. Waugh (1988) estimated that a cohort of diabetics who had their most proximal amputation in 1981 occupied more than 16,000 hospital bed days over a 5 year period. It was estimated that this would account for at least 1.2% of all hospital costs. Clearly there would also be an enormous drain on community resources including those of the general practitioner, district nurse, chiropodist, diabetologist and nursing home accommodation.

There is however some evidence that diabetic foot disease is preventable. Lippmann and Farrar (1979) concluded that lower extremity amputation rarely occurred in the absence of extrinsic injury and concluded that limb loss was not an inevitable consequence of claudication. Similarly Edmonds et al (1986) have shown that since the inception of a diabetic foot clinic, amputation rates for their hospital have approximately halved. Indeed the National Diabetes Advisory Board (1981) has concluded that amputation rates could be reduced by as much as 50-70%.

Diabetic foot disease is therefore both medically and economically important. A prevalence survey is needed to identify the magnitude of diabetic foot disease and its risk factors in a typical diabetic community. Not only will it enable the size of the problem to be identified within the population but also will give an indication of what are the most important clinical determinants of diabetic foot disease, possibly enabling future strategies for prevention. The Poole Diabetic Department provides an excellent opportunity for epidemiological research for the following reasons. Firstly the population of Poole has an age/sex and racial structure typical of the UK (Gatling et al 1985). Secondly, Poole General Hospital solely serves the needs of the local population and the Diabetic Department operates a "shared care" system of management with the local general practitioners (Hill 1976). Not only has this allowed close ties with the community but also has facilitated the development of the Poole diabetic register. The latter is a

computerised database for diabetics within the Poole area which is regularly updated for deaths, patient migration and newly diagnosed subjects. It is virtually unique because it comprises all patients whether managed by the hospital or solely in the community.

The Poole diabetic cohort has previously been investigated for the prevalence of retinopathy (Houston 1982) and nephropathy (Gatling 1986). It is planned in the near future that the observations over the 10 year period will be published as a longitudinal study giving valuable data on the natural history of the major diabetic complications.

The AIMS of the study are (a) to establish the prevalence of diabetic foot disease and its risk factors in a geographically defined population identifying diabetics with:

1. clinical peripheral neuropathy
2. peripheral vascular disease
3. foot ulceration
4. amputation of the lower limb
5. foot deformity

and (b) to compare the findings with an age and sex matched non-diabetic control group.

Chapter 1

THE SYNDROME OF DIABETES MELLITUS

Diabetes mellitus is a descriptive term for a group of diseases which are characterised by the finding of hyperglycaemia. Although diabetes has been described through the centuries it was not until the late 19th century that Minkowski located the abnormality to the pancreas.

Diabetes mellitus is normally defined by biochemical criteria laid down by the World Health Organisation (1985_B). The criteria recommended for NIDDM are derived from epidemiological data, and glucose levels within the diabetic range have been shown to be associated with development of small vessel complications (Jarrett and Keen 1976). In the group who neither have normal glucose tolerance nor meet the criteria for frank diabetes mellitus there is minimal risk of small vessel complications but they are more likely to have or to develop macrovascular disease. This group may sometimes revert back to normal glucose tolerance or in a small percentage may go on to develop frank diabetes (Birmingham Diabetes Survey Working Party 1976).

Diabetes mellitus is now classified as insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM). Some prefer to use the terms type 1 and type 2 diabetes mellitus respectively. IDDM subjects are generally aged 30 or less at onset and tend to present acutely with symptoms of polyuria, polydipsia and weight loss. The hallmark of this condition is the propensity to ketosis and indeed most have evidence of ketonuria at presentation. Usually they are thin and without insulin usually die within months of diagnosis. NIDDM subjects are typically overweight, aged 40 or more and are often asymptomatic of hyperglycaemia. Diagnosis is frequently made at presentation of one of its complications or the chance finding of glycosuria at a routine medical examination.

The classification is obviously descriptive and there are often "grey areas" where a subject does not readily fit into either category. Nevertheless the classification works reasonably well in

clinical practice and will probably remain for the foreseeable future. In some instances diabetes mellitus is secondary to another disease (for example Cushing's syndrome) and as a consequence is termed secondary diabetes mellitus. Such cases are a small minority.

The aetiology of the two main types of diabetes is completely different. IDDM is the result of destruction of the beta cells of the islets of Langerhans and leads to a severe deficiency of insulin. Histological examination of the pancreas shows an inflammatory process which culminates in fibrosis and occasionally deposition of amyloid. Alpha and delta cells in the islets either persist or increase (Govan et al 1981).

There is now much evidence to suggest that type 1 diabetes mellitus is a chronic organ specific auto-immune disease. Islet cell antibodies are present in the majority of newly diagnosed insulin dependent diabetics (Tarn et al 1988). They are also present in siblings of affected individuals and the presence of islet cell complement fixing antibodies greatly increases the relative risk of developing IDDM. It should however be appreciated that islet cell antibodies may occur transiently in normal individuals and their presence does not necessarily indicate the development of diabetes in the future.

IDDM probably has both a genetic and environmental aetiology. Genes in the class 2 region of the HLA system on chromosome 6 are associated with IDDM. The relative risk of developing IDDM with HLA DR3 or DR4 is 5 and this risk increases markedly for some HLA DQ region genes (Leslie et al 1989). In practical terms however this risk is relatively minor since only one third of identical twins develop IDDM. Environmental factors are clearly important. Epidemiological work has shown that the rapid rise in incidence and prevalence in certain ethnic groups and migrants cannot possibly be attributed to a single genetic disorder alone. (Diabetes Epidemiology Research International 1987). The exact nature of this environmental agent has not yet been established but may well be due to a virus or indeed several viruses.

In NIDDM the pathogenesis is far from clear but its aetiology is largely genetic. Twin studies have shown concordance rates for NIDDM approaching 100% (Taylor 1989). Apart from unusual types of NIDDM the mode of inheritance is polygenic in nature. In the vast majority of cases there is no HLA association with NIDDM.

The pancreas in NIDDM is of reduced volume (Fonesca et al 1985) and histologically there is no discrete beta cell abnormality. Post mortem studies have however shown a reduction in beta cell mass with fibrosis and amyloid deposition in the islet (Taylor 1989). Although NIDDM subjects are often obese with concomitant insulin resistance and hyperinsulinaemia they also appear to have a defect in islet cell function. When obese subjects with normal glucose tolerance are matched with obese subjects with glucose intolerance, insulin responses are less in the glucose intolerant group following a glucose challenge. It appears that the basic defect is a fault in the first phase glucose induced secretion. Progessive islet cell failure is matched by a rise in glucose to maintain basal and second phase insulin output. A point is reached where compensation by raising the glucose concentration is not possible ie when the renal threshold for glucose is exceeded. Insulin resistance, as a result of obesity, exacerbates the glycaemia in NIDDM (Porte 1991).

The incidence of IDDM varies from country to country and even within different regions of a country. Japan has one of the lowest incidence rates at 0.54 per thousand and Finland the highest at 28.6 per thousand (Jarrett 1986). Perhaps more interesting than the absolute incidence rates for IDDM is the rate of change over the last 20 years. In some countries the incidence has doubled (Jarrett 1986). Clearly the risk of developing IDDM is heavily influenced by environmental rather than genetic factors.

Prevalence and incidence rates for NIDDM also vary markedly from country to country and indeed area to area in many countries. Probably some of the variation is accountable by methodological differences and until recently the use of varying definitions of diabetes mellitus. This has made comparisons between different

studies speculative and it is difficult to determine whether rates truly differ between regions and even whether they are increasing. West (1972) screened random samples from different populations using identical glucose challenge and found marked differences in glucose tolerance between different ethnic groups. North American Indians, Polynesians, Micronesians and Melanesians have a particularly high prevalence for NIDDM which seems to be a recent phenomenon (West 1974). Again this indicates that environmental factors must exert powerful effects in determining the prevalence of NIDDM despite its undoubted genetic aetiology.

Both IDDM and NIDDM are associated with excess mortality. In IDDM renal disease accounts for most of this excess but cardiovascular causes become significant after the age of 30 (Jarrett 1989). In NIDDM cardiovascular disease is the major cause of mortality. Indeed it may account for up to 70% of all deaths in this group. The excess mortality risk for NIDDM diminishes with age until a point is reached at 75 years when there is virtually no difference from non-diabetics (Panzram 1987). The excess mortality risk for men and women is roughly similar although some studies report a higher excess risk in women.

Diabetic Neuropathy

Diabetic neuropathy may be defined as symptoms of neuropathy accompanied by abnormal physical findings and/or objective measurement abnormalities. (Report and recommendations of the San Antonio conference on diabetic neuropathy 1988). Hitherto there had been a lack of a clear universal definition of neuropathy and this may well have hampered research into the pathogenesis and epidemiology of the condition. It may be classified in many ways, usually relating to its clinical manifestations but the simplest one may well be that advocated by Dyck et al (1987) and shown in Table 1.1. Distal symmetrical neuropathies may be further sub-divided into acute and chronic syndromes.

Histologically diabetic neuropathy is characterised by loss of myelinated and unmyelinated axons in a length related pattern. Axons may sometimes show evidence of regeneration which may be implicated in the severe pain sometimes found in peripheral neuropathy (Asbury and Fields, 1984).

The aetiology of diabetic neuropathy is uncertain. Both metabolic and vascular causes have been put forward. The former has attracted much interest in recent years although most of the work has been performed on diabetic rats. Caution is therefore needed when extrapolating the results of such data to what occurs in man. Briefly the substances sorbitol and myoinositol seem to be implicated in the pathogenesis of nerve dysfunction in diabetes. The former is elevated in diabetic nerves and the latter reduced. Decreased myoinositol concentrations affect the metabolism of membrane phoso-inositides - lipids known to be important in the function of excitable cell membranes. It is postulated that the decreased myoinositol leads to both functional and structural abnormalities (Green et al 1987). The former is manifested by slow nerve conduction velocity and the latter by nerve swelling at the node of Ranvier.

The exact relationship between sorbitol accumulation and myoinositol depletion is not known. Nevertheless aldose reductase inhibitors (the latter enzyme is necessary for the conversion of glucose to sorbitol) correct both metabolic abnormalities suggesting a link between the two. These biochemical abnormalities are exciting finds because they do raise the possibility of preventive treatment.

Evidence for vascular aetiology of diabetic neuropathy comes from both histological and physiological findings. Dyck et al (1985) found vascular changes in the endoneural capillaries which included endothelial cell proliferation and capillary closure. Additionally peripheral nerve oxygen tensions have been shown to be decreased in diabetics with chronic sensory neuropathy (Newrick et al 1986). The capillary changes, which may lead to nerve hypoxia, may offer an explanation as to why neuropathy seems to progress and develop even in well controlled subjects.

Peripheral nerves consist of myelinated and unmyelinated as well as small and large fibres subserving motor sensory and autonomic functions. Small fibres subserve pain, temperature and autonomic function and large fibres vibration and joint position sense. There is evidence that small fibres are affected before large fibres (Guy et al 1985). There is no research indicating why sensory rather than motor function is affected predominantly in diabetic neuropathy.

Often diabetic neuropathy is painful and within that category there is a sub-group characterised by rapid onset of severe pain but with few physical findings and only minor abnormalities of nerve conduction (Archer et al 1983). Fortunately the syndrome seems to be usually reversible.

Chronic neuropathy is a far more usual finding and aside from pain the major problem associated with the condition is ulceration and tissue destruction in the extremities, particularly the feet.

Physical findings in diabetic neuropathy tend to be predicted by the fibre loss. For example, the predominantly small fibre type is characterised by loss of pinprick and temperature perception but reflexes are relatively preserved. Predominantly large fibre neuropathy is characterised by loss of position sense and vibration usually with absent reflexes. Although small fibre neuropathy seems to occur in isolation it is doubtful whether the same applies purely to large fibre loss (Thomas and Brown 1987).

Arthropathy also occurs in diabetic neuropathy although it is uncommon (Sinha et al 1972). This complication seems primarily associated with loss of pain and sensation although autonomic neuropathy has also been implicated in its pathogenesis. In contrast to other diseases associated with neuropathy, such as syphilis, neuropathic joints in diabetes tend to occur more distally. In particular the tarsal and ankle joints are usually involved.

Peripheral Vascular Disease

This is a term used to denote macrovascular disease of the arteries of the upper and lower extremities. The basic pathology seems to be histologically identical to that found in non-diabetics ie arterial wall thickening due to fibrosis and atheroma of the intima along with replacement of smooth muscle fibres in the media. The combination of arterial thickening and atheroma is known as atherosclerosis. Atherosclerosis may affect arteries down to 2 mm in diameter (Muir 1985). The histological lesions consist of plaques containing variable proportions of lipid and fibrous tissue. Plaques may undergo haemorrhage or may rupture and ulcerate with subsequent thrombosis. The haemorrhagic plaque may seriously narrow the arterial lumen resulting in ischaemia and thrombosis may cause organ infarction by complete occlusion of the vessel.

The precise aetiology of atherogenesis is unknown and is probably multifactorial. There are however many risk determinants for atheroma derived mainly from research into coronary artery disease. Few epidemiological studies investigating risk factors for peripheral vascular disease have been performed - even in non-diabetic populations. The Framingham study suggests that age, systolic pressure, cigarettes, serum cholesterol, blood glucose and vital capacity are independent predictors of symptomatic peripheral vascular disease in the general population (Kannel and McGee 1985). Predictors of peripheral vascular disease in diabetic populations per se (with adequate classification and definitions of diabetes) are virtually non-existent.

Peripheral vascular disease is manifested clinically by intermittent claudication, absent pulses and gangrene. Further discussion regarding the pathological and clinical differences between peripheral vascular disease in diabetics and controls as well as its role in the pathogenesis of diabetic foot disease will be discussed in the next chapter.

Media Calcification of Peripheral Arteries

This is a degenerative disease of unknown aetiology affecting the media, particularly in the large arteries of the lower limb. The intima is unaffected although there may be concomitant atheroma. Although generally regarded as an exaggerated feature of ageing (Muir 1985) there is evidence that it is more common in diabetics matched for age (Pyorala and Laakso 1983). In addition the media calcification has been reported to be associated with the duration of diabetes independently of age (Pyorala and Laakso 1983). Although it is generally felt to be an "innocent" radiological finding there is some evidence that it has physiological significance (Christensen 1968). Its role in the pathogenesis of distal ischaemia, if any, is unknown.

CLASSIFICATION OF NEUROPATHY TABLE 1.1

(AS PROPOSED BY DYCK ET AL 1987)

I. SYMMETRIC DISTAL POLYNEUROPATHY

II. SYMMETRIC PROXIMAL NEUROPATHY

III. ASYMMETRIC NEUROPATHY
(> 25% DIFFERENCE BETWEEN SIDES)

- A. CRANIAL
- B. TRUNK - RADICULOPATHY OR MONONEUROPATHY
- C. LIMB PLEXUS OR MONONEUROPATHY C SYNONYMS: DIABETIC AMYOPTROPHY, FEMORAL NEUROPATHY, LIMBOSACRAL PLEXUS NEUROPATHY
- D. MULTIPLE MONONEUROPATHY
- E. ENTRAPMENT NEUOPRATHY (EG CARPAL TUNNEL SYNDROME)
- F. ISCHAEMIC NERVE INJURY FROM ARTERIAL OCCLUSION

IV. ASYMMETRIC NEUROPATHY AND SYMMETRIC DISTAL POLYNEUROPATHY (MIXTURES OF I, II AND III)

Chapter 2

DIABETIC FOOT DISEASE - PATHOGENESIS, AETIOLOGY, EPIDEMIOLOGY AND MANAGEMENT

Foot disease in diabetes mellitus encompasses foot ulceration and gangrene often culminating in amputation. Diabetics are particularly prone to these problems but they are not confined to diabetics per se (Nabarro 1988). Previous research has indicated that peripheral neuropathy and peripheral vascular disease are the major determinants of diabetic foot disease but the exact aetiology and pathogenesis of foot ulceration has not yet been established. Studies so far have been cross-sectional rather than longitudinal and risk factors therefore have been assumed rather than proven. Furthermore since group studies have been highly selected, usually hospital based, their results may well be biased.

Pathogenesis of Diabetic Foot Disease

Diagram 2.1 shows how foot ulcers may develop with the interaction of different pathological processes. It should be noted that this diagram is simplistic and gives the impression that the two main processes, ie abnormal blood flow and neuropathy, occur in isolation. In clinical practice this is often not the case.

Neuropathy

Both peripheral, autonomic and somatic neuropathy are thought to contribute to foot ulceration through independent mechanisms. The relative importance of each type is disputed.

Autonomic Neuropathy and Diabetic Foot Ulceration

Clinical evidence of autonomic involvement in the lower limbs is manifested by dry cracked skin, dilated dorsal veins and callus tissue under high pressure points. The dry cracked skin has been attributed to decreased sweating and the dilated dorsal veins to arterio-venous shunting. The oxygen content of blood samples from these veins is increased in keeping with the hypothesis (Boulton et

al 1982_B). Sympathetic fibres are known to cause vasoconstriction and clearly through this mechanism blood flow to the foot could be altered in the context of autonomic neuropathy.

It has been shown by Archer et al (1984) that blood flow to the foot in diabetics with peripheral neuropathy is increased up to five times compared to normal subjects at the same temperature. They found the increased flow greatest in severe painless neuropathy where 60% of patients had foot ulceration. They also however found the abnormality in the painful neuropathy group. Furthermore even subjects in the non-neuropathic diabetic group also demonstrated marked increases. It was concluded that sympathetic defects resulting in high peripheral blood flow were common in diabetics in general.

Other studies have demonstrated over-perfusion of the foot. Scarpello et al (1980) demonstrated, using pulse wave form velocities, a significantly increased flow to the foot in diabetics with ulcers compared to non-diabetics, non neuropathic diabetics and diabetics with neuropathy but without ulceration. Since pulse wave velocity is dependent on arterial wall rigidity it was postulated that in the ulcer groups there may be incipient peripheral vascular athero-sclerosis accounting for this difference. All patients in the study had a normal valsalva ratio.

Edmonds (1986A) also found significant abnormalities in pulsatility index in patients with ulcers compared to patients with neuropathy and controls. It was concluded that although probably autonomic neuropathy could not alone cause ulceration it was nevertheless strongly associated with its development. Another conclusion could have been however that they were merely looking at a more severe neuropathy group, ie severe enough to cause ulcerative changes, and more likely to involve all types of nerve fibres.

Similar findings were reported by Corbin et al (1987). Reduced peripheral resistance was found in diabetics with neuropathy and foot ulcers, diabetics with neuropathy but no ulcers and also diabetics with neither ulceration or neuropathy. However, in the

ulcer group the blood flow abnormalities were markedly worse. Interestingly peripheral somatic nerve dysfunction was also more severe in the diabetic group who had ulcers but autonomic function tests were similar between the diabetics with neuropathy and ulceration and those with neuropathy but no ulceration.

The conclusions that can be drawn from these studies are that blood flow to the foot is abnormal in diabetics with neuropathic ulceration and there is increased flow in the capillaries with shunting of blood possibly due to sympathetic denervation.

What is the relevance of these blood flow abnormalities? Rayman et al (1986) have shown that although the perfusion of the foot is increased the actual vascular response to injury is less than that in age/sex matched healthy controls. This impairment is independent of glycaemic control and could not be attributed to a decrease in capillary number. Clearly abnormal vascular response to trauma may be important in ulcer formation but whether this abnormality is related to chronic over-perfusion remains to be established. Rayman et al (1986) have also shown that high blood flow exists even when the foot is below the level of the heart. The latter would suggest impairment of the veno-arteriolar reflex which occurs when venous pressure increases and leads to an increase in arterial resistance. It is thought to prevent oedema occurring in normal individuals.

Edmonds et al (1986_B) have suggested that loss of this reflex may cause neuropathic oedema. The oedema could obviously interfere with nutrient exchange leading to ulceration but oedema is, however, rare in clinical practice. In contrast Flynn et al (1989) have recently demonstrated capillary under-perfusion on standing indicating no loss of capillary vasoconstriction. It would help to explain why neuropathic oedema is rare and also indicates that the ischaemia may occur as a result of this under-perfusion.

Clearly perfusion of the foot is grossly abnormal but its importance in the pathogenesis of ulcer formation is uncertain. The role of autonomic neuropathy as a pre-requisite for ulcer formation is not yet proven. Validated direct measurements of sympathetic impairment are needed to detect early subtle abnormalities.

Somatic Neuropathy in Foot Ulceration

Somatic neuropathy has long been recognised to be of great importance in the genesis of foot ulceration. Oakley et al (1956) were impressed by the clinical absence of large vessel disease in many cases of ulceration and considered neuropathy a discrete aetiological factor in foot ulceration. The questions that need to be addressed are: "Is somatic neuropathy a pre-requisite for foot ulceration" and, if so, "what features of the neuropathy precede or predispose the diabetic to ulceration?" The precise answer to the first part of the question is not known at the present time since no inception cohort studies have been undertaken to evaluate risk factors for diabetic foot disease over a period of time. In the absence of longitudinal studies the impact of either somatic or indeed autonomic neuropathy is speculative.

Cross-sectional studies do however suggest that somatic neuropathy is a prime aetiological factor in the pathogenesis of foot ulceration. Martin (1953) emphasised the need to identify neuropathy as a discrete cause of foot ulceration in addition to infection and vascular insufficiency.

Kelly et al (1958) reviewed 47 patients who had undergone treatment for neuropathic ulceration of whom approximately 50% were diabetic. Ellenberg (1968) described 36 cases of neuropathic ulcer and noted all patients had a profound sensory loss and absent ankle jerks. Most also complained of numbness but painful sensations seem to have subsided by the time they developed ulcers. Both Ellenberg and Kelly noted the ulcers were always under high pressure points (mainly the metatarsal heads) and considered mechanical factors must be of importance in addition to anaesthesia. Both were impressed by "the architecture of the feet" describing hammer toes and prominent metatarsal heads.

Delbridge et al (1983) in a review of neuropathic ulcers also considered mechanical forces in addition to changes in connective tissues a pre-requisite for foot ulcer formation. Rafferty et al (1986) investigated two groups of patients, one with a history of past or present ulceration and the other with no such history. Of

the ulcer group 80% had neuropathy compared to 40% in the non-ulcer group. Of the latter only one third had autonomic neuropathy.

More recent research has looked further into which type of fibre and modality loss predominates in neuropathic ulceration. Certainly from the studies to date it was seen that not all neuropathy leads to ulceration and this may reflect difference in severity or could be due to particular features of some types of neuropathy. Another possibility is that a catalyst is necessary to trigger a sequence of events leading to ulceration in somatic neuropathy.

Said (1980) investigating non-diabetic neuropathic ulceration investigated 16 patients clinically and histologically. Clinically pain and temperature perception was always diminished or absent and muscle strength always normal. Vibration and position sense was abnormal in approximately half the patients. Histologically large fibres were primarily involved followed by small myelinated and unmyelinated fibres. Indeed unmyelinated nerve fibre densities were normal in some cases which is at variance with the clinical findings.

Thermal and vibration sensation was evaluated by Guy et al (1985) in diabetics. It was found that thermal sensation may be impaired in isolation but the reverse was never found. In groups with ulcers and Charcot's joints there was severe impairment of both modalities indicating both large and small fibre involvement. The clinical and pathological study performed by Said et al (1983) investigated 5 patients with dissociated sensory loss of pain and temperature. Two of these patients had plantar ulcers. Small fibre loss was apparent in all biopsies but in the two cases of ulceration (one of Charcot's arthropathy) large fibre loss was severe. Clearly care must be exercised in drawing any definite conclusions from such small studies.

Young et al (1986) investigated the relationship between somatic and autonomic neuropathy in various diabetic groups. They found large fibre abnormalities tended to predominate in painless neuropathy associated with foot ulceration. Acute and chronic

painful neuropathy groups were compared to the painless ulcer group and the degree of autonomic neuropathy was similar in all three categories. A possible conclusion from the study is that small fibre involvement is always present in diabetic neuropathy but in some cases large fibre neuropathy occurs in addition. The latter would indicate more severe degrees of neuropathy and would be more likely to give rise to ulceration.

Boulton et al (1986) investigated various quantitative parameters thought to be associated with foot ulceration including measures of large fibre function (vibration thresholds) and small fibre function (valsalva ratio and skin resistance). Vibration thresholds had the strongest correlation with ulceration although autonomic function was also abnormal. Clearly these results would again indicate that both large and small fibre abnormalities are involved in ulceration. Since a large fibre abnormality may indicate advanced neuropathy it is not surprising that vibration had the best correlation with ulceration. Boulton et al also noted that all in the ulcer group had clinically impaired pain perception but since this could not be quantified it was not considered further in the analysis.

In conclusion somatic neuropathy is associated with foot ulceration and diminished pain perception always seems to be present. In actual ulceration with neuropathy there also seems to be large fibre involvement and this finding is not confined solely to diabetic neuropathy. Why large fibre neuropathy should predispose to ulceration is not known but a possibility is that it reflects a more advanced stage of neuropathy where tissue destruction is liable to occur.

Distal Motor Neuropathy

Distal neuropathy affects the motor system to only a limited extent. This, therefore, in most cases allows free mobility of the subject with neuropathy. Clearly this mobility may lead to high pressures under the foot and explains why most ulcers occur over high pressure bearing areas.

Muscle wasting due to denervation does occur (Fagerberg 1963) even though there is often no weakness. Lippmann et al (1976) considered that this motor involvement commonly leads to weakness of intrinsic muscles of the foot leading to unopposed action of the long extensor tendons. Eventually this wasting culminates in the typical cavus deformity often found in somatic neuropathy. Inter-phalangeal flexion and metatarsal phalangeal hyperextension, and eventually dislocation, occurs giving rise to the high arched foot with claw toes. The protective fibrofatty pad under the metatarsal heads is dislocated distally allowing much greater pressures under this area. Ellenberg (1968) and Kelly et al (1958) noted the wide forefoot with digital deformity presumably resulting from very high metatarsal head pressures.

Pressure and Diabetic Foot Ulceration

The observation of ulceration occurring at high pressure points in the neuropathic foot has led to much research into the measurement of these pressures and their role in the pathogenesis of ulceration. Barrett and Mooney (1973) using the Hams footprint test found static loading of up to 60 pounds per square inch in plantar ulcers and concluded that pressure in addition to anaesthesia was necessary for ulcer formation. The study was limited however because only static pressure measurements were performed. Stokes et al (1975) looked at dynamic pressure loading underfoot to determine whether there was a difference between groups with neuropathic ulcers and groups with neuropathy but without ulcers. They found maximal pressures at the site of ulceration and a trend of highest loading onto the forefoot with a reduction on the toes. This trend tended to correlate with the degree of severity of neuropathy and supported the concept of intrinsic muscle wasting leading to greater forefoot loading. Similar results were found by Ctercteko et al (1981) who also compared vertical pressures underfoot in control and ulcer groups. The control groups consisted of normal subjects and neuropathic individuals without ulceration. The site of maximal force correlated with the site of the ulcer but there was no direct relationship between peak force and ulceration, ie, there was overlap betwen ulcer and control

groups. They concluded that foot deformity per se leads to high pressure which although often present in neuropathy is not exclusive to this condition. Sensory impairment was a pre-requisite for ulceration. Conclusions should be guarded because measurements were made barefoot and were concerned with only vertical forces. At the shoe-foot interface there could be other mechanical factors such as shear force.

In order to determine the relative importance of high pressure in the pathogenesis of ulceration it is necessary to follow such groups over time. The study by Ctercteko et al was cross-sectional and ulcers could well develop with time in unaffected peak force areas.

Boulton et al (1987_A) addressed the problem by following up patients with neuropathy over a 3 year period. The study showed that high foot pressure areas may disappear, appear or change distribution. Six patients had recurrent ulcers, 5 of which were under previous high pressure points. The paper did not indicate whether ulcers occurred under high pressure points in neuropathy cases where hitherto there had been no history of ulceration.

Rheumatoid arthritis is a condition which mimics foot deformity of diabetic neuropathy. Masson et al (1989) investigated whether high pressure per se associated with foot deformity caused plantar ulceration. Patients with rheumatoid arthritis were compared with diabetics both having similar foot deformities. Approximately one third of the diabetics had previous plantar foot ulceration but none of the arthritis group had such a history. The frequency of high pressure areas was identical in the two groups but the rheumatoid group had little evidence of neuropathy compared to the diabetics.

Clearly the work of Ctercteko et al (1981) and Masson et al (1989) strongly suggests that high plantar pressures are not primary causes of plantar ulceration. Somatic neuropathy, possibly by loss of pain and proprioception, is the permissive factor for ulceration. Pressure, whether constant over hours or repetitive moderate stress, is a trigger for tissue necrosis and ulcer

formation. Local factors such as dry cracked skin and infection may serve to fuel this destructive process. Foot deformity whether caused directly by neuropathy and small muscle wasting or acquired from other causes unrelated to diabetes, must however be considered a highly important factor in ulcer development.

Circulatory Disorders

Large Vessel Peripheral Vascular Disease

This is a term used to describe athero-sclerotic lesions in the arterial circulation of the lower limbs. Clinically it is manifested by absent peripheral pulses, intermittent claudication and gangrene. The basic pathological lesions in the arteries do not differ qualitatively from non-diabetics (see Chapter 1). There are however differences in clinical presentation. The site of occlusion in peripheral vascular disease is important clinically because proximal lesions are more likely to be amenable to surgery should it be necessary. Studies that have compared large vessel disease in diabetics and non-diabetics are relatively few but the general finding is that peripheral vascular disease in diabetics tends to be more distal.

Strandness et al (1964) compared 42 diabetics with 35 non-diabetics, each having evidence of peripheral vascular disease. The groups were further divided into amputation and non-amputation categories. The site of obstruction in the arteries was determined by both a clinical and non-invasive means and all amputations were examined histologically. They found that the diabetic category had a significantly higher involvement in the arteries below the knee but only in the amputation group. The main difference between diabetics and non-diabetics in the non-amputation group was the presence of neuropathy in the former.

Conrad (1967) performed a pathological study on diabetic and non-diabetic amputations using a cast method. Twenty successive amputations were examined. It was found that diabetics had much greater occlusion of arteries below the knee although surprisingly

the foot vessels were involved less in the diabetic group. Haimovici (1967) performed an angiographic study on 321 lower extremities in 189 patients. Approximately 50% were diabetic. Again there was a greater incidence of infrapopliteal involvement in the diabetic group particularly involving more than one artery.

Arterial occlusion of the foot vessels was examined by intra-operative post reconstruction angiography by Karacagil et al (1989). Most of the patients undergoing surgery had rest pain or gangrene. They found there was no difference between the involvement of foot arteries between diabetics and non-diabetics. Clearly this was a specialised group of patients and may not be extrapolated to diabetics with peripheral vascular disease in general. Nevertheless it supports the work of Conrad who did not find more severe disease in pedal arteries in diabetics, at least in amputations.

In non-diabetics peripheral vascular disease may manifest clinically from absent pulses to frank gangrene and ulceration. Marinelli et al (1979) thought that occlusion of the distal vessels, ie tibial and peroneal arteries, often did not give rise to claudication. They also suspected that peripheral neuropathy would abolish claudication. It was found that 31% of diabetics who had peripheral vascular disease defined by non-invasive criteria did not have claudication. There was however no control group of non-diabetics for comparison. It is well known in the latter population that a large percentage of peripheral vascular disease remains asymptomatic (Widmer 1964).

It is well established that when an artery gradually occludes collateral vessels are formed. Conrad (1967) has shown that collateral vessels are present in roughly equal proportions in both diabetics and non-diabetics. Despite the presence of collaterals diabetics with peripheral vascular disease may well be at greater risk of ulceration, as we shall see later. Possibly the presence of super-added neuropathy may allow potentially disastrous events to occur. For example tight shoes are more likely to be tolerated in

diabetics allowing the external pressure of the shoe to exceed the perfusion pressure to the foot. Warm baths may well be tolerated by the diabetic greatly increasing oxygen demand to the already devitalised tissues. In the setting of severe peripheral vascular insufficiency this demand may not be met resulting in tissue necrosis (Lippmann and Farrar 1979_B).

The neuropathy and more distal peripheral vascular disease may well account for the worse prognosis of occlusive arterial disease in diabetics. The presence of small vessel disease which may also be relevant will be discussed in the next section. Other than these latter three findings there seems to be no difference between peripheral vascular disease in non-diabetics and diabetics alike.

Small Vessel Disease and Foot Ulceration

The role of small vessel disease in the genesis of foot ulceration is disputed. Some authors consider arterioles in the definition of small vessels whilst others confine the terms solely to capillary abnormalities. Goldenberg et al (1959) examined 152 amputation specimens, from mid thigh to a single toe, of which 92 were from diabetics. They found a lesion of small arteries and arterioles which they believed to have a causal relation to diabetes. The lesion consisted of endothelial cell proliferation often leading to complete occlusion of the lumen with PAS staining material throughout the proliferating endothelium. Capillary changes were also noted including those subserving nerves. Skin and muscle capillaries were also affected.

The study by Goldenberg et al was retrospective and two prospective studies by Strandness et al (1964) and Conrad (1967) failed to confirm these findings. Banson et al (1964) did not confirm endothelial proliferation but did note dermal basement membrane thickening in diabetics, both in amputation specimens and at necropsy. Surprisingly there was no correlation with the duration of diabetes. Moore et al (1965) in a similar prospective study, examining skin from amputations and biopsies, also found capillary basement membrane thickening and indeed also endothelial cell proliferation.

Arterioles were also affected. The prevalence of these lesions was greater in diabetics with foot lesions than without and the authors concluded that they played a significant part in the causation of ulceration.

Non-histological investigation of microvascular disease being implicated in the causation of foot ulceration has also been attempted. Faris (1975) found a significant correlation between ankle toe pressures and diabetic foot lesions in the absence of large vessel disease. These patients also had evidence of peripheral neuropathy. It could be wrong to assume that pressure drop between ankle and toe could only be due to occlusion of small vessels. If sympathetic denervation were present a loss of peripheral resistance could account for the difference. More recently Irwin et al (1988) performed a similar study investigating the possibility of small vessel disease in the causation of foot ulcers where neuropathy and large vessel occlusion had apparently been excluded. The small vessel disease group were thought in retrospect to have neuropathy, although initially had been referred by physicians as cases of foot ulcers with no attributable cause. Resting toe flow rates were increased in patients with supposed small vessel disease although there was a modest pressure drop between ankle and toe. The findings of both Faris and Irwin could be attributed to severe autonomic neuropathy and not occlusive microvascular disorder.

The literature is thus confusing as regarding a specific occlusive small vessel lesion leading to foot ulceration. There seems to be reasonable evidence of basement membrane thickening of the microcirculation but no definite evidence of occlusive disease pathognomonic of diabetes. Basement membrane thickening may be important in the pathogenesis of ulceration but at the present time this is speculative (Logerfero 1987).

Infection and Diabetic Foot Disease

Probably infection is not a primary factor in the pathogenesis of diabetic foot ulceration. More likely it is a complicating factor when either, or both, of the two primary aetiological agents are present. A clinico-pathological study of foot ulcers performed by Jones et al (1987) isolated a variety of organisms from foot ulcers including staphylococci, streptococci, coliforms, pseudomonas aeruginosa, anaerobes and various non-pathogenic bacteria. There was no correlation between the type of lesion and the amount of organisms per swab.

Bacteroides, proteus, streptococci, staphylococcus aureus, clostridia and escherichia coli were the commonest pathogens isolated by Louie et al (1976) using what was described as "optimal microbiologic techniques". It was noted that anaerobic bacteria were isolated from 19 out of 20 foot ulcers. They also suggest anaerobic pathogens are significant in deep lesions. No specific pathogen could however be linked to extension of the pathological process when they analysed stable and complicated cases of foot ulcers. In conclusion chronic lesions with no evidence of cellulitis or osteomyelitis were unlikely to benefit from anti-microbial therapy.

Infection adversely affects diabetic control and as Kozak (1984) indicates, poor control may predispose to infection. Studies have been performed which suggest that poor diabetic control may affect the granulocyte leading to abnormalities of adherence (Bagdade et al 1978), engulfment and intracellular killing (Nolan et al 1978).

The abnormalities quoted were reversible at least partially by improving metabolic control. This would indicate that correction of poor diabetic control is an important aspect of management in diabetic foot disease even though infection per se is probably not the initial instigator of ulceration.

A knowledge of the frequency, the prognosis and the characteristics of the population who develop diabetic foot disease is of paramount importance if appropriate preventative strategies and resource allocations are to be instituted. Clearly endpoints of diabetic foot disease are not exclusive to diabetics in that ulceration and amputation also occur in non-diabetics. Similarly neuropathy and peripheral vascular disease will also be prevalent in the general population. We therefore need to know the excess frequency of these variables in the diabetic population by comparison with rates in non-diabetics. The populations studied are also important. Hospital diabetic clinic attenders will not be representative of the diabetic population in the community and nor will those seen predominantly in general practitioner clinics.

In considering excess frequency rates for any of the variables concerned with diabetic foot disease we need to know the following:

1. the prevalence of diabetes within the general population studied,

2. the frequency of the variable within the diabetic population and

3. the frequency of the variable within an age and sex matched reference group randomly drawn from the general population.

When reviewing the literature with regard to the frequency of neuropathy, peripheral vascular disease, amputation and foot ulceration in the following sections, where appropriate, emphasis will be placed on those studies which fulfil the above criteria.

Neuropathy

Frequency

There are few population studies concerned with the prevalence of diabetic neuropathy. Previous studies are predominantly hospital clinic based and there is no uniformity in the definition of

neuropathy. The diagnostic methods used to establish its presence also differ markedly ranging from sophisticated electro-physiological tests through to somewhat subjective physical findings. A list of such studies is given in Table 2.1, mainly to illustrate the diversity in prevalence of neuropathy encountered, when such lack of uniformity exists, and also to emphasise the importance of using standardised diagnostic criteria in representative diabetic populations.

Limited numbers of diabetic population studies do exist and some with non-diabetic control groups. Nilsson et al (1967) identified 598 diabetics who had been seen in the hospital medical department or who were under the care of general practitioners within the catchment area of the Central Hospital Kristianstad (Sweden). The community patients constituted 10% of the total number of patients identified. The catchment area for the hospital was 95,717. This figure seems unrealistic as hospital catchment areas are seldom so precise. The prevalence of diabetes mellitus was therefore of the order of 0.62% which seems low compared to estimated known diabetic prevalence rates in the UK. Strict definitions of diabetes mellitus were, however, employed and they disregarded transient elevations of glucose in the context of acute illness. Possibly they excluded subjects who were diabetic by present day criteria. Furthermore only diabetics aged between 20 and 79 were included. Nilsson examined vibration perception and ankle jerks but no attempt was made to define neuropathy or to elicit any symptoms. Nevertheless a control group consisting of age and sex matched non-diabetics was used for a comparison with groups of short and long duration diabetics. The overall frequency of abnormal neurological findings in the groups is however not readily apparent. The presentation of the data is rather crude and is presented in Table 2.2. For example, the presence of areflexia is calculated for each individual age group according to sex and is a percentage. The percentages are then meaned which clearly does not equal the overall percentage of areflexia for each sex. The numbers in the control group are not specifically mentioned and are apparently the results of a previous study. Despite these limitations there does seem to be a trend of increased neurological abnormality in diabetics compared with controls in all age groups.

Palumbo et al (1978) actually defined and calculated the cumulative frequency of neuropathy in a cohort of diabetics living in Rochester, Minnesota. In 1970 the prevalence of diabetes mellitus was 1.6% and was determined by scrutinising the medical records of all sources of care available in and around Rochester. The criteria used for the diagnosis of diabetes mellitus are, not surprisingly, different from present day WHO definitions. Undoubtedly some diabetics were excluded in the older age group and some younger subjects included who were not diabetic. Neuropathy was defined as symmetric symptoms or decreased vibratory sense with or without hyporeflexia. This is a very broad definition and as Mayne et al (1965) established previously, vibration perception loss and areflexia are a common occurrence in non-diabetic populations. In the Palumbo study 108 patients were found to have neuropathy of which 72% was of a distal polyneuropathy variety. This yielded a cumulative incidence of 7.6% after 25 years.

Knuiman et al (1986) using loss of pin-prick perception as a definition of neuropathy, found a prevalence of 15.3%. The population consisted of 1084 caucasian diabetics living in rural areas within 50 - 800 km of Perth, Australia. The exact prevalence of diabetes within the region was not known but from prevalence data for known diabetes mellitus in Australia it was estimated that 70% of all diabetics within the study area were screened. Clearly this may be inaccurate since purely rural centres were studied. Furthermore 70% is a low screening percentage and is compounded by the fact that those who attended were automatically a selected group. Pin-prick perception is subjective and there was more than one observer. Almost certainly this would have led to inter-observer differences. Loss of pain perception also occurs in non-diabetic populations and unfortunately no control group was available for comparison.

To date, therefore, the frequency of neuropathy on a population basis with an acceptable present day definition is not available, particularly with reference to an adequate control group.

Prevalence data only tell us the magnitude of the problem in a population at one particular point in time. It does, of course, merely reflect survivors and may greatly underestimate the true

problem of neuropathy in diabetics if the latter has any effect on survivorship (which it may reference Ewing D J et al 1985).

Therefore prevalence data are useful in terms of resource allocation but may not give true information regarding the increased risk of developing neuropathy (or indeed anything else) in diabetics compared to non-diabetics. By similar logic it may also give a false impression of the characteristics of diabetics with neuropathy.

Incidence rates may be a measure of the risk of developing a condition - usually expressed as the number of new cases occurring per year in a given geographically defined area. The problem in such calculations stems from identifying the population at risk. A longitudinal cohort study measuring incidence rates for neuropathy and comparing them to a non-diabetic control group will give a measure of the increased risk of developing neuropathy in diabetics. No such prospective cohort studies are available at the present time.

Risk Factors for Neuropathy

Duration of Diabetes

The basic question to be addressed is whether diabetes is a cause of neuropathy. Clearly if a disease directly leads to a particular condition such as neuropathy then the risk of the condition would be expected to increase with duration of the disease. There is a wealth of literature considering the relationship between the duration of diabetes and neuropathy (listed in Table 2.3) but all these studies are flawed for several reasons.

Firstly, most are not population based and as previously mentioned if we look at neuropathy in clinic populations we are of course looking at a biased group. There may equally be many more subjects of a similar duration with no evidence of neuropathy in the community. Secondly they are often cross-sectional and as previously suggested this has problems because we are only looking at a survival group. Thirdly, in non insulin dependent diabetics it is often impossible to ascertain exactly when the onset of

diabetes occurred. It is well known that NIDDs may be diabetic for several years before diagnosis. Mincu (1980) for example investigated complications of diabetes in newly diagnosed subjects with particular reference to pre-diagnostic symptoms. For neuropathy it was noted that 11.62% had evidence of neurological complications. It was noted that the pre-diagnostic period (ie the time elapsed between first symptoms and diagnosis of the disease) correlated positively with the frequency of diabetic polyneuritis and ranged from 4% at 5 months to 19% at 15 months pre-diagnostic period. Obviously they may have been diabetic for even longer than the symptomatic period. This problem, particularly in the older age groups, may account for some of the discrepancies between the studies.

From population studies it is noteworthy that Knuiman et al (1986) found a positive correlation between sensory neuropathy, and duration and age of onset of diabetes. The population study by Nilsson et al (1967) also claimed to show a positive correlation between neurological abnormalities and duration although the correlation coefficients stated do not seem to support this. Some studies have looked at the frequency of neuropathy occurring in cohorts of diabetics over periods of time. Pirart (1978) followed up a non-population based cohort of diabetics over a 20 year period and found the prevalence rate for neuropathy less than 10% at diagnosis increasing to 40% at 20 years and 50% at 25 years. ALthough a longitudinal study he emphasises the problems with such studies by mentioning that sample erosion was a major problem (only 26 cases from an inception cohort of 2,759 remained after 25 years). He also indicates that erosion was not haphazard and that the aged, seriously ill and those with "mild" diabetes tended to default on follow-up. The magnitude of the effect of removing these patients from the population cannot be estimated from these prevalence data. Nevertheless Pirart also calculated incidence data for neuropathy over the 25 year period and found that it had increased from about 3 cases per 100 patients per year initially to approximately 18 cases per 100 previously unaffected patients at 25 years duration. The problems of sample bias and patient follow-up of course still apply.

The population study by Palumbo et al (1978) in non insulin dependent diabetics over the age of 30 found the cumulative incidence of neuropathy at 5 years duration to be 4% which increased to 15% at 20 years. Clearly no comparison may be directly made with Pirart's study since cumulative incidence in practice does not equal prevalence and the two studies differed in subject groups and definition of neuropathy. Nevertheless it would seem from the scant evidence available that there is an association between neuropathy and duration of diabetes mellitus.

Glycaemic Control

If diabetes mellitus causes neuropathy it would be expected that the degree of glycaemic control would be an important variable for its development. Again numerous problems are encountered when investigating the association between degree of glycaemia and neuropathy. These include defining the degree of control, defining what constitutes neuropathy and in experimental studies ensuring that sample sizes are adequate. Is there any evidence from experimental or observational studies that the degree of glycaemia is important in the development of neuropathy?

Previous studies have shown (Mulder et al 1961, Porte et al 1981 and Ward et al 1971) that even at diagnosis diabetics demonstrate abnormalities of nerve conduction and these defects may be partially diminished by starting treatment. Although Young et al (1986) showed that electro-physiological abnormalities may help to predict who will later develop frank neuropathy they are not synonymous with the diagnosis of peripheral neuropathy. They may as Windebank (1986) suggested merely reflect acute metabolic or osmolar abnormalities associated with hyperglycaemia. Holman et al (1983) at Oxford studied 74 insulin dependent diabetics divided into two groups. One group was treated by intensive insulin therapy and the other by conventional insulin regimens. Patients were randomly assigned to each group and diabetic control was assessed by four-monthly glycated haemoglobin estimations. The group was followed up over a two year period. Vibration thresholds were used to assess sensory nerve function and it was significantly

better preserved in the intensive treatment group (even though HbA1 levels did fall in the control group). This study shows that good diabetic control may help to preserve one facet of nerve function but does not tell us whether poor control leads to neuropathy.

Service et al (1986) addressed the problem by performing a similar study to that of Holman et al but included a full assessment for neuropathy. There was no difference between either the intensive treatment or conventional treatment groups. The numbers in this study were small (15 in the rigorously controlled group and 18 in the conventionally treated group) and therefore the power of the study may have been low. Also 5 of the intensive treatment group did not meet the target for excellent control but 8 of the 18 conventionally treated group fulfilled the latter glycaemic control criteria.

As yet there is, therefore, no experimental evidence to suggest that excellent diabetic control prevents the onset of neuropathy. There have been however numerous observational studies investigating the relationship between diabetic control and the presence of neuropathy. The early ones are essentially unhelpful, mainly because there was no satisfactory index of diabetic control. More recent studies using glycated haemoglobin are more useful but most are still concerned with selective groups of diabetics. Palumbo in 1978 in the Rochester, Minnesota population study found that the frequency of distal polyneuropathy was less in diabetic patients with good or excellent control (10% versus 24% of cases with neuropathy). The patients were all NIDDs and the criteria for excellent diabetic control was based on the percentage of fasting glucose levels of less than 8.3 mmol/l. Since fasting glucose levels in NIDDM correlate well with HbA1 results it is a reasonable method of assessing control in such patients.

Boulton et al (1982_A) compared 36 pairs of diabetics with and without neuropathy. The patients came from the hospital diabetic clinics but were matched for age, sex, duration and type of diabetes mellitus. There were also strict definitions as to the diagnosis of peripheral neuropathy. Significantly higher HbA1

estimations were found in the neuropathy group compared with the controls, although the sub-group with NIDDM failed to show this association. In contrast McCann and Davis (1979) found no such relationship. They used a different method for measuring glycated haemoglobin and were not so precise in their definition of neuropathy. However it should be appreciated that glycated haemoglobin is only relevant to the preceding 6 to 8 weeks and several estimations over a period of time would be more useful. Clearly within the confines of a cross-sectional study this is not possible.

Boulton et al (1985) whilst determining the prevalence of symptomatic neuropathy in a clinic population, found no significant difference in diabetic control between those with and without neuropathy. The motor conduction velocities did, however, show a significant correlation with HbA1 estimations. As previously discussed the exact relevance of this finding is not clear.

Knuiman et al (1986), looking specifically for risk factors associated with diabetic complications, found an association between diabetic control (as assessed by glycated haemoglobin) and sensory neuropathy independent of age, type and duration of diabetes.

The conclusion regarding diabetic control and neuropathy at the present time must be that whilst electro-physiological parameters of nerve function correlate well with poor metabolic control, the relationship with definite neuropathy is not so certain. Problems with the present studies are that they are mainly cross-sectional and not truly representative of the total diabetic population.

Age

Age has similarly been cited as a risk factor for neuropathy. Clearly the aging nervous system makes differentiation between normal and abnormal difficult. It emphasises the need for control groups of non-diabetics which are age matched.

Studies that have compared neurological findings in diabetics with non-diabetics have broadly found similar findings. Mirsky et al (1953) found that vibration threshold increased in both groups but the diabetics behaved "as if they were approximately 20 years older". Steiness (1957) reported similar findings but noted the significant correlation with duration of diabetes in contrast to Mirsky et al.

Matthews (1955) and Mayne (1965) found abnormal physical signs occurring often in the ageing nervous system of non-diabetics. Furthermore Mayne (1968) in a follow-up study of diabetic patients with symptomatic neuropathy compared them with a group of diabetics drawn at random from the diabetic clinic. The discriminatory value of absent ankle jerks, impaired vibration and diminished position sense between the two groups was so poor that Mayne concluded that the three findings were not a feature of symptomatic neuropathy. However although the two groups were matched for age and sex 18% of the random group had symptoms of neuropathy.

What is clear from the above discussion is that in both diabetics and non-diabetics there is an increased prevalence of abnormal neurological signs in elderly subjects and care should be taken in defining neuropathy in either group.

Alcohol

Alcohol may cause neuropathy independently of diabetes (Behse et al 1977) and obviously diabetics consuming large quantities of alcohol would be expected to at least have the same risk as non-diabetics. Young et al (1986) found a significant relationship between alcohol consumption and foot ulceration in neuropathic diabetics. There is however no evidence for a synergistic effect of alcohol and diabetes in the genesis of neuropathy available at the present time.

Height

Height, theoretically, may be expected to be a risk factor for neuropathy. Since diabetic neuropathy has a distal length-related pattern of involvement, it implies a greater vulnerability of longer nerve fibres. The question of whether greater height predisposes to the development of neuropathy has seldom been addressed in the literature. Bonkalo (1950) found no difference between heights in groups with and without neuritis. Sosenko et al (1986) found a significant correlation between height and diminished vibration threshold. Clearly the question remains open at the present time.

Neuropathy and Other Diabetic Complications

Since duration of diabetes appears important in the development of neuropathy it would be surprising if there was no association between neuropathy and other small vessel complications which are known to increase in frequency from time of diagnosis. Fagerberg (1959) performed an analysis of the association between vascular complications and neuropathy in diabetics. Strict definitions of each complication were employed and patients were divided into two groups - with and without neuropathy. All but four, however, were inpatients and hence a highly selected group. In all age groups there was a highly significant correlation between neuropathy and both retinopathy and nephropathy. Pirart (1978) also found an association between neuropathy and the other two main small vessel complications. Particularly striking was the highly significant temporal relationship between the three in clinical presentation. Shichiri (1964) found absent patella reflexes were only correlated to retinopathy and not nephropathy. The study by Boulton et al (1985) investigating symptomatic neuropathy in IDDs also found that there was a significant association between retinopathy and neuropathy. Nephropathy was excluded however because of the possibility of uraemia per se causing neuropathy.

Assessing the relationship between different syndromes of diabetic polyneuropathy and retinopathy Young et al (1986) found a significant relationship with both chronic painful neuropathy and recurrent foot ulceration. The latter was associated with a more severe form of neuropathy. Walsh et al (1975) also found an association between foot ulcers and retinopathy in newly diagnosed diabetics.

In summary, studies that have considered the relationship between small vessel complications and neuropathy suggest a strong correlation between the two. Neuropathic foot ulceration seems particularly associated. It does not, however, necessarily suggest that the same small vessel pathological process is occurring in both conditions.

Prognosis in Diabetic Polyneuropathy

Information regarding the natural history and prognosis in distal sensory neuropathy is virtually non-existent. It is important not to confuse transient nerve conduction abnormalities that may occur at diagnosis with established neuropathy. Mayne (1968) followed up 73 patients over periods ranging from 2 to 4.75 years. All had symptoms of neuropathy but they were not graded. In the commonest type of neuropathy (chronic sensory) over 50% of patients either deteriorated or remained the same in terms of symptoms and signs. No mention was made of ulceration or amputation in this group over the period. Clearly without adequate grading of symptoms and signs this study is highly subjective.

Boulton et al (1983) examined the natural history of chronic painful distal diabetic neuropathy over a 4 year period. All patients in the study fulfilled strict criteria for the diagnosis of neuropathy and symptoms were scored on a 10 cm horizontal graphic rating scale (0 = no pain, 10 = maximum pain). Electro-physiological measurements were also performed. It was found that symptoms of neuropathy persisted and electro-physiological recordings deteriorated.

In acute painful neuropathy which should be classified as a separate entity to chronic distal polyneuropathy, the prognosis seems to be good. Archer et al (1983) found all symptoms in 9 such cases subsided within 10 months of onset.

The prognosis in terms of symptomatology in chronic, as opposed to acute, neuropathy seems to be poor, probably underlining the fact that irreversible nerve damage has occurred. The incidence of long term sequelae such as ulceration or amputation in this group of diabetics is not available and will probably reflect the level of care given by both doctor and patient.

Peripheral Vascular Disease

Frequency

Many of the problems that bedevil the accurate determination of frequency and excess risk of peripheral vascular disease in diabetes mellitus are similar to those encountered in considering neuropathy. Population studies are few and there has been a lack of concensus regarding the definitions used to denote the presence of peripheral vascular disease. Early studies are primarily concerned with post mortem and clinical findings whereas more recently emphasis has been placed on non-invasive doppler investigation. The latter method has not only circumvented the problems of pulse palpation but has enabled accurate determination of the total burden of both symptomatic and asymptomatic peripheral vascular disease within populations.

When considering cardiovascular morbidity in diabetics it is important, as Jarrett (1989) has previously indicated, to differentiate between the two different types of diabetes mellitus. In IDD's the impact of uraemia upon mortality is so great that it is essential to consider them separately. Unfortunately the literature to date has rarely enabled this distinction to be made.

Early work to determine if there was a greater frequency of atheroma in the peripheral arteries in diabetics included a major study by Bell (1950). The frequency of gangrene in the extremities of diabetic and non-diabetic persons was determined by scrutinising 43,359 post mortem records over a 41 year period (1910 to 1951) at the University of Minnesota. Non athero-sclerotic causes of gangrene were excluded. In males gangrene was found 38 times more commonly and in females 40 times more commonly than non-diabetics. Clearly diabetes may not have been excluded in a number of non-diabetics and many of the diabetics may not have fulfilled present day criteria for the diagnosis of diabetes mellitus. Nevertheless the study represents an extensive analysis of post mortem data and suggests that there is an overwhelming propensity to gangrene in diabetics.

Zdanov et al (1976) showed an increase in the raised lesions in the abdominal aorta of diabetics but Sternby (1968) found no excess compared to non-diabetics. The latter was confined to persons dying above the age of 60 whereas the Zdanov study included all ages and therefore was more representative. The latter group compared those subjects on insulin to those on diet or tablets and found no significant difference.

Clinical studies have concentrated mainly on the presence of intermittent claudication, absent pulses or amputation. The latter will be discussed separately because of the possibility of including cases of neuropathy.

Incidence rates for peripheral vascular disease come from two main population studies. The Framingham study (Garcia 1974) compared the excess incidence of intermittent claudication amongst diabetics to what would be expected in non-diabetics. The incidence in females from the observed/expected ratio was 3.75 and for males 4.84. Although adjusted for age, smoking habits were not taken into account. In 1979 Kannel and McGee respectively examined the risk of glucose tolerance to cardiovascular disease in the Framingham cohort. Relative risks for intermittent claudication adjusted for age, systolic blood pressure, smoking, cholesterol and ECG LVH were 4.2 for males and 5.0 for females.

An increased incidence of peripheral vascular disease in diabetics compared to non-diabetics was reported in the Israeli ischaemic heart disease study (Herman et al 1977); again a population study, although confined to males. They found intermittent claudication was 2.2 times higher in previously diagnosed diabetics and 2.3 times higher in newly diagnosed diabetics. Although the incidence rates between the Framingham and the Israeli studies differ in absolute terms the pattern of excess risk remains.

Intermittent claudication is only one subjective aspect for assessing peripheral vascular disease. Marinelli et al (1979) has shown that it represents only a small percentage of the total peripheral vascular disease within diabetic populations. Melton et al (1980) studied the incidence and prevalence of peripheral vascular disease by using the absence of at least one pulse as a diagnostic criterion. The study was population based centred around newly diagnosed diabetics over the age of 30 living in the Rochester, Minnesota area. Approximately 8% of diabetics had clinical evidence of peripheral vascular disease at diagnosis and the incidence subsequently was 21.3 per thousand person years for men and 17.6 per thousand person years for women. Unfortunately no comparison was made to a non-diabetic control group and hence no excess risk for diabetic status was determined. The incidence rate increased with age and was greater for men than women at all ages. After 10 years the cumulative incidence was 15.4% reaching 45% at 20 years. Studies using purely the absence of pulses as a method of diagnosing peripheral vascular disease must however be treated with caution because of inter-observer variation and because absent pulses may occur in up to 12% of the normal population (Barnhorst and Barner 1968).

Another method to assess the incidence rate for peripheral vascular disease is to ascertain the number of admissions to hospital. Tibell (1971) searched registers for the diagnosis of peripheral vascular disease (ie the diagnosis of peripheral arterial insufficiency, intermittent claudication and leg ulcers). He found over the period 1949-65 373 diabetics were admitted out of a total of 967 cases of peripheral vascular disease. Only 7 of these were

found to be diabetic before the age of 40. The latter low figure was to be expected since only approximately 20% of diabetic populations are known to be insulin dependent and the mortality from uraemia means that few will reach an age where peripheral vascular disease becomes more common. It cannot be assumed that insulin dependent diabetics are less liable to develop peripheral vascular disease. Tibell using the diabetic prevalence data of Silwer and Oscarsson (1958) calculated the first admission rates for diabetics and compared them to non-diabetics. Whilst Tibell's work is extremely useful regarding the type of diabetic admission there are major problems with the study in terms of reliably estimating excess rates of peripheral vascular disease. Firstly Silwer and Oscarsson's 1958 prevalence estimate (5.1 diabetics per 1,000 population) is very low and almost certainly does not reflect all the cases within the area. The authors expected that the percentage of known diabetics must be an underestimate and state that "despite all our endeavours the figures obtained must be minimal". Secondly there may well be referral bias conferred by the status of being diabetic and thirdly only a small fraction of symptomatic peripheral vascular disease is ever referred to hospital (Reid et al 1974).

Prevalence data concerning peripheral vascular disease in diabetics is listed in Table 2.4. The different rates reflect methodological problems in diagnosing peripheral vascular disease and the different subject groups. Unfortunately very little control data are available particularly for non-invasive doppler studies. Indeed no comprehensive prevalence studies using non-invasive techniques have been performed in diabetic populations.

From Table 2.4 there are studies that merit further discussion. The two population studies ie Nilsson et al (1967) and Melton et al (1980) have the same criteria for diagnosis of peripheral vascular disease and allow some comparison. Nilsson's study also has a control group. The results of each study are shown in Table 2.5. Although in the younger age groups there is a broad agreement in the 60 to 79 age group there is a marked difference between the two studies. Possibly the contrasting results reflect methodological difficulties in determining whether a pulse is present or absent.

Not shown in Table 2.4 is the WHO (1985) multi national study to determine the prevalence of macrovascular disease in 14 different centres around the world. Amputation and claudication were considered as endpoints of peripheral vascular disease. Unfortunately 9 of the centres were recruited from clinic populations which obviously may not have been truly representative of the diabetic population as a whole within each country (although there was a strict sampling definition). The highest prevalence rates for intermittent claudication at just under 10% was found in Moscow and the lowest in Japan at under 1%. Such marked differences would be unlikely to be due to sampling biases. These results tend to mirror differences in prevalence rates in non-diabetics from the same regions. Inevitably we must conclude that local ethnic and cultural influences interacting with general risk factors for atherosclerosis are powerful determinants of peripheral vascular disease. Diabetes acting independently seems to make little difference.

Risk Factors for Peripheral Vascular Disease

From the previous discussion it is clear that diabetics are more susceptible to peripheral vascular disease. It is important to know whether this is due to an excess of general risk factors or whether diabetic status independently is the cause. If it is an independent risk factor it would also be desirable to know whether the degree of diabetic control, the type of diabetes or the duration of diabetes is important.

In addressing the first question the Framingham study gives us valuable information. In this study (Kannell and McGee 1979) the relative risk for developing claudication was 4.2 in males and 5.0 in females. These figures are however not adjusted for other putative risk factors for peripheral vascular disease. The age adjusted risk was 4.0 in men and 6.4 in women. This would suggest that diabetic status regardless of sex confers an added risk of developing claudication. It does not however prove that diabetes is an independent risk factor. Many other putative risk factors such as LDL/HDL levels or haemostatic factors were not accounted for.

Many cross-sectional studies have compared the relationship between general risk factors and peripheral vascular disease in diabetics. Beach et al (1979) defined peripheral vascular disease by non-invasive methods in 506 diabetics and divided them into IDDs and NIDDs. The latter was sub-divided into those treated by insulin and those on diet and oral hypoglycaemic agents. In IDDs and NIDDs on insulin the LDL triglyceride and LDL cholesterol were found to be important risk indicators whilst in NIDDs inverse HDL cholesterol correlated with peripheral vascular disease. Overall there were increased lipoprotein levels in the diabetics compared to an age and sex matched non-diabetic group.

Beach et al (1982) further investigated the relationship between peripheral vascular disease in diabetics with smoking and hypertension. There was also a control group of non-diabetics. They found a clear correlation between peripheral vascular disease and both hypertension and smoking.

Janka et al (1980) screened 623 non-selected diabetic outpatients using non-invasive methods. Statistical analysis revealed, after adjusting for age, that peripheral vascular disease was significantly correlated to blood pressure. Smoking was not considered in the analysis.

Age, and male sex, are risk factors for developing peripheral vascular disease in non-diabetics and similar findings are found in diabetics. Bell (1950) found gangrene was more common in older age groups. Beach et al (1980) noted the prevalence of peripheral vascular disease increased by 7.5% per decade. Melton et al (1980) found the highest incidence rate for peripheral vascular disease in the 80+ age group irrespective of duration of diabetes.

Diabetics do not tend to exhibit, to the same extent, the male sex bias towards developing peripheral vascular disease. Beach et al (1979) found after accounting for smoking differences, there was no increased prevalence in males. Similarly the Framingham study revealed that the relative risk for females was greater than for males but the authors never claimed the difference was significant (given the small numbers in each group it probably was not). Both

Beach's study, and that of Janka, are of course not population based and may well give a biased picture. Furthermore to demonstrate an excess of the supposed risk factors in diabetics, we really need to compare groups of diabetics and non-diabetics with peripheral vascular disease. The studies by Beach et al and Janka et al do not give us this information.

Zimmerman et al (1981) studied four groups of subjects. The groups consisted of non-diabetics with and without peripheral vascular disease, and diabetics with and without peripheral vascular disease. Non-invasive methods were used to define the nature and extent of arterial occlusion. Interestingly no association with peripheral vascular disease was found with total cholesterol, HDL or LDL levels. Triglyceride levels were however correlated and were highest in the diabetic group. Although there was no association with hypertension, smoking was significantly more common in diabetics with peripheral vascular disease compared to those without it. The same applied to the non-diabetic groups.

It would seem therefore that diabetic status confers an added risk for developing peripheral vascular disease and the general risk factors are similar to those in non-diabetics. Although the evidence is conflicting there does seem to be an excess of general risk factors in diabetics compared to non-diabetics with peripheral vascular disease.

If diabetes is an independent risk factor we should expect to see a relationship between the duration of diabetes and degree of control. There may also be a difference between IDDM and NIDDM particularly as insulin levels, which are reputed to be atherogenic, are different between the two types of diabetes.

Few studies have specifically addressed the question of duration of diabetes and the prevalence or incidence of peripheral vascular disease. The population study by Nilsson et al (1967) found no significant correlation between the prevalence of absent pulses and duration of diabetes.

Beach et al (1982) and Janka et al (1980) in their non-population based studies found similar results. In the former study duration was significantly correlated only in IDDM and NIDDM treated by insulin. Janka et al found that only distal peripheral vascular disease (ie disease below the popliteal) was significantly correlated with duration. Interestingly a significantly higher percentage of insulin treated patients were in this group.

In the Rochester, Minnesota study (Melton et al 1980) (which must be predominantly NIDDM) the incidence of peripheral vascular disease rose with increasing duration of diabetes and the association was independent of age. In contrast in the Israeli study Herman et al (1977) showed the incidence in male NIDD's was virtually identical in newly diagnosed NIDDM and those already known to be diabetic. The problem of course in trying to relate diabetes to any diabetic complication in NIDDM is establishing the date of onset. The diagnosis date may well be associated with antecedent hyperglycaemia for several years.

The relationship between the degree of glycaemia and peripheral vascular disease is not known. Janka et al (1980) found that distal peripheral vascular disease was significantly related to blood glucose levels although the method used to assess diabetic control was poor. Beach et al (1982) found no correlation between HbA1 and peripheral vascular disease in either IDDM or NIDDM. There have been no longitudinal studies comparing the incidence of peripheral vascular disease in groups of diabetics with good and poor glycaemic control.

In coronary artery disease there is some evidence that insulin may be atherogenic (Pyorala 1979). There is virtually no work previously performed addressing the relationship between insulin profiles and peripheral vascular disease. A recently published incidence study based in a Finnish population have found a correlation between fasting insulin at baseline and the development of intermittent claudication. This correlation remained significant following multiple logistic regression analysis. However, as the authors indicate that high fasting insulin could merely be as a result of insulin resistance and the theory that insulin levels per se are atherogenic in peripheral vascular disease are far from proven (Uusitupa et al 1990).

It seems, therefore, that evidence linking duration of diabetes with peripheral vascular disease is very limited. Further longitudinal studies to determine incidence rates are needed and no definite conclusions may be made meantime. Similarly no relationship between glycaemic control or insulin levels with peripheral vascular disease has definitely been established.

Finally does the type of diabetes influence susceptibility to peripheral vascular disease? Unfortunately insufficient data are available to answer this question. Generally IDDM are young subjects and sadly, seldom do sufficient numbers reach old age. Paz-Guevara et al (1975) found that 40% of IDDM subjects with duration of diabetes greater than 40 years had evidence of peripheral vascular disease. From Table 2.5 it can be seen that this is a very high prevalence rate.

Prognosis for Peripheral Vascular Disease in Diabetics

Prognosis of peripheral vascular disease can be assessed by two outcomes - amputation and death. Malone et al (1977) compared life expectancy following aortofemoral arterial grafting. 47% of non-diabetics were alive 10 years after grafting compared to 0% in diabetics. However we are not told what percentage of subjects had diabetes. The numbers may well have been small and patients undergoing aortofemoral grafting represent a special group and may not be representative of diabetics with peripheral vascular disease in general.

Some of the above criticisms apply to the study by De Weese et al (1977) although their findings are similar to Malone. They followed 103 patients with 113 autogenous femoro-popliteal by-pass grafts over a 10 year period. Again this is a selected group of patients, ie generally those with more severe disease. Nevertheless 25 of the 103 subjects were diabetic, of whom only 8% were alive after 10 years. This contrasted with the survival of 35% of non-diabetics. 56% of diabetics had arterio-sclerotic heart disease at the time of operation compared to 27% in the non-diabetics.

From De Weese's paper, mortality was very high in diabetics and since there was a preponderance of ischaemic heart disease the latter may well have been a major cause. Hertzer (1981) investigated fatal myocardial infarction following lower extremity re-vascularisation in 273 subjects. Of 256 patients who survived the operation 84 were diabetic. After 5 years the mortality in diabetics was 37% compared to 20% in non-diabetics. Myocardial infarction was the cause of death in over 50% of the diabetics compared to 38% in non-diabetics. The difference was highly significant. This study is extraordinary because all patients undergoing lower limb vascularisation also had a pre-operative coronary angiogram! The work of Tibell (1971) also suggests a high mortality in diabetics who actually present to hospital. He found that only 50% of diabetics, with first time admission to hospital with leg vascular disease, survived 3 years.

Steer et al (1983) followed up groups of diabetics and non-diabetics with rest pain, ulceration and gangrene over a period ranging from 10 months to just under 4 years. The groups were matched for age and sex. Mortality in the diabetic group was not significantly greater. Adverse survival factors were rest pain and ulceration regardless of diabetic status. They also best predicted subsequent limb loss. Hughson et al (1978) investigated factors determining outcome in 160 patients discharged from hospital after admission for peripheral vascular disease in the Oxford region. Patients were followed up for a total of 8 years after which 56% of diabetics had undergone amputation compared with 20% of non-diabetics. However amputation and mortality are heavily dependent on age and we have no means to determine whether the diabetics were older than the non-diabetics. Furthermore smoking habits are implicated in the prognosis and again no information was available to determine whether there was a difference between diabetics and non-diabetics.

A problem with all the above studies is that they deal with subjects who seek medical help specifically for vascular problems. Hughson et al (1978) and Reid et al (1974) have shown only a minority of patients in fact seek medical help as a result of

intermittent claudication. Of course these are based upon general populations and diabetics may be more prone to seek advice from a doctor. Clearly however one must be cautious in extrapolating results from selected studies to prognosis in the diabetic population at large.

Bendick et al (1983) attempted to monitor the progression of atheroma by non-invasive means in a group with 274 subjects screened from a population of 514 diabetics. Of the 274, 34% had progression of their disease. Age and systolic blood pressure were the two most important determinants of progression. Diabetic control had no influence.

Kreines et al (1985) followed up NIDDs for 14 years to determine the cause of peripheral vascular disease. The sample was very unrepresentative consisting of 451 women and 165 men. The diagnostic categories for peripheral vascular disease were intermittent claudication, absent foot pulses, arterial calcification and amputation. Amputation was very rare. Its initial prevalence was 0.6% and over the 13 years only a further 1.3% occurred. As the authors suggest this low incidence rate may well have been due to a quarterly clinic review rate (which seems excessive). Intermittent claudication commonly did not progress to amputation but this probably, as it does in non-diabetics, reflects high mortality. The latter was significantly increased in the arterial calcification and absent pulse categories but surprisingly no mortality data was given for intermittent claudication subjects as such.

In summary, at least in patients who seek medical help with peripheral vascular disease, there is an increase in mortality compared to non-diabetics. The excess mortality is mainly due to myocardial infarction. As with non-diabetics peripheral vascular disease does not frequently appear to progress to amputation probably because they do not survive long enough.

Amputation in Diabetics

Amputation is important, not only because of the human suffering that it inevitably causes but also because of the huge financial burden that it imposes. It is therefore necessary to know the total problem in the general diabetic population and the excess risk to diabetics.

Studies into the frequency of amputation in diabetics must be population based. Such studies are very difficult to perform as previously outlined. It is necessary to ascertain the size of the population denominator, the diabetic population within the area and all admissions for amputation in both diabetics and non-diabetics. Furthermore in many areas more than one hospital serves the needs of the population and some (particularly teaching hospitals) take referrals from outside the area. In view of these problems few such studies have been performed. Table 2.6 lists the more recent population studies and the percentage of diabetic amputations. It also, where possible, indicates the prognosis following amputation.

Hanson's study (1964) tried to detect all amputations that occurred amongst the population of Gothenberg in Sweden. The operation schedules of several different departments of surgery were checked for clinical characteristics of amputees. The prevalence of diabetes within the general population was not known and hence incidence rates for amputation in diabetics could not be calculated. No definitions of diabetes were given. Only amputations proximal to the ankle joint were included. A similar study was performed by Hierton et al (1973). Again retrospective checking of case records from all the hospitals in Uppsala County, Sweden was carried out. Many of the criticisms of the Hanson study apply also to Hierton's. In particular the number of diabetics found must be suspect, not only because of the differing definitions of diabetes but also because of the inaccuracy of checking records retrospectively for diagnoses.

Neither study referred to smoking habits which probably reflects ignorance concerning smoking and peripheral vascular disease that may have prevailed at that time.

Christensen's study (1976) in the County of Aalborg and the study by Liedberg et al (1983) investigating amputations amongst the population of Malmohus, Sweden were also retrospective studies. The incidence of diabetic amputations varied markedly but we do not know whether this reflects different prevalence rates for diabetes, different definitions of diabetes (for example Liedberg et al found diabetics by searching case records for insulin and diabetic drugs whilst Christensen doesn't even state how he found them) or if it was due to demographic changes within the population. No details regarding smoking habits are given in either paper - any differences may have been important. Certainly Liedberg's definition of diabetes could have missed some diabetics.

If we also look at the recent study by Kald et al (1989) which analyses the medical records of amputees over the 1980-82 period, the incidence rate has further risen to 20.7 per thousand (see Table 2.6). This latter study was somewhat smaller than those of Christensen and Liedberg. Nevertheless there is an increasing trend in incidence which may at least partially be explained by demographic changes and probably methodological problems with each study. It is disappointing that no estimates for the prevalence of diabetes were available which would have enabled the increased risks for amputation to be calculated.

Finch et al (1980) however noted the number of amputations that occurred over a 3½ year period at the peripheral vascular unit in Oxford. According to Steer et al (1983) this unit deals with all peripheral arterial disease and diabetic foot problems in the Oxford region. Since the prevalence of diabetes has been investigated by Neil et al (1987) in the Oxford region an idea of the increased incidence rate may be calculated. Unfortunately the Oxford hospital is a major teaching hospital and may well have a cross boundary flow. Also, interestingly the amputation rates in Steer's and Finch's study differ although they are over virtually an identical time period.

Presumably this reflects different definitions of diabetes (although none are given) and renders further analysis of amputation very suspect.

Two studies have addressed the relative risk for amputation in diabetics and non-diabetics. Most and Sinnock (1983) calculated the relative risk for amputation in diabetics in the USA as 15. Amputation rates for 6 States were determined by hospital discharges collated by a diabetes control programme in each state. The prevalence of diabetes was determined by data from the 1978 Health Interview Study. Estimates of amputations in non-diabetics were derived from previous hospital discharges and survey data in 1977. Although a useful paper in that it gives some idea of the increased amputation risk conferred by being diabetic, its accuracy is debatable. It only deals with amputations per se, not actual numbers of diabetics. Many may undergo progressive amputations, eg toes to foot to below knee amputation. As previously mentioned hospital discharges are often inaccurate and we have no way of determining how inaccurate. 73% of all discharges were examined and in some states it was as low as 44%. In addition, although probably a small number, some of the discharges would inevitably be due to reasons other than gangrene and ischaemia.

Waugh (1988) also attempted to establish the relative risk for diabetic amputations in the Tayside region using two methods. One method used the Scottish morbidity record (SMR) after one admission for amputation and the other used an SMR linkage method based on 5 years of discharges. The latter selected major amputations during the year of 1981 but ascertained all admissions for those patients over a 5 year period. The prevalence of known diabetes was estimated by sending a short questionnaire to GP's within the area. Diabetes was identified as those on treatment or a fasting glucose greater than 8 mmol/l. The population figures for the region were from the 1981 census. The results are shown in Table 2.7. There are problems with this study but it has circumvented many of the difficulties encountered with Most and Sinnock's work. Firstly this is a patient based study and not amputation based.

Secondly the coding selection negates the problem of traumatic and other types of amputation being included.

The problems with the study however include (1) the prevalence rate for diabetes could be widely inaccurate. 0.8% is lower than the prevalence for diabetes in Poole and Oxford (Neil et al 1987) and probably reflects methods used. For example diabetic registers may be out of date and inaccurate without further personal checks by the investigator. (2) The SMR method requires accurate coding. This may not be possible because it is seldom performed by clinicians (and even if it was there is no guarantee it would be accurate!) Efforts were made to validate the SMR codes in the study and a number of discrepancies were found.

The difference in relative risk between Most and Sinnock's and Waugh's studies may arise from reasons already stated but also because one population may have different factors that would influence risk. For example smoking habits or an excess of premature ischaemic heart disease would clearly alter the relative risk. Nevertheless the two studies do demonstrate that diabetics are far more likely to undergo amputation than their non-diabetic counterparts.

Prevalence Data

There are virtually no population studies concerning the prevalence of amputation. Neil et al (1989_B) found the prevalence of amputation 3.1% in the Oxford survey. However only 75% of the population were examined and this would inevitably bias the number of amputees found unless they were actively sought by visiting their homes (the percentage visited at home is not stated).

Characteristics of Diabetic Amputees

Table 2.8 shows a breakdown of the amputations according to age and sex from various studies. No other data are available regarding amputees from caucasian population studies. From the limited information that we do have the sex ratio is approximately unity and amputation

is most frequent in the 70 to 79 year age group. This should of course not be confused with incidence in each category which tends to be greater in the 80+ age group.

Prognosis

From Table 2.6 it may be seen that the survival rate for both diabetics and non-diabetics is approximately 50% within 2 years, almost certainly due to concomitant ischaemic heart disease.

A recent study investigating the fate of contralateral limbs suggested that 50% of survivors will undergo a contralateral amputation after 2 years (Bodily and Burgess 1983). It is not surprising since the main determinants of amputation, ie peripheral vascular disease and neuropathy, tend to be bilateral.

Diabetic Foot Ulceration

Frequency

Population studies showing the prevalence of foot ulceration are equally limited. Comparisons with age and sex matched non-diabetic populations are non-existent. Clearly this is not surprising since the most probable aetiological factors, ie neuropathy and peripheral vascular disease, are also seldom researched in population cohorts. Jones et al (1985) studied foot lesions in a Diabetic Clinic. To determine the extent of the problem a survey was conducted of all infected necrotic or ulcerated lesions between 1.4.82 and 1.11.84. It was found that 54 patients suffered a total of 106 lesions. 83% of the lesions were associated with neuropathy and 13 had amputations. Unfortunately we have no idea of how many diabetics attended the clinic overall and therefore, no idea of the prevalence in a clinic population.

Peacock et al (1985) in a prevalence survey by questionnaire revealed that only 25 out of 66 patients with ulceration were known to hospital. They posted the questionnaires to GP's, chiropodists and district nurses to ascertain the number of their diabetics

presently being treated for foot ulceration. The problem with this type of survey is that the diagnosis of diabetes may not have been accurately established. It does however emphasise the particular importance of population based studies in investigating diabetic foot problems.

A questionnaire survey was also performed by Rosenquist (1988). 742 diabetics were selected from a register of 30,617 patients who had been hospitalised during 1969 to 1979. It was therefore not a population study. The recipients of the questionnaire were selected so that they represented 9.5% of diabetics less than 55 years of age and 3.3% of diabetics over 55 years of age. 83.2% of the diabetics responded and 10.2% reported severe foot disease. We are not told precisely what constituted severe foot disease. Also questionnaires sent to patients may well result in bias favouring the articulate and more motivated. As the author stated the late responders tended to have more severe symptoms.

Holewski et al (1989) studied 100 consecutive male patients attending a diabetic clinic for the prevalence of foot pathology. The mean age was 59.6 years and mean duration of diabetes was 13.9 years. The prevalence of past and present ulceration was 1.9%. This contrasts with a true population based study by Neil et al (1989_B) conducted in the Oxford region who found a prevalence of 5%. Some of the problems with this study have previously been discussed but it does give some idea of the extent of the problem in the diabetic community. Longitudinal studies of foot ulceration in diabetic populations have not been performed.

Diabetic foot ulcers may be graded by the Wagner classification (Wagner 1987) depending on depth and severity of ulceration. Although clinical examination yields much information regarding the extent of ulceration, underlying osseous involvement may be further investigated by x-ray and isotope bone examination. Osteomyelitis may often be confused with neuro-osteoarthropathy and in which case Gallium isotope scans may be of some benefit (Wheat 1985).

The diagnosis of peripheral vascular disease may be determined non-invasively by simple doppler pressure measurements. A pressure of less than 1.0 at the ankle is indicative of peripheral vascular disease (Yao 1970). Such non-invasive testing is superior to pulse palpation (Marinelli et al 1979) but is unreliable when there is significant medial vascular calcification as a falsely elevated ankle pressure may be obtained (Emanuele et al 1981). Segmental pressures and doppler wave form analysis may further determine arterial stenoses, and doppler pressures following exercise may further increase diagnostic yields (Carter 1964).

Neuropathy may be quantified by sensory thresholds (vibration and temperature perception) and nerve conduction studies. These investigations serve as an adjunct to clinical examination. The latter correlates well with neurophysiological measurements (Dyck et al 1985) and nerve pathology (Dyck et al 1980). Clearly however for comparison between centres and for follow-up studies the quantitative measurements are of greater value. It should be remembered however that abnormal sensory thresholds or nerve conduction findings are not synonymous with a diagnosis of neuropathy. The latter has a strict definition which includes symptoms (San Antonio recommendations 1988). Since ulcers tend to occur in cases of more severe somatic neuropathy, in practical terms probably clinical examination is as good as any other method in determining who is at risk of ulceration (Young 1987). The value of pressure measurements underfoot remains to be established and probably for the present remains a purely research tool. (Boulton 1987). Clinical examination for areas of callus is probably equally as effective and certainly simpler.

Treatment strategies for diabetic foot disease are primarily directed at prevention. Lippmann indicated the folly of subjecting patients to vascular reconstruction without any basic knowledge of the fundamentals of good footcare (Lippmann 1979_A). Edmonds et al (1986) quantified the results of a foot clinic. Using methods of intensive chiropody, aggressive control of sepsis, provision of appropriate footwear and patient education, they demonstrated that amputation rates were halved. Ward (1987) considers that most cases of neuropathic ulceration in the absence of significant peripheral vascular disease should not culminate in amputation. What is needed however is co-operation between many different healthcare professionals so that effective prompt intervention may be achieved.

Neuropathic ulcers are generally treated by a combination of measures which include

1. regular chiropody for the removal of callus and debridement of ulcers

2. rest to relieve pressure

3. antibiotics to eradicate superadded infection

4. in patients where mobility is essential, total contact plaster cast to allow resumption of normal lifestyle whilst the ulcer is healing.

Preventive measures encompass adequate footwear to offload high pressure points. There are now durable high energy absorbing insole materials available (Boulton et al 1984). Probably the most important aspect of prevention is patient education enabling the patient personally to have responsibility for his own footcare.

Treatments for neuropathy per se are limited. Aldose reductase inhibitors have little useful impact in established neuropathy although may have some beneficial effects on symptomatology (Gillon et al 1986). Whether they may prevent neuropathy developing in possible high risk subjects is not known. As diabetic control

seems to be implicated in the development of diabetic neuropathy, scrupulous control of diabetes must clearly be an objective of management for most diabetics.

Peripheral vascular disease, as previously discussed, carries a poor prognosis in terms of mortality and diabetics have more distal disease which predicts a poor outlook for graft patency. (Dean et al 1979, Crawford 1981, De Weese and Rob 1977). Nevertheless patency rates for by-pass grafts in diabetics with threatened limb loss are similar to non-diabetics (Thomas et al 1988), and Karacagil et al (1989) have suggested, in view of the similar patency of foot vessels between diabetics and non-diabetics, the same management approach should be adopted. Generally arterial vascular reconstruction is performed in subjects with lifestyle limiting claudication, rest pain or threatened limb loss. It may be argued, in view of the poor survival outlook, that a more aggressive approach should be adopted in diabetics to improve quality of life. Clearly since the general risk factors for peripheral vascular disease seem to apply to non-diabetics, the preventive measures such as cessation of smoking, control of blood pressure, reduction in lipid levels and regular exercise should be advocated to all diabetics at an early age.

Fig 2.1

A Suggested Pathogenesis of Diabetic Foot Ulceration

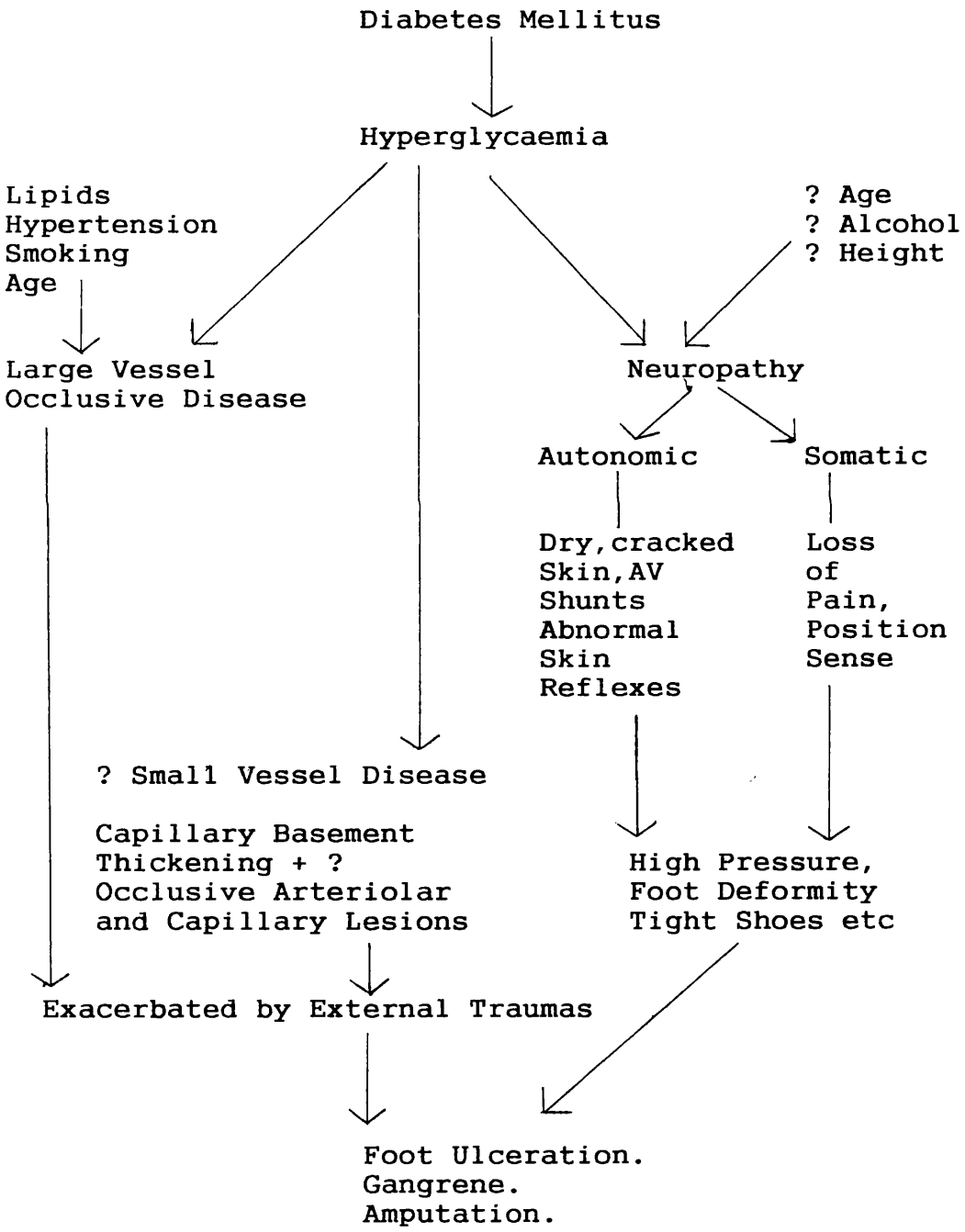


TABLE 2.1 - PREVALENCE OF DIABETIC NEUROPATHY

Study	Diagnostic Criteria	Subject Group	Prevalence	Age Range
Murphy F D 1931	Unknown	Hospital Clinic (unselected)	0.60%	
Rundles W 1945	Unknown	Hospital & clinic attenders (newly diagnosed)	4.1%	
Broch O J 1947	Symptoms of neuropathy	Hospital & clinic attenders	20.6%	
Bonkalo A 1950	Objective signs of neuropathy	Hospital clinic - unselected	49.3%	7-84
Fagerberg S E 1959	Symptoms + 2 abnormal signs	Hospital inpatients (unselected)	63%	
Matthews J D 1955	Symptoms + signs	Hospital Clinic	37%	
Mulder D W 1961	Objective loss + EMG criteria	Hospital Neurology Clinic - unselected	41.7%	
Collyer R T 1961	Absent ankle jerks	IDDs whose age of onset <13 yrs - unselected	52%	
Kelsey-Fry I 1962	Objective signs not including ankle jerks or vibration	Hospital Clinic	8.9%	
Friedman S A 1967	Objective signs of neuropathy	Hospital Clinic - consecutive patients	88%	
Mincu I 1979	Unknown	Hospital based - newly diagnosed	11.2%	

TABLE 2.1 CONT.

Study	Diagnostic Criteria	Subject Group	Prevalence	Age Range
Dryberg T 1981	Abnormal autonomic function tests	IDD Clinic subjects aged 30-50 years	27%	30-50
Boulton A J 1985	Symptoms + loss of ankle jerks	IDDs in hospital clinic	10.7%	15-59
Knuiman M W 1986	Loss of pin prick	Population based	15.3%	
O'Brien T A 1988	Absent or impaired ankle jerks + vibration threshold > 95th centile	IDDs ? hospital clinic	23.5%	12-85
Neil H A W 1989_A	Autonomic function tests	Population based	16.7%	
Neil H A W 1989_B	Abnormal vibration thresholds	Population based < 75 years	23%	
Lehtinen J M 1989	Symptoms + signs or nerve conduction velocities	Newly diagnosed NIDDs in health centres	2.3% clinical criteria 15.2% electro-physio-logcial criteria	45-64 years

TABLE 2.2

Comparison of vibration sense in normals and diabetics

Nilsson's data (1967)

	PRESENT			ABSENT		
Series						
Males	C	A	B	C	A	B
60-79	71.4	34.3	40.0	11.4	28.6	30.0
40-59	95.2	91.4	88.0	0	5.8	4.9
20-39	100.0	100.0	100.0	0	0	0
Mean	88.9	75.2	71.0	3.8	11.5	11.6
Females						
60-79	92.6	71.0	40.0	0	7.9	35.0
40-59	94.1	76.6	76.7	5.9	0	5.3
20-39	100.0	100.0	100.0	0	0	0
Mean	95.6	82.5	72.2	2.0	3.7	11.7

Ankle Jerks - comparison of ankle jerks in normals and diabetics

Nilsson's data (1967)

	PRESENT			ABSENT		
Series						
Males	C	A	B	C	A	B
60-79	75.0	45.9	32.5	21.4	27.0	27.5
40-59	92.9	75.0	52.4	4.8	11.1	14.3
20-39	0	90.0	76.2	0	0	9.5
Mean	89.3	70.3	53.7	8.7	12.7	17.1
Females						
60-79	71.4	57.5	12.8	25.0	15.0	33.3
40-59	97.2	53.3	53.3	0	10.0	6.7
20-39	0	84.6	78.9	0	0	0
Mean	89.5	65.1	48.3	8.3	8.3	13.3

C = controls
A = short duration diabetic
B = long duration diabetic

TABLE 2.3 - NEUROPATHY VERSUS DURATION OF DIABETES

Study	Subject Group	Significant Relationship to Neuropathy Yes/No
Steiness I B 1957	Hospitalised diabetics	Yes
Fagerberg S E 1957	Hospitalised diabetics	Yes
Shichiri M 1964	Hospitalised diabetics and Outpatients	No
Mulder D W 1961	Neurology clinic attenders (diabetics)	No
Nilsson 1967	Population of Diabetics around Kristianstad	Yes
Palumbo 1978	NIDD population (cumulative incidence study)	Yes
Pirart 1979	Hospital diabetic clinic cohort	Yes
Neilsen N V 1979	Hospital out and inpatients	Yes
Dryberg T 1981	Hospital diabetic clinic attenders	Yes
Boulton A J 1985	Hospital clinic attenders IDDs	Yes
Knuiman M W 1986	Diabetic population (rural Australia)	Yes
Neil H A W 1989	Population (around Oxford)	No

TABLE 2.4 - PREVALENCE OF PERIPHERAL VASCULAR DISEASE

Study	Diagnostic Criteria	Study Group	Prevalence Diabetic	Control Group
Brandman O 1953	Absent foot pulses bilaterally	Diabetics aged 17 - 64 clinic based	25.4%	-
Semple R 1953	Intermittent claudication or bilateral absent or diminution of pulse volume after exercise	Clinic based aged 50 - 79	42%	-
Bryfogle J W 1957	Intermittent claudication or visible lesions	Clinic based - no specific age range	15.7%	-
Nilsson 1967	Absent pulses	Population based	See text	See text
Paz-Guevara A T, 1975		IDDs > 40 years duration	40%	
Melton J L 1980	Absent pulses	Population	10.5%	-
Beach K W 1980	Doppler pressure Index < 0.95 IDDs & NIDDs & age/sex matched non-diabetic controls	Clinic based No age category	NIDD 34% IDD 18%	20%
Janka H 1980	Ankle pressure 30 mmHg < brachial pressure	Clinic based non-selected	15.9%	-
Siitonen O 1986	Doppler pressure Index < 0.9	Newly diagnosed NIDDs aged 45-64 age/sex matched non-diabetic control group	Males 7.3% Females 1.2%	Males 2.3% Females 1.0%

TABLE 2.5

PREVALENCE OF PERIPHERAL VASCULAR DISEASE BY PULSE PALPATION IN 2 POPULATION STUDIES

Nilsson's Study (1967)

% frequencies of absent pulses

Males	Palpable			Not palpable		
Age	N	A	B	N	A	B
60-79	60	40.0	45	2.9	31.4	32.5
40-59	95.2	80.1	66.7	0	11.1	7.1
20-39	96.8	90.0	100	0	0	0
Females						
60-79	60.7	52.6	33.3	7.1	15.8	15.4
40-59	80.6	76.7	53.3	5.6	0	0
20-39	88.2	81.8	73.7	0	0	5.3

N = non diabetic controls
A = short duration diabetes
B = long duration diabetes

Melton's Study 1980

	Diabetics
Males	Prevalence of impalpable pulses
Age	
60-79	9.2%
40-59	0.7%
30-39	0%
Females	
60-79	7.2%
40-59	1%
30-39	0%

TABLE 2.6

POPULATION BASED AMPUTATION SURVEYS

Study	Period Observed	% of Diabetic Amputations	Diabetic Amputations (Incidence/* 100,000	Prognosis
Hansson 1964	1947-56 and 1961	43.2%	-	Not specifically stated
Hierton and James 1973	1967-69	60%	-	1 year survival: Diabetic 60% Non-diabetic 45%
Christensen S 1976	1961-71	43.3%	7.3	2 year survival: Diabetic 20% Non-diabetic 30%
Finch et al 1980	1974-78	32%	-	2 year survival: Diabetic 45% Non-diabetic 62%
Borssen and Lithner 1983	1971-77	56%	-	2 year survival: Diabetic 40% Non-diabetic 70%
Liedberg and Persson 1983	1979	37%	11.3	-
Most and Sinnock 1983	1976-78	45%	-	-
Waugh N 1988	1981	35%	15.0	2 year survival: Diabetic 46% Non-diabetic 50%
Kald A et al 1989	1980-82	45%	20.7	-

* General population

TABLE 2.7

WAUGH'S 1988 DATA - RELATIVE RISK FOR AMPUTATION IN DIABETICS

		DIABETIC			NON-DIABETIC		
Source of Diabetes Notification	Year	Number	%of all major amputees	Rate/ 10,000	Number	Rate/ 10,000	Relative Risk
Amputation Admission (SMR form alone)	1980 -82	93	27	101	250	2.2	46
Record Linkage Study (5 years SMR data)	1981	32	35	105	58	1.5	70

TABLE 2.8

AGE AND SEX CHARACTERISTICS OF DIABETIC AMPUTEES

	M/F ratio		Amputation Age				
	No		0-49	50-59	60-69	70-79	80+
Hanson 1964	143	1.0	1 0.8%	12 8.3%	59 41.3%	62 43.3%	9 6.3%
Christensen 1976	151*	not known	4 3%	20 13%	55 36%	55 36%	18 13%
Liedberg etal 1983		60	1.17 12%	7 12%	7 20%	12 33%	2021 35%

* only approximate figures from a graph

Chapter 3

SUBJECTS AND METHODS

Subjects - Study Population Identification

The study population consisted of all patients registered with 45 general practitioners working from 10 general practices. The geographical area shown in Figure 3.1 has both rural and urban areas. The population has the same age and sex characteristics as those of the United Kingdom (1981 census). (See Chapter 4). In zone A all the general practitioners were included in the study and in zone B approximately 25%.

The diabetic population (known) in this survey was identified by the following methods:

1. Using the computer list of all diabetics for the 10 practices. The list was regularly updated for new patients, patient deaths and patients who had moved away from the study area. This computer list is termed the Poole Diabetic Register.
2. The previous register of all patients found by Drs Houston and Gatling (Houston 1982, Gatling et al 1985).
3. Checking the diabetic registers that existed in each of the 10 practices.
4. Regular checks with each practice for new patients when the practice diabetics were being reviewed.

All patients identified were checked with the case notes to make sure they fulfilled WHO criteria for the diagnosis of diabetes mellitus (WHO 1985). If hospital records did not contain the necessary information the general practitioner records were also checked. Where information was still not available patients were either excluded from the study or a repeat glucose tolerance test performed.

The diabetic patients identified were sent a letter inviting them to attend the hospital for a physical examination. If patients were unable or unwilling to travel they were offered the facility to be seen at their home. Each patient who did not attend was sent one further appointment and if they still did not respond they were contacted personally to enquire if they would accept a home visit.

Calculation of Known Diabetes Mellitus Within the Study Population

A point prevalence for diabetes mellitus was calculated in each practice when most of the subjects in that practice had been seen for the purposes of the study.

The point prevalence of known diabetes mellitus was determined by dividing the number of known diabetics within the practice by the total number of patients registered with that practice. The latter was calculated by either counting the age/sex register (which was continually updated by each practice) or by the number of patients registered on the practice computer (available in two practices).

The total prevalence for known diabetes mellitus within the study population was thus calculated by determining the mean of the individual point prevalences for each practice. An age specific prevalence for diabetes mellitus was also calculated for each 5 year age band of the general population by dividing all the diabetics in each age category by the number of subjects registered.

Control Population Determination

A cohort of age and sex matched non-diabetic controls was drawn from the same study population. The purpose of the controls was to determine the prevalence of foot disease and the putative risk factors in a non-diabetic population.

The control population was selected by obtaining the name of a person on the age/sex register which was immediately before or after a diabetic patient. The control population was limited to

subjects aged 30 years or older since no abnormalities regarding diabetic foot disease were found below this age in the diabetic group.

All controls were checked to ensure that they were not known to be diabetic and each was sent a letter explaining the purpose of the study with an invitation to attend for a physical examination. As with the diabetics any subject who was unwilling or unable to attend the hospital appointment could arrange for a home visit. Controls were only sent one appointment which was the wish of the general practitioners.

The non-diabetic status was initially determined by the absence of glycosuria. If glycosuria was present the subject was asked to have a formal 75g glucose tolerance test to exclude diabetes mellitus. Any control found to have an abnormality such as peripheral vascular disease or neuropathy was screened for diabetes mellitus by measuring the plasma glucose 2 hours after a main meal. All with glucose concentrations equal to or greater than 7.8 mmol/l were asked to have a formal glucose tolerance test.

It is realised that this was not an ideal method for excluding diabetes mellitus in the control population and this will be discussed fully in a later chapter.

Patient Review - Diabetics

Review Protocol

On arrival at the clinic each patient was asked to complete a WHO cardiovascular questionnaire for angina, possible myocardial infarction, intermittent claudication, stroke and hypertension (see Appendix 2 for further details). If the patient had difficulty in completing the questionnaire for any reason they were given assistance by Mrs O M Foley, the research nurse. The patients were then asked to undress and their height (to the nearest centimetre) and weight (to the nearest kilogram) were recorded.

Visual acuity was then measured by the research nurse. The patient was seated at 6 metres from an illuminated Snellen chart. The refractive errors were corrected by the patient's own glasses or a pinhole (whichever gave the best result). The lowest line in which the patient correctly identified half or more of the letters was the measure of the patient's visual acuity. If the acuity was less than 6/60 then counting fingers at one metre was attempted, progressing as necessary,to detection of hand movements and perception of light only.

The pupils were then dilated with 1% Tropicamide to a pupil diameter of at least 3 mm so as to be ready for direct fundoscopy using an ophthalmoscope later on in the examination.

A full history was then taken by the doctor to ascertain the information listed in Table 3.1. Diabetes was classified as insulin dependent if the patient had at least one episode of diabetic ketoacidosis documented or who had had insulin treatment initiated at diagnosis or within one month of diagnosis or who had never been off insulin for longer than one month. All other diabetics were considered non insulin dependent. The limitations of this classification will be discussed later. Symptoms of neuropathy were elicited by direct questioning. Each patient was asked if they regularly experienced numbness, tingling, burning, aching or tenderness in their feet. If they did they were also asked whether the symptoms were bilateral and of greater than one year's duration. The latter question was to avoid symptoms related to episodes of poor diabetic control, transient syndromes of painful neuropathy and conditions that may mimic neuropathy. Only symptoms which were bilateral and present for at least one year's duration were considered to be due to neuropathy. A previous history of foot ulceration was recorded and checked by scrutinising previous general practitioner, hospital and chiropody records. Only ulcers diagnosed at, or after the diagnosis of diabetes mellitus was made were included in the analyses. All amputations were noted and the most proximal site was used for determining the prevalence if a previous amputation had been performed.

Following the history interview each patient was examined and the data that was sought are listed in Table 3.2.

The blood pressure measurement was performed after asking the patient to lie flat and relax for 5 minutes. The right arm was always used unless there was some obvious contra-indication. A 12 cm pneumatic cuff was placed around the arm, level with the patient's heart. A large cuff was used for obese patients. The systolic pressure (mm mercury) was recorded at the point when the Korotkov sounds returned. The diastolic pressure was recorded at phase V, ie the point where the sounds disappeared. The blood pressure was then repeated after the patient had stood upright for 2 minutes by the side of the couch. A random zero syphygmomanometer was always used throughout the study.

Peripheral neuropathy was determined by:

i light touch perception (using a piece of cotton wool)
ii pain perception (using a straight sterile pin)
iii vibration perception (using a bio-thesiometer) and
iv reflexes (ankle/knee - using reinforcement if necessary)

The definition of neuropathy for the purposes of this study is given at the end of the chapter. The sites for determining light touch and pain were the dorsum of the first toe, the plantar and dorsal surfaces of the foot and both malleoli. A dichotomous classification was used, ie either the sensory modality was normal or abnormal at, at least, one site bilaterally. Only sharp localised pain was considered normal for pain perception. In the case of light touch the cotton wool could be felt or not felt. The reason for using this type of classification was to minimise the subjectiveness of interpretation.

The vibration perception threshold (VPT) was determined by demonstrating the vibration in the patient's finger initially (assuming it was not affected by neuropathy). The probe of the bio-thesiometer was then placed on the tip of the first toe supported by its own weight and kept as vertical as possible.

Throughout the examination the patient remained as flat as possible. It is well established that the loading of the biothesiometer probe affects the VPT (Lowenthal and Hockaday 1987) and the method used in this study standardised for probe loading. The vibration amplitude was gradually increased until the patient could just perceive the vibration. The point on the relative amplitude scale at which the patient could just perceive the vibration was termed the VPT. A trial run was always performed and then the mean of two recordings was determined for the first toe and medial malleolus of both feet.

Ulceration was examined and classified according to the Wagner classification (for further details see the end of the chapter). The site and duration of ulceration was always recorded and where possible the aetiology of the ulcer noted.

All types of foot deformity were recorded as shown below:

1. Claw toes
2. Hallux valgus
3. Hallux rigidus
4. Hammer toes
5. Pes cavus
6. Charcot deformity
7. Previous foot surgery
8. Other

Any foot deformity was considered a potential risk factor for diabetic foot disease if there was evidence of high pressure (eg callus or areas of erythema) from wearing of footwear at that point.

Peripheral pulses were included as femoral, popliteal, dorsalis pedis and posterior tibial pulses. The femorals were also auscultated for bruits. Each pulse was recorded as either present or absent; again this was designed to minimise errors in interpretation.

Ankle doppler pressures were determined in both legs. An 8 MHz doppler probe was used in all doppler pressure measurements. Each pressure was determined with the patient lying as flat as possible. The right brachial artery systolic doppler pressure was measured initially using a 12 cm pneumatic cuff. This was placed around the upper arm and the doppler probe positioned over the artery to obtain the best doppler signal. The cuff was then inflated to obliterate the signal. The doppler systolic pressure (measured in mmHg) was considered to be the pressure at which the signal just returned on gradual release of the cuff. An identical method was used to measure the systolic pressure in the dorsalis pedis and posterior tibial arteries with the cuff applied just above the ankle in each case. The best systolic pressure in each leg was recorded and divided by the brachial pressure to give the pressure index (PI).

Laboratory investigations performed on all diabetics are listed in Table 3.4A. Additional investigations as listed in Table 3.4B were also performed in patients who were considered at risk of diabetic foot disease.

The criteria for the latter are listed at the end of the chapter. Obviously patients who were too frail or who had been seen at home because of difficulties in travelling were not included for further investigation.

Autonomic function tests were not recorded in patients who had cardiac rhythm disturbance (checked by the author on the ECG monitor before the test was performed), those with severe respiratory disease and those subjects with proliferative retinopathy.

The exact details of the method used for determining autonomic function tests are listed in Appendix 3. The tests were performed by the Poole Hospital Medical Physics Department. Recordings were performed during:

1. a resting state
2. forced breathing for one minute and
3. valsalva manoeuvre.

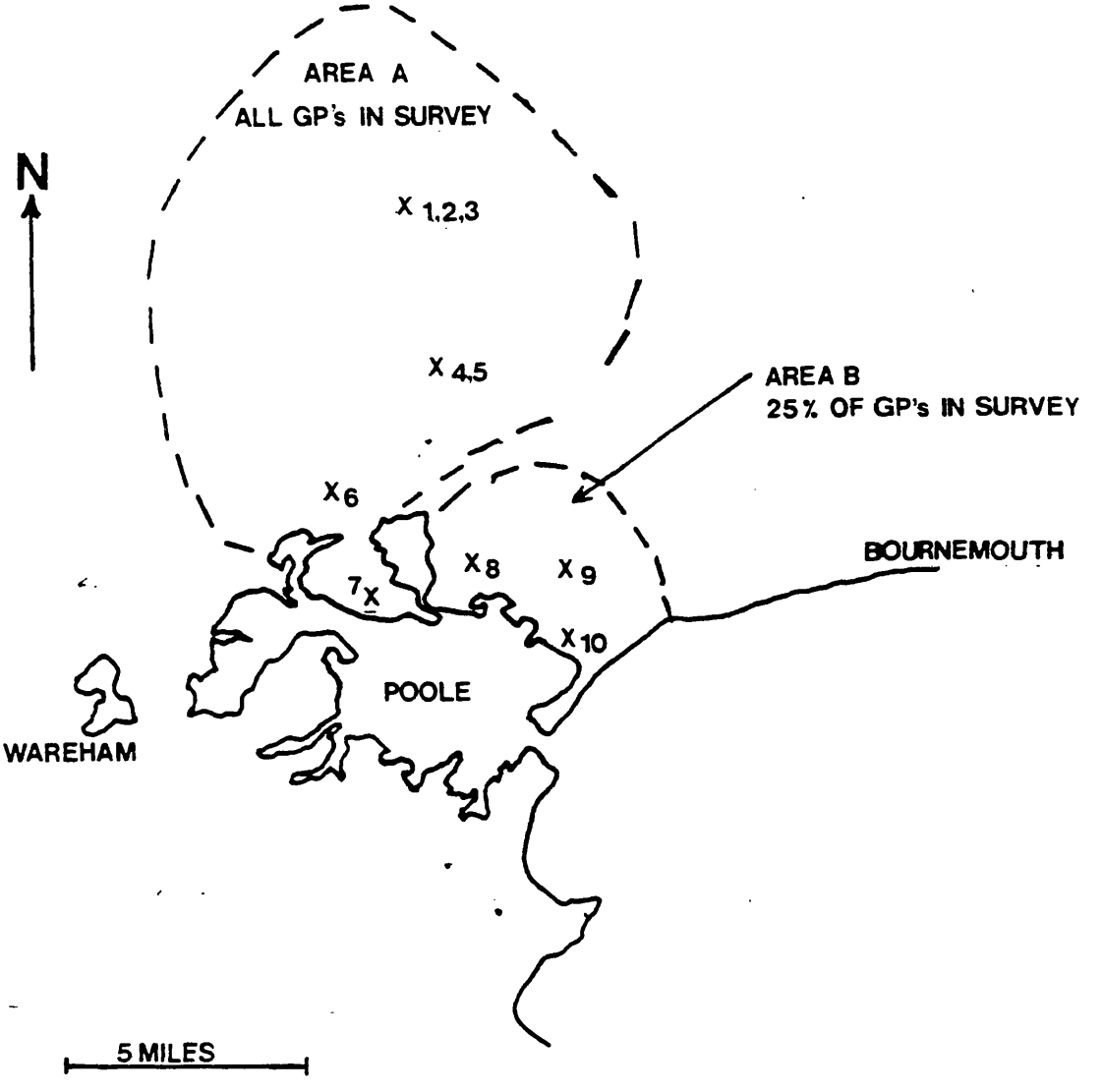
If the patient was unable to comply with the protocol for the valsalva manoeuvre the result was excluded from the analysis of autonomic neuropathy. The normal ranges for the autonomic function tests are listed at the end of the chapter (Ewing and Clarke 1987) and are obtained from the literature.

X-rays were always taken when ulceration existed or Charcot's joints were suspected.

Controls - Review Protocol

The control population was interviewed and examined in exactly the same way by the same observer (ie the author) as the diabetic population. Exceptions are that they did not have additional investigations if they were found to have risk factors for foot disease. There are therefore no autonomic function test data available. Cholesterol was measured only in controls with evidence of peripheral vascular disease.

MAP SHOWING GEOGRAPHICAL AREA AND THE LOCATION OF PRACTICES INVOLVED IN THE SURVEY (FIG. 3.1)



1,2,3	WIMBORNE	8	POOLE CENTRAL
4,5	BROADSTONE	9	PARKSTONE
6	UPTON	10	LILLIPUT
7	HAMWORTHY		

TABLE 3.1

DIABETIC REVIEW

INFORMATION FROM HISTORY

1. Diabetic history
   - type of diabetes
   - date of diagnosis
   - treatment

2. History of smoking

3. History of present alcohol intake (units/week)

4. History of neuropathy - symptoms

5. History of ischaemic heart disease

6. History of peripheral vascular disease

7. History of cerebrovascular disease

8. Hypertension history - including medication

9. Previous and present foot ulceration
   - site
   - duration

10. Previous surgery amputation
    - digital
    - part foot
    - below knee
    - above knee

11. Past medical history

TABLE 3.2

DIABETIC REVIEW

INFORMATION FROM EXAMINATION

1. Blood pressure
   - lying
   - standing (after 2 minutes)

2. Peripheral vascular disease
   - pulses
   - femoral bruits
   - resting ankle doppler pressures
   - ischaemia of feet

3. Peripheral neuropathy
   - ankle/knee reflexes
   - light touch
   - pain
   - vibration

4. Foot deformity

5. Foot ulceration
   - site
   - duration
   - grade

6. Fundi
   - grade
   - classification

7. Visual acuities

TABLE 3.3

CONTROL POPULATION - REVIEW

INFORMATION OBTAINED FROM HISTORY

1. History of smoking

2. History of alcohol intake - present (units/week)

3. Symptoms of neuropathy

4. History of ischaemic heart disease

5. History of stroke

6. History of peripheral vascular disease

7. History of hypertension

8. Previous foot ulceration - site/duration

9. Previous amputation and vascular surgery - date/type

10. Past medical history

INFORMATION FROM EXAMINATION

1. Blood pressure - lying
   - standing

2. Evidence of peripheral vascular disease
   - palpation of pulses
   - femoral bruits
   - dopplers - rest & exercise

3. Evidence of peripheral neuropathy

4. Foot deformity

5. Foot ulceration

LABORATORY INVESTIGATIONS

Urine - glycosuria) Ames
      - proteinuria) multistix

IN SELECTED PATIENTS

- 2 hour post meal plasma glucose
- glucose tolerance test 75g
- cholesterol - non fasting
- T4

TABLE 3.4

LABORATORY INVESTIGATIONS

A - PERFORMED ON ALL DIABETICS

1. Proteinuria - Ames Multistix

2. Plasma glucose - taken two hours after a meal

3. Haemoglobin A1

4. Serum creatinine

5. Serum cholesterol

B - IN DIABETICS AT RISK OF FOOT ULCERATION/AMPUTATION

6. Haemoglobin/haematocrit

7. Autonomic function tests - beat to beat variation - response to (a) forced breathing
(b) valsalva manoeuvre

8. T4 + TSH

TABLE 3.5

1. WAGNER CLASSIFICATION FOR FOOT ULCERATION
IE AN OPEN LESION AT OR BELOW THE MALLEOLLI
(ref Wagner 1987)

1. Superficial ulcer ie skin or soft tissues

2. Deep ulcer ie extending to bone, ligament, joint capsule, deep fascia

3. Deep abscess/osteomyelitis

4. Some portion of the foot is gangrenous

5. Complete involvement so that no foot healing or local procedure is possible.

II. DEFINITION OF PERIPHERAL NEUROPATHY

Clinical: Symptoms of one year's duration in the lower limb bilaterally with one or more of the following signs:

- absent ankle jerks (in patients < 70 years) bilaterally
- vibration threshold > 2 SD's from the mean for each age group up to 75 years (ref Bloom 1984)
- absent light touch or pain perception

Sub-clinical: No symptoms but at least 2 abnormal signs

III. DEFINITION OF PERIPHERAL VASCULAR DISEASE

1. Doppler pressure index of < 0.9

2. Previous, documented by-pass surgery for lower limb occlusive disease even if PI after surgery is 1.0 or more

IV. DEFINITION OF AUTONOMIC NEUROPATHY

1. Valsalva Ratio of 1.20 or less

2. Heart Rate (RR interval) variation during deep breathing of 10 beats per minute or less.

BOTH 1 AND 2 NEED TO BE PRESENT TO CONSTITUTE AUTONOMIC NEUROPATHY

TABLE 3.6

DIABETICS AT RISK OF FOOT ULCERATION

CRITERIA FOR ADDITIONAL INVESTIGATION

1. History of ischaemic heart disease/cerebrovascular disease/ peripheral vascular disease

2. Doppler pressure ratio of 0.9 or less

3. Absent posterior tibial pulse (at a minimum)

4. Some evidence of peripheral neuropathy
   - absent ankle jerks (in patients aged < 70 years) bilaterally
   - elevated vibration threshold bilaterally
   - absent pain or light touch perception
   - symptoms of neuropathy of at least 1 year's duration bilaterally

5. Past or present foot ulceration

6. Foot deformity

Chapter 4

RESULTS OF SUBJECT IDENTIFICATION

Diabetics

Table 4.1 shows the age and sex structure of the study population with comparison to the figures for the United Kingdom (1981 UK census). There is a small excess of 65 - 74 year olds and the trend becomes more marked in the 75 years and over category. In the very young age categories (up to 15 years) the converse occurs with the study population having slightly lower rates than the UK. These discrepancies apply to either sex.

1,150 diabetics were identified of whom 1,077 were reviewed (93.7%). Figure 4.1 shows results of previous surveys performed by Houston (1982) and Gatling (1986). The population within the defined area has risen to 97,039 and the number of GPs to a total of 45. The prevalence of diabetes mellitus was thus 1.19% and sub-dividing into sex categories revealed a rate of 1.31% for men and 1.07% for women. The age and sex characteristics of the total diabetic population identified are shown in Table 4.2. Almost one half the diabetics are over the age of 60 and the male/female ratio was 1.13.

Age specific rates for diabetes mellitus accrete steadily up to 50 years of age after which there is a marked increase. This is particularly so for males who have rates approximately 50% higher than their female counterparts (see Table 4.4).

Of the diabetics 21.2% were classified as insulin dependent and 77.9% as non insulin dependent. A further 0.9% could not be categorised because of insufficient information. The age and sex distribution of the two types of diabetes is shown in Figs 4.2 - 4.4. The clear bimodal distribution of the two types of diabetes is demonstrated. In insulin dependent diabetes as well as NIDDs the general trend was for an excess of males in most age categories. For IDDM the male/female was 1.16 and for NIDDM it was 1.13.

A pie chart (figure 4.5) shows that 34.9% of the diabetics were treated by insulin, 25.7% by diet only and 38.4% by diet and oral hypoglycaemic agents. Only 30% of diabetics were regularly reviewed by the hospital clinic.

Controls

Initially 751 supposedly non-diabetic controls were drawn from the study population of whom 41 were found either to have recently died or had moved. A further 225 subjects refused to attend and 5 were found to be diabetic leaving a total of 480 who were reviewed. (Tables 4.7 and 4.8). Three of the diabetics were found from testing for glycosuria and two by glucose levels after a meal. Table 4.6 shows a comparison of the age and sex breakdown of the controls and diabetics who attended for review. The sex structure is similar except in the very elderly age groups where there was a bias towards males. Similarly the percentages in each age category showed little difference except in the 80 years and over category where there were proportionally more diabetics.

Discussion

This study deliberately sought all diabetics who had diabetes mellitus as defined by WHO criteria within a defined population. The fact that only 36% of diabetics regularly attended the hospital clinic attests the importance of community rather than hospital based surveys. The Poole Hospital system of requesting that all diabetics regardless of age or mode of treatment are initially referred for education and examination before discharge back to the community aided identification of subjects. Relying purely on diabetic prescription methods may well be inaccurate since diet only treated diabetics may be missed. Similarly GP registers may well be out of date. This survey used several different methods for locating diabetics and it is unlikely that many cases were missed. Certainly the presence of 25.7% of diet only treated diabetics is high compared to previous surveys in Poole (Houston 1982, Gatling 1986). Theoretically this group would be the most likely category to be overlooked. The age characteristics of the study population follow a trend noted in Gatling's study (1986).

The latter survey noted a preponderance of elderly subjects but the trend is more marked in this current study. The reasons for this may be partly explained by demographic changes in the population as a whole. The Government White Paper (1989) suggests an expected increase in the 75 and over age group and possibly the 1991 census will reflect similar changes to that found in Poole. Nevertheless parts of the Poole area tend to be retirement areas and therefore more likely to have an older population.

It is conceivable that area B may not be truly representative of the area since only 25% of the GP's were involved within the area. However, these practices were chosen at random and all practices within the area were involved in the Poole shared care scheme regardless of whether they were participating in the study. It is unlikely, therefore, that there should be any real bias in terms of subjects registered with the practices actually studied.

The population of 97,039 must be considered accurate as the age/sex registers were updated by computerised Family Practitioner Committee lists every 3 months. Also 3 of the practices had only just had their patient registers updated and transferred onto the practice computers.

The prevalence of diabetes mellitus was found to be 1.04% by Houston (Houston 1982) and 1.01% by Gatling (Gatling 1986). The increase to 1.19% in this study may reflect the demographic changes within the population since methods of subject identification were similar in each case. There have been few recent studies that afford any comparison because of (a) differences in the definition of diabetes, (b) differences in the methods used for detection and (c) atypical population groups. A hospital based survey (Falconer 1971) found the prevalence of diabetes mellitus to be 0.63%. Although GPs were contacted, less than 5% of new diabetics were added to the hospital record of diabetics. It would seem unlikely that such a small percentage of subjects were treated purely in the community and may account for why they found only 13% of the diabetics were aged 65 or over.

Prevalence of known diabetes mellitus within general practices has been determined in several studies (Doney 1976, Fletcher 1977, Yudkin 1980, Dorman et al 1983, Tasker 1984, Williams 1985, Burrows et al 1987, Thompson et al 1988) and varies between 0.59 and 1.2%. Most of these studies were of small size and large variations may occur between practices (Burrows et al 1987). In these studies definitions of diabetes varied and in many cases we do not know how representative the populations were to that of the UK.

Prevalence data for populations in the USA and Australia also differ widely (Palumbo et al 1976, Klein et al 1983, Glatthaar et al 1985, Bender et al 1986) and generally they are higher than the results from this survey. Whether these differences are real or due to methodological practice may not accurately be determined.

Gatling (1986) noted a high age specific rate in males over the age of 45 and this finding is confirmed in the present study. One explanation previously offered for this occurrence has been the greater frequency of routine medicals performed for insurance and employment purposes. There is also a greater male to female ratio which seems to be a relatively recent change (Malins et al 1968) and would be in keeping with the former hypothesis. However the trend occurs through to the very elderly age groups and may well represent a real difference.

The classification of diabetes is not precise and there is as yet no definitive measure that will identify all genuine cases of IDDM and NIDD. The methods employed in this survey as proposed by Keen and Ng Tung Fui (1982) is a practical approach useful for large studies. It is realised in some instances that small numbers of diabetics will be inappropriately classified.

The method used initially to exclude the presence of diabetes in the non-diabetic population was crude. Glycosuria is not a reliable method to exclude the presence of diabetes mellitus. Where definite pathology was found a 2 hour post meal glucose was performed and a formal glucose tolerance test subsequently arranged for all subjects with a plasmaglucose of 7.8 mmol/l or more. There

is no satisfactory screening method for diabetes mellitus (Forrest et al 1986) and a glucose tolerance test was not feasible except in limited numbers. If the prevalence of undiagnosed diabetes mellitus is 1%, then of 480 subjects seen 5 would be expected to be diabetic. This study found 5 subjects to be diabetic but almost certainly some cases will have been missed since there was a preponderance of elderly subjects in the study where the prevalence of diabetes mellitus is highest.

These prevalence data emphasise that diabetes is a particular problem in elderly age groups and in the light of demographic changes in the population of the United Kingdom as a whole will be useful in estimating the increased demand on health care facilities by this group of patients.

TABLE 4.1

AGE DISTRIBUTION OF ALL PATIENTS REGISTERED WITH 45 GP'S

AGE (YEARS)	NO OF PATIENTS REGISTERED	%	% UK
< 5	5,202	5.4	6.1
5 - 14	11,480	11.8	14.7
15 - 29	19,610	20.2	22.5
30 - 44	20,668	21.3	19.5
45 - 64	21,528	22.2	22.3
65 - 74	10,007	10.3	9.2
75+	8,549	8.8	5.7
	97,039	100.0	100.0
MALES			
< 5	2,606	5.6	6.4
5 - 14	6,012	12.9	15.5
15 - 29	9,918	21.3	23.5
30 - 44	9,954	21.4	20.2
45 - 64	10,498	22.6	22.4
65 - 74	4,420	9.5	8.2
75+	3,138	6.7	3.8
TOTAL	46,546	100.0	100.0
FEMALES			
< 5	2,596	5.2	5.8
5 - 14	5,468	10.8	13.9
15 - 29	9,692	19.2	21.6
30 - 44	10,714	21.2	19.0
45 - 64	11,030	21.8	22.3
65 - 74	5,587	11.1	10.0
75+	5,411	10.7	7.4
TOTAL	50,493	100.00	100.00

TABLE 4.2

AGE AND SEX CHARACTERISTICS OF DIABETIC POPULATION IDENTIFIED

AGE	M	F	ALL
0- 4	0	2	2
5-14	8	7	15
15-29	37	23	60
30-39	32	25	57
40-49	38	50	88
50-59	82	66	148
60-69	151	113	264
70-79	175	159	334
80+	88	93	181
UNKNOWN		1	
TOTAL	611	539	1150

TABLE 4.3

CUMULATIVE FREQUENCY OF DIABETICS WITH RESPECT TO AGE

AGE	FREQUENCY	%	CUMULATIVE FREQUENCY
0- 4	2	0.2	0.2
5-14	15	1.3	1.5
15-29	60	5.2	6.7
30-39	57	5.0	11.7
40-49	88	7.7	19.4
50-59	148	12.9	32.3
60-69	264	23.0	55.3
70-79	334	29.0	84.3
80+	181	15.7	100.0

TABLE 4.4

AGE SPECIFIC RATE FOR DIABETES MELLITUS

AGE	NO OF SUBJECTS REGISTERED	NO OF DIABETICS	RATE PER 1000
0 -4	5,202	2	0.4
5-14	11,480	15	1.3
15-29	19,610	60	3.1
30-39	12,742	57	4.5
40-49	13,741	88	6.4
50-59	10,364	148	14.3
60-69	10,875	264	24.3
70-79	8,628	334	38.7
80+	4,480	181	40.4
UNKNOWN		1	
TOTAL	97,039	1,150	
MALES			
0- 4	2,606	0	0
5-14	6,012	8	1.3
15-29	9,918	37	3.7
30-39	6,061	32	5.3
40-49	6,763	38	5.6
50-59	5,130	82	16.0
60-69	4,980	151	30.3
70-79	3,667	175	47.7
80+	1,492	88	59.0
TOTAL	46,546	611	
FEMALES			
0- 4	2,596	2	0.7
5-14	5,468	7	1.3
15-29	9,692	23	2.4
30-39	6,681	25	3.7
40-49	6,978	50	7.2
50-59	5,234	66	12.6
60-69	5,895	113	19.2
70-79	4,961	159	32.0
80+	2,988	93	31.1
		+ 1	
TOTAL	50,493	538	

TABLE 4.5

AGE AND SEX BREAKDOWN OF ALL DIABETICS IDENTIFIED ACCORDING TO TYPE

IDDs

AGE	NO	% OF AGE GROUP (IE OF TOTAL DIABETICS IN CATEGORY)	M/F RATIO
0-4	2	100	0.00
5-14	16	100	1.00
15-29	58	96.7	1.64
30-39	52	91.2	1.48
40-49	41	45.8	0.64
50-59	19	13.1	1.10
60-69	31	11.7	1.20
70-79	21	6.3	1.62
80+	4	2.2	0.00
TOTAL	244		

NIDDs

0-4	0	0	-
5-14	0	0	-
15-29	2	3.3	1.0
30-39	5	8.8	0.25
40-49	42	54.2	0.91
50-59	126	86.9	1.27
60-69	232	88.3	1.37
70-79	312	93.7	1.09
80+	177	97.8	0.99
TOTAL	896		

TABLE 4.6

COMPARISON OF AGE/SEX BREAKDOWN OF CONTROLS WITH DIABETICS AGED 30+

Age (years)	Diabetics aged 30+ No.	(%)	M/F ratio	Controls No.	(%)	M/F ratio
30-39	49	(4.8)	1.33	15	(3.1)	1.14
40-49	76	(7.5)	0.62	37	(7.7)	0.61
50-59	137	(13.5)	1.32	75	(15.6)	1.42
60-69	253	(24.9)	1.30	143	(29.8)	1.38
70-79	324	(31.9)	1.08	146	(30.4)	1.12
80+	176	(17.3)	0.96	64	(13.3)	1.56
	1015	(100.0)	1.10	480	(100.0)	1.23

TABLE 4.7

CONTROLS

TOTAL DRAWN	=	751	
DEAD OR MOVED AWAY	=	41	
PROVED TO BE DIABETIC	=	5	
ATTENDED	=	480	
DID NOT ATTEND	=	225	F = 109 M = 116
HOME VISITS FOR CONTROLS	=	31 (6.5%)	

TABLE 4.8

BREAKDOWN OF CONTROLS INTO AGE AND SEX - NOT SEEN

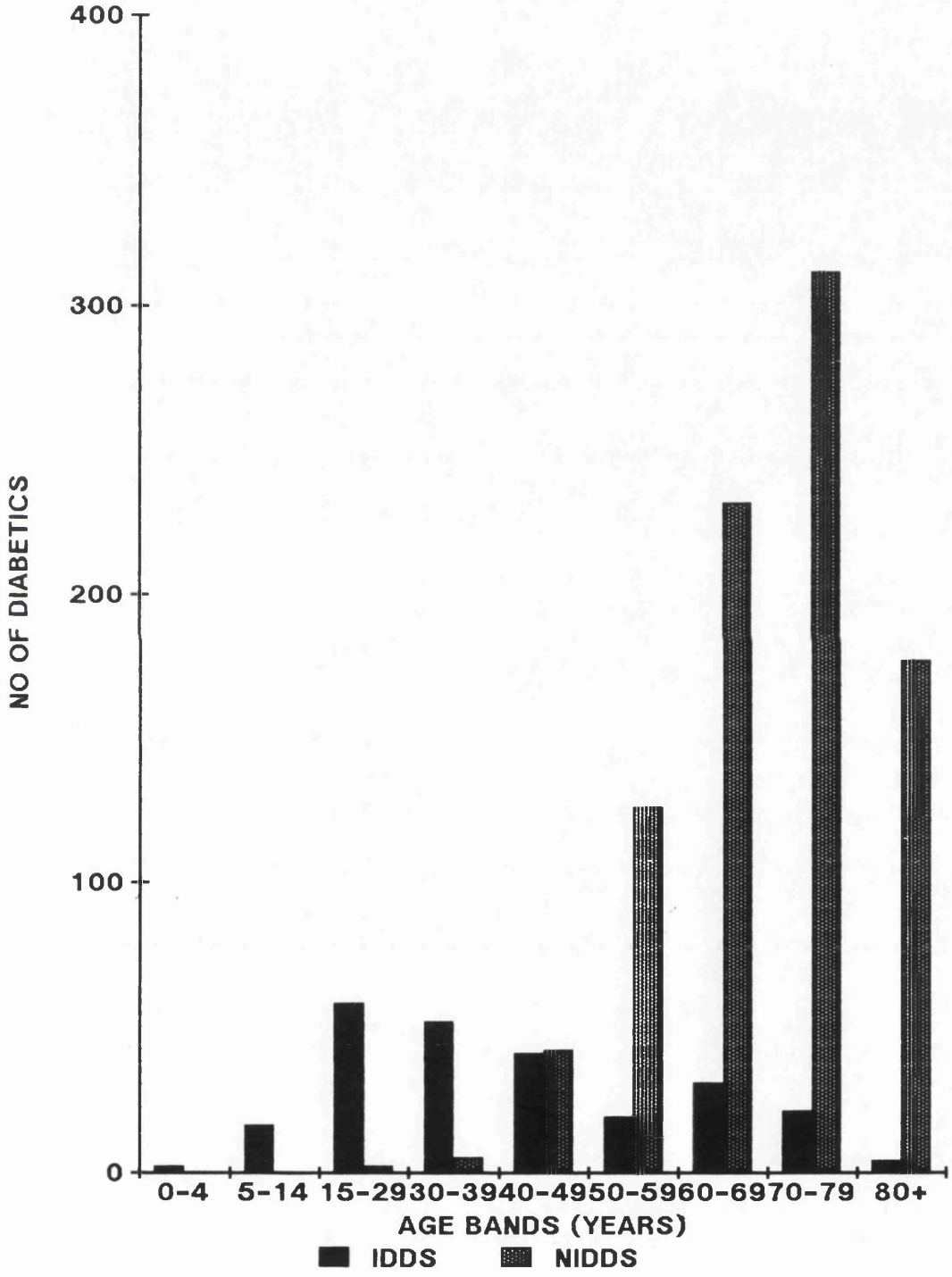
	M	F
30-44	10	13
45-64	43	42
65-74	31	21
75+	31	43
TOTAL	116	109

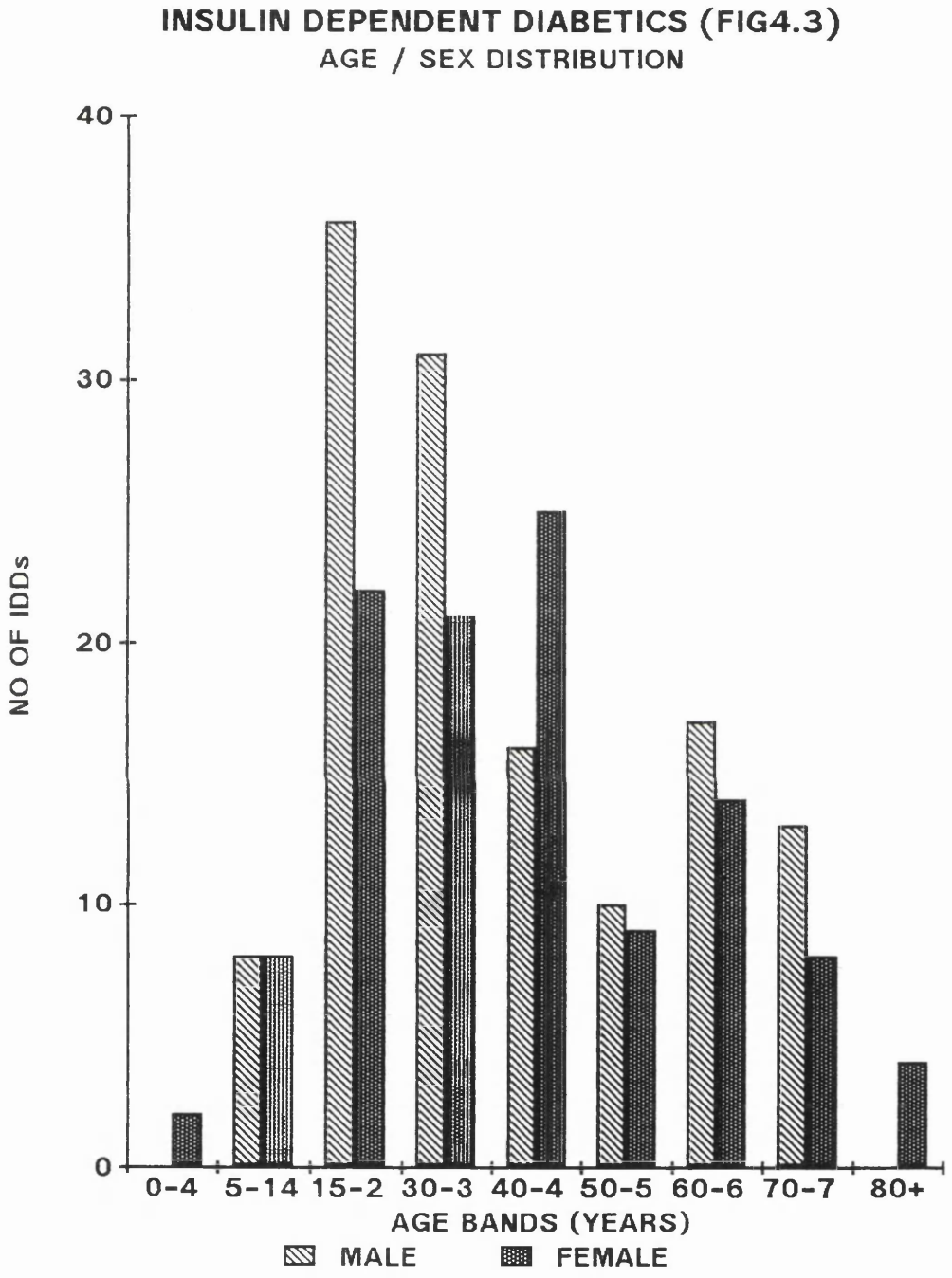
Fig 4.1.

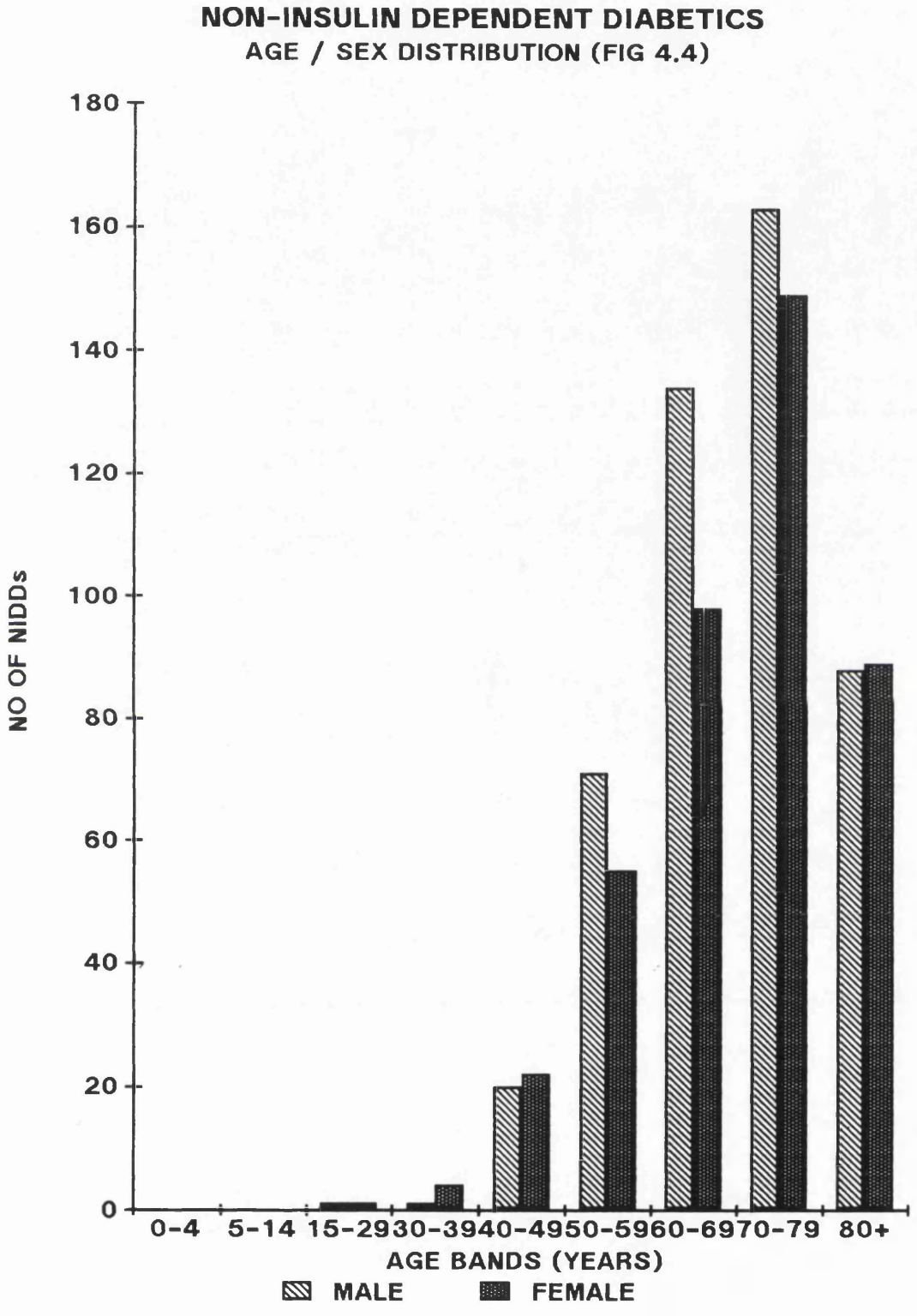
THE PREVALENCE OF DIABETES MELLITUS FROM THE 3 POOLE HOSPITAL DIABETIC DEPARTMENT SURVEYS

1979/80 Houston retinopathy survey	717 diabetic subjects identified General population 82,000 Prevalance of diabetes mellitus = 0.87%	273 dead 434 alive 3 embarked 7 untraced 717 total
1983/84 Gatling nephropathy survey	917 diabetic subjects identified General population 90,660 Prevalence of diabetes mellitus = 1.01%	211 dead 699 alive 7 embarked 917 total
1988/89 Present survey	1150 diabetic subjects identified General population 97,039 Prevalence of diabetes mellitus = 1.17%	

AGE DISTRIBUTION OF DIABETICS
ACCORDING TO TYPE (FIG 4.2)

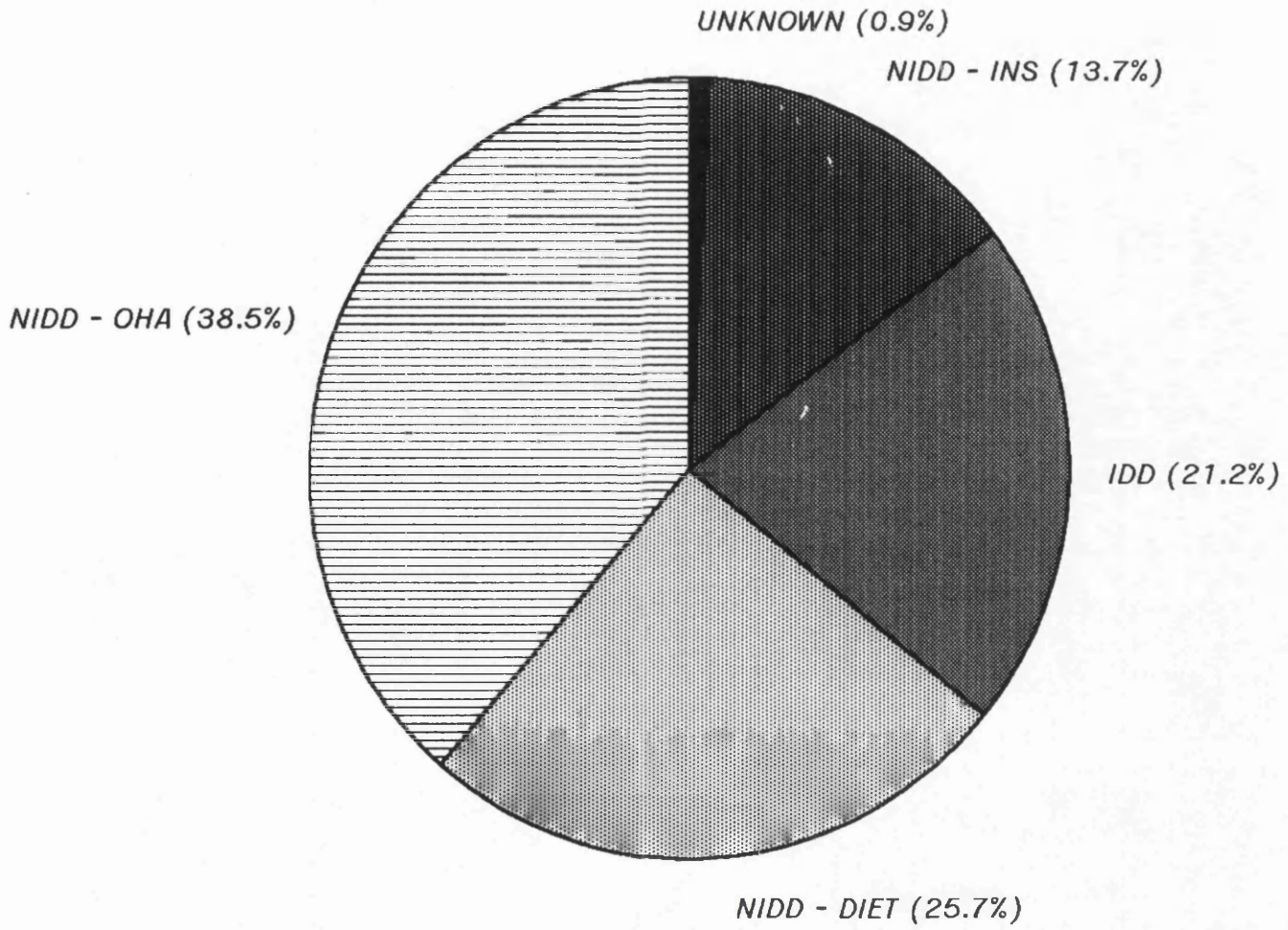



INSULIN DEPENDENT DIABETICS (FIG4.3)
AGE / SEX DISTRIBUTION
NO OF IDDs
40
30
20
10
0
0-4
5-14
15-2
30-3
40-4
50-5
60-6
70-7
80+
AGE BANDS (YEARS)
MALE
FEMALE


NON-INSULIN DEPENDENT DIABETICS
AGE / SEX DISTRIBUTION (FIG 4.4)
NO OF NIDDs
180
160
140
120
100
80
60
40
20
0
0-4
5-14
15-29
30-39
40-49
50-59
60-69
70-79
80+
AGE BANDS (YEARS)
MALE
FEMALE

DIABETIC TREATMENT STRATEGIES

TOTAL POPULATION IDENTIFIED (FIG 4.5)



Chapter 5

GENERAL CHARACTERISTICS OF THE DIABETIC AND CONTROL POPULATIONS

Diabetic Characteristics

Review Rate

Of 1,150 subjects identified 1,077 were reviewed. Of these, 130 patients (12%) were seen at home and the remainder at hospital research clinics. The age and sex breakdown of diabetics not reviewed is shown in Table 5.1. From existing hospital records 30 of these subjects were classified as insulin dependent, 29 as non insulin dependent and 14 were unclassifiable from data available. Since these patients refused to co-operate in the study the scrutinisation of GP records was deemed inappropriate without written consent.

The following description refers purely to those subjects seen either at home or at the hospital.

Type of Diabetes

19.7% (213 subjects) were deemed to be insulin dependent and 80.2% (864 subjects) to be non insulin dependent.

Ethnicity

All subjects were caucasian of whom 3 were Asians.

Age/sex structure

The age and sex characteristics are shown in Table 5.2 - 5.4 and Fig 5.1. Over 50% of all diabetics were aged 60 or over. It is noteworthy that there is a small percentage of non insulin dependent diabetics in the 15 - 39 age group. As expected only a very small percentage of diabetics over the age of 60 are classifiable as insulin dependent.

The bimodal age distribution for the two types of diabetes is clearly demonstrated in Fig 5.1.

The mean age at diagnosis and at review for IDDM and NIDDM is shown in Table 5.5. The difference between the sexes for either the age at diagnosis or at review was minimal.

Duration

The duration of diabetes is shown in Table 5.6, figs 5.2 and 5.3. 61% of NIDDs have a duration of 9 years or less compared with only 18.8% for IDDs.

Treatment

The breakdown of the diabetics into treatment categories is shown in Fig. 5.4. Just over one third of all subjects were treated by insulin. Of the remainder approximately one quarter were treated by diet only.

Diabetic Control

Diabetic control was assessed by glucose measurements 2 hours after a main meal (wherever possible) and HbA1 levels (see Appendix 4 for method of estimation). Table 5.7 shows the mean glucose values according to age. There is a marked difference in blood glucose concentration between the young and the elderly. This trend however is not so obvious when comparing mean HbA1 values (Table 5.9). Comparing mean glucose to type of diabetes mellitus reveals that glucose levels are highest in the insulin dependent and insulin treated categories (Table 5.8). Obviously the majority of the very elderly diabetics will be treated by diet or diet with an oral hypoglycaemic agent (OHA). Mean HbA1 levels were lowest in the diet treated categories and highest for the insulin dependent group. Only 29.2% of IDDs had an HbA1 within the normal range compared to 47% of NIDDs (see Tables 5.10, 5.11). The levels of statistical significance between different types of treatment of diabetes and mean HbA1 and glucose levels are shown in Table 5.12. Generally the difference between IDDs and NIDDs in terms of diabetic control was highly significant ($P < 0.0001$).

Specific Complications of Diabetes Mellitus

Retinopathy

The prevalence of retinopathy according to type of diabetes is shown in Table 5.13. Maculopathy was much more common in the non insulin dependent diabetics. The prevalence of retinopathy with duration is shown in Table 5.14. Over 50% of insulin dependent diabetics with a duration of 20 years or more had some form of retinopathy. One half of NIDDs with a duration of 15 years or more had retinopathy and indeed 21% were found to have retinopathy within 5 years of diagnosis.

Nephropathy

Proteinuria (ie 0.3 g/l or more of protein per litre) was found in 3.4% of all diabetics. 45 diabetics (4.1%) were found to have a creatinine of 150 umol/l or more. 15.6% of diabetics with proteinuria had chronic renal failure (creatinine of > 150 umol/l). (see Tables 5.15 - 5.16).

Comparison of the Control and Diabetic Populations for General Characteristics

BMI

The mean body mass index values (weight divided by height^2) for IDDs was 24.33 kg/m^2 and for NIDDs 26.84 kg/m^2. The difference was highly significant ($P < 0.001$). For controls the body mass index was 24.92 (kg/m^2). The difference between diabetics and controls after adjusting for age was highly significant. ($P < 0.001$). There was no significant difference in height between the diabetic and control populations ($P = 0.52$).

Age/Sex

The age and sex characteristics of the diabetics and controls reviewed are shown in Figure 5.5. In the extreme age ranges there are proportionally less controls ie the 30 - 39 and 80+ agegroups.

A greater percentage of 60 - 69 year olds were reviewed in the control group but the male/female ratio is very similar between both populations except in the 80+ age category where there were 50% more males than females.

Blood Pressure

The prevalence of hypertension and the percentage of subjects taking anti-hypertensive medication for the diabetic and control groups is shown in tables 5.18, 5.19 and 5.21. The difference in the prevalence of hypertension between diabetics and controls is statistically not significant ($P = 0.29$). Similarly the prevalence of hypertension in either type of diabetes was not significantly different compared to controls after adjusting for age. However 32.8% of diabetics and only 22.4% of controls were on anti-hypertensive medication. This difference is highly significant ($P < 0.001$). Dividing into the type of diabetes revealed that this difference was confined to NIDDs only. The male/female ratio for subjects on anti-hypertensive medication is almost equal for diabetics but males predominate in the control group. Mean systolic and diastolic blood pressure levels according to age is shown in table 5.20.

The mean systolic blood pressure was greater in diabetics but in controls there was a higher mean diastolic pressure. Multiple regression analysis taking into account the disparity of age between the two groups found that the difference between diabetics and controls for either systolic or diastolic pressure was highly significant ($P < 0.001$). These differences in blood pressure compared to controls occurred in both types of diabetes.

Smoking Habits

Current and past smoking habits in the two populations are shown in tables 5.22 and 5.23. Little difference was revealed regarding smoking habits between the 2 groups. A greater percentage of IDDs compared to NIDDs are smokers particularly in the 11 - 20 cigarettes per day category. Past smoking habits revealed that 35% of NIDDs and 47.6% of IDDs have never smoked. After adjusting

for age there is no difference between controls and diabetics regarding the maximum number of cigarettes smoked per day (ever - P = 0.22).

Alcohol Intake

Current drinking habits are shown in table 5.24. A greater percentage of diabetics are regular non drinkers compared to controls ($P < 0.001$). Considering the diabetic subjects by type 43.2% of IDDs compared to 58.7% of NIDDs are non drinkers.

Coronary Artery Disease.

The prevalence of coronary artery disease in each group is shown in table 5.25. There was no significant relationship between duration of diabetes and coronary artery disease in NIDDM. In IDDM however the relationship was highly significant ($P = 0.0006$). (See Table 5.28).

Cerebrovascular Disease.

The prevalence of cerebrovascular disease in each group according to sex is shown in table 5.26. The Mann-Whitney test revealed no significant relationship between duration of diabetes and cerebrovascular disease in either type of diabetes ($P = 0.63$ for IDDM and $P = 0.26$ for NIDDM) (see table 5.28).

Discussion

93.7% of all known diabetics in the cohort were reviewed. Such a high review rate was achieved by having a large number of home visits to all groups who were unwilling or unprepared to attend the hospital. It was felt necessary to try and see as many of this group of patient as possible because of the nature of the study. Inevitably patients with lower limb abnormalities are less likely to travel either to the GP surgery or to hospital. As a

consequence the number of home visits had to be a significant proportion of those actually seen. Of those who were not reviewed many were young insulin dependent diabetics who would be less likely to have complications of diabetes.

The Age at Diagnosis

The age at diagnosis of diabetes mellitus is predictable by type. The results of this survey do not differ appreciably from that of the previous survey in Poole (Gatling 1986). The mean age in that study was 25.4 years at diagnosis for IDDM as compared to 24.8 years in this study. A comparison with other British surveys is limited particularly with regard to population studies. A community survey in Oxford (Neil et al 1987) revealed a similar age at diagnosis. Other surveys have been hospital based and are at least 20 years old (Falconer et al 1971, O'Sullivan 1967). There is good evidence for an increase in the prevalence of known diabetes (Neil et al 1987) and it has been shown that only a minority of patients attend hospital clinics (Yudkin et al 1980). Therefore, comparisons with much older, non-population based studies, are of doubtful value.

Age at Review.

The age breakdown of diabetics at review clearly shows a discrete group of subjects who are young non insulin dependent diabetics. Such a group was found by Gatling (1986) and has been well described previously. The age and sex breakdown of the diabetics reviewed is similar to the previous Poole survey (Gatling 1986) and the Oxford survey (Neil et al 1989).

Although approximately 50% of IDDs were aged 40 or over in absolute terms there were very small numbers of subjects in the upper age levels. Care should therefore be exercised in extrapolating findings from a relatively small population of elderly IDDs to predict occurrences in larger populations.

Duration of Diabetes

The mean duration of diabetes is clearly less for NIDDs than IDDs and this is similar to the previous surveys in Poole (Houston 1982, Gatling 1986). This probably reflects the prolonged periods of antecedent hyperglycaemia and the greater age at diagnosis in non insulin dependent diabetics.

Type of Diabetes Mellitus and Modes of Treatment

The percentage of insulin dependent and non insulin dependent diabetics found in this survey support the general belief that approximately 80% of diabetic populations are non insulin dependent. Methods of treatment in this survey are similar to most other population surveys in terms of treatment ratios (Tasker 1984, Burrows et al 1987, Neil et al 1989) and previous surveys in Poole (Houston 1982, Gatling 1986) are also very similar. Clearly the percentage of diabetics on insulin treatment tends to reflect the attitude of the diabetologist. At Poole there is an aggressive approach to the management of poorly controlled non insulin dependent diabetics but this may not be the case in other centres.

Diabetic Control

Diabetic control was assessed by 2 hour interval glucose levels ie glucose levels taken 2 hours after a main meal, and haemoglobin A1 concentrations. There were significant differences between types of treatment and mean values for HbA1 and glucose concentrations. Similar results have been found in other studies (Yudkin et al 1980, Gatling 1986). In non insulin dependent diabetes the mode of treatment generally reflects difficulty in achieving adequate control. Normally such patients are started on diet and progress through increasing doses of oral hypoglycaemic agents and eventually in many cases require insulin treatment. It is therefore not surprising to find significant differences between different treatment regimens in this category of patient.

It is not appropriate to compare mean glucose and HbA1 levels between different studies. This is because in the case of glucose, timing of the sample is of paramount importance and in the case of HbA1 there is no uniformity of normal ranges between laboratories. However some comparison can be made regarding the percentage of subjects who had an HbA1 within the normal range. 43.4% of the subjects in this study had an HbA1 within normal limits for the Poole hospital laboratory. Yudkin et al (1980) found only 19% of hospital patients and 21.9% of patients under the care of the GP had HbA1s within normal limits. It was also found that mean levels of HbA1 were highest in social classes 3, 4 and 5 and they noted that they had a greater proportion of such classes in their study area. The previous survey in Poole found a similar percentage of HbA1 results within normal limits compared to the present survey (Gatling 1986).

Diabetic Complications

Retinopathy

The overall prevalence of retinopathy in this study does not appreciably differ from previous surveys in the Poole area (Houston 1982, Gatling 1986). Houston however found a lower prevalence of maculopathy although the definitions used were not identical since a different visual acuity was used and cases of ischaemic maculopathy were discounted. Similarly the prevalence of any retinopathy and new vessel disease was almost identical in the Oxford study (Neil et al 1989).

Nephropathy

The prevalence of nephropathy as defined by proteinuria of equal or greater than 0.3 g/l was lower than that found by the previous Poole survey. Nevertheless the only two other comparable population studies (Higgs et al 1989, Neil et al 1989) do in fact reveal very similar results. Clearly prevalence studies using single urine specimens are liable to lead to conflicting results since proteinuria in diabetic nephropathy may well be intermittent. Interestingly the prevalence of chronic renal failure is almost identical to recently published data from a similar population study (Higgs et al 1989).

Hypertension

There was no difference in the prevalence of hypertension between the control and diabetic populations. Since there were no controls aged less than 30, direct comparisons between types of diabetes and non diabetics is not possible. However using statistical methods to adjust for age allowed some comparison to be made. The vast majority of the diabetics in this study over the age of 30 are NIDDs and it is important to differentiate between the two types of diabetes because of the effects of diabetic nephropathy in IDDs. Gatling (1986) using lower criteria found a much higher prevalence of hypertension. The Oxford study (Neil et al 1989) using a similar definition to this survey found a prevalence of 43%. This figure seems very high and certainly higher than the recent study performed in the Bath area (Higgs et al 1989). The discrepancies between studies could be due to the percentage of subjects taking anti-hypertensive medication or could be due to methodological differences. The latter could include multiple observers and differences in equipment, for example whether a random zero sphygmomanometer was used.

There was a much greater frequency of diabetics on anti-hypertensive medication compared to controls ($P = < 0.001$). It does not necessarily indicate that hypertension is more frequent in the diabetic population. Clearly diabetics are far more liable to be started on such treatment due to the numerous opportunities for review by a physician. The fact that there was no difference between the two populations in terms of elevated blood pressure tends to confirm findings in the literature which relate to blood pressure in NIDDM. The Chicago Heart Association Detection Project (Pan et al 1986) found, after adjusting for age and weight, no significant difference between diabetics and non diabetics. However other studies (Jarrett et al 1978, Barrett-Connor et al 1981, Wilson et al 1986) have found small differences in blood pressure between diabetics and controls; although in one a significant difference was found only for women (Barrett-Connor et al 1981) and in another only for systolic pressure (Wilson et al 1986).

When considering the mean systolic and diastolic pressures there were clear differences between diabetics and controls. However it would be wrong to place too much emphasis on such findings because of the many differences between the two groups. Not only because of potential confounding factors such as body mass index but also the vast difference in prevalence of anti-hypertensive medication and possible differences in stress at the time of examination (diabetics are generally more used to having their blood pressure taken).

Smoking Habits

It is interesting to note that both diabetics and controls smoke far less than the general population in 1984 (OPCS survey 1984). If one looks at previous smoking habits it is evident that in both groups a large percentage have stopped smoking. The OPCS survey is of course over 5 years old and covers a much larger section of the population. Furthermore smoking habits vary with age and social class (OPCS survey 1984). The latter was not studied in our survey and may well be different. Nevertheless in this survey both diabetics and non diabetics seem to be aware of the dangers of smoking. It is perhaps disappointing that more diabetics smoke than controls although the maximum number of cigarettes smoked per day (ever) is not significant between the two populations.

Alcohol

The 1979 OPCS survey reveals that 44% of all women and 24% of all men are non or occasional drinkers only. This is in marked contrast to the present survey's findings which shows that both diabetics and controls have much higher percentages of non drinkers. Possibly the general public are becoming more aware of the dangers of excessive alcohol intake.

When comparing the controls with the diabetic population the significant trend towards lower alcohol consumption is both encouraging and possibly to be expected. Diabetics are warned that alcohol may have harmful synergistic effects in the development of hypoglycaemia and alcohol must also be counted as a source of calories in an already restricted diet.

Coronary Artery Disease

The prevalence of Rose questionnaire positive heart disease was almost identical to that in the Oxford study if myocardial infarction and angina are combined. It is interesting that the prevalence of coronary artery disease is not related to the duration of diabetes except in IDDs. Obviously the effects of aging per se and concomitant renal disease may account for the latter finding.

Cerebrovascular Disease

The prevalence of stroke in this study is higher than in the Oxford survey (Neil et al 1989). This may reflect the higher review rate conferred by more frequent home visits. However stroke is a broad term encompassing many different pathologies and may be mimicked by several other diseases. No attempt was made in this study to ascertain further information regarding a putative stroke. Comparisons with other studies, therefore, are limited. It is noteworthy that no associations existed between duration of diabetes. Similar findings have previously been reported in both insulin dependent and non insulin dependent diabetics (Welborn et al 1984).

Conclusions

This data gives a useful update for the general characteristics of a diabetic population and also provides a comparison with an age and sex matched non diabetic group drawn from the same general population. The non-diabetic group is valuable in that it gives an estimation of the increased burden imposed on the community conferred by the diagnosis of diabetes mellitus. At the time of writing no other such studies have been performed with an adequate control group. It is interesting that some of the known risk factors for macrovascular disease such as hypertension and smoking are not significantly different between the two populations in this survey. The importance of these findings as applied to the prevalence of diabetic foot disease will be discussed fully in a later chapter.

TABLE 5.1

AGE AND SEX DISTRIBUTION OF
DIABETICS NOT REVIEWED

	MALE	FEMALE	TOTAL	% OF TOTAL DIABETICS IN CATEGORY
< 5	0	2	2	100%
5-14	3	4	7	30.4%
15-29	5	1	6	10%
30-39	4	4	8	14%
40-49	9	3	12	13.6%
50-59	4	7	11	7.4%
60-69	8	3	11	4.2%
70-79	7	3	10	1.9%
80+	2	3	5	2.7%
UNKNOWN		1	1	
TOTAL	42	31	73	

TABLE 5.2

AGE/SEX BREAKDOWN OF DIABETICS

Age (years)	Males No.	(%)	Females No.	(%)
0- 4	0	(0.0)	0	(0.0)
5-14	5	(0.9)	3	(0.6)
15-29	32	(5.6)	22	(4.3)
30-39	28	(4.9)	21	(4.1)
40-49	29	(5.1)	47	(9.3)
50-59	78	(13.7)	59	(11.6)
60-69	143	(25.1)	110	(21.7)
70-79	168	(29.5)	156	(30.7)
80+	86	(15.1)	90	(17.7)
TOTAL	569	(100.0)	508	(100.0)

TABLE 5.3

AGE/SEX BREAKDOWN OF DIABETICS ACCORDING TO AGE

Age (years)	IDDM No.	IDDM % of age group	IDDM M/F ratio	NIDDM No.	NIDDM % of age group	NIDDM M/F ratio
0- 4	0	-	-	0	-	-
5-14	8	100.0	1.67	0	0.0	-
15-29	52	96.3	1.48	2	3.7	1.00
30-39	45	91.8	1.50	4	8.2	0.33
40-49	38	50.0	0.52	38	50.0	0.73
50-59	16	11.7	1.67	121	88.3	1.28
60-69	30	11.9	1.14	223	88.1	1.32
70-79	20	6.2	1.50	304	93.8	1.05
80+	4	2.3	0.00	172	97.7	1.00
TOTAL	213	19.8	1.15	864	80.2	1.11

TABLE 5.4

AGE DISTRIBUTION ACCORDING TO TYPE OF DIABETES

Age (years)	IDDM No.	IDDM (%)	IDDM Cum.	IDDM (%)	NIDDM No.	NIDDM (%)	NIDDM Cum.	NIDDM (%)
0- 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
5-14	8	(3.8)	8	(3.8)	0	(0.0)	0	(0.0)
15-29	52	(24.4)	60	(28.2)	2	(0.2)	2	(0.2)
30-39	45	(21.1)	105	(49.3)	4	(0.5)	6	(0.7)
40-49	38	(17.8)	143	(67.1)	38	(4.4)	44	(5.1)
50-59	16	(7.5)	159	(74.6)	121	(14.0)	165	(19.1)
60-69	30	(14.1)	189	(88.7)	223	(25.8)	388	(44.9)
70-79	20	(9.4)	209	(98.1)	304	(35.2)	692	(80.1)
80+	4	(19.9)	213	(100.0)	172	(19.9)	864	(100.0)
TOTAL	213	(100.0)			864	(100.0)		

TABLE 5.5

GENERAL CHARACTERISTICS

IDDM

	Males	Females	All
No. of patients	114	99	213
Age at review (years):			
mean value	41.4	44.8	43.0
range	71	82	85
Age at diagnosis (years):			
mean value	24.4	25.2	24.8
range	71	72	73
Duration of diabetes (years):			
mean value	17.0	19.7	18.2
range	53	49	53

NIDDM

	Males	Females	All
No. of patients	455	409	864
Age at review (years):			
mean value	69.4	69.8	69.6
range	68	76	76
Age at diagnosis (years):			
mean value	59.3	60.6	59.9
range	86	82	92
Duration of diabetes (years):			
mean value	10.1	9.2	9.7
range	81	41	81

TABLE 5.6

DISTRIBUTION OF DIABETICS ACCORDING TO DURATION

IDDM

Duration (years)	Males No.	(%)	Females No.	(%)	All No.	(%)
0- 4	16	(7.5)	8	(3.8)	24	(11.3)
5- 9	24	(11.3)	16	(7.5)	40	(18.8)
10-14	21	(9.9)	16	(7.5)	37	(17.4)
15-19	14	(6.6)	15	(7.0)	29	(13.6)
20-24	13	(6.1)	13	(6.1)	26	(12.2)
25-29	5	(2.3)	10	(4.7)	15	(7.0)
30-34	7	(3.3)	7	(3.3)	14	(6.6)
35-39	6	(2.8)	6	(2.8)	12	(5.6)
40-44	1	(0.5)	6	(2.8)	7	(3.3)
45-49	4	(1.9)	1	(0.5)	5	(2.3)
50+	3	(1.4)	1	(0.5)	4	(1.9)
TOTAL	114	(53.5)	99	(46.5)	213	(100.0)

NIDDM

Duration (years)	Males No.	(valid%)	Females No.	(valid%)	All No.	(valid%)
0- 4	146	(16.9)	129	(15.0)	274	(31.9)
5- 9	119	(13.8)	132	(15.3)	251	(29.1)
10-14	77	(8.9)	64	(7.4)	141	(16.4)
15-19	53	(6.1)	39	(4.5)	92	(10.7)
20-24	26	(3.0)	28	(3.2)	54	(6.3)
25-29	16	(1.9)	8	(0.9)	24	(2.8)
30-34	11	(1.3)	4	(0.5)	15	(1.7)
35-39	3	(0.3)	2	(0.2)	5	(0.6)
40-44	1	(0.1)	2	(0.2)	3	(0.3)
45-49	0	(0.0)	0	(0.0)	0	(0.0)
50+	2	(0.2)	0	(0.0)	2	(0.2)
Total valid	454	(52.7)	408	(47.3)	862	(100.0)
Missing data	1		1		2	

TABLE 5.7

BLOOD GLUCOSE CONCENTRATIONS (DIABETICS)

1048 (ie 97.3%) out of 1077 cases have a value for blood glucose concentration

Age group	No. (valid)	Mean glucose	SD glucose
5-14	6	10.58	8.76
15-29	52	11.75	7.69
30-39	49	10.52	5.48
40-49	74	11.08	5.45
50-59	133	10.57	4.63
60-69	250	9.44	4.24
70-79	318	9.40	4.14
80+	166	8.69	3.94

TABLE 5.8

MEAN BLOOD GLUCOSE CONCENTRATIONS ACCORDING TO TREATMENT

Type of DM	No. (valid)	Mean glucose	SD glucose
IDD	207	11.46	6.34
NIDD diet	264	8.19	3.54
NIDD OHA	425	9.53	4.01
NIDDI	152	10.36	4.60

TABLE 5.9

HBA1 VALUES (DIABETICS)

1041 (ie 96.7%) out of 1077 cases have a value for HbA1

Age group	No. (valid)	Mean HbA1	SD HbA1
5-14	8	8.69	0.99
15-29	53	9.66	1.81
30-39	48	9.24	1.63
40-49	74	9.50	1.89
50-59	133	9.12	1.88
60-69	250	8.77	1.59
70-79	311	8.79	1.60
80+	164	8.95	1.58

TABLE 5.10

MEAN HbA1 VALUES ACCORDING TO TREATMENT

Type of DM	No. (valid)	Mean HbA1	SD HbA1
IDD	209	9.51	1.73
NIDD diet	261	8.38	1.40
NIDD OHA	420	8.92	1.73
NIDDI	151	9.36	1.58

TABLE 5.11

DEGREE OF DIABETIC CONTROL ACCORDING TO TYPE OF DIABETES

	IDDM		NIDDM		All diabetics	
HbA1 range*	No.	(%)	No.	(%)	No.	(%)
0.0- 8.5	61	(29.2)	391	(47.0)	452	(43.4)
8.6-10.5	94	(45.0)	328	(39.4)	422	(40.5)
10.6-12.5	40	(19.1)	87	(10.5)	127	(12.2)
>12.5	14	(6.7)	26	(3.1)	40	(3.8)
	209	(100.0)	832	(100.0)	1041	(100.0)

*Upper limit of normal range = 8.5%

TABLE 5.12
RESULTS OF *T*-TESTS COMPARING GLUCOSE AND HBA1 LEVELS

Glucose	HbA1
1. IDDs vs NIDDs	1. IDDs vs NIDDs
IDD mean: 11.46 (207 cases)	IDD mean: 9.51 (209 cases)
NIDD mean: 9.32 (841 cases)	NIDD mean:8.83 (832 cases)
Difference of means: 2.14	Difference of means: 0.684
t=5.98, df=1046, p<0.0005	t=5.34, df=1039, p<0.0005
95% confidence interval for difference in means: 1.44 to 2.84	95% confidence interval for difference in means: 0.433 to 0.936
2. NIDD OHA vs NIDDI	2. NIDD OHA vs NIDDI
NIDD OHA mean: 9.53 (425 cases)	NIDD OHA mean: 8.92 (420 cases)
NIDDI mean: 10.71 (152 cases)	NIDDI mean: 9.36 (151 cases)
Difference of means: -1.18	Difference of means: -0.438
t=2.99, df=575, p=0.003	t=2.74, df=569, p=0.006
95% confidence interval for difference in means: -1.95 to -0.404	95% confidence interval for difference in means: -0.753 to -0.124
3. NIDD diet vs NIDDI	3. NIDD diet vs NIDDI
NIDD diet mean: 8.19 (264 cases)	NIDD diet mean: 8.38 (261 cases)
NIDDI mean: 10.71 (152 cases)	NIDDI mean: 9.36 (151 cases)
Difference of means: -2.52	Difference of means: -0.975
t=6.24, df=414, p<0.0005	t=6.49, df=410, p<0.0005
95% confidence interval for difference in means: -3.31 to -1.72	95% confidence interval for difference in means: -1.27 to -0.68
4. NIDD diet vs NIDD OHA	4. NIDD diet vs NIDD OHA
NIDD diet mean: 8.19 (264 cases)	NIDD diet mean: 8.38 (261 cases)
NIDD OHA mean: 9.53 (425 cases)	NIDD OHA mean: 8.92 (420 cases)
Difference in means: -1.34	Difference in means: -0.536
t=-4.44, df=687, p<0.0005	t=4.23, df=679, p<0.0005
95% confidence interval for difference in means: -1.93 to -0.746	95% confidence interval for difference in means: -0.785 to -0.287

TABLE 5.13

PREVALENCE OF RETINOPATHY
(see Appendix 6 for definitions)

	IDDM		NIDDM		All diabetics	
	No.	(valid%)	No.	(valid%)	No.	(valid%)
None	127	(67.6)	505	(69.3)	632	(68.9)
Background	58	(28.9)	165	(21.3)	223	(22.8)
Ischaemic	13	(6.6)	25	(3.2)	38	(3.9)
Proliferative	11	(5.5)	9	(1.2)	20	(2.1)
Maculopathy	15	(7.6)	45	(6.8)	60	(7.0)
Non-diabetic Maculopathy	4	(1.9)	76	(8.8)	80	(7.4)

TABLE 5.14

PREVALENCE OF ANY RETINOPATHY (ACCORDING TO DURATION)

Duration (years)	IDDM No.	(%)	NIDDM No.	(%)	All diabetics No.	(%)
< 1	0	(-)	0	(0.0)	0	(0.0)
1- 4	2	(8.7)	52	(21.0)	54	(19.9)
5- 9	2	(5.3)	52	(24.2)	54	(21.3)
10-14	5	(15.6)	43	(39.1)	48	(33.8)
15-19	9	(36.0)	37	(50.0)	46	(46.5)
20-24	12	(54.5)	20	(47.6)	32	(50.0)
25-29	11	(73.3)	11	(55.0)	22	(62.9)
30-39	12	(60.0)	9	(60.0)	21	(60.0)
40-49	6	(66.7)	0	(0.0)	6	(54.5)
50+	2	(50.0)	0	(0.0)	2	(40.0)
Missing values	25		135		160	

TABLE 5.15

PREVALENCE OF PROTEINURIA

All diabetics (missing values = 73)

	Proteinuria present		Proteinuria absent	
	No.	(%)	No.	(%)
IDD	8	(4.0	190	(96.0)
NIDD	26	(3.2)	780	(96.8)
All	34	(3.4)	970	(96.6)

TABLE 5.16

Diabetics with renal impairment (>150 mmol/l)

	Proteinuria present		Proteinuria absent	
	No.	(%)	No.	(%)
IDD	1	(50.0)	1	(50.0)
NIDD	6	(14.0)	37	(86.0)
All	7	(15.6)	38	(84.4)

TABLE 5.17

Diabetics without renal impairment (<150 mmol/l)

	Proteinuria present		Proteinuria absent	
	No.	(%)	No.	(%)
IDD	7	(3.8)	179	(96.2)
NIDD	19	(2.6)	719	(97.4)
All	26	(2.8)	898	(97.2)

TABLE 5.18

PREVALENCE OF HYPERTENSION

Age (years)	IDD No.	(%)	% of hyper-tensive IDDs	NIDD No.	(%)	% of hyper-tensive NIDDs
0-19	0	(0.0)	0.0	0	(0.0)	0.0
20-29	0	(0.0)	0.0	0	(0.0)	0.0
30-39	0	(0.0)	0.0	0	(0.0)	0.0
40-49	0	(0.0)	0.9	5	(13.2)	4.1
50-59	1	(6.3)	14.3	16	(13.3)	13.1
60-69	4	(13.3)	57.1	32	(14.5)	26.2
70-79	1	(5.3)	14.3	38	(13.1)	31.1
80+	1	(25.0)	14.3	31	(19.6)	25.4
	7	(3.3)	100.0	122	(14.6)	100.0
Missing values	2			31		

TABLE 5.19

PREVALENCE OF HYPERTENSION - DIABETICS VERSUS CONTROLS

Age (years)	Diabetics No.	(%)	% of hyper-tensive diabetics	Controls No.	(%)	% of hyper-tensive controls
0-19	0	(0.0)	0.0	0	(-)	0.0
20-29	0	(0.0)	0.0	0	(-)	0.0
30-39	0	(0.0)	0.0	0	(0.0)	0.0
40-49	5	(6.7)	3.9	0	(0.0)	0.0
50-59	17	(12.5)	13.2	4	(5.5)	5.8
60-69	36	(14.3)	27.9	20	(14.1)	29.0
70-79	39	(12.6)	30.2	30	(20.8)	43.5
80+	32	(19.8)	24.8	15	(24.2)	21.7
Missing values	129	(12.4)	100.0	69	(14.6)	100.0
	33			4		

TABLE 5.20

MEAN BLOOD PRESSURE

Age (years)	Diabetics Diastolic mean/mmHg	Diabetics Systolic mean/mmHg	Controls Diastolic mean/mmHg	Controls Systolic mean/mmHg
0- 4	-	-	-	-
5-14	61.50	99.25	-	-
15-29	74.43	124.23	-	-
30-39	77.10	129.19	82.27	118.30
40-49	82.05	136.44	83.03	121.47
50-59	86.61	146.40	89.99	135.92
60-69	86.06	156.26	89.30	145.98
70-79	83.99	158.62	90.03	155.56
80+	85.79	165.74	88.86	162.80
Missing values	32	33	8	8

TABLE 5.21

HYPOTENSIVE THERAPY

	On treatment No.	(%)	M/F ratio	Not on treatment No.	(%)	M/F ratio	Missing values
IDDM	26	(12.6)	1.17	181	(87.4)	1.18	6
NIDDM	322	(37.7)	0.96	532	(62.3)	1.22	10
All diabetics	348	(32.8)	0.98	713	(67.2)	1.21	16
Controls	107	(22.4)	1.55	371	(77.6)	1.16	2

TABLE 5.22

CURRENT SMOKING HABITS

	IDDM		NIDDM		All diabetics		Controls	
	No.	(valid%)	No.	(valid%)	No.	(valid%)	No.	(valid%)
Non-smoker	158	(74.2)	743	(86.1)	901	(83.7)	416	(86.8)
Pipe smoker	0	(0.0)	6	(0.7)	6	(0.6)	2	(0.4)
Cigar smoker	2	(0.9)	2	(0.2)	4	(0.4)	0	(0.0)
1- 5*	5	(2.3)	13	(1.5)	18	(1.7)	7	(1.5)
6-10*	10	(4.7)	24	(2.8)	34	(3.2)	7	(1.5)
11-20*	24	(11.3)	42	(4.9)	66	(6.1)	28	(5.8)
21-30*	13	(6.1)	22	(2.5)	35	(3.3)	12	(2.5)
> 30*	1	(0.5)	11	(1.3)	12	(1.1)	7	(1.5)
Total valid	213	(100.0)	863	(100.0)	1076	(100.0)	479	(100.0)
Missing data	-		1		1		1	

TABLE 5.23

PAST SMOKING HABITS

	IDDM		NIDDM		All diabetics		Controls	
	No.	(valid%)	No.	(valid%)	No.	(valid%)	No.	(valid%)
Non-smoker	101	(47.6)	299	(35.2)	400	(37.7)	193	(40.4)
Pipe smoker	2	(0.9)	12	(1.4)	14	(1.3)	4	(0.8)
Cigar smoker	3	(1.4)	4	(0.5)	7	(0.7)	2	(0.4)
1- 5*	15	(7.1)	75	(8.8)	90	(8.5)	44	(9.2)
6-10*	19	(9.0)	106	(12.5)	125	(11.8)	58	(12.1)
11-20*	41	(19.3)	159	(18.7)	200	(18.8)	101	(21.1)
21-30*	28	(13.2)	130	(15.3)	158	(14.9)	40	(8.4)
> 30*	3	(1.4)	65	(7.6)	68	(6.4)	36	(7.5)
Total valid	212	(100.0)	850	(100.0)	1062	(100.0)	478	(100.0)
Missing data	1		14		15		2	

*Maximum number of cigarettes smoked per day

TABLE 5.24

CURRENT DRINKING HABITS

	IDDM		NIDDM		All diabetics		Controls	
	No.	(valid%)	No.	(valid%)	No.	(valid%)	No.	(valid%)
Non-drinker	92	(43.2)	504	(58.7)	596	(55.6)	217	(45.2)
1-14*	107	(50.2)	296	(34.5)	403	(37.6)	201	(41.9)
15-21*	5	(2.3)	30	(3.5)	35	(3.3)	20	(4.2)
22-35*	6	(2.8)	14	(1.6)	20	(1.9)	30	(6.3)
36-50*	2	(0.9)	4	(0.5)	6	(0.6)	6	(1.2)
> 50*	1	(0.5)	10	(1.2)	11	(1.0)	6	(1.2)
Total valid	213	(100.0)	858	(100.0)	1071	(100.0)	480	(100.0)
Missing data	-		6		6		-	

	Diabetics					
	Males			Females		
	No.	(valid%)	(cum.%)	No.	(valid%)	(cum.%)
Non-drinker	245	(43.2)	(43.2)	351	(69.6)	(69.6)
1-14*	260	(45.9)	(89.1)	143	(28.4)	(98.0)
15-21*	28	(4.9)	(94.0)	7	(1.4)	(99.4)
22-35*	17	(3.0)	(97.0)	3	(0.6)	(100.0)
36-50*	6	(1.1)	(98.1)	0	(0.0)	(100.0)
> 50*	11	(1.9)	(100.0)	0	(0.0)	(100.0)
Total valid	567	(100.0)		504	(100.0)	
Missing data	2			4		

	Controls					
	Males			Females		
	No.	(valid%)	(cum.%)	No.	(valid%)	(cum.%)
Non-drinker	104	(39.2)	(39.2)	113	(52.6)	(52.6)
1-14*	108	(40.8)	(80.0)	93	(43.3)	(95.8)
15-21*	18	(6.8)	(86.8)	2	(0.9)	(96.7)
22-35*	24	(9.1)	(95.8)	6	(2.8)	(99.5)
36-50*	6	(2.3)	(98.1)	0	(0.0)	(99.5)
> 50*	5	(1.9)	(100.0)	1	(0.5)	(100.0)
Total valid	265	(100.0)		215	(100.0)	
Missing data	-			-		

*Number of units of alcohol consumed per week

TABLE 5.25

PREVALENCE OF CORONARY ARTERY DISEASE

	CAD present			CAD absent		
	No.	(valid%)	M/F ratio	No.	(valid%)	M/F ratio
IDDM	15	(7.0)	0.88	198	(93.0)	1.18
NIDDM	150	(17.5)	1.21	709	(82.5)	1.10
All diabetics	165	(15.4)	1.17	907	(84.6)	1.11
Controls	53	(11.0)	2.53	427	(89.0)	1.14

TABLE 5.26

PREVALENCE OF CEREBROVASCULAR DISEASE

	CVD present			CVD absent		
	No.	(valid%)	M/F ratio	No.	(valid%)	M/F ratio
IDDM	5	(2.3)	4.00	208	(97.7)	1.12
NIDDM	60	(7.0)	1.31	800	(93.0)	1.10
All diabetics	65	(6.1)	1.41	1008	(93.9)	1.10
Controls	18	(3.8)	17.00	462	(96.2)	1.16

TABLE 5.27

REGRESSION ANALYSES TO DETERMINE THE SIGNIFICANCE OF DIFFERENCES BETWEEEN VARIABLES IN THE CONTROL AND DIABETIC POPULATIONS AFTER ADJUSTING FOR AGE

(Age included in the regression equation)

Dependent Variable	Factor	Coefficient (SE)	P value
1. Alcohol intake (units/week)	Diabetics = 1 Controls = 0	-1.886 (0.545)	<0.001
	NIDDs = 1 Controls = 0	-1.707 (0.584)	<0.01
	IDDs = 1 Controls = 0	-1.926 (1.028)	0.06
2. Smoking (max smoked per day)	Diabetics = 1 Controls = 0	1.030 (0.833)	0.22
	NIDDs = 1 Controls = 0	2.229 (0.890)	0.01
	IDDs = 1 Controls = 0	-0.928 (1.404)	0.66
3. Body Mass Index (kg/M^2)	Diabetics = 1 Controls = 0	1.425 (0.241)	<0.001
	NIDDs = 1 Controls = 0	2.121 (0.247)	<0.001
	IDDs = 1 Controls = 0	-0.411 (0.390)	0.29

TABLE 5.27 (cont.)

Dependent Variable	Factor	Coefficient (SE)	P value
4. Hypertension* > 160/95 mmHg	Diabetics = 1 Controls = 0	-0.174 (0.163)	0.29
	NIDDs = 1 Controls = 0	-0.079 (0.165)	0.63
	IDDs = 1 Controls = 0	-0.554 (0.432)	0.20
5. Hypotensive therapy*	Diabetics = 1 Controls = 0	0.581 (0.131)	<0.001
	NIDDs = 1 Controls = 0	0.664 (0.132)	<0.001
	IDDs = 1 Controls = 0	0.286 (0.277)	0.30
6. Systolic blood pressure (mmHg)	Diabetics = 1 Controls = 0	7.355 (0.197)	<0.001
	NIDDs = 1 Controls = 0	7.920 (1.285)	<0.001
	IDDs = 1 Controls = 0	6.762 (2.052)	<0.001
7. Diastolic blood pressure (mmHg)	Diabetics = 1 Controls = 0	-4.555 (0.662)	<0.001
	NIDDs = 1 Controls = 0	-3.184 (0.687)	<0.001
	IDDs = 1 Controls = 0	-8.349	<0.001

A minus (-) coefficient indicates that the variable is inversely related to diabetic status.

*Logistic regression analysis used as it is a discrete variable.

TABLE 5.28

MANN-WHITNEY U TEST

This was used to determine whether a relationship existed between the duration of diabetes and the presence or absence of coronary artery disease/cerebrovascular disease for IDDM and NIDDM.

The 2-tailed significance levels calculated are shown below:

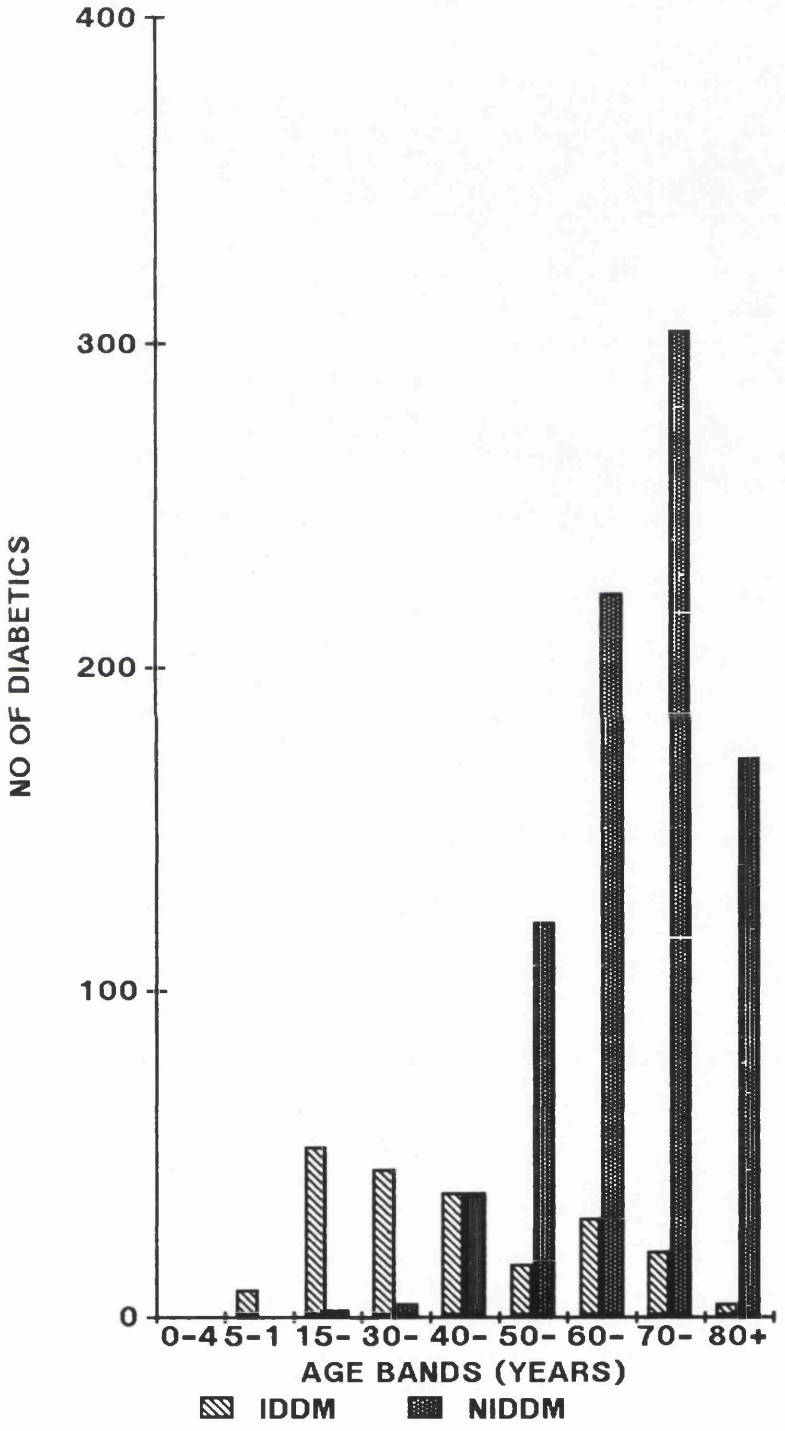
(a) For coronary artery disease in IDD diabetics, p=0.0006

(b) For coronary artery disease in NIDD diabetics, p=0.6417

(c) For cerebrovascular disease in IDD diabetics, p=6356

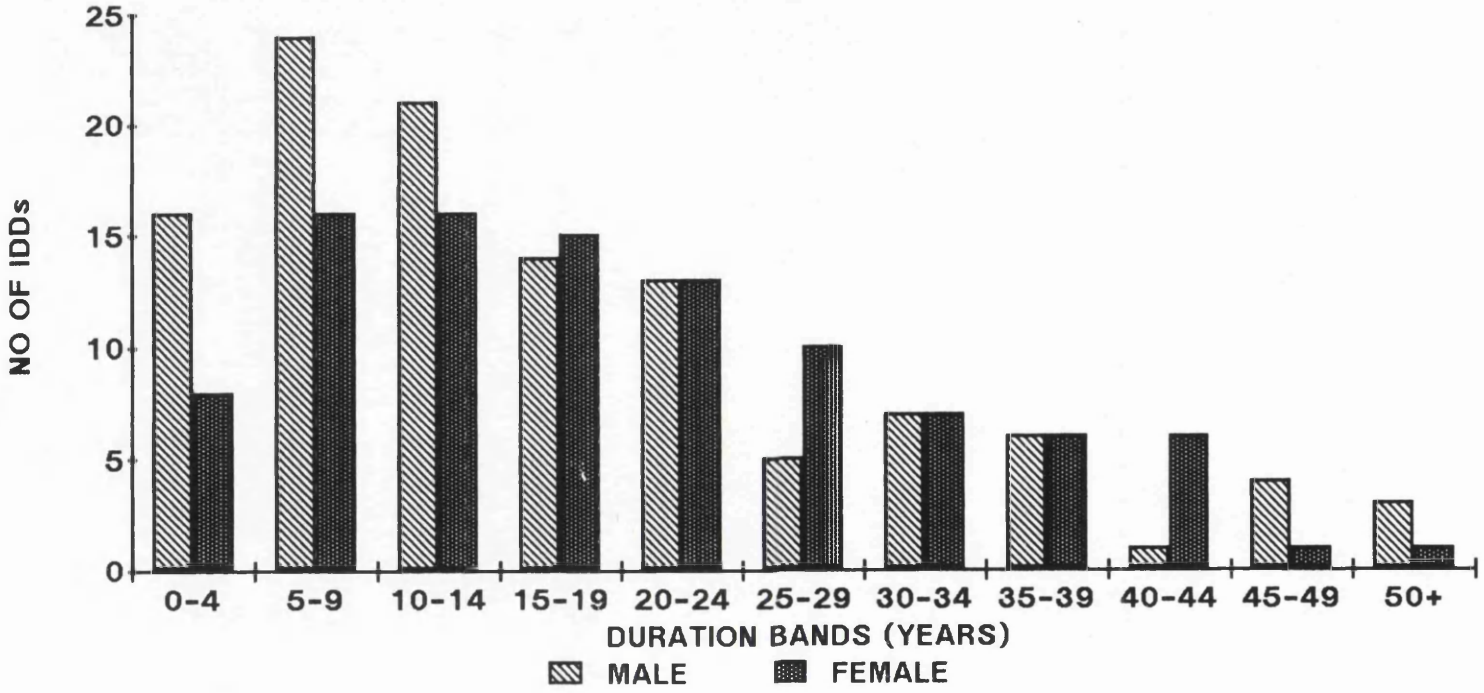
(d) For cerebrovascular disease in NIDD diabetics, p=0.2600

DISTRIBUTION OF DIABETICS REVIEWED
ACCORDING TO AGE AND TYPE (FIG 5.1)



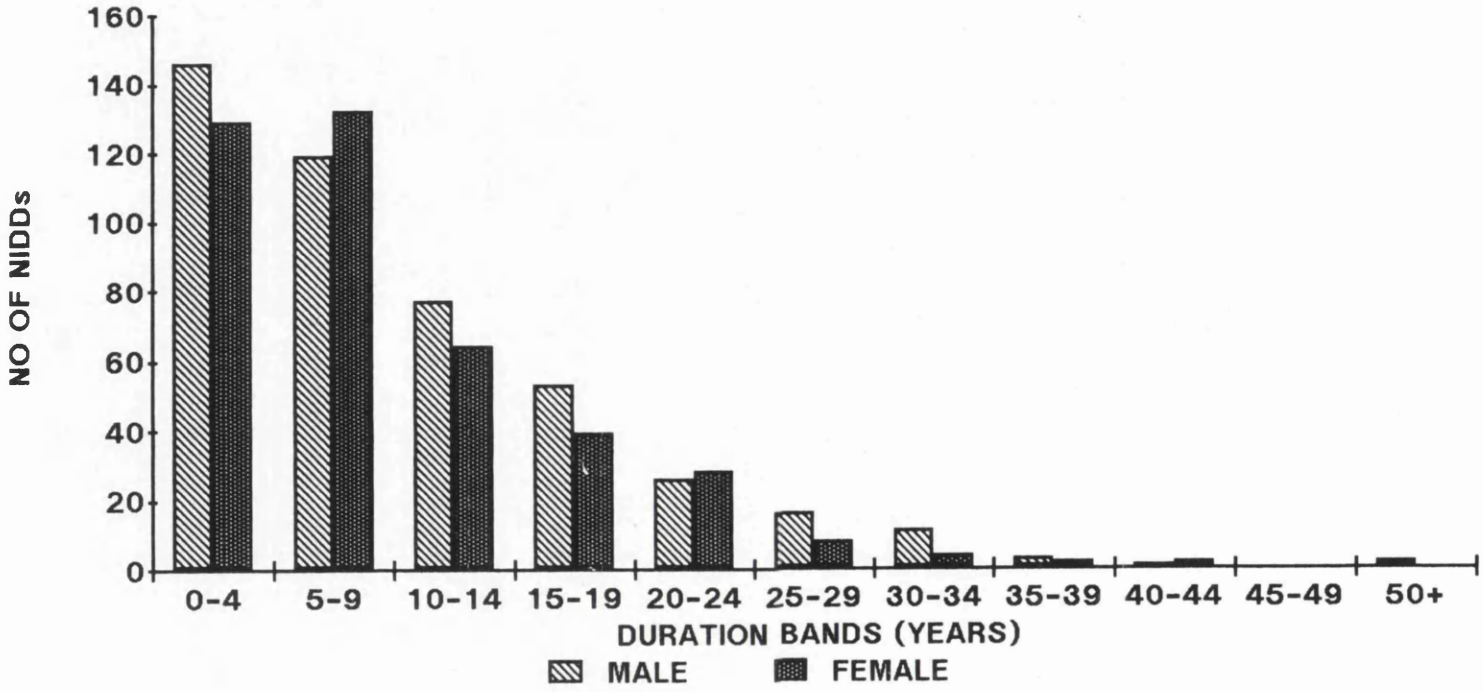
DURATION OF DIABETES (FIG 5.2)

DISTRIBUTION IN IDDM ACCORDING TO SEX



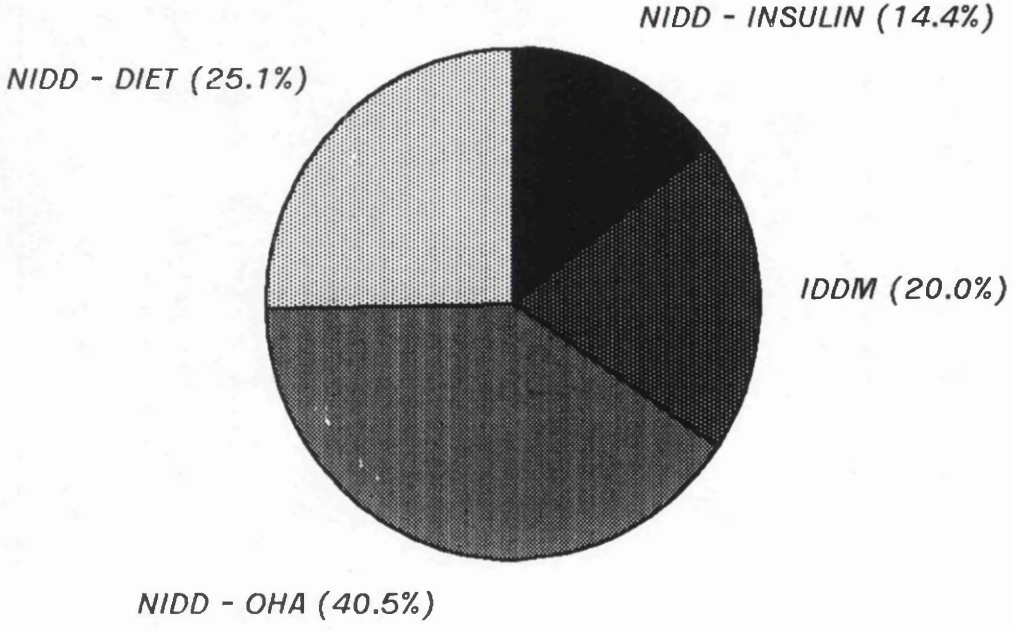
DURATION OF DIABETES (FIG 5.3)

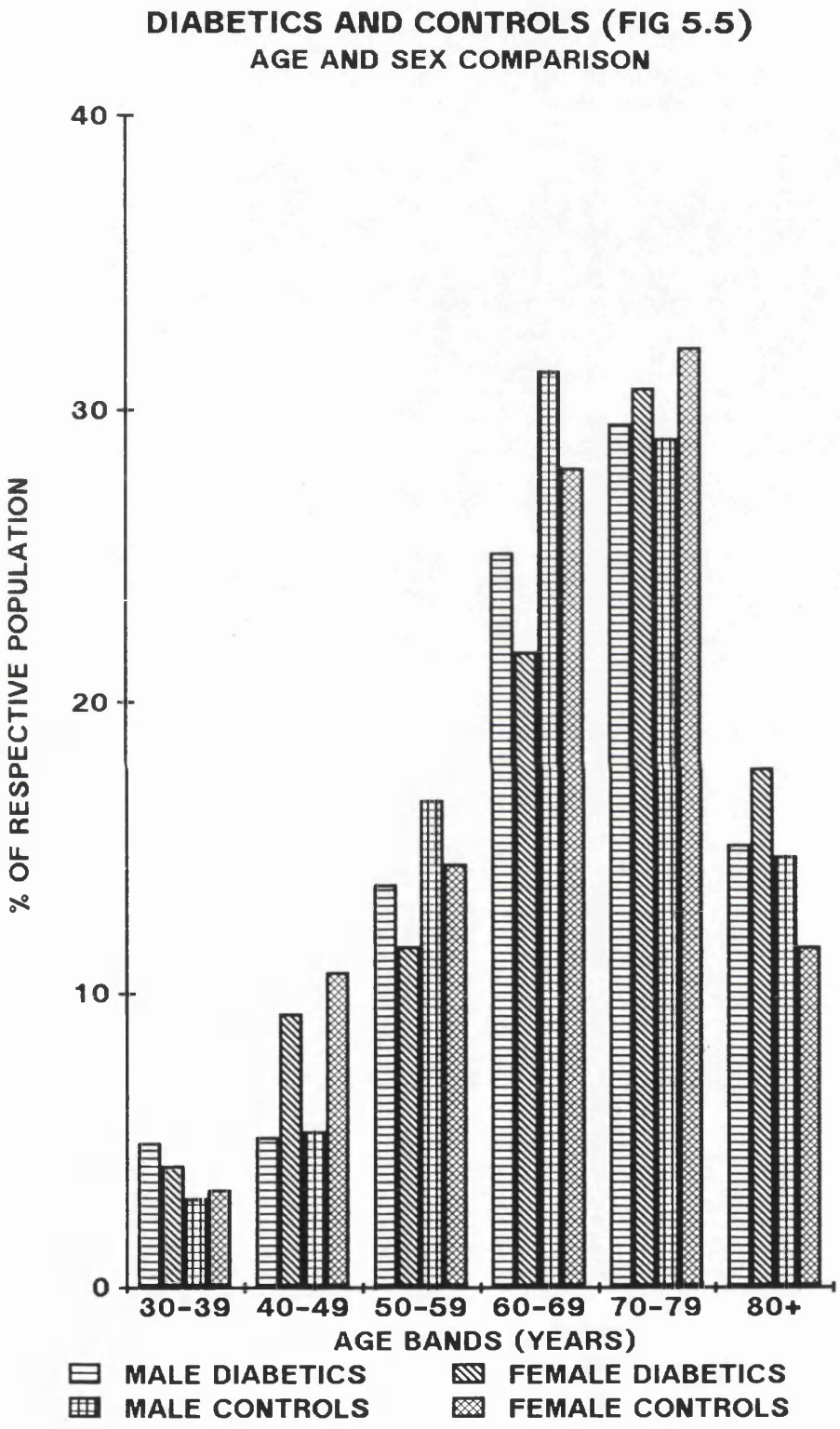
DISTRIBUTION - NIDDM ACCORDING TO SEX



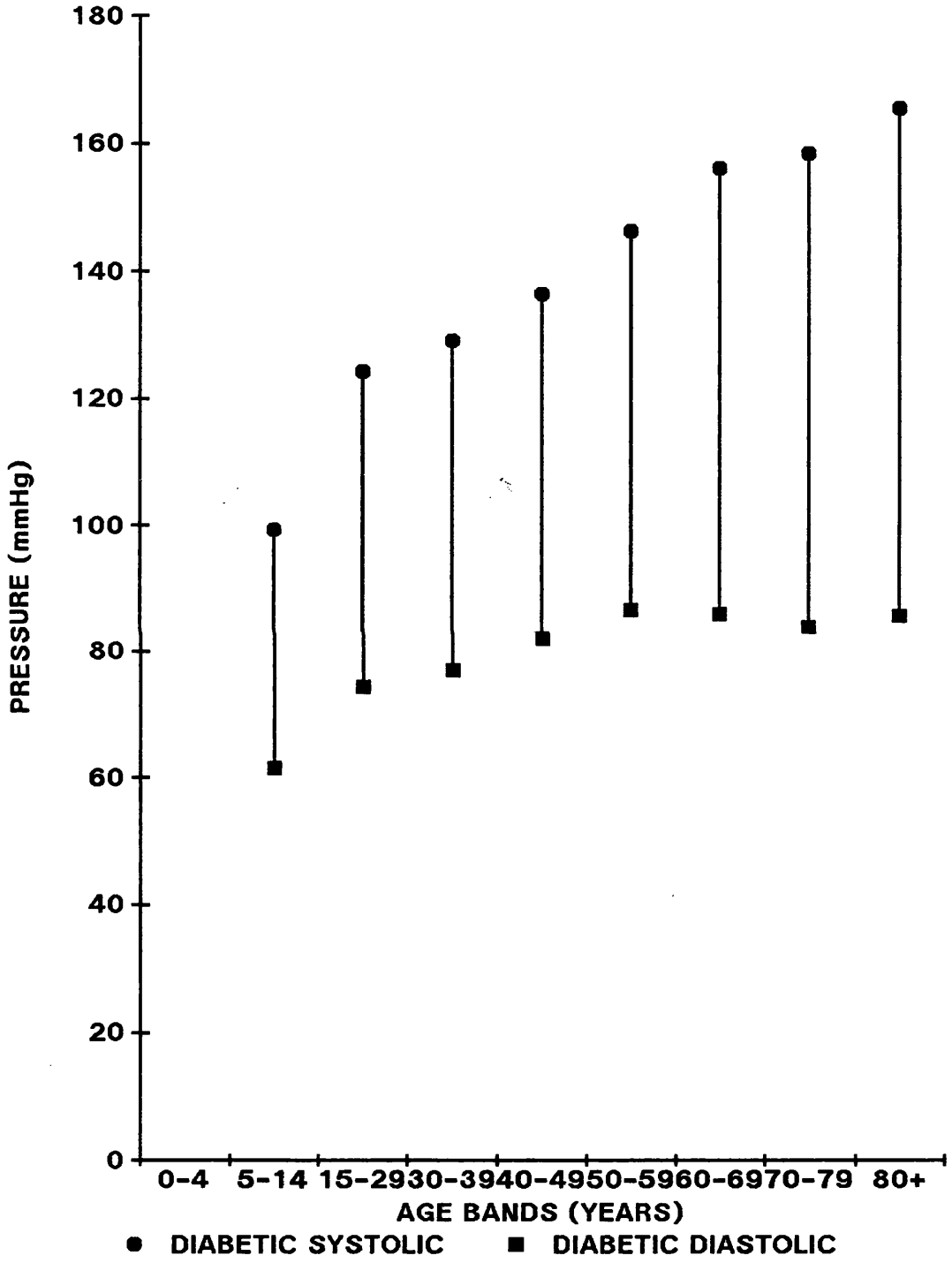
TREATMENT STRATEGIES

DIABETICS REVIEWED (FIG 5.4)



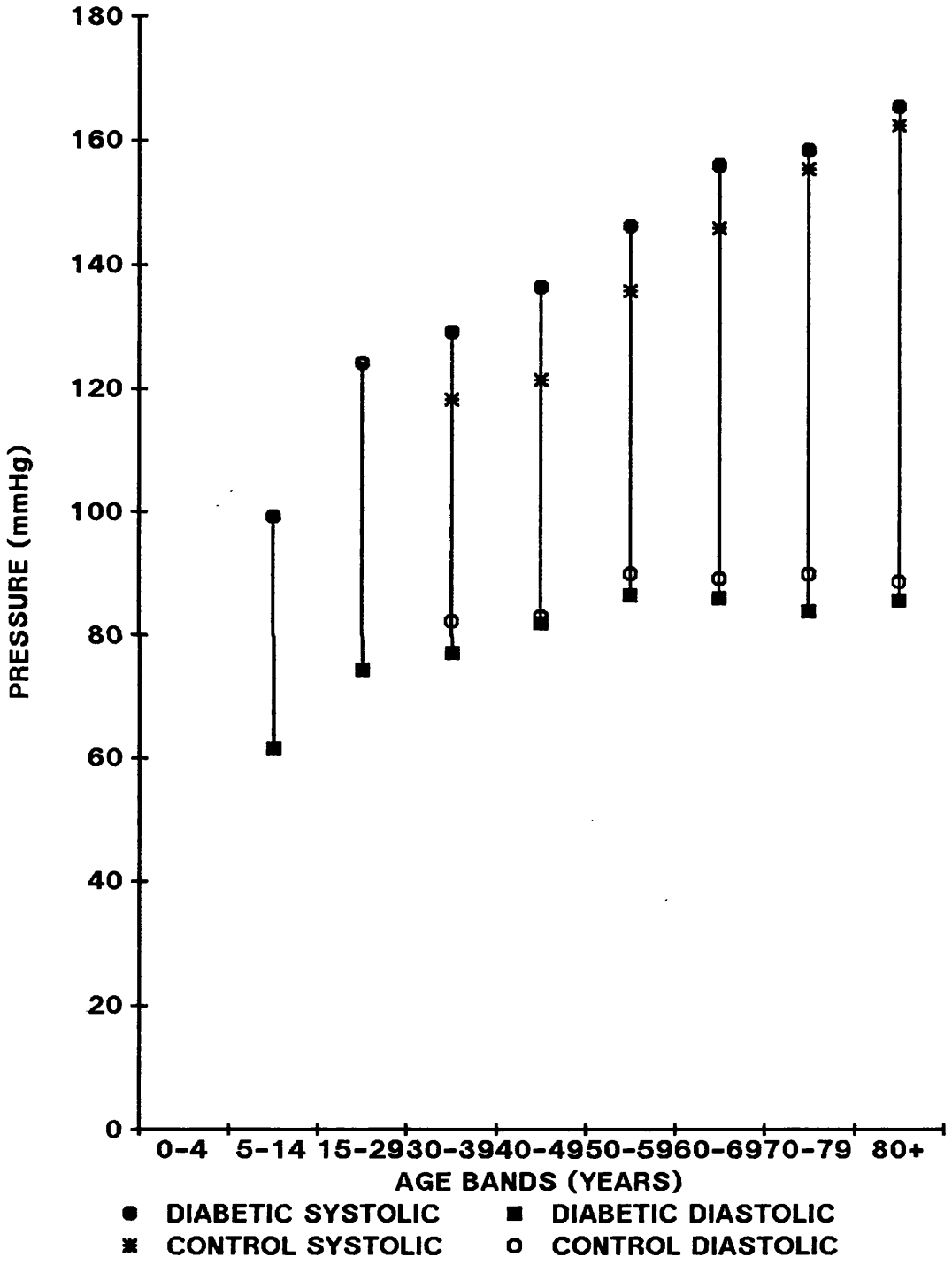

DIABETICS AND CONTROLS (FIG 5.5)
AGE AND SEX COMPARISON
% OF RESPECTIVE POPULATION
40
30
20
10
0
30-39
40-49
50-59
60-69
70-79
80+
AGE BANDS (YEARS)
MALE DIABETICS
MALE CONTROLS
FEMALE DIABETICS
FEMALE CONTROLS

MEAN SYSTEMIC PRESSURE
DIABETICS (FIG 5.6)



MEAN SYSTEMIC PRESSURE (FIG 5.7)

DIABETICS Vs CONTROLS



Chapter 6

THE PREVALENCE OF LOWER LIMB PERIPHERAL NEUROPATHY

Results

Symptomatic Neuropathy

According to age - in diabetics

Symptomatic neuropathy as previously defined was found in 10.9% of all diabetics. Table 6.1 and Fig. 6.1 shows the prevalence of neuropathy with age. The age and sex characteristics of the diabetics with peripheral neuropathy are also shown in Figure 6.2. There were no cases in either males or females under the age of 30 and the prevalence increased substantially between the 5th and 6th decades in women and the 6th and 7th decades in men. There is a gradual almost linear decline in symptomatic neuropathy in diabetic women over the age of 60. This trend does not occur in men and the prevalence continues to rise until the age of 80. In very elderly males the prevalence drops sharply and becomes similar to that in females.

According to sex and type of diabetes

Typically the prevalence of symptomatic neuropathy in males was slightly higher than in females overall and particularly so for the older age categories (see Fig 6.2). However, the difference was not significant ($P > 0.1$). Table 6.2 shows the prevalence of symptomatic neuropathy according to type of diabetes. The difference was not significant after accounting for age ($P=0.89$ - see Table 6.16). Within each type of diabetes the sex structure was quite different. In IDDs there was a trend towards a greater prevalence of neuropathy in females but in the NIDD category almost twice as many males had symptomatic neuropathy compared to females. The difference in prevalence of symptomatic neuropathy according to sex in NIDDs was statistically significant ($P = 0.03$, see Table 6.15). For IDDM there was not a statistically significant difference.

Control Group

In the control group the prevalence of symptomatic neuropathy was only 1.5% (Table 6.3). In neither sex was there any evidence of neuropathy below the age of 60. The difference in prevalence between controls and diabetics of either type was highly significant (Table 6.16).

Total Neuropathy

Prevalence by Age

The prevalence of any neuropathy ie symptomatic plus sub-clinical according to age is shown in table 6.4. The prevalence rate of neuropathy shows a general tendency to increase with age and when cases of objective neuropathy are combined with symptomatic neuropathy there is no suggestion of a reduction in prevalence rates in the elderly (as found in purely symptomatic neuropathy). Objective sensory loss without symptoms is relatively common in non-diabetics (see fig 6.3). Indeed the prevalence of symptomatic neuropathy in the very elderly non-diabetics was zero which contrasts with 9.4% of non-diabetic individuals with sub-clinical neuropathy.

Prevalence by Duration

The prevalence of neuropathy according to duration of diabetes is shown in table 6.7 Chi squared test for trend revealed a significant association between duration of diabetes and neuropathy for IDDM ($p < 0.001$) and NIDDM ($p < 0.01$). Even after adjusting for age by multiple regression analysis (with age included in the regression) there still remained a significant association in NIDDM ($p < 0.01$) but in IDDM the association just failed to achieve statistical significance ($p=0.07$).

Prevalence by Sex

Table 6.4 shows the prevalence of total cases of neuropathy in diabetics according to age and sex. For both men and women the prevalence tends to increase with age and generally neuropathy is

more common in men. The difference is, however, not significant ($P > 0.1$). Considering the diabetes by type, as with symptomatic neuropathy, there was a significantly greater prevalence of neuropathy in NIDD males compared to NIDD females ($P < 0.05$) but in IDDM the converse occurred with a greater prevalence in females. This difference was not, however, significant ($p>0.2$).

The prevalence of neuropathy in the control group according to sex is shown in Table 6.6. On univariate analysis using Chi squared there was no significant difference between male and female controls with neuropathy.

Prevalence by Type of Diabetes

Predictably in view of the different age structure the crude prevalence of neuropathy in non-insulin dependent diabetics was greater than in insulin dependent diabetics although there was no significant difference after accounting for age ($p=0.07$). Indeed for most age categories the prevalence of neuropathy in IDDM was greater than for NIDDM (see fig 6.4). In either type of diabetes the prevalence, after adjusting for age differences, was significantly greater than for non-diabetics (see Table 6.16).

Neuropathy Variables

Since any definition of neuropathy must be to some extent arbitrary, it may be more relevant to compare individual modalities of neuropathy between diabetics and controls. The odds ratios for absent light touch, pain perception, ankle and knee jerks were larger for IDDs versus controls than for NIDDs versus controls (see Table 6.16).

Vibration

Table 6.8 and Figs 6.5, 6.6 show the mean vibration thresholds for diabetics and controls according to age. In both groups values increase with age. For both insulin dependent diabetics, non insulin dependent diabetics and diabetics considered as a whole the mean value of vibration threshold is significantly different when compared to the control group ($P < 0.001$).

Ankle/Knee Reflexes

In both controls and diabetics the prevalence of absent limb jerks in the lower limbs increases with age. Even in diabetics absent knee jerks were quite rare although significantly more common than in controls. Similarly the frequency of at least one absent ankle jerk was significantly more common in diabetics than controls.

The majority of diabetics over the age of 70 had at least one absent ankle jerk but it was also a relatively common finding in non-diabetics (see Tables 6.9, 6.10 and Figs 6.7, 6.8). In both groups over the age of 70 there was an increase in loss of ankle jerks and although the numbers are much smaller a similar finding is observed with knee jerks.

Light Touch and Pain Perception

From Tables 6.11 and 6.12 and Figs 6.9 and 6.10 it is apparent that although the prevalence of absent light touch and pain perception is clearly much lower in the controls than the diabetics the trends are similar for both groups. The absence of both modalities increases steadily with age and absent pain perception occurs more frequently than absent light touch. In non-diabetics the absence of either modality is rare even in the very elderly age groups. No diabetics under the age of 30 were found to have either absent light touch or pain and in the control groups such abnormalities were only found in subjects aged 50 or more. The different prevalence rates between diabetics and controls were highly significant when comparing non-diabetics to either IDDs, NIDDs or diabetics as a whole.

Subjective Neuropathy

The prevalence of purely subjective symptoms of neuropathy was 2.5% in diabetics and 2.7% in controls. This difference in prevalence was not statistically significant except in IDDs (after adjusting for age - see Table 6.16).

Regression Analysis for Neuropathy to determine potential risk factors

The relationship between objective neuropathy and selected variables following multivariate analysis is shown in Table 6.17. The odds ratios are also stated. It is particularly important to note the magnitude of the odds ratio rather than the degree of statistical significance. The latter may merely reflect a significant difference between a clinically minor effect. Where the confidence limits at the lower end reach 1.0 obviously caution should be exercised in their interpretation. These caveats are applicable to all discussions in this thesis regarding the regression analyses.

For diabetics as a whole, age, height, alcohol intake, diabetic control, foot deformity and any form of retinopathy were significant. Considering the diabetics by type in insulin dependent diabetes age no longer becomes significant and duration, as for the diabetic group as a whole, exhibits no association. Height, foot deformity and retinopathy still remain associated, the latter two particularly so. Diabetic control is also not a significant factor in the insulin dependent category.

For NIDDM the findings are very similar to those found for diabetes as a whole. This probably reflects the very high percentage of NIDDs in the total diabetic population. Duration shows no statistically independent association with objective neuropathy in keeping with insulin dependent diabetes. A powerful relationship was found for retinopathy and foot deformity with objective neuropathy in both groups of diabetics. They are both highly significant and seem to be independent of age and duration of diabetes.

Regression analysis on the control population revealed significant relationships only with age, male sex and foot deformity.

Prevalence of Neuropathy

The prevalence of diabetic neuropathy in the study was determined using strict criteria ie symptoms plus objective physical findings. Clinical findings are considered essential in any definition of neuropathy (Report and Reccommendations of the San Antonio conference 1988). Furthermore Dyck et al (1985) have shown that clinical examination correlates well with pathological changes within the nerve. The present study primarily was concerned with identifying subjects with clinical evidence of neuropathy which may yield information relevant to patient management. With this purpose in mind very sensitive indicators of nerve abnormality such as conduction studies are not necessary. Clinical examination should be sufficient to identify significant levels of neuropathy ie to identify those subjects liable to tissue destruction. It is realised however that even with a dichotomous classification for the presence or absence of modalities, variation in interpretation will occur. This makes comparisons with other studies difficult. The use of a control group and one observer may have circumvented some of the difficulty by enabling a direct comparison with diabetics and non-diabetics drawn from the same population.

Other studies have revealed prevalence rates ranging from 0.6 to 63% (see Table I Chapter 2). As previously outlined this vast difference between rates is largely methodological. Those studies that were population based revealed rates between 2.3% (Lehtinen et al 1989) and 34% (Maser et al 1989). Although these are population surveys they dealt with specialised groups of subjects within the population. For example Lehtinen et al (1989) only looked at newly diagnosed non insulin dependent diabetics within a defined population area and Maser et al confined their study to IDDs. Table 6.14 shows the more recent population studies for the prevalence of neuropathy according to type of diabetes.

Even population studies involving subjects with similar types of diabetes and employing broadly similar definitions reveal large

variations in prevalence. For example, Franklin et al (1990) using almost exactly similar definitions for neuropathy found the prevalence in American NIDDs (of whom 28.4% were Hispanics) to be almost 60% greater than this survey. Clearly the above statements regarding interpretation of physical findings may account for the difference but it is interesting that the control population yields a very similar prevalence of neuropathy to this survey, ie 3.5% vs 2.9%. The review rate for the control population was also very similar but only 81.7% of diabetics were examined compared with 95% in this survey. Possibly this relatively low review rate may have biased the result but a real difference may exist between the two populations of diabetics (eg ethnic differences). Similar prevalence data from the UK at the time of writing is unfortunately not available.

There are of course many more studies dealing with particular groups of patients in defined clinical settings. In a typical outpatient department consisting only of insulin dependent diabetics Boulton et al (1983) found a prevalence of 10.7%. A similar definition for diabetic neuropathy was however employed in this survey compared to the present study. Not only was the survey limited to insulin dependent diabetics but they also gave defined age categories. If one was to include all the cases of neuropathy in the present survey between the stated age categories of the study by Boulton et al this would yield a prevalence of 6%. This clearly demonstrates the problems of selecting groups of patients. The Diabetic Clinic is very unrepresentative of the diabetic population at large and in this particular instance it is a teaching hospital clinic which may well exacerbate the problem by having a high proportion of secondary referrals.

There are no other UK studies which have studied neuropathy with similar definitions to the present study. However there are further studies, some population based, which do afford some comparison as regards loss of individual modalities of nerve function. The population study by Neil et al (1989) found the prevalence of impaired distal vibration to be 23%. Although a similar definition for abnormal vibration threshold was used in this survey compared with the present study any attempt to compare

the results directly may not be valid. Estimating vibration thresholds depends heavily on technique and ideally one observer should be used.

Knuiman et al (1986) found a prevalence of peripheral neuropathy of 13% using a definition of absent pinprick sensation. The faults of this study have already been discussed but the results tend to correlate quite well with those found in the present study. There are no studies looking specifically at loss of light touch.

Nilsson et al (1967) in a population study assessed the prevalence of absent ankle jerks and diminished vibration. Unfortunately the presentation of results does not enable an accurate comparison but the study does demonstrate in keeping with the present survey that absent ankle reflexes are much more frequent at all ages than in age/sex matched non-diabetic controls.

The importance of knowing the prevalence of neuropathy or any constituent of neuropathy in diabetics is to ascertain the greater frequency at which it occurs in the diabetic population compared to the general population. The present study has demonstrated the increased frequency of abnormal neurological findings in diabetics compared to controls. To do this is particularly important because it is generally accepted in non diabetic subjects that ageing of the nervous system is inevitable and indeed is thought to be fundamental to our understanding of the ageing process (WHO 1981). Causes may be repeated minor traumas or possibly vascular impairment rather than just a purely degenerative ageing process. The exact aetiology is immaterial to this discussion but it does suggest that the general population is susceptible to a background neuropathy just by virtue of the ageing process in addition to other known causes of neuropathy such as drug ingestion, metabolic (other than diabetes), carcinoma and infections. There seems to be no reason why diabetics should not be prone to these other causes of neuropathy in addition to the physical changes that occur due to the ageing process.

The findings in the control population demonstrate that there is indeed a significant background neuropathy in the general population. It also demonstrates that all parameters of loss of

nerve function increase with age. Whilst this has been studied for vibration threshold (Steiness 1957, Mirsky 1957, Jarrett et al 1969) and ankle reflexes (Critchley 1931, Howell 1949) little has been published regarding pain and touch sensation in the ageing nervous system. However, Howell (1949) suggested the latter does occur although much less commonly that loss of limb jerks and vibration perception (Potvin et al 1980). Possibly, in view of the rarity of loss of light touch and/or pain, it may not be considered a "normal aspect" of ageing but nevertheless in this study approximately 7% of controls over the age of 70 had loss of either one of these modalities. In 4 cases there was an identifiable cause (3 hypothyroidism and 1 congenital) although in the remainder the findings were unexplained.

In the diabetics there was also evidence to suggest that causes other than diabetes may have caused or contributed to the neuropathy (those who were also diagnosed as hypothyroid, for example). All cases of neuropathy in diabetics were attributed to diabetes but clearly this must over-estimate the true prevalence of diabetic neuropathy. However it was deemed impossible to delineate the exact cause where other conditions co-existed. One of the aims of this study was to demonstrate the increased frequency of risk factors for foot disease and therefore the increased prevalence of neuropathy in diabetics regardless of cause. These findings emphasise that strict definitions for neuropathy should be employed and other treatable causes should be investigated before a diabetic is labelled as having diabetic neuropathy.

Finally the prevalence of neuropathy far exceeded the prevalence of past or present ulceration in diabetics. Clearly this suggests that only a minority of diabetics develop neuropathic ulceration. This may reflect the severity of the neuropathy but caution must be exercised because it is a prevalence survey. A longitudinal study to follow up all cases of neuropathy would be valuable in determining which of the subjects go on to develop ulceration. Correlates of foot ulceration per se will be discussed later.

Risk Factors for Neuropathy

In view of the different aetiologies and age distribution of IDDM and NIDDM it was felt that the diabetics should be divided into type as well as considering the diabetic group as a whole. Clearly one of the disadvantages is the inevitable reduction in sample size and possibly, therefore, a loss of power.

Age

The regression analysis for diabetics as a whole revealed a significant association between age and peripheral neuropathy. Most studies have revealed an increasing prevalence with age but it is, of course, difficult to exclude the effects of duration and hence diabetic exposure from ageing per se. When the diabetics were divided into type there was no statistically independent association between age and neuropathy in IDDs in contrast to NIDDs. This could imply that ageing effects are important in elderly diabetics as in non-diabetics. It should be noted that age was also (just) significantly correlated with neuropathy in the control group.

From the graphs of symptomatic neuropathy the prevalence seems to decrease in the upper age categories. This, of course, does not necessarily imply that the risk decreases for developing symptomatic neuropathy in the very elderly groups. Neuropathy may, for example, have an effect on mortality and hence true risk would not be evaluated from these prevalence data.

Once again there are very few population studies which afford any comparison. Knuiman et al (1986) using a different definition of neuropathy found that duration of diabetes rather than age was significantly associated with neuropathy regardless of type of diabetes. However they noted that sensory neuropathy was also correlated to age at diagnosis and found that those who were diagnosed later in life tended to develop the condition. This raises the possibility of the confounding effect of age.

Duration

Duration of diabetes was associated with an increasing prevalence of neuropathy for both types of diabetes but was not statistically an independent variable. A relationship with neuropathy has also been shown in several recent studies (Palumbo et al 1978, Boulton et al 1985, Knuiman et al 1986, DCCT 1988, Maser et al 1989 and Franklin et al 1990) and some have also revealed a relationship following multivariate analysis (Knuiman et al 1986, DCCT 1988, Maser et al 1989).

Recent studies in IDDM using similar definitions of neuropathy to the present survey generally agree that duration of diabetes is a risk factor for the presence of neuropathy (DCCT 1988, Maser et al 1989) and although strictly not a population study, Maser et al purport that their subject group is representative of insulin dependent diabetics resident in Allegheny County, USA. These studies were larger than the present survey and this may explain the difference with our results. Unfortunately there are no UK studies for comparison at the time of writing.

For NIDDM there are only 2 recent population studies that attempt to define neuropathy clinically (Palumbo et al 1978, Franklin et al 1990). Although they have both found an association with duration of diabetes neither specifically indicate whether this is independent of age, or indeed other variables. Once again there are no population studies in NIDDM employing similar definitions of neuropathy to the present survey that have been performed in the UK.

Sex

The finding of a significant difference between the prevalence of neuropathy in males compared to females in NIDDM has been previously reported (Franklin et al 1990). Additionally in keeping with the present survey, one of the few insulin dependent studies found no association between sex and the presence or absence of neuropathy (Maser et al 1990). However, sex was not a statistically independent variable in either type of diabetes following multivariate analysis. Clearly the possible confounding

effects of greater height or alcohol intake/susceptibility may be contributing to the univariate association in NIDDM. The different sex prevalence in IDDs may have been due to the smaller sample size but equally other factors, possibly related to the different age structure of the groups may be important. It may be relevant that male gender was an independent statistically significant risk factor for the presence of neuropathy in controls. There is, theoretically, no reason why diabetics should not be exposed to this background neuropathy.

Diabetic Control

The other aspect of diabetes exposure, aside from duration, is of course the severity. Haemoglobin A1 levels in this study were significantly and independently correlated in NIDDM but not in IDDM. No relationship was found with 2 hour interval blood glucose. Clearly in all cross-sectional surveys there are difficulties in accurately assessing glycaemic control, particularly in the older studies when glycated haemoglobin measurements were not available. In IDDM using similar definitions of neuropathy to the present survey have yielded conflicting results when assessing the degree of glycaemia with the presence or absence of neuropathy. Since definitions of neuropathy were similar some of the discrepancy in results may well be due to the problem of assessing plasma glucose levels over long periods of time. In NIDDM, however, results have been more consistent and are in agreement with the present survey (Palumbo et al 1978, Franklin et al 1990). Generally these studies and the present survey are much larger than in the IDDM surveys and possibly fluctuations in glucose concentrations over prolonged periods are less marked in NIDDM (Holman and Turner 1980) and therefore easier to assess in a cross-sectional survey. Ideally a prospective population study is needed to attempt to solve the question regarding the association between glycaemia and neuropathy. At the present time it would seem that whilst there is reasonable evidence for a positive association for NIDDM no definite conclusions can be made for IDDM.

Diabetic complications

This study confirmed the strong association between neuropathy and

diabetic retinopathy. Similar findings have been reported by other studies both recent and old (Pirart 1978, DCCT Research Group 1988, Masser et al 1989). Interestingly the association between retinopathy and neuropathy seems to be independent of exposure to diabetes. Possibly retinopathy may act as a marker for subjects who are more vulnerable to neuropathy and as yet unknown factors may link the two. No correlation with proteinuria or creatinine concentrations was found in this study for either IDDs or NIDDs. The rest of the literature either does not address the problem because of the possible link between renal failure per se and neuropathy (Boulton et al 1985) or is conflicting (DCCT 1988, Maser et al 1989). These studies are of course only concerned with insulin dependent diabetics and as is the case in retinopathy there are no population based studies available for comparison investigating both types of diabetes.

Foot deformity

Foot deformity is significantly and independently associated with neuropathy in IDDs, NIDDs and controls. Although not directly studied elsewhere in the literature this association should not be surprising. As has previously been discussed foot deformity is liable to occur in neuropathy because of intrinsic muscle wasting. Its importance must be that in conditions where mobility is largely retained such as diabetic neuropathy the association with foot deformity ultimately increases the likelihood of foot ulceration. The significance of foot deformity and ulceration will be discussed in a later chapter.

Alcohol intake

Alcohol intake has previously been suggested by Young et al (1986) to increase the risk of foot ulceration in diabetics with neuropathy. Certainly neuropathy can be caused by alcohol in its own right and an association between alcohol intake in both insulin and non insulin dependent diabetics was found in this study. There is exceedingly little published data specifically investigating the relationship between alcohol intake and neuropathy in diabetics. Franklin et al (1990) found no significant association between diabetics with neuropathy and those who had previously consumed

alcohol. Clearly this is a rather crude measure of alcohol consumption and does not take into account the amount of alcohol regularly consumed. Maser et al (1989) found in contrast to the present survey that alcohol intake was weakly (no confidence limits stated) and inversely related to the presence of neuropathy by univariate analysis. However, after multiple logistic regression analysis they failed to find any significant association. Nevertheless the present study, being a large population based enquiry, does give valuable data on the significance of alcohol intake in diabetics with neuropathy. Clearly excessive alcohol consumption must be regarded as a potential risk factor for diabetic neuropathy.

Height

Height exhibited a significant correlation with neuropathy both in IDDs and NIDDs. Again there is very little previously published work regarding the relationship between these two variables. No relationship was found between height and neuropathy in control subjects and it suggests that an innate factor of diabetic neuropathy renders increasing height an important characteristic in the pathogenesis of diabetic neuropathy. Although there are no population studies to corroborate the findings of this survey two large studies involving purely insulin dependent diabetics revealed conflicting results (Maser et al 1989 and DCCT 1988). Quite possibly the differences are reflected by patient selection. Clearly any population which was not representative of diabetics at large could easily give spurious results. However one study revealing no correlation (Masser et al 1989) suggests that it includes 70% of all patients who were diagnosed with diabetes at less than 17 years of age in a defined area of the USA.

Finally, although it is interesting to compare regression analysis between controls and diabetics, caution must always be exercised because of the fewer number of observations in the control group compared to diabetics. However the control group is in fact larger than the insulin dependent diabetic group when the diabetics are considered by type. Also it should be noted that these variables associated with neuropathy are only putative determinants. Clearly longitudinal studies would be necessary to confirm their validity.

TABLE 6.1

PREVALENCE OF SYMPTOMATIC NEUROPATHY IN DIABETICS

Age (years)	Male diabetics No.	(% prev.)	Female diabetics No.	(% prev.)	All diabetics No.	(% prev.)
0-19	0	(0.0)	0	(0.0)	0	(0.0)
20-29	0	(0.0)	0	(0.0)	0	(0.0)
30-39	2	(7.1)	0	(0.0)	2	(4.1)
40-49	2	(6.9)	2	(4.3)	4	(5.3)
50-59	6	(7.7)	7	(11.9)	13	(9.5)
60-69	23	(16.1)	12	(10.9)	35	(13.8)
70-79	30	(17.9)	16	(10.3)	46	(14.2)
80+	9	(10.5)	8	(8.9)	17	(9.7)
	72	(12.7)	45	(8.9)	117	(10.9)
Missing cases	0		0		0	

TABLE 6.2

PREVALENCE* ACCORDING TO TYPE OF DIABETES

	IDDM No.	(%)	NIDDM No.	(%)	All diabetics No.	(%)
Present	16	(7.5)	101	(11.7)	117	(10.9)
Absent	197	(92.5)	763	(88.3)	960	(89.1)
Total	213	(100.0)	864	(100.0)	1077	(100.0)

TABLE 6.3

PREVALENCE* IN CONTROLS

Age (years)	Male controls No.	(% prev.)	Female controls No.	(% prev.)	All controls No.	(% prev.)
30-39	0	(0.0)	0	(0.0)	0	(0.0)
40-49	0	(0.0)	0	(0.0)	0	(0.0)
50-59	0	(0.0)	0	(0.0)	0	(0.0)
60-69	3	(3.6)	1	(1.7)	4	(2.8)
70-79	2	(2.6)	1	(1.4)	3	(2.1)
80+	0	(0.0)	0	(0.0)	0	(0.0)
	5	(1.9)	2	(0.9)	7	(1.5)
Missing cases	0		0		0	

*OF SYMPTOMATIC NEUROPATHY

TABLE 6.4

PREVALENCE OF PERIPHERAL NEUROPATHY* IN DIABETICS

Age (years)	Male diabetics No.	(% prev.)	Female diabetics No.	(% prev.)	All diabetics No.	(% prev.)
0-19	0	(0.0)	0	(0.0)	0	(0.0)
20-29	0	(0.0)	0	(0.0)	0	(0.0)
30-39	4	(14.3)	0	(0.0)	4	(8.2)
40-49	2	(6.9)	5	(10.6)	7	(9.2)
50-59	8	(10.3)	7	(11.9)	15	(10.9)
60-69	30	(21.0)	19	(17.3)	49	(19.4)
70-79	39	(23.2)	24	(15.4)	63	(19.4)
80+	21	(24.4)	17	(18.9)	38	(21.6)
	104	(18.3)	72	(14.2)	176	(16.3)
Missing cases	0		0		0	

TABLE 6.5

PREVALENCE OF NEUROPATHY ACCORDING* TO TYPE OF DIABETES

	IDDM No.	(%)	NIDDM No.	(%)	All diabetics No.	(%)
Present	27	(12.7)	149	(17.2)	176	(16.3)
Absent	186	(87.3)	715	(82.8)	901	(83.7)
Total	213	(100.0)	864	(100.0)	1077	(100.0)

TABLE 6.6

PREVALENCE OF NEUROPATHY* IN CONTROLS

Age (years)	Male controls No.	(% prev.)	Female controls No.	(% prev.)	All controls No.	(% prev.)
30-39	0	(0.0)	0	(0.0)	0	(0.0)
40-49	0	(0.0)	0	(0.0)	0	(0.0)
50-59	0	(0.0)	0	(0.0)	0	(0.0)
60-69	3	(3.6)	1	(1.7)	4	(2.8)
70-79	3	(3.9)	1	(1.4)	4	(2.7)
80+	5	(12.8)	1	(4.0)	6	(9.4)
	11	(4.2)	3	(1.4)	14	(2.9)
Missing cases	0		0		0	

*Includes all cases of symptomatic and sub-clinical neuropathy.

TABLE 6.7.

PREVALENCE OF NEUROPATHY* ACCORDING TO DURATION OF DIABETES

Duration (years)	IDDM* (%)	NIDDM** (%)
0- 4	0	17.8
5-10	5	11.6
11-15	5.4	18.4
16-25	21.8	24.0
>25	19.2	20.4

Chi-squared test for trend - IDDM = 12.90, df=1
p<0.001
- NIDDM = 9.85, df=1
p<0.01

Using logistic regression analysis to adjust for age

IDDM Variable	Coefficient (SE)	OR	P value
Age (years)	0.039 (0.014)	1.04	0.004
Duration (years)	0.03 (0.017)	1.03	0.07

NIDDM (Variable)	Coefficient (SE)	OR	P value
Age (years)	0.027 (0.008)	1.03	0.002
Duration (years)	0.026 (0.01)	1.03	0.01

*Includes all cases of symptomatic and sub-clinical neuropathy.

NEUROPATHY VARIABLES

TABLE 6.8

MEAN VIBRATION PERCEPTION THRESHOLD VALUES

Age group	Diabetics Great toe	Diabetics Medial malleolus	Controls Great toe	Controls Medial malleolus
30-39	10.51	12.85	6.63	9.27
40-49	13.03	15.52	8.78	11.80
50-59	17.81	20.66	12.23	15.10
60-69	24.22	26.67	16.63	20.49
70-79	32.15	35.28	21.54	26.11
80+	38.84	41.84	29.25	36.28
Missing cases	16	12	3	3

TABLE 6.9

ANKLE/KNEE REFLEXES: DIABETICS

Age (years	Ankle reflexes Either absent No.	(%)	Knee reflexes Either absent No.	(%)
0-29	0	(0.0)	0	(0.0)
30-49	16	(12.8)	6	(4.8)
50-69	81	(20.9)	21	(5.4)
70+	298	(60.4)	50	(10.2)
	395	(37.0)	77	* 7.2)
Missing cases	16		14	

TABLE 6.10

ANKLE/KNEE REFLEXES: CONTROLS

Age (years)	Ankle reflexes Either absent No.	(%)	Knee reflexes Either absent No.	(%)
30-49	1	(1.9)	0	(0.0)
50-69	31	(14.2)	4	(1.8)
70+	81	(38.6)	9	(4.3)
	113	(23.5)	13	(2.7)
Missing cases	0		0	

TABLE 6.11

LIGHT TOUCH/PAIN PERCEPTION: DIABETICS

Age (years)	Light touch perception Either absent		Pain perception Either impaired	
	No.	(%)	No.	(%)
0-29	0	(0.0)	0	(0.0)
30-49	6	(4.8)	7	(5.6)
50-69	39	(10.0)	52	(13.3)
70+	86	(17.6)	102	(20.7)
Total	131	(12.3)	161	(15.0)
Missing data	11		9	

TABLE 6.12

LIGHT TOUCH/PAIN PERCEPTION: CONTROLS

Age (years)	Light touch perception Either absent		Pain perception Either impaired	
	No.	(%)	No.	(%)
30-49	0	(0.0)	0	(0.0)
50-69	4	(1.8)	6	(2.8)
70+	14	(6.7)	16	(7.6)
Total	18	(3.8)	22	(4.6)
Missing data	1		0	

TABLE 6.13

PREVALENCE OF PURELY SUBJECTIVE NEUROPATHY

	Present		Absent	
	No.	(%)	No.	(%)
Diabetics	27	(2.5)	1050	(97.5)
Controls	13	(2.7)	467	(97.3)

TABLE 6.14

RECENT POPULATION BASED STUDIES

Study	Definition of Neuropathy	Prevalence
IDDM		
Knuiman et al 1986	Absent pain perception	7.7%
Maser et al 1989	Symptoms + 1 abnormal sign or 2 abnormal signs	34%
Present Survey 1990	Symptoms + 1 abnormal sign or 2 abnormal signs	12.7%
NIDDM		
Knuimann 1986	Absent pain perception	18.2%
Franklin 1990	Symptoms + 1 sign or 2 signs	27.8%
Present Survey 1990	Symptoms + 1 abnormal sign or 2 abnormal signs	17.2%

TABLE 6.15

DIFFERENCES IN THE PREVALENCE OF NEUROPATHY ACCORDING TO SEX AND TYPE OF DIABETES

(a) Symptomatic Neuropathy

(i) Diabetics

	Males	Females
Absent	527	463
Present	72	45

Chi squared (Yates correction) = 2.52 p>0.1 (1 df)

(ii) NIDDs

	Males	Females
Absent	391	372
Present	64	37

Chi squared (Yates correction) = 4.78 p=0.03 (1 df)

(iii) IDDs

	Males	Females
Absent	106	91
Present	8	8

Chi squared (Yates correction) = 0.001, p=0.97 (1 df)

(iv) Controls

	Males	Females
Absent	260	216
Present	5	2

Chi squared (Yates correction) = 2.237, p>0.5 (1 df)

(b) Total Neuropathy

(i) Diabetics

	Males	Females
Absent	495	436
Present	104	72

Chi squared (Yates correction) = 1.81 p >0.1

(ii) NIDDs

	Males	Females
Absent	365	350
Present	90	59

Chi squared (Yates correction) = 3.96 p<0.05 (1 df)

TABLE 6.15 (Cont.)

(iii) IDDs

	Males	Females
Absent	100	86
Present	14	13

Chi squared (Yates correction) 0.0004, p>0.5 (1 df)

(iv) Controls

	Males	Females
Absent	254	215
Present	11	3

Chi squared (Yates correction) = 2.350, p>0.1 (1 df)

TABLE 6.16

REGRESSION ANALYSES TO DETERMINE THE SIGNIFICANCE OF DIFFERENCES BETWEEN NEUROPATHY VARIABLES IN THE CONTROL AND DIABETIC POPULATIONS AFTER ADJUSTING FOR AGE

(Age is included in the regression equation)

Dependent Variable	Factor	Coefficient (SE)	P Value
1. Total Neuropathy	Diabetics = 1 Controls = 0	1.910 (0.284)	<0.001
	NIDDs = 1 Controls = 0	1.849 (0.287)	<0.001
	IDDs = 1 Controls = 0	2.626 (0.396)	<0.001
2. Symptomatic Neuropathy	Diabetics = 1 Controls = 0	2.133 (0.393)	<0.001
	NIDDs = 1 Controls = 0	2.154 (0.396)	<0.001
	IDDs = 1 Controls = 0	2.517 (0.513)	<0.001
3. Purely Subjective Neuropathy	Diabetics = 1 Controls = 0	-0.066 (0.342)	0.85
	NIDDs = 1 Controls = 0	-0.264 (0.368)	0.52
	IDDs = 1 Controls = 0	1.043 (0.521)	0.05
4. Either ankle jerk missing	Diabetics = 1 Controls = 0	0.793 (0.138)	<0.001
	NIDDs = 1 Controls = 0	0.710 (0.144)	<0.001
	IDDs = 1 Controls = 0	1.496 (0.281)	<0.001

TABLE 6.16 (Cont.)

Dependent Variable	Factor	Coefficient (SE)	P Value
5. Either knee jerk absent	Diabetics = 1 Controls = 0	1.045 (0.306)	<0.001
	NIDDs = 1 Controls = 0	0.910 (0.313)	<0.01
	IDDs = 1 Controls = 0	1.979 (0.447)	<0.001
6. Light touch - either missing	Diabetics = 1 Controls = 0	1.313 (0.260)	<0.001
	NIDDs = 1 Controls = 0	1.230 (0.263)	<0.001
	IDDs = 1 Controls = 0	2.190 (0.398)	<0.001
7. Pain perception - either missing	Diabetics = 1 Controls = 0	1.345 (0.236)	<0.001
	NIDDs = 1 Controls = 0	1.306 (0.239)	<0.001
	IDDs = 1 Controls = 0	1.976 (0.373)	<0.001
8. Mean Great Toe vibration perception	Diabetics = 1 Controls = 0	8.599 (0.524)	<0.001
	NIDDs = 1 Controls = 0	7.948 (0.556)	<0.001
	IDDs = 1 Controls = 0	8.907 (0.780)	<0.001
9. Mean Medial Malleolus vibration perception	Diabetics = 1 Controls = 0	7.219 (0.519)	<0.001
	NIDDs = 1 Controls = 0	6.508 (0.551)	<0.001
	IDDs = 1 Controls = 0	8.044 (0.834)	<0.001
10. Symptomatic Neuropathy	IDDs = 1 NIDDs = 0	0.046 (0.332)	0.89

TABLE 6.17

NEUROPATHY - MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR POTENTIAL RISK FACTORS

A. Group Diabetics (IDDs + NIDDs)
Dependent variable - neuropathy

Variable	Coefficient	SE	P Value	Odds Ratio	95% CI
Age* (years)	0.0212	0.0083	0.01	1.0214	0.0051-1.0376
Duration (years)	0.0052	0.0103	0.601	1.0053	0.9852-1.0254
Alcohol** (units)	0.0264	0.0093	0.005	1.0267	1.0084-1.0449
Height*** (cm)	0.0595	0.0117	<0.001	1.0613	1.0383-1.0842
HbA1**** (%)	0.2049	0.0622	0.001	1.2274	1.0982-1.3565
Foot deformity(1)	2.1947	0.2568	<0.001	8.9769	8.4735-9.4802
Retinopathy (1)	0.9256	0.2208	<0.001	2.5183	2.0855-2.9510

B. Group IDDs
Dependent variable - Neuropathy

Age* (years)	0.0208	0.0191	0.2762	1.0210	0.9835-1.0584
Duration* (years)	0.0113	0.0236	0.63	1.0113	0.9650-1.0575
Height*** (cm)	0.0623	0.0317	0.05	1.0642	1.0028-1.1263
Foot deformity(1)	2.3857	0.6272	<0.001	10.8664	9.6370-12.0957
Any retin-opathy(1)	2.1962	0.6507	<0.001	8.9904	7.7150-10.2657

TABLE 6.17 (Cont.)

C. Group - NIDDs
Dependent Variable - Neuropathy

Variable	Coefficient	SE	P Value	Odds Ratio	95% CI
Age*	0.0233	0.0117	0.05	1.0236	1.006-1.0465
Duration*	-0.0038	0.0142	0.78	0.9962	0.9683-1.0240
Alcohol*	0.0271	0.0097	0.005	1.0275	1.0028-1.0521
Height***	0.0595	0.0126	<0.001	1.0614	1.0367-1.0860
HbA1****	0.1931	0.0684	0.005	1.2130	1.0789-1.3470
Foot deformity(1)	2.1794	0.2834	<0.001	8.8409	8.2854-9.3963
Any retinopathy(1)	0.7623	0.2407	0.002	2.1431	1.6713-2.6148

Group - Controls
Dependent Variable - Neuropathy

Age Years)	0.0616	0.0325	0.06	1.0636	0.9999-1.1272
Sex (2)	1.5381	0.6756	0.03	4.6557	3.3311-5.9798
Foot deformity(1)	1.9316	0.7995	0.02	6.9002	5.3331-8.4672

(1) = present
(2) = male

* - odds ratio per year
** - odds ratio per unit of alcohol consumed/week
*** - odds ratio per cm
****- odds ratio per %

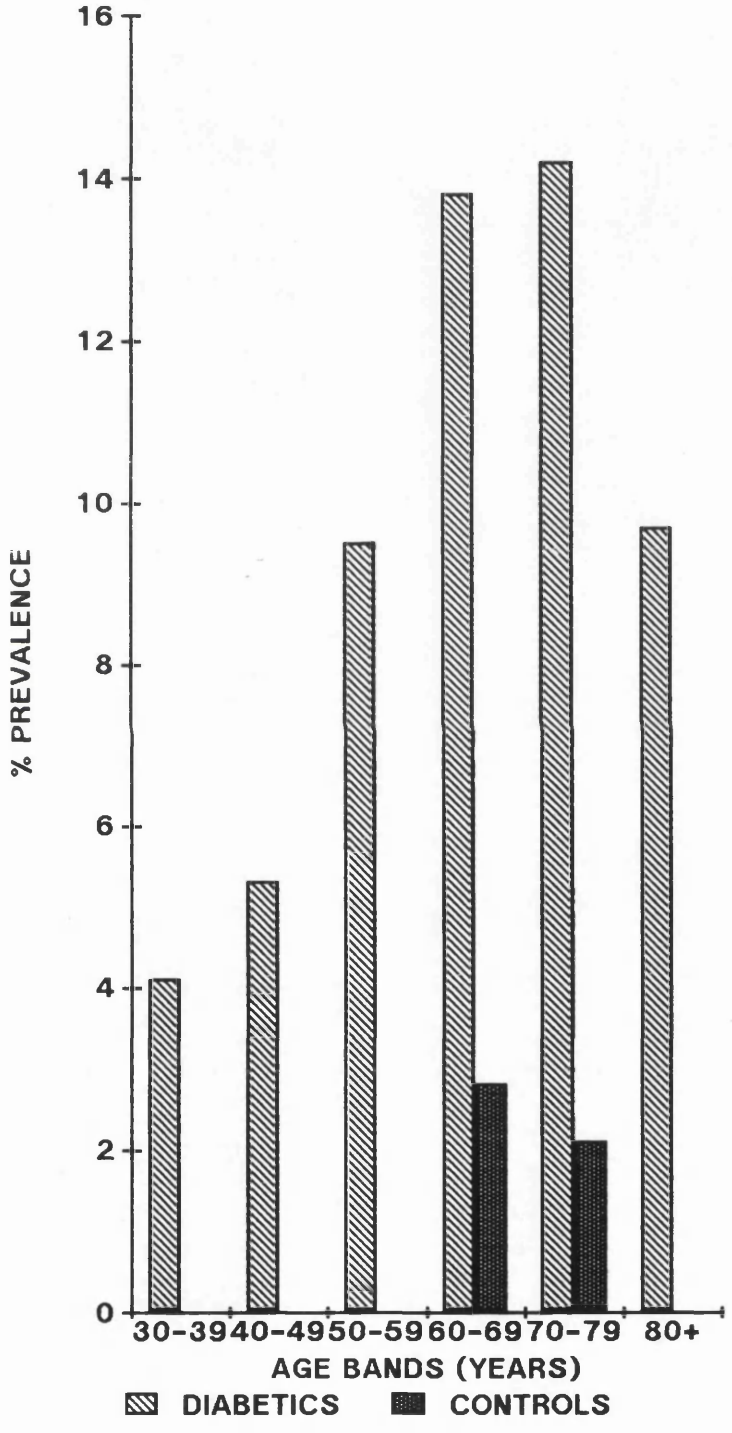
TABLE 6.18

SUMMARY OF THE PREVALENCE DATA FOR NEUROPATHY AND ITS VARIABLES

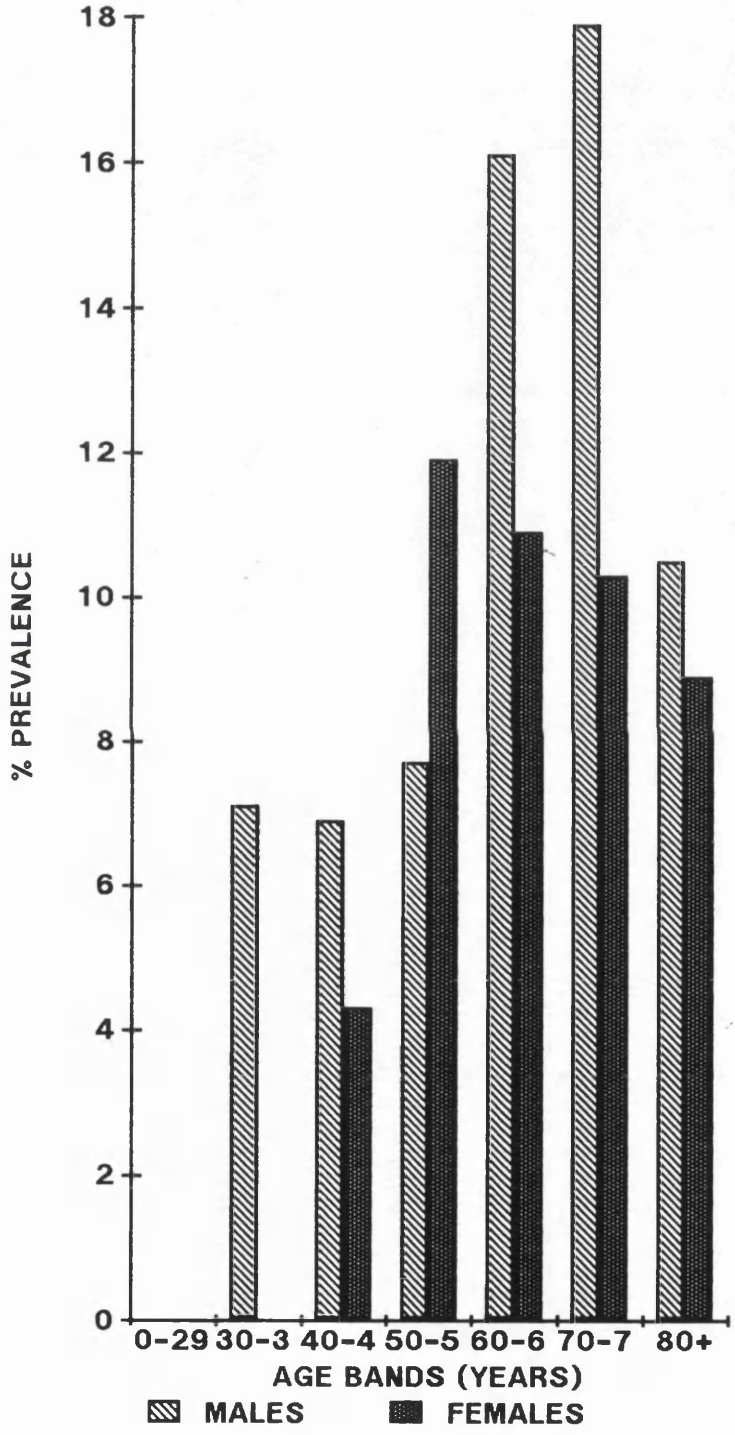
	Diabetics % Prevalence (95% CI)	Controls % Prevalence (95% CI)	IDDM % Prevalence (95% CI)	NIDDM % Prevalence (95% CI)
Neuropathy	16.3 (14.1-18.5)	2.9 (1.4-4.4)	12.7 (8.2-17.2)	17.2 (14.7-19.7)
Symptomatic Neuropathy	10.9 (9.0-12.8)	1.5 (0.4-2.6)	7.5 (4.0-11.0)	11.7 (9.6-13.8)
Absent knee jerks	7.2 (5.6- 8.8)	2.7 (2.0-3.4)	-	-
Absent ankle jerks	37.0 (34.1-39.9)	23.5 (19.7-27.3)	-	-
Absent light touch	12.3 (10.3-14.3)	3.8 (2.1-5.5)	-	-
Impaired pain perception	15.0 (12.9-17.1)	4.6 (2.7-6.5)	-	-

SYMPTOMATIC NEUROPATHY - PREVALENCE

DIABETICS Vs CONTROLS (FIG 6.1)

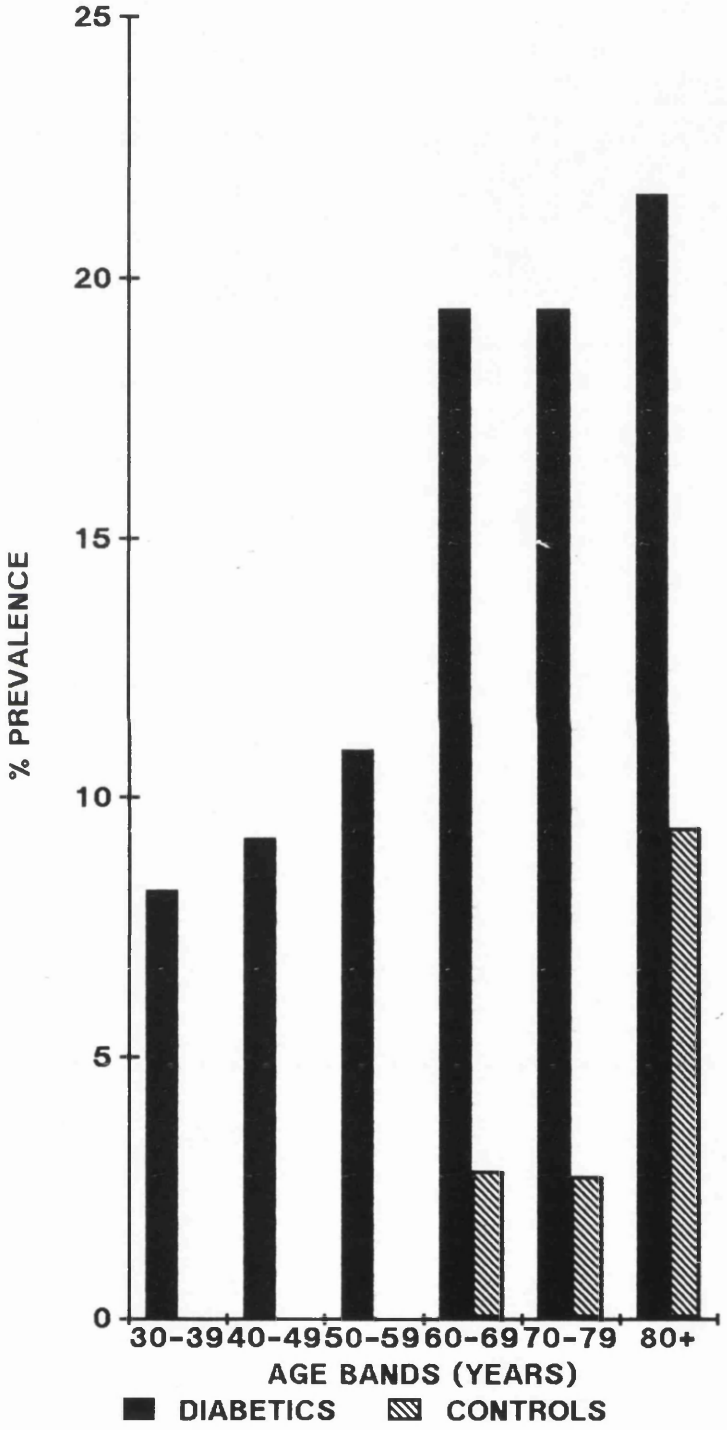


SYMPTOMATIC NEUROPATHY IN DIABETICS
ACCORDING TO AGE AND SEX (FIG 6.2)



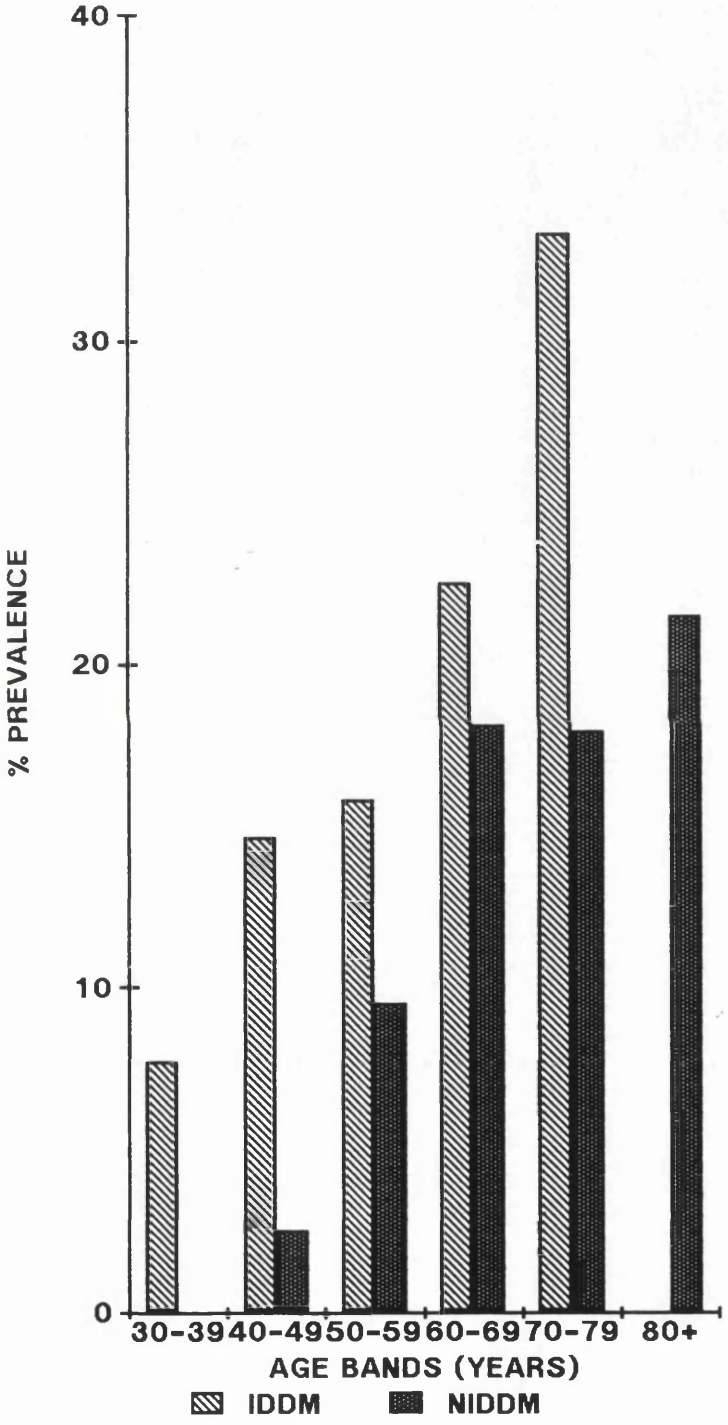
PREVALENCE OF NEUROPATHY (FIG 6.3)

DIABETICS Vs CONTROLS



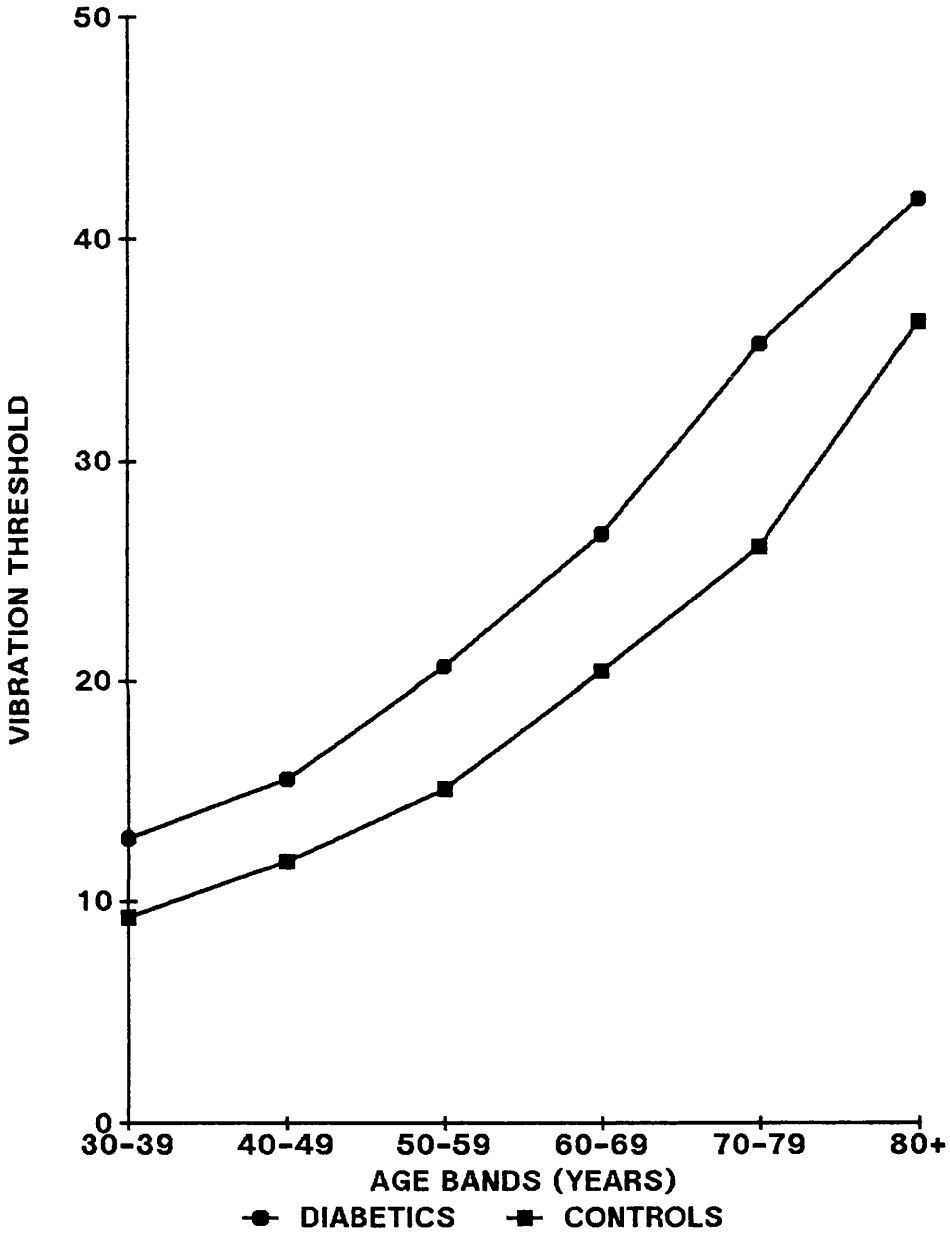
PREVALENCE OF NEUROPATHY (FIG 6.4)

IDDM Vs NIDDM



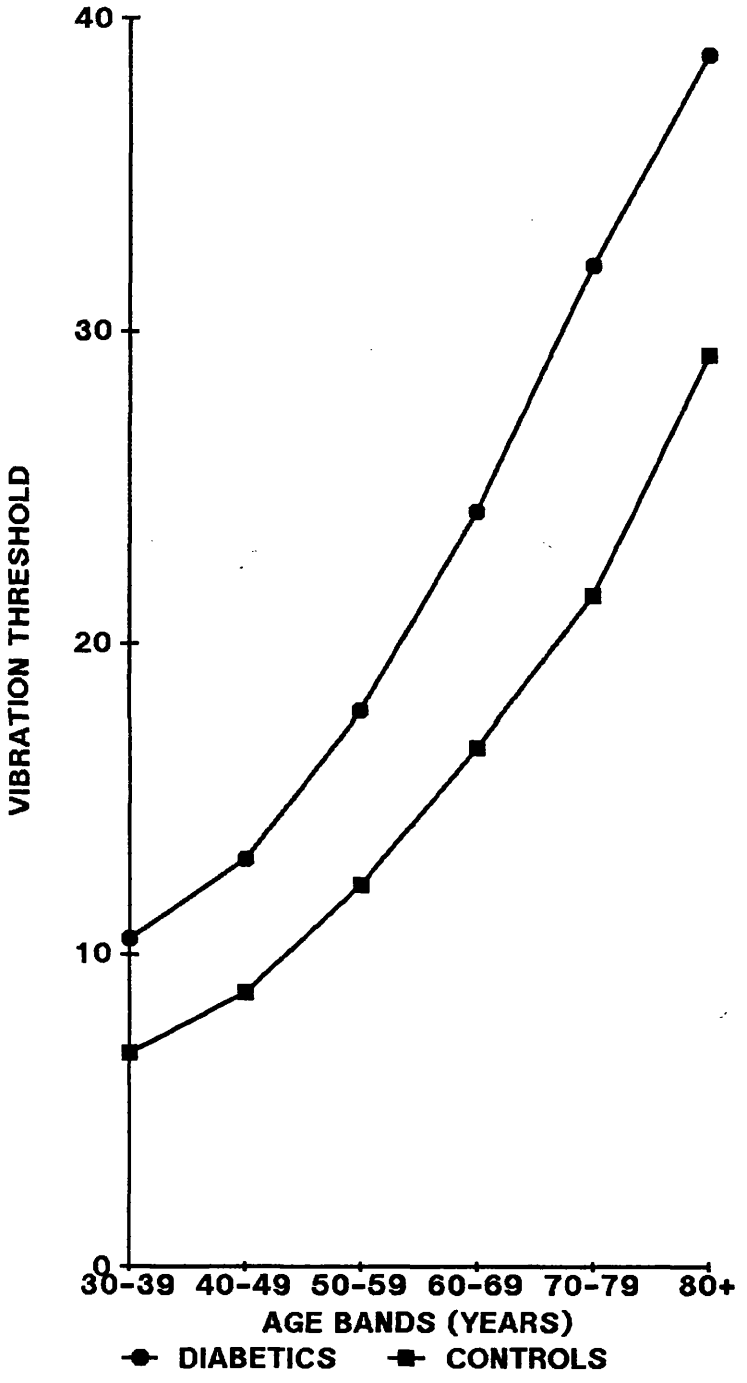
MEAN VIBRATION THRESHOLD (FIG 6.5)

MEDIAL MALLEOLUS - ACCORDING TO AGE



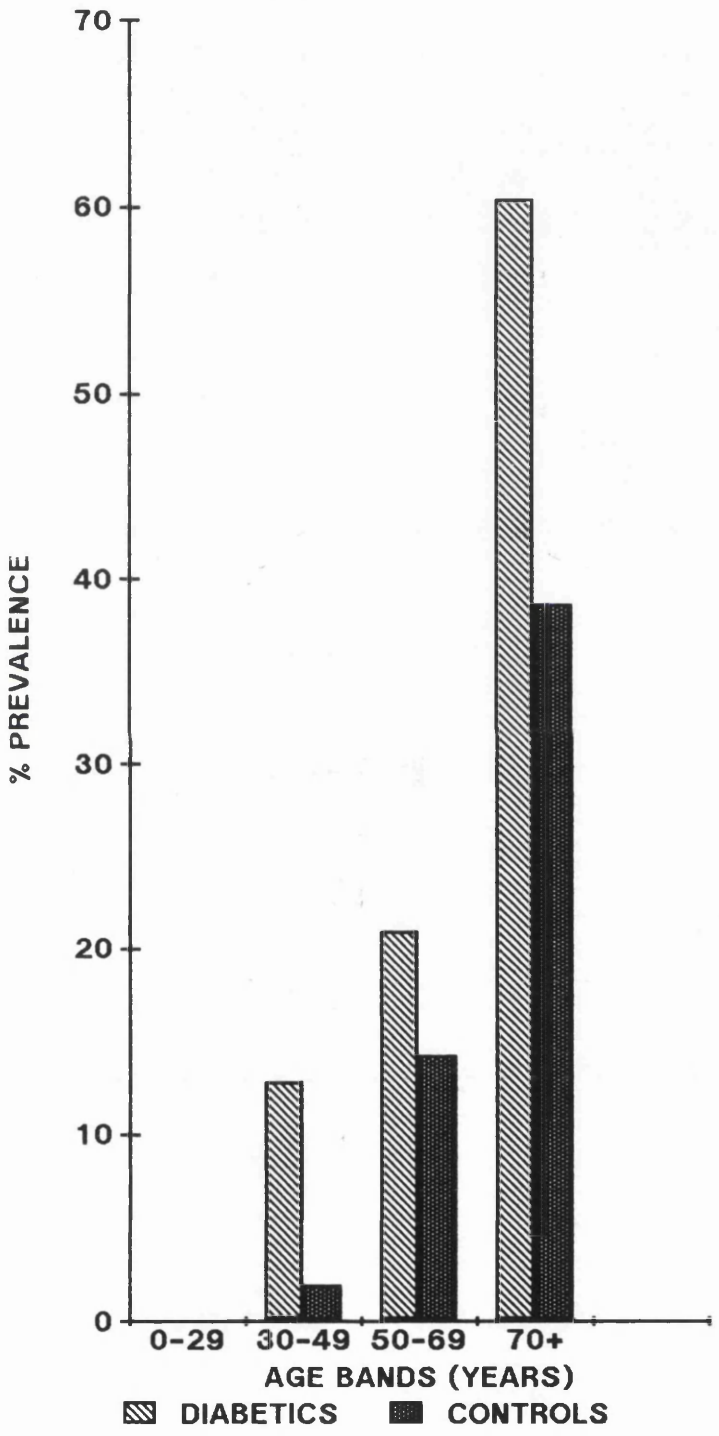
MEAN VIBRATION THRESHOLDS (FIG 6.6)

GREAT TOE - ACCORDING TO AGE



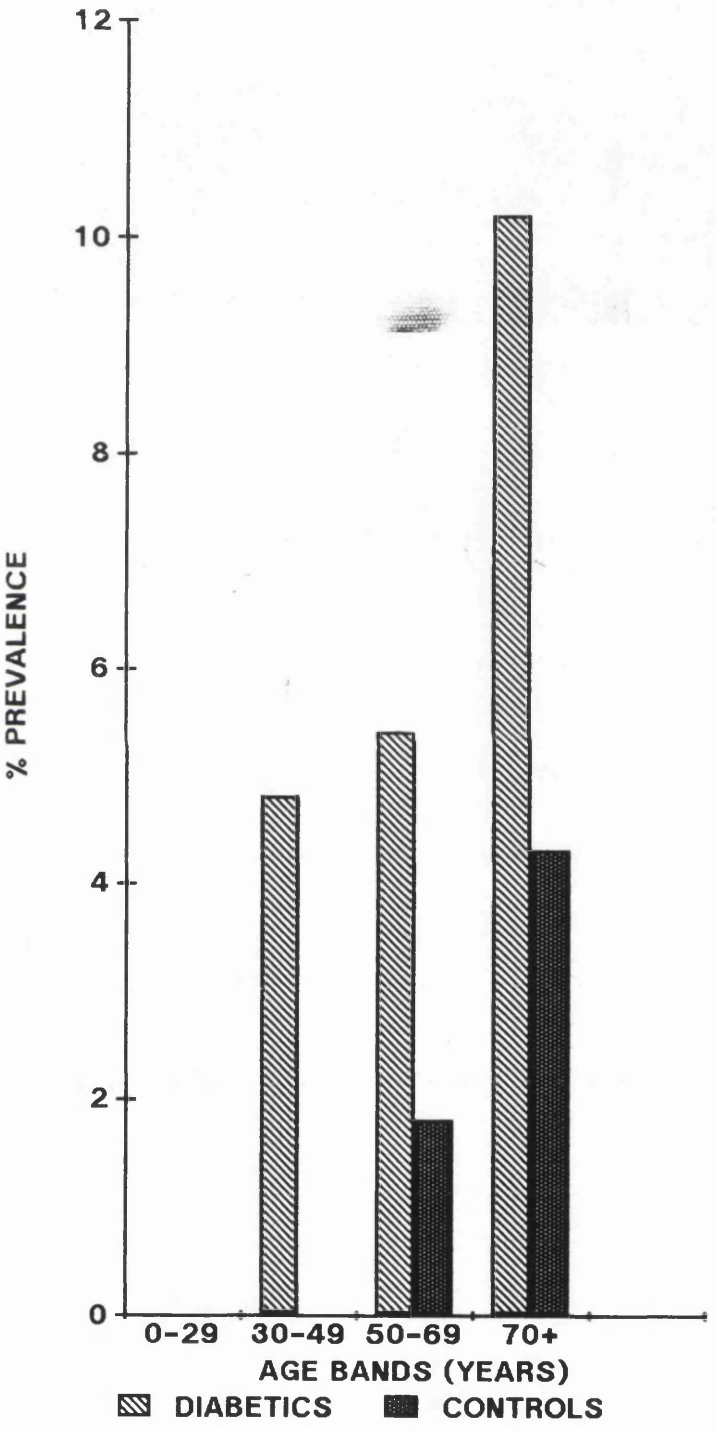
ABSENT ANKLE JERKS (FIG 6.7)

DIABETICS /CONTROLS ACCORDING TO AGE



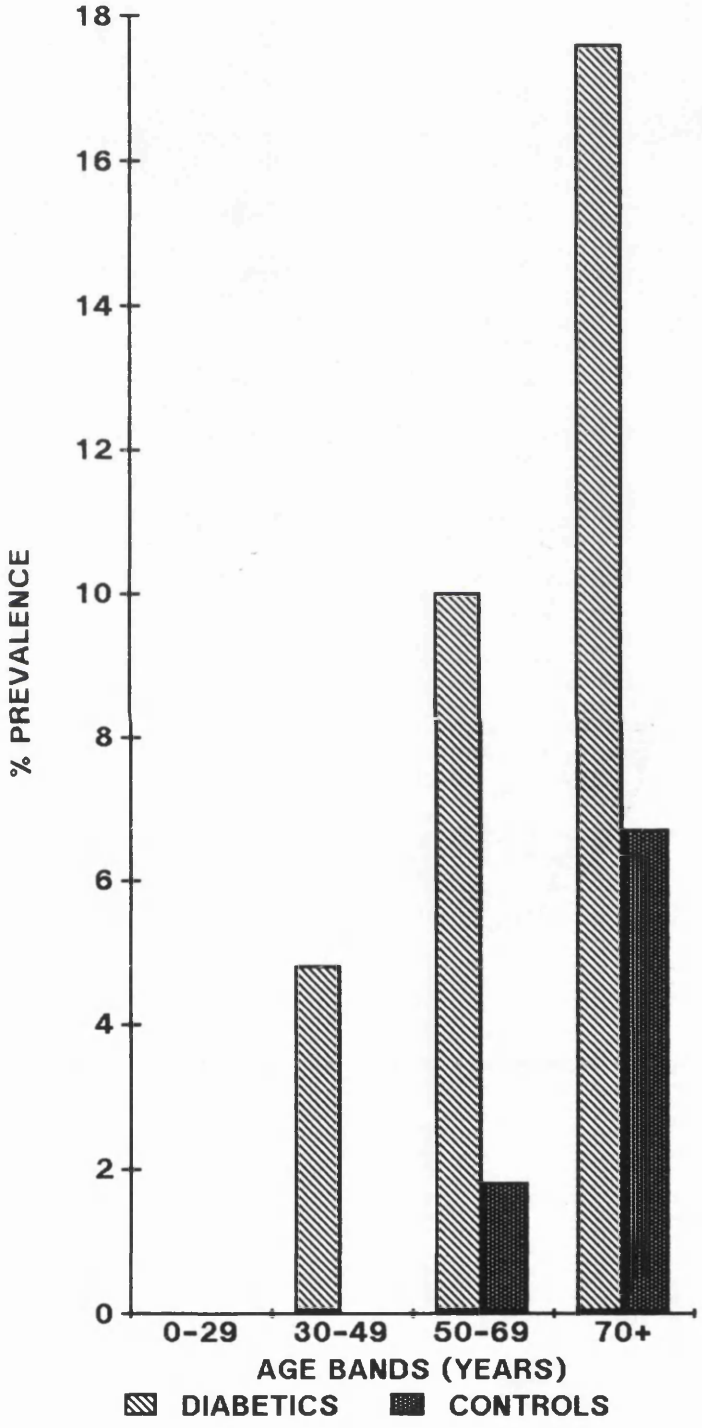
ABSENT KNEE JERKS (FIG 6.8)

DIABETICS/CONTROLS ACCORDING TO AGE



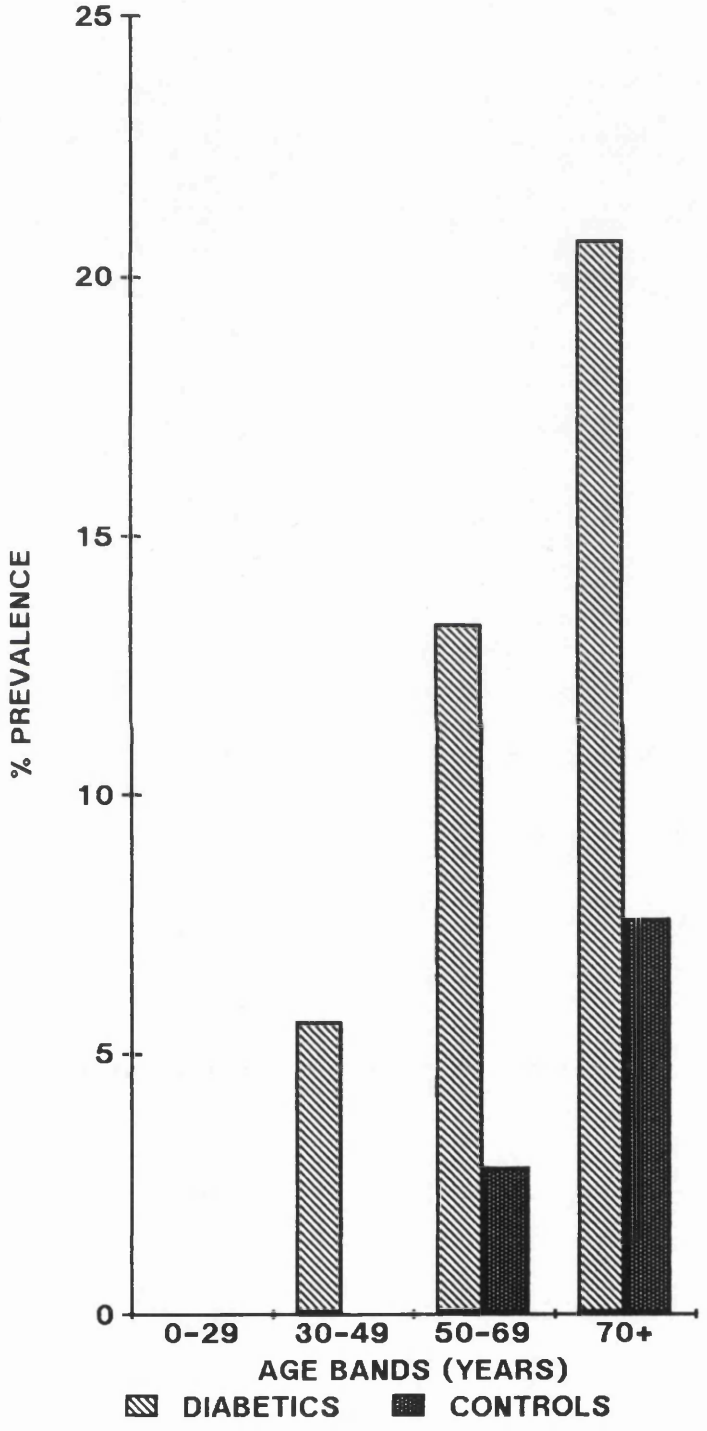
ABSENT LIGHT TOUCH PERCEPTION (FIG6.9)

DIABETICS/CONTROLS ACCORDING TO AGE



DIMINISHED PAIN PERCEPTION (FIG 6.10)

DIABETICS/CONTROLS ACCORDING TO AGE



Chapter 7

PREVALENCE AND RISK FACTORS FOR PERIPHERAL VASCULAR DISEASE IN DIABETICS

Results

Prevalence - by age and sex

20.6% (95% CI 18-23) of diabetics and 9.6% (95% CI 7.0-11.2) of controls were found to have evidence of peripheral vascular disease using the criterion of the doppler pressure ratio being less than or equal to 0.9 (see Table 7.1). It is obvious that diabetics tend to develop peripheral vascular disease at a younger age than their age/sex matched non-diabetic counterparts but the tendency for the prevalence to increase with age occurs in both groups (Fig 7.1). In the diabetic population the prevalence of peripheral vascular disease in males and females is similar whereas in controls there was a tendency towards a greater prevalence in males compared to females (see Table 7.1). However, there was no significant difference between the prevalence according to sex in either group (see Table 7.5).

Prevalence by type of diabetes

Considering diabetics by type, not surprisingly, the prevalence of peripheral vascular disease in NIDDs was markedly greater than in IDDs (see Table 7.2). However, after accounting for the disparity in age between the two types of diabetes (using logistic regression analysis) it was found that the difference in prevalence was not significant ($P = 0.18$). There is no significant difference between prevalence rates in each sex even though from the crude data of Table 7.2 it appears that peripheral vascular disease is more common in male IDDs (compared to female IDDs). In NIDDs, however, there was in fact slightly more (but not significant) females with peripheral vascular disease compared to males. The prevalence in both types of diabetes was significantly greater than for the control group after adjusting for differences in age.

Prevalence of Claudication Amongst Cases with Peripheral Vascular Disease

Table 7.3 shows the prevalence of claudication in diabetics and controls who were proven to have peripheral vascular disease by doppler investigation. There was no significant difference between the two groups (chi squared = 0.050 P = NS 1df). The prevalence of claudication was strikingly low in both groups indicating that the vast majority of peripheral vascular disease is asymptomatic. Furthermore the prevalence of claudication by sex tended to mirror the changes found for peripheral vascular disease by sex ie that overall the prevalence of claudication in males and females was similar whereas in controls there was a greater prevalence in males compared to females.

Site of Peripheral Vascular Disease

Table 7.4 shows the prevalence by site of the peripheral vascular disease ie whether it is suprapopliteal or infrapopliteal. The definition of each is given in Appendix 8. Unfortunately some cases could not be classified as either suprapopliteal or infrapopliteal peripheral vascular disease and this tends to reflect the difficulty in palpating the pulse. For either IDDM or NIDDM there was no significant difference in the prevalence of infrapopliteal disease compared to controls (see Table 7.6).

A comparison of clinical parameters of peripheral vascular disease with doppler pressure ratios

The prevalence, sensitivity and specificity of pulse palpation and intermittent claudication compared to doppler pressure ratios is shown in table 7.9. The "gold standard" for the presence of peripheral vascular disease was a doppler pressure ankle/brachial ratio of 0.9 or less. For pulse palpation peripheral vascular disease was defined as 2 or more absent pulses in the same leg. It can be seen that both intermittent claudication and pulse palpation have a poor sensitivity but an excellent specificity in diabetics and controls.

Risk Factors for Peripheral Vascular Disease

Regression analysis on risk factors for peripheral vascular disease in diabetics and controls is shown in Table 7.7. As with neuropathy diabetics have been divided into insulin dependent and non insulin dependent. Considering time related variables separately from other putative risk factors, age, demonstrates a powerful association with peripheral vascular disease in controls and all types of diabetes. Duration of diabetes exhibits no relationship to peripheral vascular disease in either type of diabetes.

The other aspect of diabetes exposure apart from duration, ie degree of control, was considered in IDDs and NIDDs and if HbA1 is used as the parameter of diabetic control then again there is no relationship between peripheral vascular disease and diabetic control. Two hour interval glucose concentrations were however significantly related to peripheral vascular disease in non insulin dependent diabetics. Since they were not fasting specimens it cannot be assumed that these glucose measurements reflect degree of diabetic control. They do however give some idea of the degree of hyperglycaemia exhibited after a glucose challenge albeit rather crude.

In non-diabetics cigarette smoking was a powerful risk factor for peripheral vascular disease. However, smoking was not significantly associated with peripheral vascular disease in either insulin dependent or non insulin dependent diabetics.

Mean systolic pressure was only weakly correlated with peripheral vascular disease in NIDDs and not at all in controls and IDDs. However for diabetics as a group there was a significant association. Contrasting other risk factors with the type of diabetes and peripheral vascular disease does in fact show clear differences. Cholesterol is a significant risk factor in NIDDs whereas proteinuria is a very powerful independent risk factor in IDDs. Coronary artery disease and cerebrovascular disease were correlated with peripheral vascular disease in NIDDM. Body mass index was inversely correlated with peripheral vascular disease in NIDDM.

Prevalence

This is the first population study to assess the prevalence of peripheral vascular disease in diabetics by using doppler pressure techniques.

The prevalence of peripheral vascular disease in both types of diabetes was significantly greater than for controls after adjusting for age differences between the groups. It should be appreciated, however, that in the case of the insulin dependent diabetic group the numbers of subjects in the elderly categories (where the prevalence of peripheral vascular disease may be predicted to be the highest) were very small. Indeed only 17 IDDs in total suffered from peripheral vascular disease. Care should, therefore, be exercised when extrapolating the data back to much larger groups. Possible trends, for example, a greater prevalence in male as opposed to female IDDs may have proved to be significant if the power of the sample size was greater. To study a larger population of IDDs would not have been feasible during this survey and to gain a large sample of elderly IDDs would have meant screening a massive population.

In diabetics over the age of 70 approximately one third will have evidence of peripheral vascular disease of which only a third will have claudication. The latter therefore is a very poor screening tool for the presence or absence of peripheral vascular disease. Yao et al (1969) have demonstrated that the pressure index is a reliable means of detecting peripheral vascular disease. However in diabetics it may underestimate the true prevalence because of media calcification causing falsely elevated values for pressures in the lower limb.

Although there are no non-invasive studies of the prevalence of peripheral vascular disease in diabetics using a quantitative definition there are some which use pulse palpation or the presence of intermittent claudication (Melton et al 1980, Nilsson et al 1967, Neil et al 1989, WHO multi-national study of vascular disease in diabetics 1985). The problem is that both pulse palpation and

intermittent claudication have been shown in the present survey to have a low sensitivity, although excellent specificity, compared to doppler pressure ratios. This problem has previously been demonstrated by Marinelli et al (1979). Also any study investigating the prevalence of peripheral vascular disease by pulse palpation also faces the potential difficulty of inter-observer variation. There are of course many non-population studies investigating the prevalence of peripheral vascular disease and indeed some of these employ non-invasive doppler methods (Janka et al 1980, Marinelli et al 1979, Beach et al 1980) but of course being selected groups may not be not directly comparable with this survey.

Site

It is commonly assumed that diabetics are more susceptible to disease below the knee (Strandness et al 1964, Conrad 1967, Haimovici 1967). The present study has not demonstrated this tendency and it is the first population study to attempt to compare the site of occlusion in the diabetic population with an age/sex matched control group. The previous studies have all investigated differences in small highly selected groups. Haemovici's subjects were those who underwent an angiogram and hence probably had been referred for surgery. Strandness et al found that the greater number of subjects with solely absent foot pulses were in those diabetics who underwent amputation and Conrad only studied amputated limbs using casts of the arterial system. These factors may well account for the discrepancy with the present survey. However the present study did not use doppler or arteriographic means to localise the site of obstruction and therefore had to rely on pulse palpation. Although errors were minimised by using a dichotomous classification with only one observer it still has to be realised that pulse palpation is very subjective and can only indicate severe occlusive disease. Nevertheless the results of the study would suggest that the excess frequency of peripheral vascular disease in diabetics is due to supra-popliteal disease and that there is no obvious predilection to infrapopliteal disease in diabetics.

Sex

The finding that female diabetics lose their protected status (Beach et al 1979, Kannel and McGee 1979) was confirmed in the present study for both types of diabetes. Unfortunately there are no studies which have previously been published which have allowed any direct comparison. Most studies have also lumped diabetics into one category rather than considering the diabetics by type. Beach et al (1980) in a non population study did divide diabetes into type and found almost identical percentages of peripheral vascular disease in insulin dependent diabetic men and women. In contrast there was a male predominance in NIDDM. However after accounting for the effects of smoking there was no sex bias.

Risk Factors for Peripheral Vascular Disease

There have been numerous attempts in the literature to relate peripheral vascular disease to putative risk factors in diabetic subjects. There has been considerable variation in findings and probably this reflects different subject groups and different means by which peripheral vascular disease has been determined. The present study is useful because not only does it cover an entire diabetic population but reference can also be made to a non-diabetic control group. Unfortunately, due to limited financial resources in the study, we were unable to measure cholesterol in non-diabetics.

Smoking

Perhaps the most striking difference between diabetics and controls was the relationship to smoking. In diabetics, smoking has often failed to show any statistical association with peripheral vascular disease in cross-sectional studies (WHO 1985, Welborn et al 1984) and the failure to demonstrate any association has been suggested to be due to the crudity of the smoking questionnaire (Welborn 1984). The questionnaire used in the present survey was the Standard Rose questionnaire (Rose 1977) and there genuinely seems to be a different effect of smoking in diabetics and non-diabetics who develop peripheral vascular disease. One possible explanation is that being a prevalence survey it is merely looking at the

survivors and possibly smoking in diabetics has a devastating impact on mortality and therefore they do not live long enough to develop the disease. Conversely diabetes may have such a powerful effect in influencing the development of peripheral vascular disease that it "swamps" the additional risk of smoking and as a consequence any added risk is missed. Another possibility could be that diabetics with peripheral vascular disease represent a separate disease entity linked by some unknown factor or factors. Clearly any of these suggestions are speculative and no definite conclusions may be made. However a recent small Finnish incidence study in NIDDM has suggested that claudication developing in males after 5 years was more common in subjects smoking at baseline (Uusitupa et al 1990). A significant association was also found after multiple regression analysis. Care should be exercised in interpreting the results of this study because only 14 males and 3 females developed claudication over the 5 year period. The regression analysis was performed on a group containing both the diabetics and a control group also studied, presumably because of the small number of cases of claudication in both groups. Further information regarding smoking and peripheral vascular disease from incidence studies is not available but the Finnish study raises the possibility that smoking may relate more to symptomatic peripheral vascular disease in diabetics.

Age/duration of diabetes

Age has long been established as being important in the manifestation of peripheral vascular disease (Bell 1950, Beach 1980, WHO 1985) and this survey confirmed such findings in both types of diabetes and controls. Even in diabetics peripheral vascular disease before the age of 40 was a rarity. Duration of diabetes however has not been uniformly shown to be independently correlated with peripheral vascular disease. Some studies investigating highly selected groups have shown a correlation with duration (Janka et al 1980, Beach et al 1979) but large population studies are inconsistent. The WHO prevalence study (WHO 1985) and the population study based in Rochester, Minnesota (Palumbo et al 1980) revealed an association with duration whereas a study based in rural Australia found no such relationship (Welborn et al 1984). Incidence studies investigating risk factors in diabetics who

develop claudication (as opposed to pulse palpation) yield conflicting results. The Framingham data (Brand et al 1989) and the Israeli study (Herman et al 1977) found no relationship with the duration of diabetes (indeed it is worth noting that both these studies found that claudication was a risk factor for subsequent diabetes) whereas a recent population study in NIDDM found the incidence of claudication, 5 years after diagnosis, greater in diabetics than in non-diabetic controls. At the start of the study there was no significant difference between the two groups (Uusitupa et al 1990). Possibly these studies are not directly comparable to this one in that the definition for peripheral vascular disease was markedly different. It would of course be wrong to be totally dismissive of any relationship between duration of diabetes and peripheral vascular disease and further longitudinal studies would be necessary to confirm or refute a definite link between the two.

Diabetic control

The other aspect of diabetes exposure is the degree of diabetic control. Two aspects of diabetic control were measured in this study; the HbA1 and the 2 hour interval glucose ie a glucose level taken 2 hours after a main meal. The latter, even in non insulin dependent diabetics, is a dubious assessment of diabetic control in contrast to the fasting glucose. There has been very little previous literature concerning diabetic control and peripheral vascular disease but the few studies that have addressed the problem have found conflicting results (Beach and Strandness 1980 and Welborn et al 1984). Once again they may not be directly comparable to this study because of different subject groups and different definitions of peripheral vascular disease. Glucose in non insulin dependent diabetes in this survey was however correlated with peripheral vascular disease. Possibly the magnitude of glucose excursion from normal ranges albeit transiently may be an important factor in the development of peripheral vascular disease. The Framingham study found that the risk of developing intermittent claudication was greatest in the upper levels of impaired glucose tolerance (Gordon 1972) in the general population but was not related to the casual blood glucose unless it was above the upper quintile (>90 mg/dl) (Kannel 1985).

Kreines et al (1985) apparently found that the risk of developing an absent dorsalis pedis pulse in NIDDs was related to the initial glucose tolerance. From the present survey however the fact that peripheral vascular disease is not related to either duration or mean HbA1 level implies that glycaemia and peripheral vascular disease are not causally linked. However, the association would be ideally examined in a prospective study.

Diabetic complications

The powerful association of macroscopic proteinuria with peripheral vascular disease in insulin dependent diabetes mellitus is interesting. It appears to be independent of serum cholesterol and creatinine concentrations. There are no previous relevant data published though the relationship between proteinuria and coronary artery disease in IDDM has been extensively investigated (Krolewski et al 1987, Anderson et al 1983). Essentially mortality from coronary heart disease is substantially lower in those diabetics without persistent proteinuria. It has been postulated that this increased mortality in IDDM is secondary to the alterations in blood pressure levels, haemostatic factors and lipids that accompany diabetic nephropathy (Jarrett 1989). Whether this is the case for peripheral vascular disease remains unknown. However it has recently been proposed following animal experiments that albuminuria is an indicator of a general increase in vessel wall permeability perhaps acting as a precursor or amplifier for atherogenesis (Keen 1989).

Blood Pressure

Mean systolic blood pressure surprisingly was not correlated with peripheral vascular disease in controls or insulin dependent diabetics. Indeed the association even in NIDDs was weak (although considering diabetics as a group there was a definite association). Perhaps in non-diabetics the sample size may have been too small to show an association as hypertension is generally accepted as a major risk factor in atherosclerosis in the non-diabetic (Gordon 1972). Clearly reducing the sample size in the diabetic population by dividing the diabetics into either type of diabetes inevitable reduced the association between peripheral vascular disease and

systolic pressure. Hypertension has been shown in cross-sectional studies in diabetics to be associated with peripheral vascular disease (Beach 1980, Janka 1980, WHO 1985). Systolic rather than diastolic pressure was predictive of peripheral vascular disease in one of the few longitudinal studies but only of vascular calcification (Kreines et al 1985). In contrast, a population study based in Finland found that the baseline systolic and diastolic blood pressures were predictive of developing claudication in diabetics after 5 years. However no relationship was found for either variable following a multiple regression analysis but, as previously mentioned, this study had to combine the diabetics with controls to perform the regression analysis. The effects of blood pressure specifically in diabetics cannot, therefore, be assessed (Uusitupa et al 1990). The other major incidence study demonstrated, as in this survey, higher levels of systolic pressure in diabetics compared to non diabetics (Brand et al 1989). The risk of developing claudication was much greater in diabetics than non diabetics and although they adjusted the relative risks for several variables the authors do not state that blood pressure (either systolic or diastolic) was predictive of claudication in diabetics. However, in the general population systolic pressure was a significant predictor of claudication even after multivariate analysis (Kannel and McGee 1985). Of these longitudinal studies either no classification of diabetes was used (Brand 1989) or only NIDDs were studied (Kreines et al 1985, Uusitupa et al 1990). This study has suggested that there may be differences in potential risk factors for peripheral vascular disease between the two types of diabetes and further longitudinal studies in IDDs and NIDDs with more quantifiable definitions of peripheral vascular disease are needed. However from the evidence available both from the present survey and from the previous literature it would seem that systolic pressure is associated with the presence of peripheral vascular disease in diabetics.

Cholesterol (total)

Previous surveys also reveal conflicting results for the correlations with body mass index and serum cholesterol. Both are reported to be risk factors for atherogenesis in non-diabetics (Kannel and McGee 1985). It was a pity that cholesterol could not

be measured in the non-diabetic controls. It would also have been desirable to measure triglyceride levels and lipoprotein composition in the diabetics but again for practical and financial reasons this was not possible. The present survey confirms the findings of Uusitupa et al (1990) of an association between peripheral vascular disease and cholesterol. The WHO study (WHO 1985) found no correlation and the study in rural Australia (Welborn 1984) found a significant association only with macrovascular disease as a whole. Whilst a selected cross-sectional survey found an association between LDL cholesterol and peripheral vascular disease in NIDDM (Beach et al 1979) the Finnish population study (Uusitupa et al 1990) suggests that VLDL cholesterol is the more important fraction in determining the development of claudication in NIDDs. Indeed the Finnish study found an association with many lipid variables and the strongest association on univariate analysis was for triglyceride levels. The problem is that as blood pressure and lipid abnormalities are associated it may be difficult to sort out the actual determinants using statistics.

BMI

It is curious that BMI should be inversely related to peripheral vascular disease. Few population studies have specifically investigated BMI in diabetics with peripheral vascular disease. Cross-sectional studies have either found no association (Welborn et al 1984) or a positive correlation in women only (WHO 1985). The incidence study of claudication in NIDDs (Kreines et al 1985) apparently found a relationship between weight and non palpable dorsalis pedis pulse but the authors do not state whether the relationship is positive or negative! The Framingham study found that weight in men had an inverse relationship in terms of the risk of developing claudication (Kannel et al 1985). This study was concerned with a general population however. BMI in the Finnish study (Uusitupa et al 1990) was marginally higher in those who developed claudication but the average was greater than or equal to 30 kg/m^2! Perhaps some of the conflicting results are due to the possibility that absolute indices of weight may be less important than the degree and distribution of body fat (which in turn correlates with HDL cholesterol) which may be more relevant. Such a

concept is postulated for mortality in coronary artery disease in diabetics (Jarrett 1990) but the problems of inter-related variables (eg BMI, blood pressure and lipids) still apply.

In conclusion this study has documented the prevalence of peripheral vascular disease whether symptomatic or asymptomatic in a diabetic population. It is the first to do so using a quantitative definition and brings into question the widely held beliefs that diabetics tend to experience less claudication and tend to have more disease below the knee. Although clearly peripheral vascular disease is more abundant in diabetics than in age/sex matched controls there appears to be no correlation with duration of diabetes or the degree of diabetic control in either type. While some of the traditional risk factors for peripheral vascular disease in non-diabetics were the same for diabetics there was one major exception in smoking habits. Since the control group was smaller than the diabetic group and the methods used to obtain data on smoking were identical, there does seem to be a genuine difference.

TABLE 7.1

PREVALENCE OF PERIPHERAL VASCULAR DISEASE
BY AGE AND SEX

Diabetics

Age (years)	Male diabetics No.	(% prev.)	Female diabetics No.	(% prev.)	All diabetics No.	(% prev.)
0-29	0	(0.0)	0	(0.0)	0	(0.0)
30-39	3	(10.7)	0	(0.0)	3	(6.1)
40-49	1	(3.4)	0	(0.0)	1	(1.3)
50-59	3	(3.9)	3	(5.1)	6	(4.4)
60-69	15	(10.6)	19	(17.3)	34	(13.5)
70-79	55	(33.3)	42	(28.0)	97	(30.8)
80+	37	(45.1)	40	(44.4)	77	(44.8)
	114	(20.4)	104	(20.8)	218	(20.6)
Missing values	11		8		19	

Controls

Age (years)	Male controls No.	(% prev.)	Female controls No.	(% prev.)	All controls No.	(% prev.)
30-39	0	(0.0)	0	(0.0)	0	(0.0)
40-49	0	(0.0)	1	(4.3)	1	(2.7)
50-59	2	(4.7)	0	(0.0)	2	(2.7)
60-69	7	(8.4)	2	(3.3)	9	(6.3)
70-79	13	(16.9)	9	(13.0)	22	(15.1)
80+	7	(17.9)	5	(20.0)	12	(18.8)
	29	(11.0)	17	(7.9)	46	(9.6)
Missing values	1		0		1	

TABLE 7.2

PREVALENCE OF PERIPHERAL VASCULAR DISEASE BY AGE, SEX AND TYPE (DIABETICS)

	IDDM		NIDDM		All diabetics	
	Males	Females	Males	Females	Males	Females
Age	No (%)	No(%)	No (%)	No (%)	No (%)	No (%)
0-29	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
30-39	3 (11.1)	0(0.0)	0 (0.0)	0 (0.0)	3 (10.7)	0 (0.0)
40-49	0 (0.0)	0(0.0)	1 (6.3)	0 (0.0)	1 (3.4)	0 (0.0)
50-59	1 (11.1)	1(16.7)	2 (3.0)	2 (3.8)	3 (3.9)	3 (5.1)
60-69	2 (12.5)	1(7.1)	13 (10.3)	18 (18.8)	15 (10.6)	19 (17.3)
70-79	7 (63.6)	2(25.0)	48 (31.2)	40 (28.2)	55 (33.3)	42 (28.0)
80+	0 (-)	1(25.0)	37 (45.1)	39 (45.3)	37 (45.1)	40 (44.4)
	13 (11.7)	5(5.2)	101 (22.6)	99 (24.6)	114 (20.4)	104 (20.8)
Missing values	3	2	8	6	11	8

TABLE 7.3

PREVALENCE OF INTERMITTENT CLAUDICATION AMONGST CASES WITH PERIPHERAL VASCULAR DISEASE

Diabetics

Age (years)	Claudication present Males No.	(%)	Females No.	(%)	All No.	(%)
0-29	0	(-)	0	(-)	0	(-)
30-39	0	(0.0)	0	(-)	0	(0.0)
40-49	0	(0.0)	0	(-)	0	(0.0)
50-59	1	(33.3)	1	(33.3)	2	(33.3)
60-69	7	(46.7)	6	(31.6)	13	(38.2)
70-79	21	(38.2)	15	(36.6)	36	(37.5)
80+	10	(27.8)	12	(30.8)	22	(29.3)
	39	(34.5)	34	(33.3)	73	(34.0)

Controls

Age (years)	Claudication present Males No.	(%)	Females No.	(%)	All No.	(%)
30-39	0	(-)	0	(-)	0	(-)
40-49	0	(-)	0	(0.0)	0	(0.0)
50-59	1	(50.0)	0	(-)	1	(50.0)
60-69	3	(42.9)	0	(0.0)	3	(33.3)
70-79	5	(38.5)	2	(22.2)	7	(31.8)
80+	2	(28.6)	1	(20.0)	3	(25.0)
	11	(37.9)	3	(17.6)	14	(30.4)

TABLE 7.4

Site of peripheral vascular disease

Site	Diabetics with PVD No.	(%)	Controls with PVD No.	(%)
Suprapopliteal	97	(44.5)	14	(30.4)
Infrapopliteal	61	(28.0)	23	(50.0)

Many cases had combinations of peripheral pulses that could not be classified as supra- or infra-popliteal.

TABLE 7.5

DIFFERENCES IN PREVALENCE OF PERIPHERAL VASCULAR DISEASE ACCORDING TO SEX AND TYPE OF DIABETES

Peripheral Vascular Disease

i. Diabetics

	Males	Females
Absent	444	396
Present	114	104

Chi squared (Yates correction) = 0.0052 $p>0.2$ (1 df)

ii. NIDDs

	Males	Females
Absent	346	304
Present	101	99

Chi squared (Yates correction) = 0.35 $p=0.55$ (1 df)

iii. IDDs

	Males	Females
Absent	98	92
Present	13	5

Chi squared (Yates correction) = 2.05 $p=0.15$ (1 df)

iv. Controls

	Males	Females
Absent	236	198
Present	29	17

Chi squared (Yates correction) 0.936 $p>0.1$ (1 df)

TABLE 7.6

REGRESSION ANALYSIS TO DETERMINE THE SIGNIFICANCE OF DIFFERENCES IN PREVALENCE BETWEEN PERIPHERAL VASCULAR DISEASE VARIABLES IN THE CONTROL AND DIABETIC POPULATIONS AFTER ADJUSTING FOR AGE

(Age is included in the regression equation)

Dependent Variable	Factor	Coefficient (SE)	Odds Ratio	95% CI	P value
1.Peripheral Vascular Disease (Ankle/ brachial pressure index <0.9)	Diabetics=1 Controls =0	0.954 (0.180)	2.60	1.82-3.69	<0.001
	NIDDs =1 Controls =0	0.925 (0.183)	2.52	1.76-3.61	<0.001
	IDDs =1 Controls =0	1.113 (0.341)	3.04	1.56-4.52	<0.001
	IDDs =1 NIDDs =0	0.408 (0.305)	1.50	0.83-2.74	0.18
2.Intermittent Claudication	Diabetics=1 Controls =0	1.048 (0.263)	2.85	1.70-4.27	<0.001
	NIDDs =1 Controls =0	1.108 (0.265)	3.03	1.80-5.09	<0.001
	IDDs =1 Controls =0	0.510 (0.533)	1.67	0.59-4.73	0.34
3.Supra-popliteal Disease	Diabetics=1 Controls =0	1.186 (0.296)	3.27	1.83-5.85	<0.001
	NIDDs =1 Controls =0	1.185 (0.298)	3.27	1.82-5.86	<0.001
	IDDs =1 Controls =0	1.223 (0.541)	3.40	1.18-	0.02
4.Infra-popliteal disease	Diabetics=1 Controls =0	0.107 (0.258)	1.11	0.67-1.85	0.68
	NIDDs =1 Controls =0	0.085	1.09	0.65-1.82	0.75
	IDDs =1 Controls =0	0.147 (0.581)	1.16	0.37-3.62	0.80

TABLE 7.7

PERIPHERAL VASCULAR DISEASE - MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR POTENTIAL RISK FACTORS

Dependent variable peripheral vascular disease

i. Group - Diabetics

Variable	Coefficient	SE	P Value	Odds Ratio	95% CI
Age*	0.0822	0.0113	<0.001	1.0847	1.06-1.11
Duration*	-0.0025	0.0101	0.72	0.9975	0.98-1.02
BMI**	-0.0643	0.0263	0.01	0.9377	0.90-0.99
Cerebro-vascular Disease (1)	1.1464	0.3658	0.002	3.1468	2.43-3.87
Coronary Artery Disease (1)	0.9776	0.2290	<0.001	2.6581	2.21-3.11
Mean systolic pressure mmHg***	0.0100	0.0043	0.02	1.0098	1.00-1.02
Glucose	0.0809	0.0235	0.001	1.0843	1.04-1.13
Serum**** cholesterol	0.1879	0.0656	0.005	1.2000	1.08-1.34
ii. Group - IDDs					
Age*	0.1149	0.0292	<0.001	1.1218	1.06-1.18
Duration*	-0.0005	0.0244	0.8535	0.9833	0.95-1.05
Proteinuria (1)	3.5135	1.9488	0.005	33.5653	31.00-36.00

TABLE 7.7 (Cont.)

iii. Group - NIDDs

Variable	Coefficient	SE	P Value	Odds Ratio	95% CI
Age*	0.0972	0.0134	<0.001	1.1020	1.08-1.13
Duration*	-0.0105	0.0125	0.40	0.9896	0.96-1.02
BMI**	-0.0543	0.0275	0.05	0.9472	0.90-0.99
Coronary Artery Disease (1)	0.9643	0.2405	<0.001	2.6230	2.12-3.12
Cerebro-vascular Disease (1)	1.0709	0.3770	0.005	2.9179	2.18-3.66
Glucose****	0.0974	0.0263	<0.001	1.1024	1.05-1.15
Serum**** Cholesterol	0.2241	0.0724	0.002	1.2512	1.11-1.39
Mean Systolic Pressure	0.0084	0.0046	0.07	1.0084	0.99-1.02

iv. Controls

Age* (years)	0.0856	0.0185	<0.001	1.0894	1.0531-1.1256
Smoking***** (max/day)	0.0359	0.0102	<0.001	1.0366	1.0166-1.0565

* odds ratio per year
** odds ratio per kg/m^2
*** odds ratio per mmHg
**** odds ratio per mmol
***** odds ratio per cigarette smoked/day

(1) = present

TABLE 7.8

SUMMARY OF PERIPHERAL VASCULAR DISEASE PREVALENCE DATA AND THE PREVALENCE ODDS FOR PERIPHERAL VASCULAR DISEASE IN THE GENERAL POPULATION CONFERED BY DIABETIC STATUS

	Prevalence (crude)	95% CI	Odds Ratio	95% CI
Diabetic status	%	%		
IDDM	7.2	3.7-10.7	3.04*	1.56-5.94
NIDDM	23.5	20.5-26.5	2.52*	1.76-3.61
Diabetics	20.6	18.2-23.0	2.6*	1.82-3.69
Controls	9.6	7.0-12.2	-	-

*p<0.001

TABLE 7.9

THE PREVALENCE, SENSITIVITY AND SPECIFICITY OF PULSE PALPATION AND INTERMITTENT CLAUDICATION COMPARED TO PERIPHERAL VASCULAR DISEASE DEFINED BY ANKLE/BRACHIAL DOPPLER PRESSURE RATIOS

Intermittent Claudication

Diabetics

Prevalence = 9.6%

	Peripheral Vascular Disease (doppler pressure 0.9 or less)	
Claudication	Present	Absent
Present	73	29
Absent	142	809

$$\text{Sensitivity} = \frac{73}{73+142} = 0.34$$

$$\text{Specificty} = \frac{809}{809+29} = 0.97$$

Controls

Prevalence = 3.75%

	Peripheral Vascular Disease (doppler pressure 0.9 or less)	
Claudication	Present	Absent
Present	14	4
Absent	32	429

$$\text{Sensitivity} = \frac{14}{14+32} = 0.30$$

$$\text{Specificity} = \frac{429}{4+429} = 0.99$$

TABLE 7.9 (Cont.)

Pulse palpation (2 or more absent in the same limb)

Diabetics Prevalence = 19.6%

Peripheral Vascular Disease
(doppler pressure ratio 0.9 or less)

Pulses	Present	Absent
Pulses Absent	152	59
Pulses Present	66	781

$$\text{Sensitivity} = \frac{152}{66+152} = 0.7$$

$$\text{Specificity} = \frac{781}{781+59} = 0.93$$

Controls Prevalence = 7.3%

Peripheral Vascular Disease
(doppler pressure of 0.9 or less)

Pulses	Present	Absent
Pulses Absent	22	13
Pulses Present	24	420

$$\text{Sensitivity} = \frac{22}{22+24} = 0.48$$

$$\text{Specificity} = \frac{420}{420+13} = 0.97$$

TABLE 7.9 (Cont.)

Applying Bayer's Theorem to determine the positive predictive value of each test using the formula as follows:

$$\text{Positive predictive value} = \frac{\text{Sensitivity x Prevalence}}{\text{Probability of positive result}}$$

For intermittent claudication

Diabetics - Positive Predictive Value = 0.71

Controls - Positive Predictive Value = 0.77

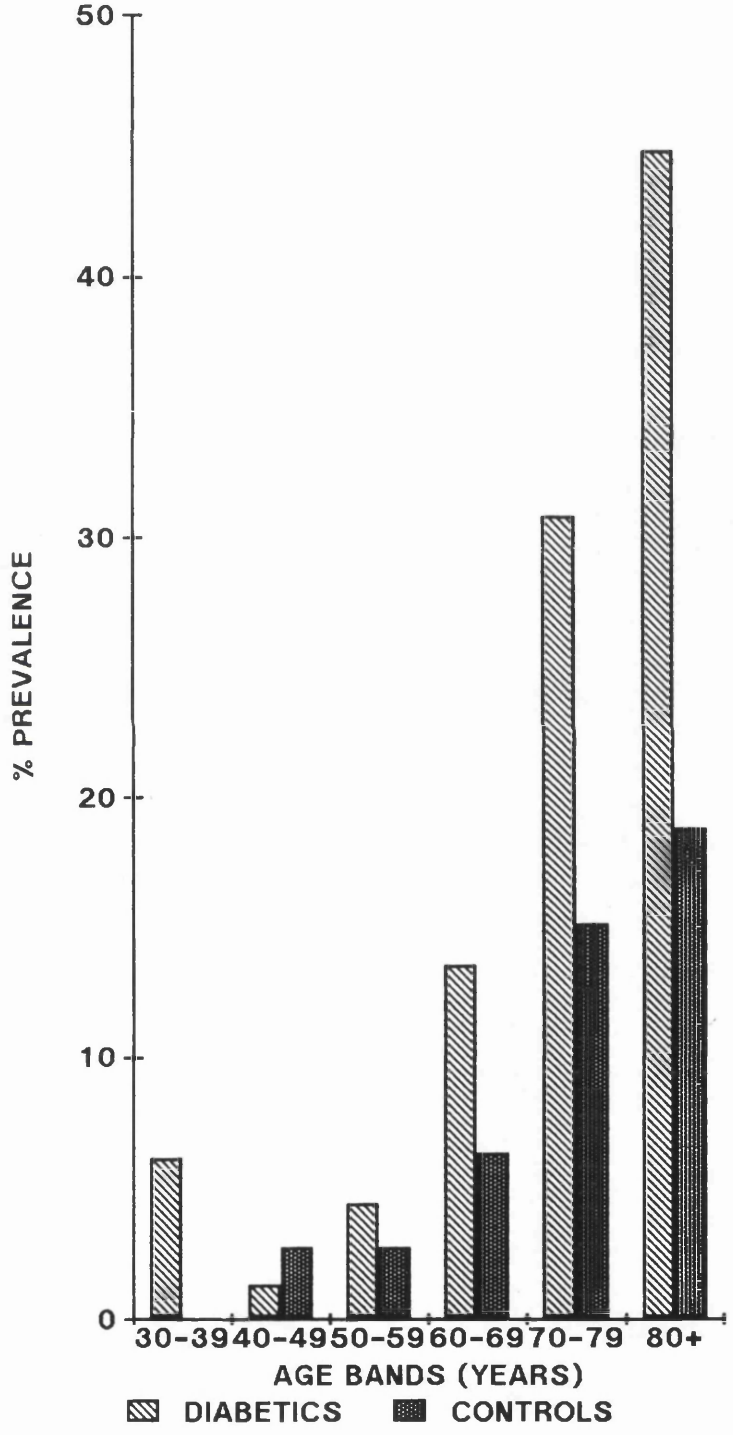
For pulse palpation

Diabetics - Positive Predictive Value = 0.72

Controls - Positive Predictive Value = 0.62

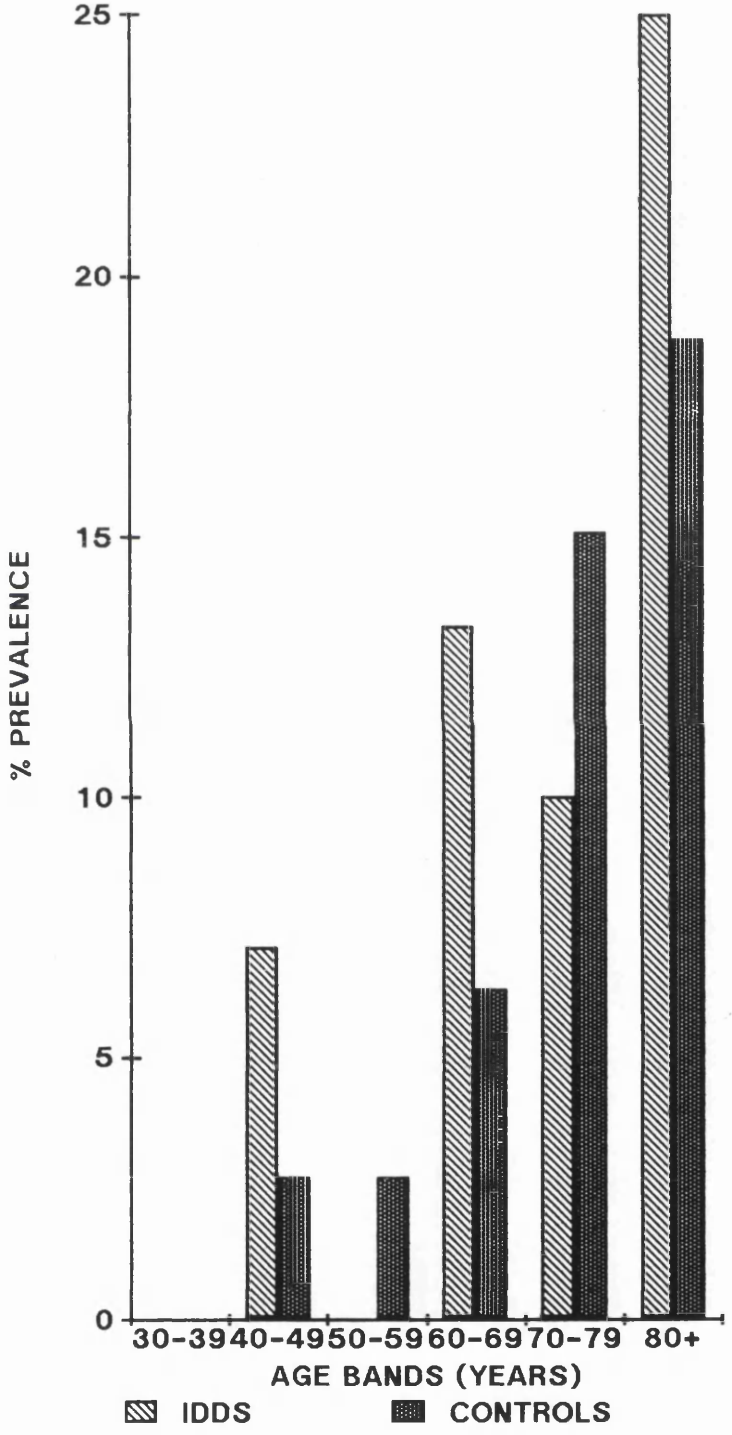
PERIPHERAL VASCULAR DISEASE

DIABETICS Vs CONTROLS (FIG 7.1)



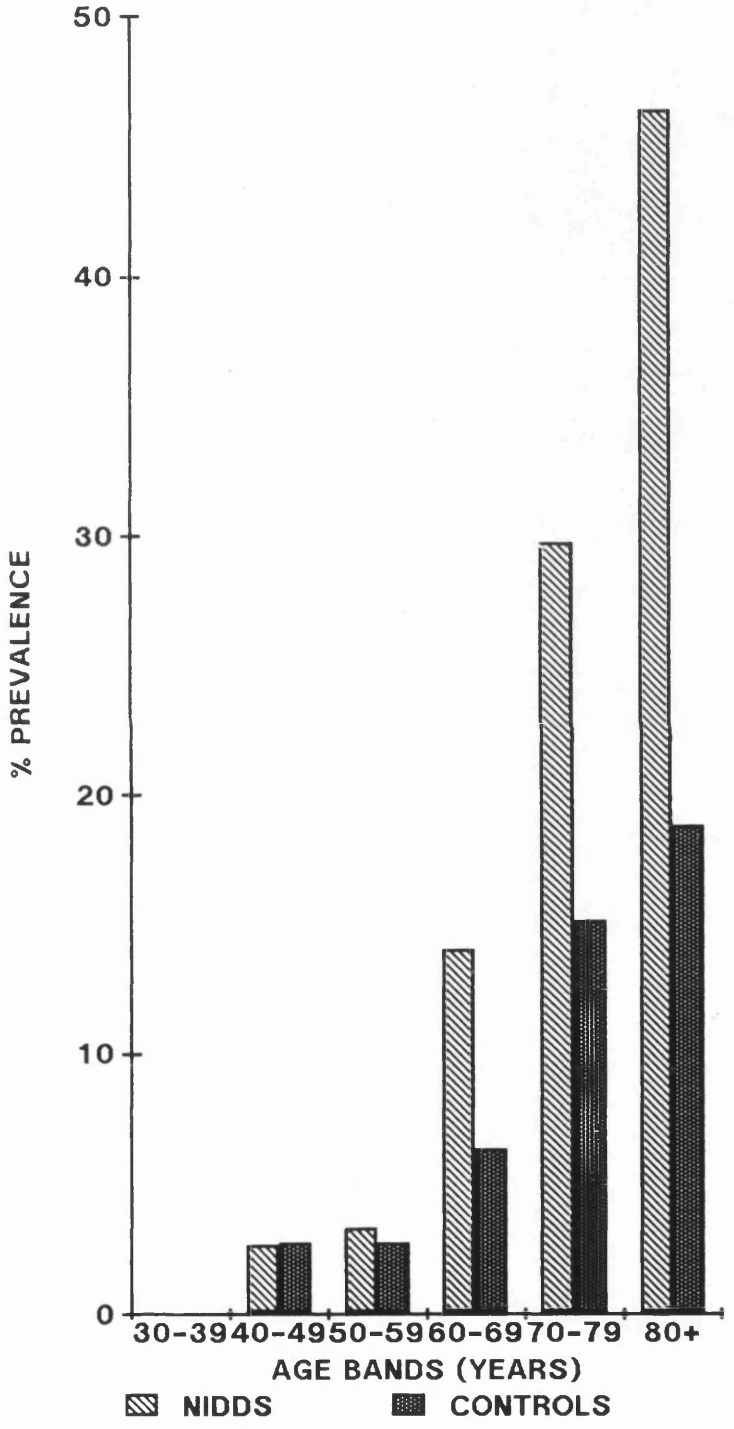
PERIPHERAL VASCULAR DISEASE (FIG 7.2)

IDDs Vs CONTROLS - PREVALENCE



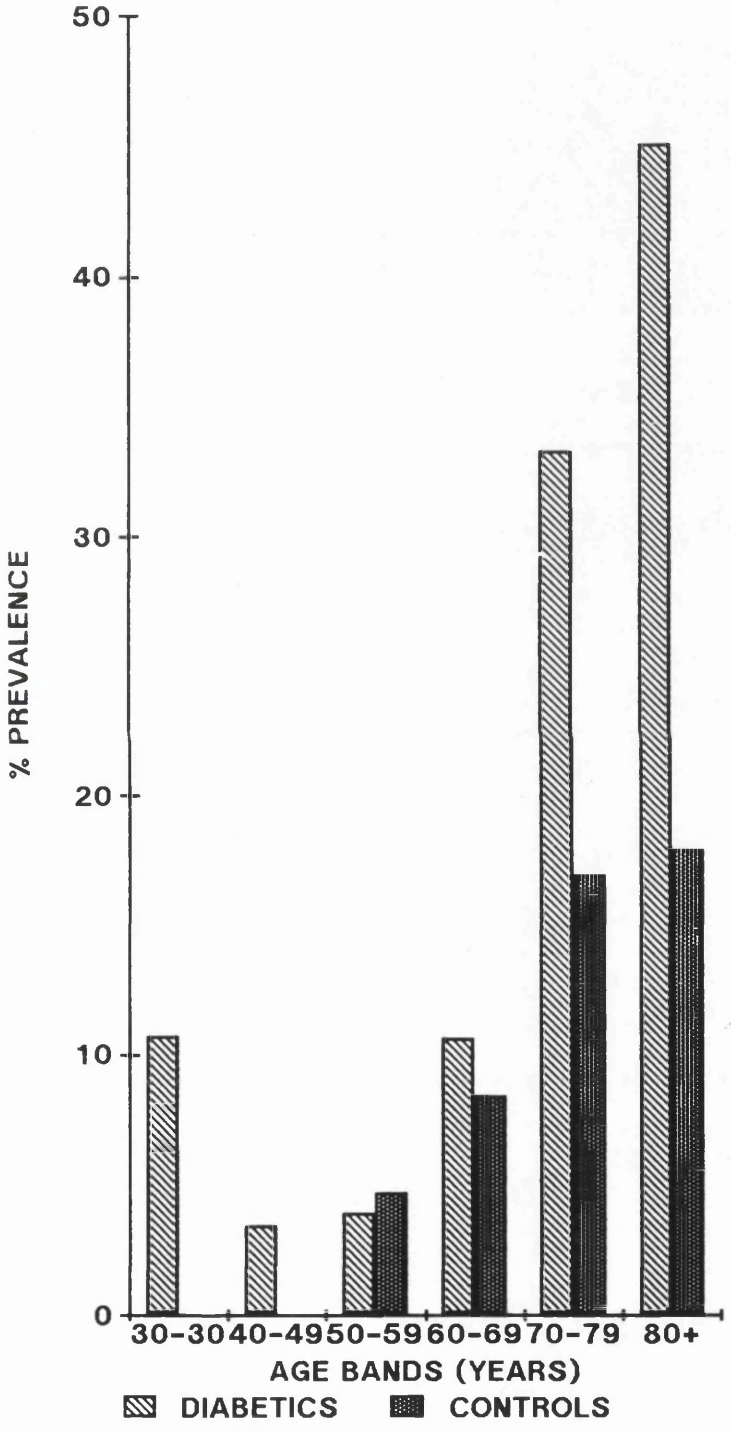
PERIPHERAL VASCULAR DISEASE (FIG 7.3)

NIDDs Vs CONTROLS - PREVALENCE



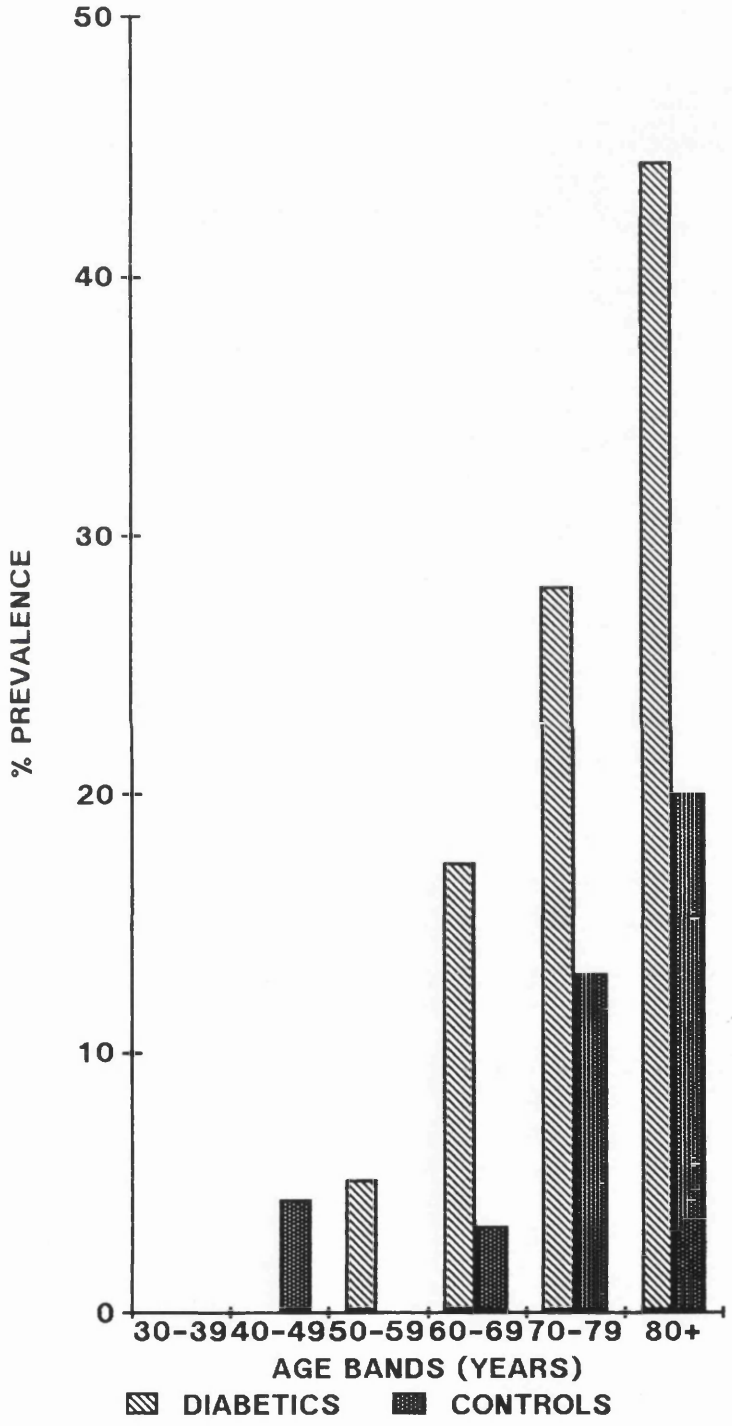
PERIPHERAL VASCULAR DISEASE (FIG 7.4)

PREVALENCE IN MALES



PERIPHERAL VASCULAR DISEASE (FIG 7.5)

PREVALENCE IN FEMALES



Chapter 8

STRUCTURAL FOOT DISEASE

Foot Ulceration, Amputation - Prevalence and Risk Factors

Prevalence of Foot Ulceration according to age and sex

The prevalence of past or present foot ulceration in diabetics and controls according to age and sex is shown in tables 8.1 and 8.2 For diabetics there was little difference between the 2 sexes in terms of prevalence and ulcers tended to become more frequent with increasing age. Table 8.3 shows the prevalence of diabetic foot ulcers present at the time of examination.

Prevalence of foot ulceration by site

Table 8.4 presents the prevalence of past or present ulceration according to type of diabetes. No adjustment was made for age and the figures are therefore crude prevalence rates.

Severity, duration and aetiology of ulceration in diabetics

Table 8.5 presents the distribution of present ulcer severity in diabetics. It is important to note that there are no type IV or V ulcers. Table 8.6 reveals the breakdown of ulcers found at the time of examination according to aetiology. In the control group only 3 cases were found to have a foot ulcer at the time of examination, one was traumatic in origin and the other 2 were found in subjects with hemiplegia. The duration of ulceration in diabetics is shown in table 8.7 (ie the time taken from onset to complete skin cover).

Place of treatment

33% of the diabetic foot ulcers were being regularly treated in hospital, 58% were treated in the community and 9% were receiving no treatment in that they were only discovered at the time of examination.

Site of ulceration

The site of ulceration in diabetics and controls is listed in order of frequency in table 8.8. The site of ulceration in the controls for both previous and present ulcers is ranked in table 8.8. As for diabetics ulcers also tend to occur under high pressure points except that the malleoli of the ankles are far more common sites of previous ulcers of non-diabetics.

Prevalence of Amputation

The prevalence of amputation according to age, sex, type of diabetes and site in the diabetic population is shown in Table 8.9. In diabetics aged over 30 it was found that only 1.4% had suffered an amputation. No males under the age of 60 had experienced an amputation and the frequency tended to increase with age. In females amputation was even rarer and also, apart from one case, was found only in subjects aged 60 or more. There was no tendency for amputation to be more prevalent in one particular type of diabetes (although no adjustment for age was made) and no amputations were found in controls.

In some cases a digital or part foot amputation had preceded a more proximal procedure in which case only the latter was counted. In all but 2 cases the amputation had been preceded by foot ulceration. Four of the amputees also had foot ulceration present at the time of examination. In one of the below knee amputees the problem was bilateral.

Prevalence of Foot Deformity

The prevalence of foot deformity in diabetics and controls is shown in Table 8.10 and 8.13. Overall there was no significant difference between the prevalence in either group (see Table 8.17). In each just under one half of all subjects had some form of foot deformity. Claw toes were significantly more prevalent in insulin dependent diabetics than in controls. There was no Charcot deformity in the control group and only 3 cases in the diabetics. A photograph of one of the Charcot feet is shown at the end of the chapter. It is noteworthy that foot deformity in both diabetics

and controls increased with age and was more common in females in both groups. The latter sex difference was statistically significant for both populations ($P < 0.001$). Table 8.17 shows the degree of significance regarding the differences in variables relating to structural foot disease after accounting for age.

Risk Factors for Foot Ulceration

The risk factors for foot ulceration in each group of subjects are listed in Table 8.18 together with odds ratios. If one considers the diabetic group as a whole then duration of diabetes, the presence of foot deformity, impaired light touch and pain perception, the presence of any retinopathy and one or more absent dorsalis pedis pulses were associated with foot ulceration. Dividing into type of diabetes revealed powerful associations with absent dorsalis pedis pulse and absent pain perception for IDDM. Indeed the odds ratio for the latter exceeded 30. In the non insulin dependent diabetic group duration of diabetes, the presence of any retinopathy, foot deformity, absent light touch perception and absent dorsalis pedis pulse were significantly associated with an increased risk of foot ulceration. Interestingly age was never found to be significant in any group. Autonomic neuropathy failed to show an association. This was perhaps due to the large number of missing values for autonomic neuropathy. However, of the cases of foot ulcer, a significant number ($P < 0.001$) had autonomic neuropathy by univariate analysis (using chi-squared) compared to those considered to be at high risk (see Table 3.6) of diabetic foot disease but no foot ulcer.

Risk Factors for Amputation

Since no amputations were found in the control group they were omitted from this analysis. In the diabetic group as a whole, age and duration of diabetes showed a significant correlation with amputation. If the sample size was reduced by dividing into insulin dependent and non insulin dependent diabetics, no significant variables were found.

Discussion

One of the aims of this survey was to identify as accurately as possible the total burden imposed by foot ulceration on an entire diabetic community and it can be reasonably assumed from this survey that most patients with foot ulceration would have been seen. Clearly very high review rates are necessary when diseases that affect mobility are being examined.

Prevalence of Diabetic Foot Ulceration

The present study has demonstrated that foot ulceration is a relatively uncommon problem even in diabetics but significantly greater than in controls. Previous work has attempted to measure the prevalence of foot ulceration. Neil et al (1988) found that 5% of the diabetic population had foot ulcers although of course the review rate for diabetic subjects was comparatively low. It is also not known whether they included both past and present foot ulceration. In a recent study investigating foot problems in diabetics aged between 15 and 50 it was found that 3% of the population had foot ulcers (Borssen et al 1989). Additionally 10% of type 1 and 9% of type 2 diabetics had healed foot ulcers. Overall this yields a total prevalence of foot ulceration (past or present) of 12.4% which considering the age of the population is very high. Whether the difference is genuine or methodological cannot be accurately ascertained but it should be noted that no definitions are given as to what constitutes an ulcer or whether they were diagnosed before or after the diagnosis of diabetes. Multiple observers were used in the study and of course this may lead to further errors in interpretation. It is interesting that within the control population the prevalence of foot ulceration was zero, identical to the present study for the same age categories.

Questionnaire surveys, either sent to patients directly (Rosenqvist et al 1982) or to general practitioners and allied health workers (Peacock et al 1985) are also useful means in determining the frequency of foot ulceration because it circumvents the problems of having to visit the patient directly. Perhaps surprisingly considering the different type of patient studied Rosenqvist et al found a prevalence of foot ulceration of 1.7%. The population

studied were those who had previously been hospitalised between 1969 and 1979. In a truly community based type survey it was found that in a general population of 200,000, 66 diabetics were noted to have had foot ulceration and were undergoing treatment (Peacock et al 1985). If it is assumed that the known prevalence of diabetes is 1.2% then the prevalence of foot ulceration is 2.75%. Clearly this would be an underestimate because not everyone will have replied to the questionnaire and certainly not every diabetic with a foot ulcer will be undergoing treatment or indeed known to the health care workers (as found in the present survey). Allowing for these shortcomings it is almost identical to the total overall prevalence of present foot ulceration in the present survey of just over 3%. On first inspection it would therefore seem unusual that Rosenqvist's hospital based prevalence data should reveal a lower figure than large scale community based surveys. Almost certainly this reflects bias involved in patient selection, questionnaire response and misinterpretation of questions by the diabetic subjects themselves.

Interestingly the study by Peacock et al (1985) is one of the few to document the greater prevalence of ulcers in diabetics compared to non-diabetics. Apparently only 93 non-diabetics were being treated for foot ulceration. This would mean an overall prevalence of 0.047% which seems extremely low compared to the present study. In an epidemiological survey based in Sweden the prevalence of leg and foot ulcers in the general population was estimated to be between 0.2 and 0.4% which is more in keeping with the present survey (Andersson et al 1984). (30% of ulcers were of the feet). Indeed in the Swedish survey the authors felt they underestimated the true prevalence of foot ulceration. What is clear from these studies and the present survey is that foot ulceration is statistically much more likely in diabetics than non-diabetics. In a typical diabetic community in the UK approximately 3% will currently be undergoing treatment for foot ulcer, either in hospital or in the community.

It is clear that ulcers tend to occur both in diabetics and in non-diabetics under high pressure points. The present study also suggests that the majority are superficial or at least only extend down to tendon or bone. However, the absence of gangrenous ulcers

may merely reflect that prevalence is a poor measure of the frequency of such cases. Obviously gangrenous ulcers may be lost rapidly from the prevalent population by mortality or amputation. The methods used to detect underlying osteomyelitis were probably inadequate in this survey. Plain x-rays will not always detect underlying bone infection and indeed the detection of the latter can be a therapeutic problem. More elaborate techniques such as gallium scanning were not available in the present survey.

Risk Factors for Diabetic Foot Ulceration

There has been much information published on the putative risk factors for diabetic foot disease. It is generally agreed that the two main risk factors are vascular insufficiency and peripheral neuropathy. As has also been previously discussed there is much debate about whether there is a discrete small vessel component specific for diabetics. Pressure, as found for example with foot deformity, although not a primary factor for the development of foot ulceration alone, is nonetheless considered important in the initiation of foot ulceration.

The lack of association with many risk factors for ulceration in insulin dependent diabetics may be due to the reduction in sample size that inevitably occurs. Clearly an attempt should be made to differentiate between the two types of diabetes in view of their very different aetiologies and epidemiological characteristics. Larger studies may therefore be needed.

Many of the significant associations found with regression analysis and foot ulceration in this survey are predictable. The modalities of neuropathy and clinical parameters of peripheral vascular disease should clearly be associated with foot ulcer. Additionally if foot ulceration is as a direct consequence of diabetes mellitus it should not be surprising that duration of diabetes is an important variable. Perhaps more interestingly in this study is the poor correlation between many variables that would be expected to be associated with foot ulcer in diabetics. In particular age, diabetic control, vibration threshold and mean doppler pressure were not significant. Clearly it may be inappropriate to consider the ulcers as one entire group, although convenient to do so

clinically, as the pathogenesis of ulcer formation and hence inevitably risk factors, must be completely different for the two main types of ulcer. Nevertheless clinically it is often impossible to decide what is the main determinant of ulcer formation in the diabetic since both vascular insufficiency and neuropathy frequently co-exist.

Age/Duration of Diabetes

Of the time related variables only duration of diabetes has independently been shown to be associated with foot ulceration in the present survey. This is perhaps a surprising finding because duration of diabetes has no correlation with peripheral vascular disease or with neuropathy following multivariate analysis. There are no previous population studies investigating risk factors for ulceration but one clinic based study did show that those diabetics with ulcers had a longer duration of diabetes though it is not clear whether this was significant (Delbridge et al 1983). Obviously in cross-sectional surveys it would be wrong to draw firm conclusions regarding risk factors but the correlation of duration of diabetes with foot ulceration would at least imply diabetes exposure is important.

Diabetic Control

No aspect of diabetic control was shown to be significantly correlated independently with ulceration and this would support previous clinic based data (Jones 1987, Delbridge et al 1983). This is perhaps surprising in view of the association between poor diabetic control and bacterial infection.

Diabetic Complications

Previous studies have also shown a strong association with other diabetic complications particularly retinopathy (Young et al 1986, Walsh et al 1975, Jones et al 1987). These studies were, of course, with selected groups of patients. It would seem that the association is independent of duration and would imply a propensity

of a sub-group of diabetics to both retinopathy and foot ulceration irrespective of the degree of diabetes exposure. In two studies (Walsh et al 1975, Glynn et al 1990) the association was found in newly diagnosed diabetics but the patients studied were mainly non insulin dependent diabetics where the true date of diagnosis could not be accurately established.

Smoking

Smoking has in some studies been associated with foot lesions (Delbridge et al 1983) but not in others (Jones et al 1987, Glynn et al 1990). Clearly since peripheral vascular disease is implicated in the pathogenesis of some types of foot ulcer it would, therefore, seem logical that there should be an association between smoking and foot ulceration. However as has been discussed previously, no correlation could be found between smoking and peripheral vascular disease in this survey.

Parameters of peripheral vascular disease

The lack of correlation between some parameters of peripheral vascular disease and foot ulceration is rather disappointing. It has been shown that resting doppler pressure is associated with foot ulceration (Delbridge et al 1983) but the former may be unreliable in patients with foot ulceration because of the higher prevalence of vascular calcification (Jones et al 1987). The latter is more likely in foot ulceration because of the link between calcification and neuropathy (Edmonds et al 1982). It emphasises the need for angiography in patients with foot ulceration if vascular insufficiency is suspected regardless of the doppler pressure.

Parameters of peripheral neuropathy

It is surprising that vibration thresholds were not associated with foot ulceration in either diabetics or controls. However other

parameters of neuropathy such as pain perception and light touch were strongly correlated. Previous literature has suggested that the vibration threshold is the most important predictor of foot ulceration (Boulton et al 1986). However, this study was in a selected, relatively young diabetic group. Young et al (1986) found that large fibre neuropathy (ie which would affect vibration perception) tended to be associated with severe, painless foot ulceration. If ulceration tends to occur in only advanced cases of neuropathy it would be expected that all modalities of neuropathy would show some correlation with ulceration. It may reflect the poor discriminatory value of vibration threshold to segregate normal from abnormal in the upper age levels since the calibration of the biothesiometer is often exceeded in the non-diabetic elderly (Bloom et al 1984). It is quite clear that absent pain perception has a powerful association with ulceration in both types of diabetes and suggests the importance of this factor in the genesis of ulceration, particularly in IDDs.

Amputation

Prevalence

Most and Sinnock (1983) and Waugh (1986) have demonstrated that diabetics have a greater risk of amputation than the general population. However the data from the present survey suggests amputation within the diabetic population is rare. The prevalence of 1.4% compares well with the only other recent UK population based study (Neil et al 1989). It is not surprising that no cases of amputation were found in the control group considering the low prevalence even in the diabetic population. It should be stressed however that prevalence is a poor measure of the number of diabetics undergoing amputation since the mortality in subjects with amputation is very high.

It is possible, although speculative, through the Poole shared care scheme that the number of cases of amputation has been decreased compared to other areas within the United Kingdom. Open access for GPs to the hospital system is available although there is no

formal diabetic foot clinic which has, of course, been show to reduce amputation (Edmonds 1986).

Risk Factors for Amputation

It has been assumed that the main risk factors for amputation are peripheral vascular disease and neuropathy. However none of the modalities of neuropathy or any of the parameters suggestive of peripheral vascular disease were significantly associated with amputation. Clearly if we wish to reduce the number of amputations, longitudinal studies to determine exactly what are the risk factors are necessary. Nevertheless this survey gives some idea of the type of diabetics who actually undergo amputation and are still alive.

It is noteworthy that all but two of the amputees had a previous history of foot ulceration before amputation. Clearly any diabetic with a foot ulcer must be considered at high risk for future limb loss. Age, not surprisingly, was significantly correlated with amputation and is an important variable for peripheral vascular disease in both insulin dependent and non insulin dependent diabetics. Duration of diabetes was also independently associated with amputation and, as with ulceration, this would suggest that diabetes exposure itself is an important risk factor for amputation and confirms a recent longitudinal study in diabetic pima Indians (Nelson et al 1988). The few European population studies which have investigated the frequency of amputation (which are predominantly Scandinavian rather than British), have also shown that age is a powerful influence on amputation (Hansen 1964, Christensen 1976 and Liedberg and Persson 1983). Similarly, Most and Sinnock (1983) and Waugh (1988) have also shown that the frequency of amputation increases with age.

There were very few significant correlations between other variables and amputation. This probably reflects the very small number of amputations found in this survey.

Prevalence of Foot Deformity

Just 3 cases of Charcot's joint were found in this study. Only cases of deformity in the presence of neuropathy with typical features of Charcot's joint and x-ray were included. It is realised that definitions of Charcot's joint may vary and hence comparison with other studies may be difficult. In a Swedish population study of all diabetics aged between 15 and 50, the prevalence of diabetic osteopathy was 2% (Borssen et al 1990). In the present survey only one case of Charcot's deformity was found under the age of 65. Whether the difference between these two studies is methodological or genuine is of course speculative but Sinha et al (1972) reviewed all cases of neuroarthropathy radiologically documented (from the records of the Joslin clinic between 1949 and 1970) and found only 101 cases, attesting to the rarity of the condition.

It is interesting that the prevalence of foot deformity overall in both the controls and diabetics was not significantly different. Individually, claw toes only had a significantly greater prevalence in IDDs (see Table 8.17). Claw toe deformity is said to be a problem in peripheral neuropathy but clearly also occurs as a function of ageing. In IDDs which are a predominantly younger group the effect of neuropathy may have had more impact than the general effects of ageing per se in NIDDs. Obviously the high prevalence of foot deformity in general cannot be attributed to peripheral neuropathy alone and seems to be the result of the ageing process. Since foot deformity was more common in females regardless of diabetic status it is possible that footwear is important in its development. Since footwear changes with fashion it is possible that a cohort effect could partly explain the high prevalence found in the present survey. This high prevalence of foot deformity has been previously documented in selected diabetic and general populations (Gould et al 1980, Spencer et al 1985, Hung and Laing 1985).

The important point to note from these prevalence data is that almost 50% of the diabetic population has foot deformity and the prevalence increases markedly with age. Since foot deformity may prove to be a risk factor for foot ulceration the elderly must surely deserve special attention with regard to prophylactic chiropody and provision of protective footwear.

TABLE 8.1

PREVALENCE OF ULCERATION ACCORDING TO AGE AND SEX

Diabetics: past and present ulceration

Age (years)	Male diabetics No.	(%prev)	Female diabetics No.	(%prev)	All diabetics No.	(%prev)
30-39	0	(0.0)	0	(0.0)	0	(0.0)
40-49	1	(3.6)	2	(4.3)	3	(4.0)
50-59	2	(2.6)	2	(3.4)	4	(2.9)
60-69	7	(5.0)	8	(7.4)	15	(6.0)
70-79	19	(11.5)	9	(5.9)	28	(8.8)
80+	12	(14.3)	12	(13.8)	24	(14.0)
	41	(7.8)*	33	(6.9)*	74	(7.4)*
Missing values	9		8		17	

*ie % prevalence amongst diabetics aged 30+

TABLE 8.2

CONTROLS: PREVALENCE OF PAST OR PRESENT ULCERATION

Age (years)	No.	(% prev)
30-39	0	(0.0)
40-49	0	(0.0)
50-59	1	(1.3)
60-69	2	(1.4)
70+	9	(4.3)
	12	(2.5)
Missing values	2	

TABLE 8.3

DIABETICS: PRESENT ULCERATION ONLY

Age (years)	Male diabetics No.	(%prev)	Female diabetics No.	(%prev)	All diabetics No.	(%prev)
30-39	0	(0.0)	0	(0.0)	0	(0.0)
40-49	0	(0.0)	1	(2.1)	1	(1.3)
50-59	0	(0.0)	1	(1.7)	1	(0.7)
60-69	4	(2.8)	1	(0.1)	5	(2.0)
70-79	10	(6.0)	2	(1.3)	12	(3.7)
80+	7	(8.1)	7	(7.8)	14	(8.0)
	21	(3.9)*	12	(2.5)*	33	(3.3)*

*ie % prevalence amongst diabetics aged 30+

TABLE 8.4

PREVALENCE OF PAST OR PRESENT ULCERATION ACCORDING TO TYPE OF DIABETES

	IDDM		NIDDM		All diabetics	
	No.		No.		No.	(valid%)
Present	16	(7.7)	58	(6.8)	74	(7.0)
Absent	193	(92.3)	793	(93.2)	986	(93.0)
Total valid	209	(100.0)	851	(100.0)	1060	(100.0)
Missing values	4		13		17	

TABLE 8.5

DISTRIBUTION OF PRESENT ULCER SEVERITY GRADE IN DIABETICS

Severity grade	No.	(%)
I	20	(60.6)
II	11	(33.3)
III	2	(6.1)
IV	0	(0.0)
V	0	(0.0)
	33	(100.0)

TABLE 8.6

DISTRIBUTION OF PRESENT ULCER AETIOLOGY IN DIABETICS

Aetiology	No.	(%)
Neuropathic	13	(39.4)
Vascular	8	(24.2)
Neuropathic and vascular	12	(36.4)
	33	(100.0)

TABLE 8.7

DURATION OF DIABETIC ULCERS

	Median Duration (months)	Interquartile Range
Present Ulceration	0.44	0.14-1.66
Past Ulceration	5.0	2.0-7.5

TABLE 8.8

PREVALENCE OF ULCERATION
Diabetics

Ranked frequencies of previous ulcer sites:

Rank	Site	Frequency
1	1st metatarsal head	11
1	Heel	11
3	Other site	10
4	Malleol of ankle	9
5	5th metatarsal head	3
5	Plantar surface great toe	3
7	2nd metatarsal head	1
7	3rd metatarsal head	1
7	4th metatarsal head	1
	Total	50

Ranked frequences of present ulcer sites:

1	Heel	11
1	Other site	11
3	1st metatarsal head	7
4	Malleol of ankle	2
5	3rd metatarsal head	1
5	5th metatarsal head	1
	Total	33

Controls

Ranked frequencies of previous ulcer sites:

Rank	Site	Frequency
1	Malleol of ankle	4
1	Other site	4
3	Heel	2
	Total	10

Ranked frequencies of present ulcer sites:

Rank	Site	Frequency
1	Heel	2
2	Other site	1
	Total	3

TABLE 8.9

PREVALENCE OF AMPUTATION

Age (years)	Male diabetics		Female diabetics		All diabetics	
	No.	(%prev)	No.	(%prev)	No.	(%prev)
30-39	0	(0.0)	0	(0.0)	0	(0.0)
40-49	0	(0.0)	1	(2.1)	1	(1.3)
50-59	0	(0.0)	0	(0.0)	0	(0.0)
60-69	2	(1.4)	1	(0.9)	3	(1.2)
70-79	4	(2.4)	2	(1.3)	6	(1.9)
80+	3	(3.5)	1	(1.1)	4	(2.3)
	9	(1.7)*	5	(1.0)*	14	(1.4)*

*ie % prevalence amongst diabetics aged 30+

By type

	No.	% prevalence
IDD	3	1.4
NIDD	11	1.3
All diabetics	14	1.3
Controls	0	0.0

By site

Site of amputation (diabetics)	No.	% prevalence
Foot (part)	4	0.3
Below knee	5	0.5
Above knee	2	0.2
Digital	3	0.3
Total	14	1.3
Missing values	0	0

TABLE 8.10

PREVALENCE OF FOOT DEFORMITY IN DIABETICS

Age (years)	Male diabetics No.	(%prev)	Female diabetics No.	(%prev)	All diabetics No.	(%prev)
0-19	1	(6.3)	0	(0.0)	1	(4.2)
20-29	0	(0.0)	2	(11.8)	2	(5.3)
30-39	4	(14.8)	1	(4.8)	5	(10.4)
40-49	0	(0.0)	9	(20.0)	9	(12.2)
50-59	19	(24.4)	20	(33.9)	39	(28.5)
60-69	48	(33.6)	58	(52.7)	106	(41.9)
70-79	85	(50.6)	105	(67.3)	190	(58.6)
80+	55	(64.7)	70	(77.8)	125	(71.4)
	212	(37.4)	265	(52.3)	477	(44.5)
Missing values	2		2		4	

TABLE 8.11

SPECIFIC FOOT DEFORMITIES: DIABETICS AGED 65 OR UNDER

Deformity	Male diabetics No.	Female diabetics No.	All diabetics No.
Hallux valgus	15	24	39
Claw toes	12	17	29
Pes cavus	6	1	7
Charcot deformity	1	0	1
Other	19	19	38
	53	61	114

TABLE 8.12

SPECIFIC FOOT DEFORMITIES: DIABETICS AGED OVER 65

Deformity	Male diabetics No.	Female diabetics No.	All diabetics No.
Hallux valgus	50	111	161
Claw toes	44	42	86
Pes cavus	5	3	8
Charcot deformity	2	0	2
Other	58	48	106
	159	204	363

TABLE 8.13

PREVALENCE OF FOOT DEFORMITY IN CONTROLS

Age (years)	Male controls No.	(%prev)	Female controls No.	(%prev)	All controls No.	(%prev)
30-39	0	(0.0)	1	(14.3)	1	(6.7)
40-49	1	(7.1)	4	(18.2)	5	(13.9)
50-59	8	(18.2)	17	(54.8)	25	(33.3)
60-69	25	(30.1)	43	(71.7)	68	(47.6)
70-79	34	(44.2)	48	(70.6)	82	(56.6)
80+	24	(61.5)	23	(92.0)	47	(73.4)
	92	(34.7)	136	(63.8)	228	(47.7)
Missing values	0		2			

TABLE 8.14

SPECIFIC FOOT DEFORMITIES: CONTROLS AGED 65 OR UNDER

Deformity	Male diabetics No.	Female diabetics No.	All diabetics No.
Hallux valgus	10	32	42
Claw toes	8	1	9
Pes cavus	0	1	1
Charcot deformity	0	0	0
Other	5	10	15
	23	44	67

TABLE 8.15

SPECIFIC FOOT DEFORMITIES: CONTROLS AGED OVER 65

Deformity	Male controls No.	Female controls No.	All controls No.
Hallux valgus	28	64	92
Claw toes	16	12	28
Pes cavus	2	1	3
Charcot deformity	0	0	0
Other	23	15	38
	69	92	161

TABLE 8.16

DIFFERENCES IN PREVALENCE OF FOOT DEFORMITY ACCORDING TO SEX

Diabetics

	Males	Females
Absent	355	243
Present	212	243

Chi squared (Yates correction) = 23.21 $p<0.001$ (1 df)

Controls

	Males	Females
Absent	173	136
Present	92	80

Chi squared (Yates correction) = 49.013 $p<0.001$ (1 df)

TABLE 8.17

REGRESSION ANALYSIS TO DETERMINE THE SIGNIFICANCE OF DIFFERENCES IN PREVALENCE BETWEEN STRUCTURAL FOOT DISEASE VARIABLES IN THE CONTROL AND DIABETIC POPULATIONS AFTER ADJUSTING FOR AGE

(Age is included in the regression equation)

Dependent Variable	Factor	Coefficient	Odds Ratio	95% CI	P value
1. Foot Ulceration	Diabetics=1 Controls =0	1.078 (0.318)	2.94	1.58-5.48	<0.001
	NIDDs =1 Controls =0	0.876 (0.326)	2.40	1.27-4.55	0.01
	IDDs =1 Controls =0	2.424 (0.449)	11.29	4.68-27.20	<0.001
2. Foot Deformity (any)	Diabetics=1 Controls =0	-0.010	0.91	0.72-1.14	0.40
	NIDDs =1 Controls =0	-0.134 (0.123)	1.19	0.69-1.11	0.27
	IDDs =1 Controls =0	0.110 (0.233)	1.12	0.71-1.76	0.64
3. Claw Toes	Diabetics=1 Controls =0	0.374 (0.199)	1.45	0.98-2.15	0.06
	NIDDs =1 Controls =0	0.344 (0.204)	1.41	0.95-2.10	0.09
	IDDs =1 Controls =0	0.804	2.23	1.08-4.61	0.03

A minus (-) coefficient indicates an inverse relationship to the variable.

TABLE 8.18

DIABETIC FOOT ULCERATION - MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR POTENTIAL RISK FACTORS

Dependent variable - past or present foot ulceration

i. Group - Diabetics

Variable	Coefficient	SE	P value	Odds Ratio	95% CI
Age (years)*	0.0113	0.0159	0.47	1.0114	0.9802-1.0425
Duration* (years)	0.0448	0.0154	0.004	1.0458	1.0156-1.0759
Foot Deformity(1)	1.8357	0.5210	<0.001	6.2696	5.2484-7.2907
Touch Perception(2)	1.0454	0.4918	0.03	2.8446	1.8806-3.8085
Pain Perception(2)	1.2748	0.4955	0.01	3.5782	2.6070-4.5493
Dorsalis Pedis Pulse(1)	1.8356	0.3551	<0.001	6.2690	5.5730-6.9649
Any Retinopathy	1.1718	0.3487	<0.001	3.2278	2.5443-3.9112
ii. Group - IDDs					
Age (years)*	0.0509	0.0286	0.075	1.0522	0.9961-1.1082
Duration* (years)	-0.0106	0.0361	0.76	0.9894	0.9186-1.0601
Pain Perception(2)	3.4944	0.8570	<0.001	32.9297	31.2499-34.6094
Dorsalis Pedis Pulse(2)	2.3227	1.0339	0.02	10.2034	8.1769-12.2298
iii. Group - NIDDs					
Age (years)*	0.0125	0.0229	0.58	1.0126	0.9677-1.0574
Duration* (years)	0.0463	0.0212	0.03	1.0474	1.0058-1.0889

TABLE 8.18 (Cont.)

Variable	Coefficient	SE	P value	Odds Ratio	95% CI
Foot Deformity(1)	2.3107	0.7698	0.003	10.0818	8.5729-11.5906
Pain Perception(2)	1.8552	0.3783	<0.001	6.3932	5.6517-7.1346
Posterior Tibial Pulse(2)	1.1880	0.5485	0.03	3.2804	2.2053-4.3554
Dorsalis Pedis Pulse(2)	1.1168	0.4807	0.02	3.0550	2.1128-3.9971
Any Retinopathy(1)	1.3776	0.3883	<0.001	3.9653	3.2042-4.7263
iv. Control Group					
Age (years)*	0.0549	0.0312	0.08	1.0565	0.9953-1.1176
Touch Perception(2)	1.8142	0.7536	0.02	6.1360	4.6589-7.6130

(1) = present
(2) = absent

* = odds ratio per year

TABLE 8.19

AMPUTATION - MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR POTENTIAL RISK FACTORS

Dependent variable - amputation

Group - diabetics

Variable	Coefficient	SE	P value	Odds Ratio	95% CI
Age (years)*	0.0250	0.0141	0.032	1.0277	1.0136-1.0418
Duration* of diabetes	0.0270	0.0091	0.001	1.0279	1.0188-1.0370

* odds ratio per year

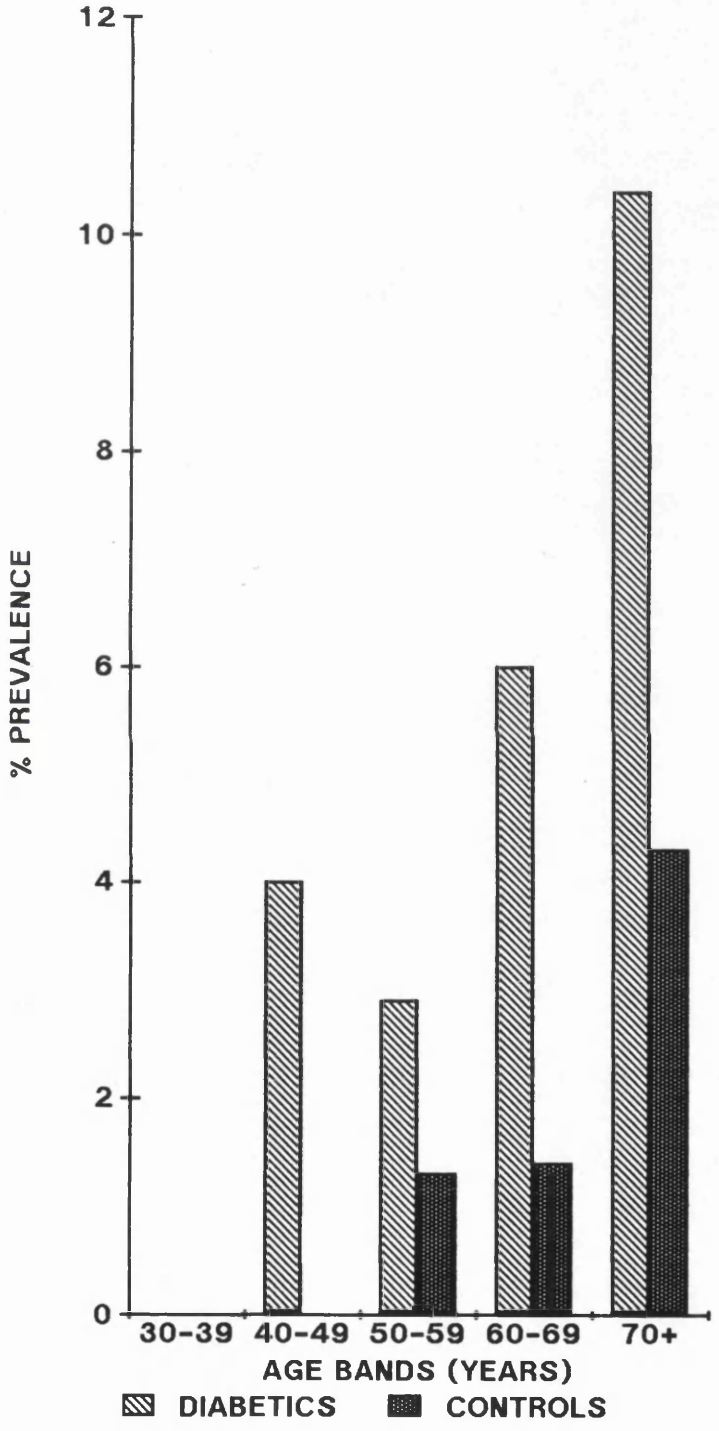
TABLE 8.20

SUMMARY OF FOOT ULCERATION, AMPUTATION AND FOOT DEFORMITY PREVALENCE DATA

	Diabetics	Controls
	% Prevalence (95% CI)	% Prevalence (95% CI)
Foot ulcers (past or present)	7.4 (5.8-9.0)	2.5 (1.1-3.9)
Foot ulcers (present at the time of review)	3.3 (2.2-4.4)	0.63 (-0.07-1.33)
Foot deformity	44.5 (41.5-47.5)	47.7 (42.7-52.2)
Amputation	1.3 (0.6-2.0)	-

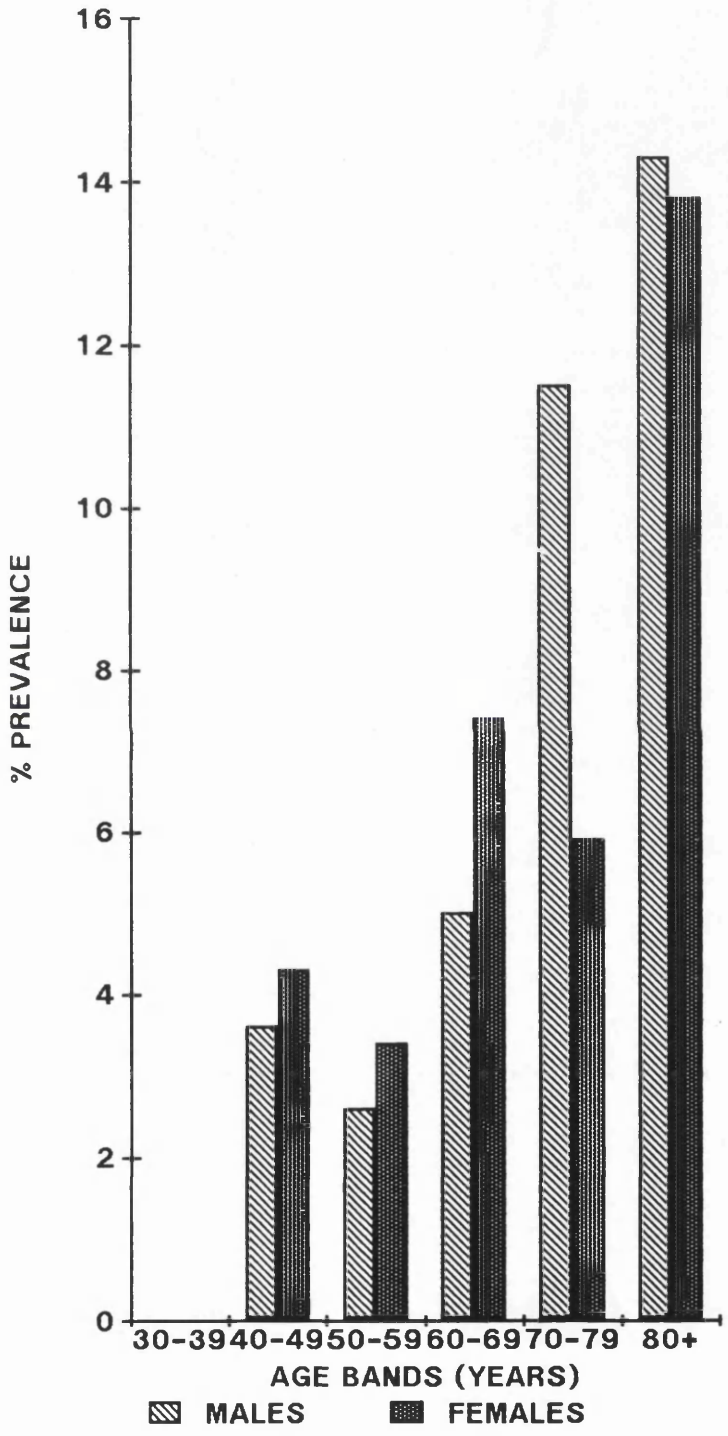
PAST/PRESENT FOOT ULCERATION(FIG 8.1)

PREVALENCE IN DIABETICS AND CONTROLS



PAST/PRESENT FOOT ULCERATION (FIG 8.2)

AGE AND SEX DISTRIBUTION IN DIABETICS



PREVALENCE OF FOOT DEFORMITY
DIABETICS Vs CONTROLS (FIG8.3)

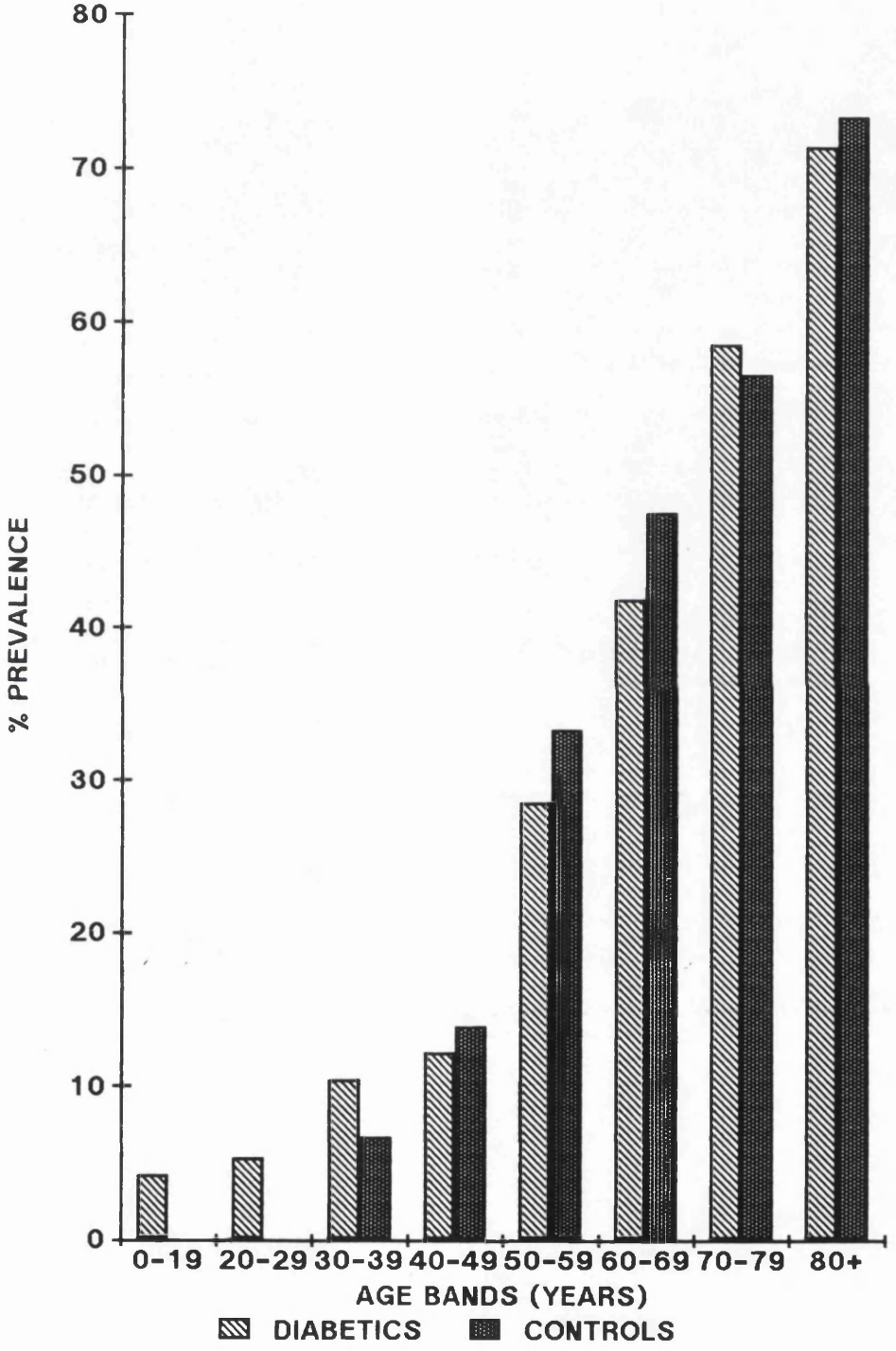
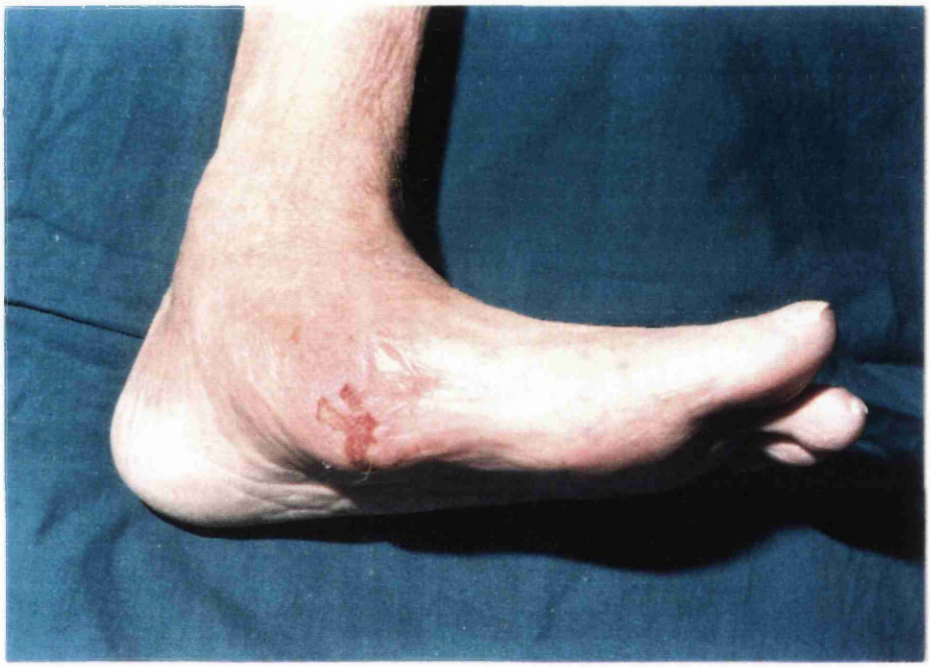


PLATE 8.1



CHARCOT JOINT

Chapter 9

CONCLUSIONS

The aims of this study were to estimate the prevalence of diabetic foot disease and its risk factors in a geographically defined population and to compare the findings with an age and sex matched non diabetic group drawn from the same general population. The results from this study, it was hoped, could be extrapolated to that of the UK. However this depends upon three assumptions. Firstly, the population has previously been shown to have a similar age and sex structure to that of the UK (Gatling 1986) but in this study the population was found to be slightly older than that revealed in the 1981 census. Whether this population change is unique to Poole remains to be seen from future national figures. Secondly, it is assumed that the diabetic population is typical of other areas of the UK. Clearly this may not be the case. Predominantly urban, inner city areas may have differing problems with their diabetic communities by virtue of a dissimilar ethnic and social structure. Furthermore it is possible that the virtually unique shared care scheme operating in Poole may bias the type of presentation seen in diabetics. Education programmes and improved diabetic control may considerably influence diabetic complications such as neuropathy. This is, of course, highly speculative. Thirdly, the control group drawn from the population may not have been typical of the general population. The fact that only 70% of the control group were reviewed may be relevant. The lower review rate could have led to bias by selecting out less healthy individuals.

The study was cross-sectional essentially because of the limited time available. Clearly a longitudinal study to determine incidence would have been preferable in view of the large losses from the prevalent diabetic population with amputation, macrovascular disease and gangrene. Nevertheless a cross-sectional survey gives useful information on the burden within the population imposed by a disease at one particular point in time and this was one of the main purposes of the study. Additionally a longitudinal study would have been more likely to determine what actually

constitutes the risk factors for diabetic foot disease but this survey may set the groundwork for such a study in the future based at Poole.

Three components of diabetic foot disease were considered ie structural foot abnormality (eg ulceration), peripheral vascular disease and peripheral neuropathy. For each case the question to be asked must be how useful were the methods of detection? In general the methods employed were those which would allow large scale screening of a population and since clinical endpoints of disease were to be estimated, simple measures common to routine diabetic clinics were used.

In the case of foot ulceration simple clinical examination allowed much information to be gained regarding the extent of ulceration. Clearly only relying on simple x-ray examination of the underlying bones undoubtedly will have missed some cases of osteomyelitis in subjects with deep ulcers. However, detection of osteomyelitis even with sophisticated scans may be very difficult in diabetics (Yuh et al 1989) and probably for the purposes of the study the issue is academic. Any foot ulcer is potentially serious and estimates for resource allocation in the management of foot disease must be based upon this assumption.

The determination of the prevalence of neuropathy rested primarily on clinical findings (except for vibration threshold). Whether clinical examination is better, as good or worse at predicting ulceration is not known. However recent definitions of neuropathy have tended to emphasise the importance of clinical manifestations of diabetic neuropathy (Report and Recommendations of the San Antonio Conference 1980). Furthermore histological and nerve function abnormalities have been shown to correlate well with clinical manifestations of diabetic neuropathy (Dyck et al 1980, Beghi et al 1988, Maser et al 1989). In practice clinical examination was the only feasible measure of neuropathy for a study of this size. The classification used in the examination was simple and although there must be some intra-observer variation, inter-observer discrepancies were eliminated.

The aetiological classification of diabetic neuropathy in this survey was not straightforward and undoubtedly some cases of neuropathy were unsatisfactorily classified. Whilst cases of sensory loss due to central nervous system lesions were excluded there remained a group of patients who had neuropathy with other co-existing disease that theoretically could also have caused the problem. Whilst the control group gives an estimation of the background neuropathy in the general population it is appreciated that diabetics may be more vulnerable to other diseases which may cause neuropathy (eg uraemia and hypothyroidism). Conversely to exclude such cases may also be inappropriate.

Peripheral vascular disease has usually been assessed in large studies by pulse palpation and/or the development of claudication. The former is unreliable (Mannelli et al 1979) and the latter will miss asymptomatic disease. However even when using doppler pressure techniques some cases of peripheral vascular disease will be missed because of falsely elevated pressures in some diabetics (Emanuele et al 1981). A classification of peripheral vascular disease incorporating both non invasive criteria and pulse palpation could have been used but a solely standardised quantitative definition was preferred. The use of the toe systolic pressure index may have been more accurate (Ramsey et al 1983) but once again was not feasible for a large epidemiological survey.

What are the implications of the study for health care? The data obtained from this survey, even allowing for some of the limitations listed above, gives valuable prevalence estimates that may be applied to the diabetic population of the UK. Particularly striking is the relationship of diabetic foot disease with age. 7 in every 100 diabetics will either have or have had a diabetic ulcer. 90% of these cases will be in subjects over the age of 60. Of the cases of amputation in the diabetic community virtually all will have been preceded by foot ulceration.

Regardless of diabetic status approximately 50% of individuals over the age of 65 will have some form of foot deformity which, if the latter proves to be an important risk factor for ulceration, inevitably must pose problems for scarce chiropody resources.

16 in every 100 diabetics will have clinical evidence of neuropathy of whom approximately 85% will be aged 60 or more. Similarly 20% of diabetics will have evidence of peripheral vascular insufficiency of whom 75% will be over the age of 60.

These figures must surely indicate that much more attention should be directed to screening the more elderly subjects in the diabetic population for potential risk factors for foot ulceration particularly in the light of evidence that specialised foot clinics have been shown to prevent limb loss (Edmonds et al 1986_B). Above all, the benefits of proven treatments in prevention such as the latter must be equated with other, perhaps more glamorous treatments, such as vascular surgery when it comes to the allocation of limited funds.

The true cost of treating diabetic foot disease and its risk factors is not really known because its frequency in the community has never accurately been established. There is no reason why these data may not be used for such calculations. They yield up-to-date information which should be useful for both hospital and GP diabetic clinics and will enable rational planning of resources for health care needs in diabetics. The NHS reforms will make accurate planning of health needs even more crucial. Further prevalence surveys of representative diabetic populations are awaited to give comparative data in other areas within the UK.

Finally an attempt was made in this survey to find correlates of the endpoints of diabetic foot disease and its main risk factors. Obviously the associations found are influenced by determinants of survival of the disease as well as causes of the disease. Studies over longer periods would undoubtedly deliver more accurate results in terms of frequency of occurrence and, at the same time, enable the investigation of the relationships between various characteristics of diabetics and the development and progression of diabetic foot disease.

APPENDIX 1

NOTES OF STATISTICAL ANALYSIS

All information gathered in this survey was loaded onto computer at Poole Hospital diabetic department and then transferred to the mainframe computer at the medical statistics department at Southampton University. Mr Mark Mullee performed the majority of the analysis. The SPSS statistical software was used for all the regression analysis.

In this survey the main population groups ie diabetics, IDDs, NIDDs and controls had different age structures. To calculate prevalence rates for variables and then to compare the frequency in diabetics with non-diabetics, it was considered necessary to account for the age difference. Many biological variables supposedly vary with increasing age. A regression analysis was therefore used rather than methods such as chi square which would not take age into account.

The regression analysis was of two types. For continuous variables (eg systolic blood pressure) where differences in magnitude were to be determined between each group, a linear multiple regression analysis was used with age included in the regression. For discrete variables a multiple logistic regression analysis was used and the result expressed as an odds ratio.

In the regression analysis of the dependent variables such as neuropathy with selected independent variables such as age and duration a multiple logistic regression analysis was always used. Continuous variables were converted to discrete variables by grouping for the purposes of the regression. Age and duration (for the diabetics) and age (for controls) were always forced into the regression model because of their possible importance in the genesis either directly or indirectly in the development of diabetic complications. After forcing age and duration into the model the importance (significance) of all the independent variables was determined by using the 'backward stepping' procedure. On the first step all variables listed on the backstep

list are entered into the model. The variable with the largest significance level greater than 0.05 is then removed. The model is re-estimated without the variable and again the variable with the largest significance level greater than 0.05 is removed. The process continues until no more variables meet removal criteria. Variables not in the model are then considered for entry based on entry criteria (<0.05). After each entry variables are once again considered for removal. Model building stops when no more variables meet entry or removal criteria.

The odds ratios approximate how much more likely (or unlikely) it is for the outcome to be present among those where x=1 (independent variable) than among those with x=0. For example, if y denotes the presence (y=1) or absence (y=0) of neuropathy and if x denotes whether or not the person has foot deformity, then an odds ratio of 2 indicates that neuropathy occurs twice as often among cases with foot deformity (x=1) than cases without foot deformity (x=0) in the study population. It approximates the relative risk. An odds ratio of less than 1.0 indicates the variable is inversely related.

The odds ratio is calculated as $_{e}ci$ where e is the exponential ie 2.7182818... and ci is the logistic regression coefficient.

The 95% confidence intervals for the odds ratios were calculated from the formula

$_{e}(ci+1.96xSE)$

where SE is the standard error of the logistic regression coefficient.

APPENDIX 2

Poole Diabetic Survey Cardiovascular Questionnaire

Please answer each question by ticking the appropriate box, eg

1. Are you a diabetic? Yes / No

2.(a) Have you ever had any pain or discomfort in your chest? Yes / No

(b) If no, have you ever had any pressure or heaviness in your chest? Yes / No

If you have answered NO to these last two questions, please proceed to question 4.

(c) Do you get it when you walk uphill or hurry? Yes / No

Never hurry or walk uphill!

If you have answered this last question NO, proceed to question 3 now.

(d) Do you get it when you walk at an ordinary pace on the level? Yes / No

(e) What do you do if you get it while you are walking?

Stop or slow down

Carry on

If you carry on after taking a GTN table under your tongue, answer question as Stop or slow down.

If you answered this last question "carry on", please proceed to question 3.

(f) If you stand still, what happens to it?

Relieved

Not relieved

(g) How soon?

10 minutes or less

More than 10 minute

(h) Where is the pain or heaviness?

Upper chest at front

Lower chest at front

Left side of chest

Other

If other, please specify where

.....

(j) Do you feel it anywhere else

Yes

No

If yes, where.....

(k) Did you see a doctor because of this pain or discomfort

Yes

No

If yes, what did the doctor say?

.....

3. Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

Yes

No

If yes, did you see a doctor because of this pain?

Yes

No

If yes, what did he say?.....

.....

4.(a) Do you get pain in either leg on walking?

Yes

No

If NO, please answer no further questions.

(b) Does this pain ever begin when you are standing still or sitting?

Yes

No

If YES, please answer no further questions.

(c) In what part of your leg do you feel it?

Pain includes calf

Pain does not include calf

(d) Do you get it if you walk uphill or hurry?

Yes

No

Never hurry or walk uphill

If NO, please answer no further questions.

(e) Do you get it if you walk at an ordinary pace on the level?

Yes

No

(f) Does the pain ever disappear while you are walking?

Yes

No

(g) What do you do if you get it when you are walking?

Stop or slow down

Carry on

If "carry on" please answer no further questions.

(h) What happens to it if you stand still?

Relieved

Not relieved

(j) How soon?

10 minutes or less

More than 10 minutes

5.(a) Have you ever had a stroke?

Yes

No

(b) If NO, have you ever had weakness or loss of strength in an arm or leg?

Yes

No

(c) If YES, how long did the weakness or loss of strength last?

More than 24 hours

Less than 24 hours

6.(a) Have you ever been told by a doctor that you have high blood pressure?

Yes

No

(b) If YES, are you on treatment to lower your blood pressure at the present time?

Yes

No

(C) When did your treatment start? 19.....

Poole Diabetic Survey Smoking Questionnaire

7.(a) Do you smoke cigarettes now?

Yes, regularly
Yes, occasionally
(less than 1 per day)
No
No, cigars only
No, pipe only

If NO, proceed to question 6.

(b) Do you inhale? Yes
No

(c) How many cigarettes do you normally smoke per day?

1- 5
6-10
11-20
21-30
More than 30

(d) What is the maximum number of cigarettes you ever smoked per day for as long as a year?

1- 5
6-10
11-20
21-30
More than 30

(e) How old were you when you began to smoke regularly?..... (age in years)

8.(a) Did you ever smoke cigarettes?

Yes, regularly
Yes, occasionally
(less than 1 per day)
No, never

(b) What is the maximum number of cigarettes you ever smoked per day for as long as a year?

1- 5
6-10
11-20
21-30
More than 30

(c) How old were you when you first began to smoke regularly?

..... (age in years)

(d) How old were you when you stopped smoking?

..... (age in years)

APPENDIX 3A

THE PROCEDURE FOR PERFORMING THE AUTONOMIC FUNCTION TESTS

(a) Check that the ECG monitoring machine is functioning normally and set so that 1mV = 1cm deflection.

(b) The patient sits or lies on a couch and relaxes with his arms by his sides.

(c) Electrodes are attached to the patient at the L & R wrists and L & R ankles.

(d) The ECG records at positions I, II, III, AVR, AVL and AVF and the ECG will be left on the position which gives the greatest deflection.

(e) The patient rests until a stable heart rate is obtained which is then recorded.

(f) Heart rate variation is then recorded whilst the patient breathes at a rate of 6 breaths per minute ie a 5 sec inspiration should be as great as possible (recording should not be performed until the patient's breathing rhythm is satisfactory).

(g) The patient rests again until his resting heart rate is stable and then is instructed in the valsalva manoeuvre.

(h) The patient then performs the valsalva manoeuvre. This entails that the patient sits or lies down and blows down a length of rubber tubing connected to a modified sphygmomanometer. The patient must not hold the tubing or move his arms. A column of mercury will be maintained at 40 mmHg for 15 seconds. The tubing will have (a) a mouthpiece, (b) a needle inserted into the side of the tubing which will act as a valve allowing air outwards. This will ensure that the patient does not maintain the pressure merely by using his cheeks. The ECG will be recorded throughout the procedure.

Calculations

(i) Maximum mean beats/minute - minimum mean beats/minute

(Normal - >15, abnormal <10)

(ii) Valsalva ratio:

$$\frac{\text{R - R interval after the manoeuvre}}{\text{R - R interval during the manoeuvre}}$$

A ratio of 1.5 or greater = normal

A ratio of 1.2 or less suggests autonomic neuropathy

APPENDIX 3B

The Biothesiometer is manufactured by the Bio-Medical Instrument Company, Chagrin Falls, Ohio.

The model used in the investigation consists of a hand-held moulded case which houses an electromagnetic vibrator mechanism, coupled to a power supply/control unit. The control unit also includes a meter, providing two alternative scales of measurement: a linear scale of voltage applied to the electromagnet and a relative amplitude scale which is proportional to the square of the applied voltage. This unit is driven by a mains-drive voltage at 100 Hz, the applied voltage being variable between 0 and approximately 50 volts.

APPENDIX 4

BIOCHEMICAL METHODS

(a) Cholesterol

Enzymatic cholesterol oxidase method using the TECHNICON CHEM Analyser.

(b) Creatinine

Jaffe reaction - using CHEM 1 auto-analyser.

(c) HbA1 Normal Range 5.5 - 8.5 (coefficient of variation = 18.7%)

FLUCKIGER METHOD - Barbituric colorimetric method.

APPENDIX 5

MULTISTIX AMES REAGENT STIX

Ames multiple reagent strips are firm plastic strips to which are affixed various separate reagent pads. Multistix measure urinary pH and the following urinary substances:

protein
glucose
ketone
bilirubin
blood
urobilinogen

Only protein, glucose and ketones used.

Manufacturers' instructions

Specimen collection and preparation: use a freshly voided, well mixed, uncentrifuged urine specimen, collected in a clean container. Procedure: completely immerse all reagent areas and in the specimen and immediately remove. Hold the strip in the horizontal position to prevent possible mixing of chemicals from adjacent reagent areas and a soiling of hands. Compare rest areas with corresponding colour charts on the bottle label at the reading times specified. Holding strip close to colour blocks, match colours carefully.

Reagents for individual tests

Protein: 0.3% w/w tetrabromopheriol blue; 97.3% w/w buffer, 2.4% w/w non reactive ingredients. Read immediately. Tests are negative in normal urines and false +ve's may occur with alkaline, highly buffered urines or in the presence of contaminating ammonium compounds.

Readings.	Trace	1+	2+	3+	4+
		0.05-0.2g/l	0.3g/l	3.0g/l	2.0g/l

Ketones. 7.1% w/w sodium nitroprusside
92.9% w/w buffer
Read at 15 seconds
Normally no ketones in urine therefore all +ve readings significant.

Glucose. 16.3% w/w glucose oxidase 0.6 w/w perioxidase, 7.0% potassium iodide, 60.7% w/w buffer, 15.4% w/w non reactive ingredients. Read at 30 seconds.

Normal urine - -ve results
False -ve's - high specific gravity, low temperature, moderately high amounts of ketones in urines with traces of glucose.

Reading.	Trace	1+	2+	3+	4+
	5.5 mmol/l-1	14	28	55	111 mmol/l

APPENDIX 6A

DEFINITIONS OF RETINOPATHY

i. No retinopathy - ie no abnormal features of diabetic retinopathy seen.

ii. Background retinopathy - dots and blots present.

iii. Exudative retinopathy - the presence of hard exudates with or without dots and/or blots and/or haemorrhages.

iv. Ischaemic retinopathy - the presence of dots and/or blots with one or more cotton wool spots (retinal infarcts) or dots and/or blots with or without exudates but with one or more ischaemic features ie deep dark round haemorrhages, sheet haemorrhages, venous loops or intra-retinal microvascular abnormalities (IRMA) (confirmed by ophthalmologist).

v. Proliferative retinopathy - new vessels with or without fibrous proliferation (confirmed by consultant ophthalmologist).

vi. Treated proliferative retinopathy - diabetics who have been treated with photocoagulation for proliferative retinopathy and now show no evidence of new vessels. The presence of new vessels has been documented in the patient's records by an ophthalmologist.

vii. Maculopathy - is defined as macula disease (either ischaemic or exudative) producing a decrease in visual acuity to 6/9 or worse. Its presence was confirmed by an ophthalmologist.

APPENDIX 6B

DEFINITIONS OF TERMS USED TO DEFINE RETINOPATHY

Dots.

Small round lesions with a sharp outline and their diameter is less than that of the superior temporal artery as it crosses the optic disc margin. These are either microaneurysms or microhaemorrhages.

Blots.

Medium sized round lesions with less clearly defined edges. They are smaller than the optic disc and are haemorrhages.

Deep dark round haemorrhages.

Circular haemorrhages with a clear cut outline and are dark red and deep in the retina. They are usually equal in size to the diameter of the superior retinal artery as it crosses the disc margin.

Sheet haemorrhages

Irregular red patches seen on the surface of the retina. They are of variable size.

Vitreous haemorrhages

These are seen as blood in the vitreous or between the vitreous body and the retina. They usually obscure the retina.

Hard exudates

These are irregular areas of yellow/white deposits with a clear sharp outline.

Soft exudates (cotton wool spots)

These are usually round lesions with an indistinct edge and are white or greyish white in colour. They represent retinal infarcts.

Venous abnormalities

Venous dilatation (gross) with irregularity and looping. This indicates the retina is ischaemic.

Intra-retinal microvascular abnormalities

Fine hair-pin like projections discrete from new vessels.

New vessels

These appear usually as a fine tangled mass of vessels either arising from the disc or in the periphery of the retina.

APPENDIX 7

DEFINITIONS OF FOOT DEFORMITY

Hallux Valgus

The great toe is deviated laterally at the metatarso-phalangeal joint. Skin over the joint is hard and often red.

Hallux Rigidus

The metatarso-phalangeal joint is thickened. There is little or no movement in either flexion or extension at this joint.

Hammer Toes

Fixed flexion deformity of the proximal inter-phalangeal joint of any toe. The distal inter-phalangeal joint is hyperextended but mobile. The metatarso-phalangeal joint is hyperextended.

Charcot Joint

Gross deformity of the foot associated with loss of pain sensation clinically. X-ray findings include subluxation, joint disorganisation and new bone formation.

Pes Cavus

High longitudinal arch with a splayed, thickened forefoot. The toes are clawed and the metatarsal heads invariably have callus tissue. The angle between the forefoot and hindfoot approaches a right angle.

Pes Planus

The longitudinal arch of the foot is reduced so that on standing its medial border is in, or near to, contact with the ground.

Claw Toes

Fixed flexion deformity of the proximal inter-phalangeal joint with similar fixed deformity of the distal inter-phalangeal joint. If the deformity occurred with a very small angle between hind and forefoot (as defined above) then the deformity was considered as part of pes cavus. The metatarso-phalangeal joint is hyperextended.

It is realised that these definitions are only semi-quantitative and mainly descriptive. Only one observer was employed. More quantitative criteria such as measuring angles precisely or x-raying all feet was not considered feasible for this survey.

APPENDIX 8

DEFINITIONS OF SITE OF PERIPHERAL VASCULAR DISEASE

Suprapopliteal disease: any subject with an ankle/brachial doppler pressure ratio of < 0.9 with all pulses below the femoral missing in the same limb.

Infrapopliteal disease: any subject with an ankle/brachial doppler pressure ratio of <0.9 with a palpable popliteal pulse but one or more foot pulses absent in the same limb.

REFERENCES

Anderson A R, Christiansen J S, Andersen J K, Kreines S & Deckert T.
Diabetic nephropathy in type I (insulin dependent diabetes): an epidemiological study
Diabetologia 1983; 25: 496-501

Andersson E, Hansson C & Swanbeck G
Leg and foot ulcers - An epidemiological survey
Acta Dermato - Venereologica (Stockholm) 1984; 64: 227-232

Archer A G, Watkins P J, Thomas P K, Sharma A K & Payan J
The natural history of acute painful neuropathy in diabetes mellitus
Journal of Neurology, Neurosurgery and Psychiatry
1983; 46: 491-499

Archer A G, Roberts V C & Watkins P J
Blood flow patterns in painful diabetic neuropathy
Diabetologia 1984; 27: 563-567

Asbury A K & Fields H C
Pain due to peripheral nerve damage: a hypothesis
Neurology (Cleveland) 1984; 34: 1587-1590

Bagdade J, Stewart M & Walters E
Impaired Granulocyte Adherence
Diabetes 1978; 27: 677-681

Barrett J P & Mooney V
Neuropathy and diabetic pressure lesions
Orthopaedic Clinics of North America
1973; 4: 43-47

Banson B B & Lacey P E
Diabetic microangiopathy in human toes
American Journal of Pathology
1964; 45: 41-48

Barhorst D A & Barner H B
Prevalence of congenitally absent pedal pulses
New England Journal of Medicine
1968; 278: 264-266

Barrett-Connor E, Criqui M H, Klauber M R & Holdbrook M
Diabetes and hypertension in a community of older adults
American Journal of Epidemiology 1981; 113: 276-284

Beach K W, Brunzell J D, Conquest L L & Strandness D E
The correlation of arteriosclerosis obliterans with lioproteins in insulin dependent and non insulin dependent diabetes
Diabetes 1979; 28: 836-840

Beach K W & Strandness D E
Arteriosclerosis obliterans and associated risk factors in insulin dependent and non insulin dependent diabetes
Diabetes 1980; 29: 882-888

Beach K W, Brunzell J D & Strandess D E (Jr)
Prevalence of severe arterioslcerosis obliterans in patients with diabetes mellitus
Arterioslcerosis 1982; 2: 275-280

Beghi E, Treviso M, Ferri P D & Mascio R
Diagnosis of diabetic polyneuropathy, correlation between clinical and instrumental findings and assessment of simple diagnostic criteria.
Italian Joural of Neurological Science 1988; 9: 577-582

Behse F & Buchthal F
Alcoholic Neuropathy: Clinical, electrophysiological and biopsy finding
Annals of Neurology 1977; 2: 95-110

Bell E T
Incidence of gangrene of the extremities in non diabetic and in diabetic persons
Archives of Pathology 1950; 49: 469-475

Bender A P, Sprafker J M, Jagger H G, Muckala K H, Marhn C P & Edwards T R
Incidence, prevalence and mortality of diabetes mellitus in Wadera, Marshall and Grand Rapids, Minnesota: The three-city study
Diabetes Care 1986; 9: 343-350

Bendick P J, Glover J L, Kuebler T W & Dilley R S
Progression of atherosclerosis in diabetics
Surgery 1983; 93: 834-838

Birmingham Diabetes Survey Working Party
Ten Year follow-up report on Birmingham Diabetes Survey of 1961
British Medical Journal 1976; 2: 35-37

Bischoff A
The natural course of diabetic neuropathy - a follow up
Hormone and Metabolic Research 1980; 9: 98-100

Bloom S, Till S, Sonksen P & Smith S
Use of a biothesiometer to measure individual vibration thresholds and their variation in 519 non diabetic subjects
British Medical Journal 1984; 288: 1793-1795

Bodily K C & Burgess E M
Contralateral limb and pateitn survival after leg amputation
American Journal of Surgery 1983; 146: 280-282

Bonkalo A
Relation between neuritis and the clinical background in diabetes mellitus
Archives Internal Medicine 1950; 85: 944-954

Borssen B & Lithner F
Amputations in diabetics and non diabetics in Umea County 1971-1977
Acta Medica Scandinavica. Suppl. 1983; 687: 95-100

Borssen B, Bergenheim T & Lithner F
The epidemiology of foot lesions in diabetic patients aged 15-50 years
Diabetic Medicine 1990; 7: 438-444

Boulton A J, Hardisty C A, North R C, Drury J & Ward J D
Estimated glycosylated haemoglobin in diabetic neuropathy
Acta Diabetologica Latina 1982_A; 19: 345-349

Boulton A J, Scarpello J H & Ward J D
Venous oxygenation in the diabetic neuropathic foot: evidence of arteriovenous shunting?
Diabetologia 1982_B; 22: 6-8

Boulton A J, Scarpello J H, Armstrong W D & Ward J D
The Natural History of Painful Diabetic Neuropathy - a 4 year study
Postgraduate Medical Journal 1983; 59: 556-559

Boulton A J, Franks C I, Betts R P, Duckworth T & Ward J D
Reduction in abnormal foot pressures in diabetic neuropathy using a new polymer insole material
Diabetes Care 1984; 7: 42-46

Boulton A J, Knight G, Drury J & Ward J D
The prevalence of symptomatic diabetic neuropathy in an insulin treated population
Diabetes Care 1985; 8: 125-128

Boulton A J, Kubrusly D B, Bowker J H, Gadia M T, Quintero, Becker D M, Skyler J S & Sosenko J M
Impaired Vibratory Perception and diabetic foot ulceration
Diabetic Medicine 1986; 3: 335-337

Boulton A J, Betts R P, Franks C I, Ward J D & Duckworth T
The natural history of foot pressure abnormalities in neuropathic diabetic subjects
Diabetes Research 1987_A; 5: 73-77

Boulton A J
The importance of abnormal foot pressures and gait in the causation of foot ulcers
In: Connor H & Ward J D; Eds
The foot in diabetes
John Wiley and Sons 1987; 11-21

Brand F N, Abbott R D & Kannel W B
Diabetes and Intermittent Claudication, and risk of cardiovascular events
Diabetes 1989; 38: 504-509

Brandman O & Redisch W
Incidence of peripheral vascular changes in diabetes mellitus
Diabetes 1953; 2: 194-198

Broch O J & Klovstad O
Polyneuritis in diabetes mellitus
Acta Medica Scandinavica 1947; 127: 515-542

Bryfogle J W & Bradley R R
The vascular complications of diabetes mellitus
Diabetes 1957; 6: 159-167

Burrows P J, Gray P J, Kinmouth A L, Payton D J, Walpole G A, Walton R J, Wilson D & Woodbine G. Journal of the Royal College of General Practitioners 1987; 37: 65-69

Carter S
Response of ankle systolic pressure to leg exercise in mild or questionable arterial disease
New England Journal of Medicine 1972; 287: 578-582

Christensen N J
Muscle blood flow, measured by Xenon and vascular calcifications in diabetics
Acta Medica Scandinavica 1968; 183:449-454

Christensen S
Lower extremity amputations in the county of Aalborg 1961-1971
Acta Orthopaedica Scandinavica 1976; 47: 329-334

Collyer R & Hazlett B
Retinopathy and neuropathy in one hundred growth-onset diabetic patients
Canadian Medical Association Journal 1961; 85: 1328-1334

Connor H
The economic impact of diabetic foot disease
In: Connor H, Boulton A J, Ward J D eds.
The foot in diabetes
John Wiley and Sons 1987; 145-149

Conrad M
Large and small artery occlusion in diabetics and non-diabetics with severe vascular disease. Circulation 1967; 36:83-91

Corbin D O, Young R J, Morrison D C, Hoskins P, McDicken W N, Housley E & Clarke B F
Blood flow in the foot, polyneuropathy and foot ulceration in diabetes mellitus
Diabetologia 1987; 30: 468-473

Crawford A H & Gabriel K R
Foot and ankle problems
Orthopaedic clinics of North America 1987; 18: 649-665

Crawford S E
Aortoiliac occlusive disease: factors influencing survival and function following reconstructive operation over a twenty five year period
Surgery 1981; 90: 1055-1067

Cronenwell J L & Lindenaur S M
Direct measurement of arteriovenous anastomotic blood flow after lumbar symphathectomy
Surgery 1977; 82: 82-89

Ctercteko G C, Dhanendran M, Hulton W C & Le Quesne L P
Vestical forces acting on the feet of diabetic patients with neuropathic ulceration
British Journal Surgery 1981; 68: 608-614

The DCCT Research Group
Factors in the development of diabetic neuropathy
Diabetes 1988; 37: 476-481

Dean R H, Yao J S, Stanton P E, Bergan J J
Prognostic indicators in femoropopliteal reconstructions
Archives of Surgery 1975,110:1287-1293

Delbridge L, Appleberg M & Reeve T S
Factors associated with development of foot lesions in the diabetic
Surgery 1983; 93: 78-82

De Weese J A & Rob C G
Autogenous venous grafts ten years later
Surgery 1977; 82: 775-783

Diabetes Epidemiology Research International
Preventing insulin dependent diabetes mellitus - the environmental challenge
British Medical Journal 1987; 295: 479-481

Doney B J
An audit of the care of diabetes in a group practice
Journal of the Royal College of General Practitioners 1976; 26: 734-742

Dormandy J, Maher M, Ascady G, Balsano F, De Leeuw P, Blombery P, Bousser M G, Clement D, Coffman J, Deutshinoff A, Bletry O, Hampton J, Mahler F, Ohlin P, Rieger H, Standen E, Turpie A G, Urai L & Verstraete M
Fate of the patient with chronic leg ischaemia
Journal of Cardiovascular Surgery 1989; 30: 50-57

Dornan C, Fowler G, Mann J I, Markus A & Thorogood M
A community study of diabetes in Oxfordshire
Journal of the Royal College of General Practitioners
1983; 33: 151-155

Dryberg T, Benn J, Sandahl Christiansen J, Hilsted J & Nerup J
Prevalence of diabetic autonomic neuropathy
Diabetologia 1981; 20: 190-194

Dyck P J, Sherman W R, Hallcher L M, Service J F, O'Brien P C, Grina L A, Palumbo P J & Swanson C
Human diabetic endoneural sorbitol, fructose and myo-inositol related to sural nerve morphometry
Annals of Neurology 1980; 8: 590-596

Dyck P J, Karnes J L, Daube J, O'Brien P & Service F J
Clinical and neuropathological criteria for the diagnosis and staging of diabetic polyneuropathy
Brain 1985; 108: 861-880

Dyck P J, Hansen S, Karnes J, O'Brien P, Yasuda H, Windebank A & Zimmerman B
Capillary number and percentage closed in human diabetic sural nerve
Proceedings of the National Academy Science, USA
1985(6); 82: 2513-2517

Dyck P J, Karnes J & O'Brien P C
Diagnosis, staging and classification of diabetic neuropathy and associations with other complications
In: Dyck, Thomas, Asbury, Winegrad, Porte eds
Diabetic Neuropathy. W B Saunders 1987; pp 36-44

Edmonds M E, Morrison N, Laws J W & Watkins P J
Media arterial calcification and diabetic neuropathy
British Medical Journal 1982; 284: 928-930

Edmonds M E, Nicolaides K H & Watkins P J
Autonomic neuropathy and diabetic foot ulceration
Diabetic Medicine 1984; 3: 56-59

Edmonds M E
The neuropathic foot in diabetes Part I: blood flow
Diabetic Medicine 1986_A; 3: 111-115

Edmonds M E, Blundell M P, Morris M E, Maelor-Thomas E, Cotton L T & Watkins P J
Improved survival of the diabetic foot: the role of a specialised foot clinic
Quarterly Journal of Medicine 1986_B; 232: 763-771

Ellenberg M
Diabetic neuropathic ulcer
Journal of the Mount Sinai Hospital 1968; 35: 585-594

Emanuele M A, Buchanan B J & Abraira C
Elevated leg systolic pressures and arterial calcification in diabetic occlusive vascular disease
Diabetes Care 1981; 4: 289-292

Ewing D, Clarke B
Diabetic Autonomic Neuropathy: A clinical viewpoint. In Dyck P J, Thomas P K, Asbury A K, Winegrad A I, Porte D eds.
Diabetic Neuropathy. W B Saunders and Company 1987; pp 66-88

Fagerberg S E
Diabetic Neuropathy - a clinical and neurological study in the significance of vascular affections
Acta Medica Scandinavica 1959; 164: suppl 345: 9-34

Fagerberg S E, Petersen I, Steg G & Wilhelmsen L
Motor disturbances in diabetes mellitus. A clinical study using electromyography and nerve conduction velocity determination
Acta Medica Scandinavica 1963; 174: 711-716

Falconer D S, Duncan L J & Smith C
A statistical and genetical study in diabetes
Annals of human genetics, London 1971; 34: 347-369

Faris I
Small and large vessel disease in the development of foot lesions in diabetics
Diabetologia 1975; II: 249-253

Finch D R, MacDougal M, Tibbs D J & Morns P J
Amputation for vascular disease: the experience of a peripheral vascular unit
British Journal of Surgery 1980; 67: 233-237

Finegold D, Latimer S A & Noble S
Polyol pathway activity
Diabetes 1983; 32: 988-993

Fletcher B R
Looking after diabetics in general practice: a trainee project
Journal of the Royal College of General Practitioners 1977;27:85-88

Flynn M D, Edmonds M E, Tooke J E & Watkins P J
Direct measurement of capillary blood flow in the diabetic neuropathic foot
Diabetologia 1988; 31: 652-656

Flynn M D, Watkins P J & Tooke J E
The first demonstration of capillary underperfusion in the diabetic neuropathic foot
Diabetic Medicine 1989; Suppl 2; 6: 7A

Fonesca V, Berger L A, Beckett A G & Dandona P
Size of the pancreas in diabetes mellitus: a study based on ultrasound
British Medical Journal 1985; 291: 1240-1241

Forrest R D, Jackson C A & Yudkin J S
Glucose intolerance and hypertension in North London: The Islington Diabetes Survey
Diabetic Medicine 1986; 3: 338-342

Franklin G M, Katin L B, Baxter J, Marshall J A & Hamman R I
Sensory neuropathy in non insulin dependent diabetes mellitus
American Journal of Epidemiology 1990; 131: 633-643

Friedman S A & Simmons E A
Diabetic Peripheral Neuropathy - clinical manifestations
Geriatrics 1967; 141-148

Garcia M J, McNamara P M, Gordon T & Kannell W B
Morbidity and mortality in diabetics in the Framingham population
Diabetes 1974; 23: 105-111

Gatling W, Houston A C & Hill R D
The prevalence of diabetes mellitus in a typical English community
Journal of the Royal College of Physicians, London 1985;19:248-250

Gatling W
The prevalence of diabetic nephropathy
MD Thesis, University of southampton 1986

Gibbins, R L, Rowlands C J & Saunders J
A management system for diabetes in general practice
Diabetic Medicine 1986; 3: 477-479

Gillon K R, King R H & Thomas P K
The pathology of diabetic neuropathy and the effects of aldose reductase inhibitors
Clinics in Endocrinology and Metabolism 1986; 15: 837-853

Glatthaar C, Welborn T, Stenhouse N & Garcia-Webb P
Diabetes and impaired glucose tolerance
The Medical Journal of Australia 1985; 143: 436-440

Glynn J R, Carr E K & Jeffcoate W J
Foot ulcers in previously undiagnosed diabetes mellitus
British Medical Journal 1990; 300: 1046-1048

Goldenberg S, Alex M, Joshi R & Blumenthal H
Non-atheromatous peripheral vascular disease in the lower extremity in diabetes mellitus
Diabetes 1959; 8: 261-273

Gordon T & Kannel W B
Predisposition to atherosclerosis in the head, heart and legs
Journal of the American Medical Association 1972; 221: 661-666

Goss D E, DeTrafford J, Roberts V C, Flynn M D, Edmonds M E & Watkins P J
Raised ankle/brachial pressure index in insulin treated diabetic patients
Diabetic Medicine 1989; 6: 576-578

Gould N, Schneider W & Ashikaga T
Epidemiological survey of foot problems in the continental United States: 1978-1979
Foot and Ankle 1980; 1: 8-10

Govan A D, MacFarlane P S, Callander R In: Govan A D, MacFarlane P S & Callander R eds
Pathology illustrated.
Churchill Livingstone 1981; pp 835-839

Government White Paper, Caring for People
Community Care in the next decade and beyond
Her Majesty's Stationery Office 1989; p 104-105

Greene D A, Lattimer S, Ulbrecht J & Carroli P
Glucose induced alterations in nerve metabolism: current perspective on the pathogenesis of diabetic neuropathy and future directions for research and therapy
Diabetes Care 1985; 8: 290-299

Greene D A, Lattimer S A & Sima A F
Sorbitol, phosphoinositides and sodium potassium - ATPase in the pathogenesis of diabetic complications
New England Journal of Medicine 1987; 316: 599-606

Guy R J, Clark C A, Malcolm P N & Watkins P J
Evaluation of thermal and vibration sensation in diabetic neuropathy
Diabetologia 1985; 28: 131-137

Haimovici H
Patterns of arteriosclerotic lesions of the lower extremity
Archives of surgery 1967; 95: 918-933

Hansson J
The leg amputee - a clinical follow-up
Acta Orthopaedica Scandinavica 1964; suppl 69: 5-102

Herman J P, Medalie J H & Goldbourt U
Differences in cardiovascular morbidity and mortality between previously known and newly diagnosed adult diabetics
Diabetologia 1977; 13: 229-234

Hertzer N R
Fatal myocardial infarction following lower extremity revascularisation
Annals of surgery 1981; 193: 492-498

Hierton T & James U
Lower extremity amputation in Uppsala County 1947-1969. Incidence and prosthetic rehabilitation
Acta Orthopaedica Scandinavica 1973; 44: 573-582

Higgs E R, Tymms D J & Reckless J P D
Results of screening for hypertension, proteinuria and nephropathy in a geographically defined diabetic population
Diabetic Medicine 1989, vol 6, suppl A4

Hill R D
Community care service for diabetics in the Poole area
British Medical Journal; 1976: I: 1137-1139

Holewski J J, Moss K M, Stess R M, Graf P M & Grunfield C
Prevalence of foot pathology and lower extremity complications in a diabetic outpatient clinic
Journal of Rehabilitation Research and Development
1989; 26: 35-44

Holman R R, Turner R C
The Basal Plasma Glucose: A simple relevant index of maturity-onset diabetes
Clinical Endocrinology 1980; 14: 279-286

Holman R R, Dornan T L, Mayon-White V, Howard-Williams J, Orde-Peckar C, Jenkins L, Steemson J, Rolfe R, Smith B, Barbour D, McPherson K, Poon P, Rizza C, Mann J I, Knight A H, Bron A J & Turner R C

Prevention of deterioration of renal and sensory nerve function by more intensive management of insulin dependent patients. A two year randomised prospective study
Lancet 1983; I: 204-208

Houston A C
Retinopathy in the Poole area: an epidemiological enquiry
Advances in Diabetes Epidemiology. Inserm symposium 1982; No 22: 199-206

Howell T H.
Senile deterioration of the central nervous system - a clinical study
British Medical Journal 1949; I: 56-58

Hughson W G, Mann J I, Tibbs D J, Woods H F & Waiton I
Intermittent claudication: factors determining outcome
British Medical Journal 1978; I: 1377-1379

Hughson W G, Mann J I & Garrod A
Intermittent claudication: prevalence and risk factors
British Medical Journal 1978; I: 1379-1381

Hung L K & Laing P C
Survey of foot deformities among 166 geriatric inpatients
Foot and Ankle 1985; 5: 156-164

Irwin S T, Gilmore J, McGrann S, Hood J & Allen J A
Blood flow in diabetics with foot lesions due to small vessel disease
British Journal of Surgery 1988; 75: 1201-1206

Janka H U, Standl E & Mehnert H
Peripheral vascular disease in diabetes mellitus and its relation

to cardiovascular risk factors: screening with the doppler ultrasonic technique
Diabetes Care 1980; 3: 207-213

Jarrett R J, Keen H, Boyns D R, Chlouverakis C & Fuller J
The concomitants of raised blood sugar: studies in newly detected hyperglycaemics
Guy's Hospital Report 1969; 118: 237-246

Jarrett R J & Keen H
Hyperglycaemia and diabetes mellitus
Lancet 1976; II: 1009-1012

Jarrett R J, Keen H, McCartney M, Fuller J H, Hamilton P J, Reid D D & Rose G
Glucose tolerance and blood pressure in two population samples: their relation to diabetes mellitus and hypertension.
International Journal of Epidemiology 1978; 7: 15-24

Jarrett R J
Descriptive epidemiology of diabetes types. In Jarrett R J ed.
Series in Clinical Epidemiology - Diabetes Mellitus - PSG Publishing Company, Inc 1986; 11-25

Jarrett R J
Cardiovascular disease and hypertension in diabetes mellitus
Diabetes/Metabolism Reviews 1989; 5: 547-558

Jarrett R J
Mortality in Diabetes
Quarterly Journal of MEdicine 1990, 277: 413-414

Jones E W, McLain S & Jeffcoate W J
Foot lesions in a diabetic clinic over a 32 month period
Diabetic Medicine 1985; 2: 304A

Jones E W, Peacock I, McLain S, Fletcher E, Edwards R, Finch R G & Jeffcoate W J
A clinico-pathological study of diabetic foot ulcers
Diabetic Medicine 1987; 4: 475-479

Kald A, Carlsson R & Nilsson E
Major amputation in a defined population: incidence mortality and results of treatment
British Journal of Surgery 1989; 76: 308-310

Kannel W B & Shurtleff D
The natural history of arteriosclerosis obliterans
Cardiovascular Clinics 1971; 3: 37-52

Kannel W B & McGee D C
Diabetes and glucose tolerance as risk factors for cardiovascular disease. The Framingham Study
Diabetes Care 1979; 2: 120-126

Kannel W B, McGee D L
Update on some epidemiological featuers of intermittent claudication: The Framingham Study
Journal of the American Geriatrics Society 1985; 33:13-18

Karacagil S, Almgren B, Bowald S & Eriksson I
Arterial lesions of the foot vessels in diabetic and non diabetic patients undergoing lower limb revascularisation
European Journal of Vascular Surgery 1989; 3: 239-244

Keely P J & Coventry M B
Neuropathic ulcers of the feet
Journal of the American Medical Association
1958; 168: 388-393

Keen H, NgTang Fui S
The definition and classification of diabetes mellitus
Clinics in Endocrinology and Metabolism 1982; 11: 279-305

Keen H, Ashton C E
Mechanisms of excess cardiovascular mortality in diabetics
Postgraduate Medical Journal 1989; 65 (suppl 1): S26-S29

Kelsey-Fry I, Hardwick C & Scott G W
Diabetic neuropathy: a survey and follow-up of 66 cases
Guy's Hospital Reports 1962; 111, 113-129

Klein R, Klein B, Moss S, DeMets D, Kaufman I & Voss P
Prevalence of diabetes mellitus in Southern Wisconsin
American Journal of Epidmiology 1984; 119: 54-61

Knuiman M W, Welborn T A, McGann V J, Stanton K G & Constable I J
Prevalence of diabetic complications in relation to risk factors
Diabetes 1986; 35: 1332-1339

Kozak G P & Rowbotham J L
Diabetic foot disease: a major problem. In: Kozak G P, Hoar S I, Rowbotham L J, Wheelock F C, Gibbons G W & Campbell D eds.
Management of diabetic foot disease. W B Saunders, Philadelphia 1984; pp 1-8

Kreines K, Johnson E, Albrink M, Knatterud G L, Levin M E, Lewitan A, Newberry W & Rose F A
The course of peripheral vascular disease in non insulin dependent diabetes
Diabetes Care 1985; 8: 235-243

Krolewski A S, Kosinski E J, Warram J H, Leland O S, Busick E J, Asmal A C, Rand L I, Christlieb A R, Bradley R F & Kahn C R
Magnitude and determinants of coronary artery disease in juvenile onset, insulin dependent diabetes mellitus
American Journal of Cardiology 1987; 59: 750-755

Lehtinen J M, Uusitupa M, Siitonen O & Pyorala K
Prevalence of neuropathy in newly diagnosed NIDDM and non diabetic control subjects
Diabetes 1989; 38: 1307-1313

Leslie R D G, Lazarus N R & Vergani D
Aetiology of insulin dependent diabetes
British Medical Bulletin 1989; 45: 58-72

Liedberg E & Persson B
Increased incidence of lower limb amputation for arterial occlusive disease
Acta Orthopaedica Scandinavica 1983; 54: 230-234

Lippman H I, Perolto A & Farrar R
The neuropathic foot of the diabetic
Bulletin of the New York Academy of Medicine 1976; 52: 1159-1178

Lippmann H I
Must loss of limb be a consequence of diabetes mellitus?
Diabetes Care 1979A; 2: 432-436

Lippmann H I & Farrar R
Prevention of amputation in diabetes
Angiology 1979B; 30: 649-658
Liedberg E & Persson B

Logerfo F W
Vascular disease, matrix abnormalities and neuropathy: implications for limb salvage in diabetes mellitus
Journal of Vascular Surgery 1987; 5: 793-796

Louie T J, Bartlett J G, Tally F P & Gorbach S L
Aerobic and anaerobic bacteria in diabetic foot ulcers
Annals of Internal Medicine 1976; 85: 461-463

Low P A, Tuck R R, dyck P J, Schmelzer J D & Yao J K
Prevention of some electrophysiologic and biochemical abnormalities with oxygen supplementation in experimental diabetic neuropathy
Proceedings of the National Academy of Science, USA 1984; 81: 6894-6898

Low P A, Zimmerman B R & Dyck P J
Comparison of distal sympathetic with vagal function in diabetic neuropathy
Muscle and Nerve 1986; 9: 592-596

Lowenthal L M & Hockaday D R
Vibratory Sensory Thresholds Depend on Pressure of Applied Stimulus
Diabetes Care, 1987; 10: 100-102

Malins J M, Fitzgerald M G & Wall M
A change in the incidence of diabetes mellitus
Diabetologia 1965; I: 121-124

Malone J M, Moore W S & Goldstone G
Life expectancy following aortofemoral arterial grafting
Surgery 1977; 81: 551-555

Marinelli M R, Beach K W, Glass M J, Primozich J F & Strandness D C
Non invasive testing vs clinical evaluation of arterial disease
Journal of the Americal Medical Association 1979; 241: 2031-2034

Martin M M
Neuropathic lesion of the feet in diabetes mellitus
Proceedings of the Royal Society of Medicine 1954; 47: 139-140

Maser R E, Nielsen V K, Bass E B, Maryoo Q, Dorman J S, Kelsey S F,
Becker D J & Orchard T J
Measuring Diabetic Neuropathy
Diabetes Care 1989; 12: 270-275

Maser R E, Steenkiste R E, Dorman J S, Nielson V K, Bass E B,
Maryoo Q, Drash A L, Becker D J, Kuller L H, Greene D A & Orchard T
Epidemiological correlates of diabetic neuropathy
Diabetes 1989; 38: 1456-1461

Masson E A, Hay E M, Stockley I, Veves A, Betts R P & Boulton A J
Abnormal foot pressures alone may not cause ulceration
Diabetic Medicine 1989; 6: 426-428

Matthews J D
Neuropathy in diabetes mellitus
Lancet 1955; I: 474-476

Mayne N
Neuropathy in the diabetic and non diabetic populations
Lancet 1986; II: 1313-1316

Mayne N
The short term prognosis in diabetic neruopathy
Diabetes 1968; 17: 270-273

McCann V J & Davis R E
Glycosylated haemoglobin concentration in patients with diabetic neuropathy
Acta Diabetologica Latina 1979; 16: 205-209

Melton J L, Macken K M, Palumbo P J & Elveback L R
Incidence and prevalence of clinical peripheral vascular disease in a population based cohort of diabetic patients
Diabetes Care 1980; 3: 650-654

Mincu I
Micro and macro angiopathies and other chronic degenerative complications in newly detected diabetes mellitus
Revue Roumaine de Medecine - Medecine Interne 1980; 18: 155-164

Mirsky A I, Futteman P & Brohkahn R H
The quantitative measurement of vibratory perception in subjects with and without diabetes mellitus
Journal of Laboratory Clinical Medicine 1953; 41: 221-235

Moore J M & Frew I D
Peripheral vascular lesions in diabetes mellitus
British Medical Journal 1965; 2: 19-23

Most R S & Sinnock P
The epidemiology of lower extremity amputations in diabetic individuals
Diabetes Care 1983; 6: 87-91

Muir R
Blood vessels and lymphatics
In Anderson J R Ed, Muir's Textbook of pathology
12th edition, Edward Arnold (Publishers) Ltd 1985, p14.1-14.5

Mulder D W, Lambert E H, Bastron J A & Sprague R G
The neuropathies associated with diabetes mellitus
Neurology 1961; 11: 275-284

Murphy F D & Moxon G F
Diabetes mellitus and its complications
The American Journal of the Medical Sciences 1931; 182: 301-311

Nabarro J D
Diabetes in the United Kingdom: some facts and figures
Diabetic Medicine 1988; 5: 816-822

National Diabetes Advisory Board
The treatment and control of diabetes
United States Department of Health Education and Welfare, Public Health Service, National Institute of Health 1980 (Publication No 81-224)

Newrick P G, Wilson A J, Jakubowski J, Boulton A J & Ward J D
Sural nerve oxygen tension in diabetes
British Medical Journal 1986; 293: 1053-1054

Neil H A W, Gatling W & Mather H W
The Oxford Community Diabetes Study: evidence for an increase in the prevalence of known diabetes
Diabetic Medicine 1987; 4: 539-545

Neil H A W, Thompson A V, John S, McCarthy S T & Mann J I
Diabetic autonomic neuropathy: the prevalence of impaired heart rate variability in a geographically defined population
Diabetic Medicine 1989A; 6: 20-24

Neil H A W, Thompson A V, Thorogood M, Fowler G H & Mann J I
Diabetes in the elderly: The Oxford Community Diabetes Study
Diabetic Medicine 1989B; 6: 608-613

Nelson R G, Gohdes D M, Everhart J E, Hartner J A, Zwerner F L, Pettitt D J, Knowles W C
Lower extremity amputations in NIDDM: 12 year follow-up study in American Indians
Diabetes Care 1988, 11:8-16

Nielson N V, Ware S & Lund F
Diabetic polyneuropathy, corneal sensitivity vibratory perception and achilles tendon reflex in diabetics
Acta Neurologica Scandinavica 1979; 5915-22

Nilsson S E, Nilsson J E, Frostberg N & Emilsson T
The Kristianstad survey II: studies in a representative adult diabetic population with special reference to comparison with an adequate control group
Acta Medica Scandinavica 1967; suppl 469: 5-42

Nolan C M, Beaty H N & Bagdade J D
Further charterisation of the impaired bactericidal function of granulocytes in patients with poorly controlled diabetes
Diabetes 1978; 27: 889-894

Oakley W, Catterall R C & Martin M M
Aetiology and management of lesions of the feet in diabetes
British Medical Journal 1956; 4999: 953-957

O'Brien I A & Corrall R J
Epidemiology of diabetes and its complications
New England Journal of Medicine 1988; 18: 1619-1620

O'Sullivan J B, Williams R F and McDonald G W
The prevalence of diabetes mellitus and related variables - a population study in Sudbury, Massachusetts
Journal of Chronic Disease. 1967; 20 535-543

OPCS Monitor
Drinking in England and Wales - an enquiry on behalf of the DHSS
pub OPCS 1980

OPCS Monitor
Cigarette Smoking 1972-1984
OPCS monitor - 1985 ref GHS 85/2

Palumbo P J, Elveback L R, Chu-Pin Chu M S, Connolly D G & Kurland L T
Diabetes mellitus: incidence, prevalence, sun worship and causes of death in Rochester, Minnesota, 1945-1970
Diabetes 1976; 25: 566-573

Palumbo P J, Elveback L R & Whisnant J P
Neurologic complications of diabetes mellitus: transient ischaemic attack, stroke and peripheral neuropathy
Advances in Neurology 1978; 19: 593-601

Pan W H, Cedres L B, Lui K, dyer A, Schoenberger J A, Shekelle R B, Stamler R, Smith D, Collette P & Stanler J
Relationship of clinical diabetes and asymptomatic hyperglycaemia to risk of coronary heart disease mortality in men and women
American Journal of Epidemiology 1986; 123: 504-516

Panzram G
Mortality and survival in type 2 (non insulin dependent) diabetes mellitus
Diabetologia 1987; 30: 123-131

Paz-Guevara A T, Hsu T H & White P
Juvenile Diabetes Mellitus after 40 years
Diabetes 1975; 24: 559-565

Page M McB & Watkins P J
Cardiorespiratory arrest and diabetic autonomic neuropathy
Lancet 1978; I: 14-16

Peacock I, Fletcher E & Jeffcoate W J
The prevalence of foot lesions - a community survey
Diabetic Medicine 1985; 2: 509A

Pirart J
Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973
Diabetes Care 1978; I: 168-188

Porte D, Graf R, Halter J, Pfeifer M & Halar E
Diabetic neuropathy and plasma glucose control
American Journal of Medicine 1981; 70: 195-200

Porte D
B cells in Type II Diabetes
Diabetes 1991 40 166-80

Potvin A R, Syndulko K, Tourtellotte W W, Lemmon J A & Potvin J H
Human neurologic function and the ageing process
Journal of the American Geriatric Society 1980; 28: 1-9

Pyorala K
Relationship of glucose and plasma insulin to the incidence of coronary artery disease: Results from two population studies in Finland
Diabetes Care 1979 2: 131-141

Pyorala K & Laakso M
Macrovascular disease in diabetes mellitus
In Mann J I, Pyorala K, Tenscher A.eds
Diabetes in epidemiologic perspective (1st edition)
Churchill/Livingstone publishers 1983; 183-247

Rafferty P, Rodigues E & Fraser D M
Aetiological factors in diabetic foot ulceration
British Journal of Clinical Practice 1986; 40: 11-14

Ramsey D E, Manke D M & Sumner D S
Toe blood pressure. A valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease
Journal of cardiovascular surgery 1983; 24: 43-48

Rayman G, Williams S A, Spencer P D, Smaje L H, Wise P H & Tooke J
Impaired microvascular hyperaemic response to minor skin trauma in type I diabetes
British Medical Journal 1986; 292: 1295-1298

Reid D D, Brett G Z, Hamilton P J, Jarrett R J, Keen H & Rose G
Cardiorespiratory disease and diabetes among middle aged male civil servants
Lancet 1974; I: 469-473

Report and Recommendations of the San Antonia Conference on Diabetic Neuropathy
Annals of Neurology 1988; 24: 99-104

Rose G, McCartney P & Reid D D
Self administration of a questionnaire on chest pain and intermittent claudication
British Journal of Preventive and Social Medicine 1977; 31: 42-48

Rosenquist U
An epidemiological survey of diabetic foot problems in the Stockholm county 1982
Acta Medica Scandinavica 1988; (suppl) 687: 55-60

Rundles R W
Diabetic neuropathy - general review with report of 125 cases
Medicine (Baltimore) 1945; 24: 111-160

Said G
A clinicopathologic study of acrodystrophic neuropathies
Muscle and Nerve 1980; 3: 491-501

Said G, Slama G & Selva J
Progressive centripetal degeneration of axons in small fibre diabetic polyneuropathy
Brain 1983; 106: 791-807

Scarpello J H, Martin T R & Ward J D
Ultrasound measurements of pulse wave velocity in the peripheral arteries of diabetic subjects
Clinical Science 1980; 58: 53-57

Service F J, Daube J R, O'Brien P C, Zimmerman B R, Swanson C J, Brennan M D & Dyck P J
Effect of blood glucose control on peripheral nerve function in diabetic patients
Mayo Clinic Proceedings 1983; 58: 283-289

Semple R
Diabetes and peripheral arterial disease - a clinical study
Lancet 1953; I: 1064-1068

Shicheri M
Clinical study on neuropathy in diabetics
Medical Journal of Osaka University
1964; 14: 223-233

Siitonen O, Uusitupa M, Pyorala, Voutilainen E & Lansimies E
Peripheral arterial disease and its relationship to cardiovascular risk factors and coronary heart disease in newly diagnosed non insulin dependent diabetics
Acta Medica Scandinavica 1986; 220: 205-212

Silwer H & Oscarsson P N
Incidence and coincidence of diabetes mellitus and pulmonary tuberculosis in a Swedish county
Acta Medica Scandinavica 1958; 161 (suppl 335): 5-48

Sinha S, Munichoodappa C S & Kozak G P
Neuro-arthropathy (Charcot Joints) in Diabetes Mellitus
Medicine 1972; 51: 191-210

Sosenko J M, Gadia M T, Fournier A M, O'Connell M T, Aguiar M C & Skyler J S
Body stature as a risk factor for diabetic sensory neuropathy
American Journal of Medicine 1986 80, 1031-

Spencer F, Sage R & Graner J
The incidence of foot pathology in a diabetic population
Journal of the Americal Podiatric Medical Association 1985; 75: 590-592

Steer H W, Cuckle H S, Franklin P M & Morris P J
The influence of diabetes mellitus upon peripheral vascular disease
Surgery, Gynaecology and Obstetrics 1983; 157: 64-72

Steiness I B
Vibratory perception in diabetics
Acta Medica Scandinavica 1957; 158: 327-335

Sternby N H
Atherosclerosis in a defined population. An autopsy survey in Malmo, Sweden
Acta Pathologica Microbiologica Scandinavica 1968; suppl 194: 7-216

Stokes I A, Faris I B & Hulton W C
The neuropathic ulcer and loads on the foot in diabetic patients
Acta Orthopaedica Scandinavica 1975; 46: 839-847

Stout R W
The role of insulin in atherosclerosis in diabetics and non-diabetics
Diabetes 1981; 30 (suppl 2): 54-57

Strandness D E, Priest R E Gibbons
Combined clinical and pathological study of diabetic and non-diabetic peripheral arterial disease
Diabetes 1964; 13: 366-372

Tarn A C, Thomas J M, Dean B M, Ingram D, Schwarz G, Boltazzo G F & Gale E A
Predicting insulin dependent diabetes
Lancet 1988; I: 845-850

Tasker P R
Is diabetes a disease for general practice?
Practical Diabetes 1984; 1: 21-24

Taylor T
Aetiology of non insulin dependent diabetes
British Medical Bulletin 1989; 45: 73-91

Thomas J H, Steers J L, Keushkenan S M, Pierce G E, Iliopolous J I & Hemreck A S
A comparison of diabetics and non diabetics with threatened limb loss
The American Journal of Surgery 1988; 156: 481-483

Thomas P K & Brown M J
Diabetic polyneuropathy. In Dyck, Thomas, Asbury, Winegrad, Porte eds. Diabetic Neuropathy publishers Saunders 1987, 56-65

Thompson A V, Neil H A W, Thorogood M, Fowler G H & Mann J I
Diabetes mellitus: attitudes, knowledge and glycaemic control in a cross-sectional population
Journal of the Royal College of General Practitioners 1988; 38: 450-452

Tibell B
Peripheral arterial insufficiency: an epidemiologic study of 2,243 hospital admissions caused by arteriosclerosis obliterans, Diabetes Mellitus, thromboanginitis obliterans and arterial embolism
Acta Orthopaeica Scandinavica 1971; 139 (suppl): 1-54

Tooke J E, Rayman G & Boolell M
Blood flow abnormalities in the diabetic foot - diagnostic aid or research tool
In Connor H, Boulton A J Ward J D (eds)
The Diabetic Foot. Publishers John Wiley and Sons 1987; pp 11-21

Uusitupa M I,Niskanen L K, Siitonen O, Voutilainen E,Pyorala K
5 year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level and abnormalities in lipoprotein composition in non-insulin dependent diabetic and non-diabetic subjects
Circulation 1990 82: 27-36

Wagner F W
The Diabetic Foot
Orthopaedics 1987; 10: 163-172

Walsh C H, Soler N G, Fitzgerald M G & Malins J M
Association of foot lesions with retinopathy in patients with newly diagnosed diabetes
Lancet 1975; I: 878-880

Ward J D, Barnes G C, Fisher D J & Jessop J D
Improvement in nerve conduction following treatment in newly diagnosed diabetics
Lancet 1971; I: 428-430

Ward J D, Armstrong W, Preston E, Best L O'Malley B & Scarpello J
Pain in the diabetic leg: a trial of Aspirin and Dypyridamole in diabetic neuropathy
Pharmtherapeutica 1981; 2: 642-647

Ward J D, Boulton A J, Simms J M, Sandler D A & KNight G
Venous distension in the diabetic neuropathic foot (physical sign of arteriovenous shunting)
Journal of the Royal Society of Medicine 1983; 76: 1011-1014

Ward J D
Essential requirements for diabetic foot care. In Connor H, Boulton A J, Ward J D (eds)
The Foot in diabetes. John Wiley and Sons 1987; pp

Walter and Israel
General Pathology, sixth edition
Publishers Churchill-Livingstone 1987

Waugh N R
Amputations in diabetic patients - a review of rates, relative risks and resource use
Community Medicine 1988; 10: 279-288

Welborn T A, Kneuman M, McCann V, Stanton K & Constable I J
Clinical macrovascular disease in caucasoid diabetic subjects: logistic regression analysis of risk variables
Diabetologia 1984; 27: 568-573

West K M
Epidemiologic evidence linking nutritional factors to the prevalence and manifestations of diabetes
Acta Diabetologica Latina 1972, 9 (suppl 1): 405-428

West K M
Diabetes in American Indians and other native populations of the New World
Diabetes 1974; 23: 841-855

West K M
Epidemiology of Diabetes and its vascular lesions
Elservier, New York 1978

WHO Study Group. Neuronal ageing and its implications in human neurological pathology.
WHO Technical Report Series no 665, Geneva 1981

WHO Multinational Study of Vascular Disease in Diabetes
Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres
Diabetologia 1985A; 28: 615-640

WHO Study Group. Diabetes Mellitus
WHO Technical Report Series No 727, Geneva 1985B

Wheat J
Diagnostic strategies in osteomyelitis
The American Journal of Medicine 1985; 78: 218-224

Widmer L K, Greenshier A & Kannel W B
Occlusion of Peripheral Arteries. A study of 6400 working subjects
Circulation 1964; 30: 836-842

Williams D R R.
Hospital Admissions of Diabetic Patients: information from hospital analysis
Diabetic Medicine 1985; 2: 27-32

Wilson P W F, Anderson K M & Kannel W B
Epidemiology of diabetes mellitus in the elderly: the Framingham Study
American Journal of Medicine 1986; (suppl SA) 80: 3-9

Windebank A J
Diabetic control and peripheral neuropathy
Mayo Clinic Proceedings 1983; 58: 344-346

Yao S T
Haemodynamic Studies in PEripheral Arterial Disease
British Journal of Surgery 1970; 57: 761-766

Yao J S T, Peterson L K & Payne K
Lower limb systolic pressure measurements. Technique and clinical applications.
Internal Angiology 1985; 4: 31-39

Young R J, Zhou Y Q, Rodriguez E, Prescott R J, Ewing D J & Clarke B F
Variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetic polyneuropathy
Diabetes 1986; 35: 192-197

Wheat J
Diagnostic strategies in osteomyelitis
The American Journal of Medicine 1985; 78: 218-224

Young R J
Identification of the subject at risk of foot ulceration. In Connor H, Boulton A J, Ward J Deds.
The foot in diabetes. John Wiley and Sons 1987; 1-10

Young R J, MacKintyre C C A, Ewing D J & Prescott R J
Prediction of neuropathy over 5 years in young insulin dependent diabetic patients
Diabetic Medicine 1988 SA

Yudkin J S, Boucher B J, Schopflin K E, Harris B T, Claff H R, Whyte N J D, Taylor B , Mellins D H, Wootliff A B, Safir J G & Jones E J
The quality of diabetic care in a London health district
Journal of Epidemiology and Community Health 1980; 34: 277-280

Yuh W T C, Corson J D, Baraniewski H M, Rezai K, Kathol M H, Sato Y, El-Khoury G Y, Hawes D R, Platz C E, Cooper R R & Corry R J
Osteomyelitis of the foot in diabetic patients: evaulation with plain film, 99m Tc-MDP bone scintigraphy and MR imaging
American Journal of Roentgenology 1989; 152: 795-800

Zdanov V S & Vihert A M
Atherosclerosis and Diabetes Mellitus
Bulletin of the World Health Organisation 1976; 53: 547-553

Zimmerman B R, Palumbo P J, O'Fallon W M, Osmundson P J & Kazmier F
A prospective study of peripheral occlusive arterial disease in diabetes
Mayo Clinic Proceedings 1981; 56: 233-242