

**A STUDY OF DIABETES IN ASIANS**

A thesis presented for the degree of Doctor of Medicine  
at the University of Leicester, 1988

**Ashok Samanta**

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I dedicate this thesis to my aunt  
MISS ANITA FERNANDEZ, who has always  
helped me achieve a sense of direction,  
with her love, guidance and support

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Ashok Samanta

A Thesis for the degree of Doctor of Medicine  
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### ABSTRACT

The thesis is a clinical study of diabetes mellitus in Asians.

CHAPTER 1: The subject is introduced and the literature reviewed. Aims are presented.

CHAPTER 2: The prevalence of known insulin dependent diabetes is ascertained in Asian children. Although lower than that in White Caucasian children, this did not reach statistical significance. The prevalence of known diabetes in adults is ascertained and found to be higher in Asians, rising significantly above the age of 45 years. Asians in all age bands are also at significantly greater risk for developing non-insulin dependent diabetes.

CHAPTER 3: The prevalence of diabetic complications is studied in a population attending the hospital diabetic clinic. Asians are shown to be at significantly higher risk for developing cataracts and kidney disease, and at lower risk for developing peripheral vascular disease and retinopathy. It is noted that heart vascular disease is higher, and cerebrovascular disease lower in Asians.

CHAPTER 4: Non diabetic Asians (first degree blood relatives of non-insulin dependent diabetics, and those without such a family history) are shown to have lowered insulin sensitivity and hyperinsulinaemia. Possible mechanisms in the pathogenesis of diabetes in Asians are discussed.

CHAPTER 5: Asian women are shown to have a significantly higher prevalence of gestational diabetes. A significant linear trend in the proportions of maternal complications is shown in Asians, across the glycaemic range following a third trimester oral glucose tolerance test. Foetal complications are shown to be higher at the extreme ends of the maternal glycaemic range.

CHAPTER 6: The acute metabolic effect of an Asian meal in normal volunteers is shown as a significantly higher and prolonged degree of glycaemia and insulinaemia when compared to an equicaloric European meal. A high consumption of sweets and snacks is shown in Asian diabetics attending a clinic in general practice, and the sociocultural implications of eating habits are discussed.

CHAPTER 7: Summary and conclusions are presented.

## ACKNOWLEDGMENTS

I am grateful to well over a thousand patients and their relatives without whose willing co-operation these studies would not have been possible; to the nursing staff of Wards 9 and 17 at the Leicester General Hospital for allowing me to use valuable "ward space"; to Miss Helen Kinghorn for helping me "process" my "samples" in the laboratory; to Mrs Mary Burden for her meticulous assistance in planning and executing that complex procedure of "data collection"; to Dr Carol Jagger for statistical advice; to the Maternity Unit at the Leicester General Hospital for allowing me access to their patients and records; to Dr Robert Turner and his staff at the Diabetes Research Laboratories, Oxford, for guiding me through the "Scylla and Charybdis" of insulin secretion and insulin resistance, and for generously allowing me to use data on subjects studied at Oxford, for comparative purposes in Chapter 4 of this thesis. To all mentioned, and indeed many others, I am deeply indebted.

My special thanks to Mrs Neera Sharma who has with the greatest of goodwill borne the vicissitudes of typing and re-typing this thesis, and who has always cheerfully and without any hesitation given me her time, despite her numerous commitments. Without her help I would have made little, if any, progress.

Last, but far from least, my thanks to Dr A C Burden ("Felix"), friend and mentor, without whose unending enthusiasm, expertise, and above all "bonne humeur", this entire venture would have not been possible.

## FOREWORD

Over the last few years, whilst engaged in the work presented in this thesis, I have often wondered about the justification of a study of diabetes in Asians. My concern, has in the main, stemmed from two questions: Are Asians different from the indigenous population in Leicester, and is there a need to conduct such studies in this particular group? I am not sure that I have definitive answers, despite some thought.

The UNESCO declaration of 1951 (1) states that "all men living today belong to a single species, Homo Sapiens, and are derived from a common stock". The statement goes on to amplify the concept of a common basis for the development of mankind, and emphasises that national, religious, geographical and linguistic differences do not necessarily provide a meaningful classificatory device for various groups of populations. Any attempt to classify populations is inherently fraught with difficulties. However, most anthropologists very broadly agree on the three major divisions of present-day mankind - the Mongoloid, the Negroid and the Caucasoid divisions. The difficulties in

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(1) Statement of the Nature of Race and Race Differences.  
UNESCO. Paris. June 1951

clearly defining any of these divisions, as well as the considerable variability that may exist, make such a classification of limited value (2). This is further confounded by the fact that many of the terms applied to different groups of people are used in an imprecise sense. In an attempt to gauge this, I randomly asked ten doctors at the Leicester Royal Infirmary, what they understood by the term "Caucasian" or "Caucasoid". Answers were very variable and ranged from "Oh, the British and Americans mainly, and maybe the French" to "Only white people". None of the answers were in any way meant to be pejorative, but simply reflected a lack of knowledge. Caucasians are supposedly those who originated from the Caucasus mountainous range (3). This is a vast region extending from the Black Sea to the Caspian Sea, and from Kuma to Turkey and Iran. Because of its location, it is "généralement considérée comme la limite entre l'Europe et l'Asie" (4). It is therefore conceivable that when migration occurred out of this area, this proceeded both eastwards and westwards, and that many of the present inhabitants of Asia and Europe are "Caucasoid" in origin.

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(2) Mason, Philip. Race Relations. Oxford University Press. Oxford. 1970.

(3) Brewer, E C. The Dictionary of Phrase and Fable. 1894. Reprinted by the Galley Press.

(4) Le Petit Robert. Dictionnaire Universel Des Noms Propres. SEPRET. Paris. 1974.

People from the Indian subcontinent then, are in the main "Caucasoid" just as the people from most European nations. For the purpose of the present study, I have used the term "White Caucasian" as applied to the indigenous population in the United Kingdom, and the term "Asian" as applied to the migrant population, originating from the Indian subcontinent. I am aware that this nomenclature is far from perfect, but is the best that I can suggest at this moment in time.

"The nature of men is identical; what divides them is their customs" (Confucius, 551-478 BC). Indeed, one of the major sources of maladjustment that may exist at the interface of different societies is due to failure to appreciate or accept a different culture. "Culture" is a multifaceted entity, and nearly a century ago Sir Edward Tylor described this as "that complex whole which includes knowledge, beliefs, art, morals, law, custom and any other capabilities and habits acquired by man as a member of society" (5). In its broadest sense, this includes human activities transmitted through various learning processes. Culture does vary with different societies, and may have an important bearing on a group's attitudes to external influences, including disease processes. In a sense it

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(5) Tylor E B. Primitive Culture. London. 1891



provides a reference framework to which an individual may apply when confronted by specific situations. However, culture is "something which can never be regarded as fixed for ever, but is constantly undergoing changes, sometimes small enough or slow enough to be almost imperceptible or to remain long unnoticed, sometimes of such scope or speed as to appear revolutionary" (6). I believe that this understanding of culture is of relevance to practising clinicians, who are directly involved with patient care. I believe that a methodical examination of disease processes in different societies helps to define the health needs of that particular society. This is further, inexorably linked by culture, to the most appropriate means of administering holistic health care. This particular philosophy has sustained the work undertaken for this thesis, and, I think, vindicates a study of diabetes in Asians.

The best intentioned studies involving ethnic groups may at times raise sensitive issues. I can only reiterate the spirit in which this work was conducted, and emphasise that it would be a source of great personal disappointment if this were to be vitiated by misinterpretation. I apologise in advance for any shortcomings in this work, and accept these as my own.

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(6) Leiris M. Race and Culture. In: Race, Science and Society. George Allen & Unwin Ltd. London. 1975

No attempt at understanding culture can even begin without some insight into the religio-philosophical background. The Indian subcontinent is rich with a diversity of religious customs and beliefs that have developed over 5,000 years. The most important legacy from the ancient past, is the doctrine of "samsara" (transmigration). This emerged some time in the first millenium BC from the idea "loke-loka enam mrityur vindet" (Death will hound the soul from world to world) (7). In the search for psychological security from this endless cycle of birth-death-rebirth there developed several schools of philosophical thought speculating on the immanent and transcendent nature of "brahman" (the Absolute) and its relation to "atman" (the Self). One of the most influential thinkers was Sankara, who in the ninth century AD developed the doctrine of "advaita" (non-duality). The eternal quest of the mystic was to be fulfilled in knowledge of "Tat tvam asi" (Thou art That), the realization of the complete identity of the "atman" with the "brahman", the monistic doctrine which denies the existence of the world as separate from the Absolute (8). This development of thought over several centuries proved a powerful factor in moulding the Indian mind, and has had widespread ramifications.

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(7) Radhakrishnan S. Eastern religions and Western thought. Oxford. 1940

(8) Basham A L. A cultural history of India. Oxford University Press. Oxford. 1975

The mind boggling concept of an endless cycle of time in an immense cosmos is lyrically and hauntingly expressed in a "tanka" of the Heian period:

"The grasses and trees  
Change their colours;  
But to the wave-blooms  
On the broad sea-plain  
There comes no autumn." (9)

This continuum from birth to death and then birth again, unending in its cycle, has been responsible for conditioning many of the sociocultural attitudes of Indians.

I look back on the years spent in preparing this work, years mixed with anxiety, apprehension and elation, and I now have before me some two hundred pages - the quintessence of my efforts. As I prepare the final stages of this thesis, I feel a sense almost of sadness, that a part of me is about to leave, perhaps forever.

"Animula vagula, blandula,  
Hospes comesque corporis,  
Quae nunc abibis in loca  
Pallidula, rigida, nudula,  
Nec, ut soles, dabis iocos . . ." (10)

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(9) Bunya Yasuhide. Poet, mid tenth century. Quoted in The Penguin Book of Japanese Verse. Penguin Books. 1964.

(10) The Emperor, Hadrien (76-138 AD). Quoted in Yourcenar M. Memoirs d'Hadrien. Gallimard. Paris. 1974.

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# CHAPTER 1

## INTRODUCTION



Diabetes mellitus has been recognised as a disease for several centuries. References of this as a malady with polyuria are made in the Egyptian Papyrus of Ebers (c 1500 BC) (Major, 1945). The disease was named "diabetes" after Aretaeus of Cappadocia (30-90 AD), who described this as a "melting down of the flesh and limbs into urine", and it was thought that body contents were thus siphoned out (Major, 1945).

Ancient Indian physicians seemed to have a better understanding of the underlying pathology. Charaka (2nd century AD) has drawn attention to the sweetness of urine in diabetes. It is believed that Charaka's teachings are based on the earlier works of Agniversa, who in turn based his writings on the principles of medicine outlined by Atreya who lived in the 6th century BC (Nayyar, 1966). It would appear, therefore, that more than two and a half thousand years ago, diabetes mellitus was a problem of sufficient magnitude in India to attract considerable attention. In about 500 AD, another Indian physician, Sushruta, coined the term "madhumeha" ("passing honey in the urine") to describe this entity. This was more than a thousand years before Thomas Willis at Oxford added the suffix "mellitus" (sweet) to the term diabetes, in order to characterise this condition in more detail (Major, 1945).

People from the Indian ("Asian") subcontinent who have settled in other parts of the world seem to have a very

high prevalence of diabetes mellitus. Jackson (1978) has shown that the prevalence of diabetes mellitus in Indians in South Africa is much higher than in the indigenous white population. In one group of Tamil Indians the prevalence was almost as high as that in the Pima Indians rising to 37% above the age of 25 years. Cassidy (1967) has shown that the prevalence of diabetes mellitus in Indians in Fiji is 5.7%, which is higher than that in the local population, and a similar increase has also been noted by Zimmet et al (1983). In a study in Singapore, Cheah et al (1979) found a significantly higher prevalence of glycosuria in Indians, and also a higher prevalence of a positive family history of diabetes.

It would appear, therefore, that the evidence from studies in migrant Asians suggests a tendency to a higher prevalence of diabetes mellitus. One possible reason for this could be the increasing affluence of such communities.

In 1962, Neel suggested that the diabetic genotype could possibly have a survival advantage in primitive societies leading a feast-and-famine existence. Those with this particular genotype held an advantage in times of famine, but were at a disadvantage in times of abundance. Recently, in a six centre collaborative study in India, Ahuja (1979) has shown that the prevalence of diabetes mellitus is about one and a half times higher in urban areas than in rural areas. If increasing affluence is associated with a rise in the prevalence of diabetes

mellitus in Asians, then a study of the clinical aspects of this condition in Asians in the United Kingdom would be of great value. There is a large migrant Asian community in the United Kingdom, and the subsequent planning of health care would, to some extent, depend on the characteristics of diseases in this group. Data from Hospital Activity Analysis (Cruickshank et al, 1980) (Donaldson and Taylor 1983) suggest that the prevalence of diabetes mellitus may be higher in Asians, and a similar impression seems to be gathered from mortality statistics (Marmot et al 1984) (Balarajan et al, 1984). A recent house to house inquiry in Southall, London, has also shown a high prevalence of diabetes in Asians (Mather and Keen, 1985). Leicester provides an ideal setting for a detailed study on diabetes and its clinical aspects in Asians, as this population in Leicester is about 14% according to the 1981 census.

The clinical features of diabetes mellitus are now recognised to be heterogeneous, and Keen and Ekoe (1984) have drawn attention to the wide geographical variation of this disease. The familiar "Caucasian" patterns of insulin dependence and non insulin dependence may be modified in non-European people. Hugh-Jones' (1955) classic description of "J-type" diabetes in Jamaicans has shown the existence of a group of young diabetics with a high insulin requirement and an absence of ketosis. The progression of

diabetes may also be different and hence mortality from diabetes, or with diabetes as a causative factor has varied widely, and is particularly high in Malta and Mauritius (WHO, 1978).

All these features emphasise the ethnic variability in diabetes, and may influence health trends of a given society. A hospital based study from Birmingham suggests that insulin requirements may be low in Asians, but does not provide any further information on true insulin dependence or on the subsequent progress of this condition. (Odugbesan and Barnett, 1985). Comparison of diabetic complications has been difficult mainly because of a lack of uniformity in definitions and criteria. The WHO multinational study has shown that a wide variability in diabetic complications may exist between different national groups (Keen and Jarrett, 1979) (Jarrett, et al 1979). For example, heavy proteinuria, severe retinopathy and retinopathic blindness seems to affect the Japanese, although they are relatively protected from atherosclerosis. Another study of long standing diabetics from Ethiopia seems to confirm the low rates of coronary heart disease in Orientals although their susceptibility to eye and kidney complications appears unchanged (Lester, 1983). These variations would suggest that geographical and perhaps ethnic differences in the susceptibility to various complications are of importance. They further underscore the need for in depth studies in specific ethnic groups.

## STUDIES IN THE ASIAN POPULATION

August Hirsch (1885) cited examples of apparent differences in the occurrence of diabetes, and noted that it was fairly common in the Eastern part of India, and along the Coromandel coast (South India). Some time later, Sen (1893) and Bose (1907) reported that diabetes was particularly common amongst affluent men in Bengal. It is clear, therefore, that as early as about a century ago important observations had already been made on the clinical impression of the prevalence of diabetes in Indians. Between 1938 and 1975, some thirty different studies were conducted to determine the prevalence of diabetes in India, and these have been recently summarized (Gupta et al, 1978). They have shown prevalence rates that have varied from 0.70 to 12.67%. The interpretation of these results has been bedevilled by the differences in methodology and diagnostic criteria, and the age range of the subjects studied by various authors. In an attempt to achieve a degree of uniformity in results, a six-centre study was conducted under the auspices of the Indian Council of Medical Research (Ahuja, 1979). Approximately 34,000 subjects were surveyed using a 50 gm glucose load, and the prevalence of diabetes was found to be 0.5% between the ages of 15-29 years, 1.0% between 30-39 years and 4% above 40 years. The overall prevalence in urban areas was approximately one and a half times that in rural areas.

The Southall study from London (Mather and Keen, 1985) has also shown, by means of a questionnaire survey of approximately 34,000 Asians, that the prevalence of diabetes rose sharply after the age of 40 years, rising to as much as 12% between the ages of 60-69 years. Both these studies provide important milestones in assessing the prevalence of diabetes in Asians. However, there are still certain areas that need to be examined. There are no specific figures on the prevalence of childhood diabetes (below the age of 15 years), nor are there data forthcoming on the relative risk for Asians of developing diabetes. For these reasons, I believe that the question of prevalence of diabetes in Asians needs to be addressed with more precision.

Several factors have been associated with diabetes mellitus. It is generally held that glucose tolerance worsens with age (West, 1978). This, however, seems to be a function of weight, and if older people remain lean, there tends to be no significant deterioration of glucose tolerance. This has been confirmed in Indians, by Tripathy et al (1965 and 1973). In a population from East Pakistan, West and Kalbfleisch (1971) observed only a modest decline in glucose tolerance, where there was no major weight gain with age. If the high prevalence of diabetes with increasing age can be related to excessive body weight then this may provide a useful preventive means to reduce

morbidity in this group. Several recent studies have shown the strength of obesity as a risk factor for diabetes (West, 1978). In Bombay, the KEM Hospital Group (1966) showed that the prevalence of diabetes was 7.86% in obese and 0.04% in non-obese subjects, and Rao et al (1966) have shown a ninefold increase in diabetes in overweight persons. Migration into an affluent society may be a factor in producing obesity and it would be useful to know the degree of excess body weight in Asian diabetics. It is possible that appropriate modification of environmental circumstances to obviate overweight may prevent the development of diabetes.

Considerable controversy has persisted over the question of diet in the aetiology of diabetes. This has been summarised by West (1978). What has not received attention is the effect that Indian herbs and vegetables may have on plasma glucose. For example, Karela (*Momordica Charantia*) is known to have a hypoglycaemic effect (Pitchumoni, 1979) (Aslam and Stockley 1979) (Leatherdale et al 1981). Ajgaonkar (1966) in his scholarly review on indigenous Indian drugs in diabetes cites six other preparations of vegetable origin that lower blood sugar. Much of the recent work to examine the hypoglycaemic effects of these substances, in particular Karela, has dealt with this in isolation. What would perhaps be of more practical value is to determine the glycaemic effects of ingredients used in Indian traditional cooking when consumed as part of a whole meal.

Diabetes is generally held to be a disease of the advantaged social classes, and Stewart Brown et al (1983) have provided evidence of an increase in insulin-dependence with higher social stratification. Much of the literature from Indian studies also points in a similar direction. Ancient Hindu physicians described diabetes as an affliction of the wealthy (Christie, 1811). The Bombay survey (KEM Hospital Group, 1966) found diabetes about six times commoner in the upper income group as compared to the poor. Ahuja (1979) has shown a higher prevalence of diabetes in urban areas where the per capita income is higher as compared to rural areas in India. Datta (1966) has found that diabetes was about 20 times commoner in rich Tamils in Pondicherry, South India, compared to the poor, and Rao et al (1966) have also found a higher prevalence in the rich. Data however, is somewhat conflicting in the report of Jackson (1972) who found that the poor had more diabetes than the rich, in Indians in Capetown. Knowledge of socioeconomic factors affecting disease processes may be of importance in the future direction of health care.

The published prevalence of coronary disease in Asian diabetics has varied considerably. Cosnett (1957) reported vascular lesions as "extremely common" in Indian diabetics in South Africa. Ibrahim in 1962, found that in a clinic in East Pakistan, coronary disease was rare. A study from Ceylon (De Zoysa, 1951) also found macrovascular disease to be rare. Pathological studies of Indians in South Africa



have shown that arteriosclerosis was comparable to that in the White population (Robertson and Strong, 1968). More recently, Jackson's (1972) studies from the Capetown area of South Africa have shown that the rate of coronary disease was about equal in both White and Indian diabetics.

In recent studies from India, rates of macrovascular disease have ranged from low to moderate (Patel et al 1966) (Lal et al 1968) (Sathe 1973) (Raychaudhari 1973). Perhaps some of this variability is due to differences in the method of data collection and the criteria used. It would be useful to collect data within the Asian ethnic group using well-defined standardized conventions, to assess this.

Very few studies have examined the prevalences of other macrovascular complications such as peripheral vascular disease or cerebrovascular disease in Asian diabetics. Peripheral vascular disease appears to be uncommon in Asians, and Tandon et al (1973) found this complication in only 9% of their diabetics in India.

The literature contains only scanty reports on small vessel disease in Asian diabetics. In 1966, Dixit et al performed a hundred renal biopsies in an unselected group of diabetics and found diffuse glomerulosclerosis in 30, and nodular glomerulosclerosis in 12. Of those with histological changes, 75% had diabetes of less than 5 years duration, and no significant relation was found with

hypertension, retinopathy or neuropathy. The overall prevalence of proteinuria was 27%. Mehra and Rajyashree (1966) reporting on diabetic retinopathy found that the overall prevalence was 34%, and that this was directly related to the duration of diabetes. Puttanna (1966), however, reported a much lower prevalence of 8%. In this series, retinopathy was graded according to severity, and there seemed to be a positive association between severe retinopathy occurring in inadequately controlled diabetes of short duration. There is a need to collect data on nephropathy and retinopathy using standardized methods to determine the extent of these complications in Asian diabetics.

It is now recognised that ethnic differences may influence the prevalence of gestational diabetes mellitus (Hadden, 1985). There is a marked paucity of data in this aspect regarding Asians, but one study (Agarwal and Gupta, 1982) shows that the prevalence of gestational diabetes in Asians is 1.88%. This seems higher than the usually accepted figure of just under 1% (Hadden, 1985). The problem of gestational diabetes in Asians needs to be explored in greater depth. The apparent increase is of potential importance, because if true, then it may highlight a group at high risk for perinatal morbidity.

The aetiology of diabetes mellitus is complex, and the final evolution of the disease may depend on a balance between genetically pre-determined and environmentally

initiated factors. As there is a high familial predisposition to non-insulin dependent diabetes, a study of non-diabetic first degree relatives may help to characterize early alterations in insulin secretion or insulin sensitivity. A dynamic assessment of these functions would be of importance in elucidating the basic mechanisms in the pathogenesis of non-insulin-dependent diabetes.

In summary, a wide heterogeneity may exist in the clinical manifestations of diabetes mellitus. This is due, at least in part, to ethnic influences. Studies based on one particular population may not necessarily be valid for a group from a different ethnic background. Many of the studies performed on Asians have involved differences in methodology that make interstudy comparisons exceedingly difficult. I propose to study the prevalence, clinical features and vascular complications of diabetes in Asians; to examine patterns of insulin secretion and insulin resistance; to address the problem of gestational diabetes and the effect of varying degrees of glycaemia on the outcome of pregnancy; and to determine the role of diet and dietary habits in diabetes in Asians. I aim to use standardised and uniform methods to allow for a valid comparison with the indigenous population. The value of such a study lies in the relevance that it may have to patient care.

## CHAPTER 2

### PREVALENCE OF DIABETES MELLITUS IN ASIANS

In 1921 Joslin applied the term "epidemic" to diabetes mellitus and was one of first persons to suggest that an epidemiological approach to the study of diabetes may be fruitful. Over the last sixty years, there have been many publications on epidemiological aspects of diabetes, and these have been recently summarized (Mann, Pyorala and Teuscher, 1983). The value of such work lies in determining the risk of developing diabetes (incidence), the risk of having the disease (prevalence), and the risk of complications and subsequent prognosis. Thus epidemiological work is of importance in establishing the natural history of diabetes, as well as predicting the magnitude of clinical workload that might be expected.

Diabetes is a heterogeneous disorder, and attempts at classification of the various types have to some extent been regarded as artificial (Mann, Pyorala and Teuscher, 1983). It is, however, usually held that diabetes occurring in childhood, before the age of 16 years, is almost invariably insulin dependent diabetes mellitus (IDDM) (Wadsworth and Jarrett, 1974), whereas that occurring later in adult life is probably non-insulin dependent diabetes mellitus (NIDDM). This is further complicated by the fact that some adult onset NIDDMs may require treatment with insulin. Allowing for the pitfalls of such a division, this classification nonetheless serves a useful purpose in that it at least separates childhood onset diabetes from adult onset diabetes, and the

consequences of these may be different. For these reasons, I have elected to study separately the prevalence of diabetes in Asian children and adults in Leicester. I have divided my prevalence study into three sections: the first dealing with childhood diabetes; the second with adult diabetes; and a final section that incorporates an overview of the prevalence of diabetes in Asians, with a discussion of my methodology and results.

#### A. PREVALENCE OF DIABETES IN ASIAN CHILDREN

It is generally held that IDDM in developing populations is rare. Unfortunately there have been no formally conducted precise studies in developing countries. Part of this may be due to inadequate resources, and also due to widely differing referral patterns, and the high mortality associated with this condition in these countries. Several other problems may also be encountered when trying to analyse such data on IDDM. Imprecise population numbers, expression of prevalence on the basis of hospital admissions and inadequate definition of the characteristics of true insulin dependence are some of the factors that have confounded the issue (Mann, Pyorala and Teuscher, 1983).

Registries for IDDM are concentrated mainly in Northern Europe and the North Eastern United States. The risk for developing IDDM is, therefore, practically unknown for the major part of the world population, concentrated in the continents of South America, Africa and Asia (La Porte et al, 1985). Data on childhood IDDM from the Indian subcontinent are sparse (Ahuja, 1979) (Gupta, Joshi and Dave, 1978). Studies on Asians in South Africa (Jackson, 1978), and in the United Kingdom (Odugbesan and Barnett, 1985) (Mather and Keen, 1985) have suggested a low prevalence of IDDM. This, however, has been based on the

impression that fewer Asians are being treated with insulin. There have been no formal studies in an Asian population of precisely ascertained classical childhood IDDM (WHO, 1985).

The 1981 census of the Office of Population Censuses and Surveys, UK, (OPCS) showed that in the City of Leicester, the immigrant Asian population was about 70,000. Leicester is ideally placed to study the prevalence of childhood IDDM.



## METHODS

### Ascertainment:

The rarity of IDDM as a disease (Wadsworth & Jarrett, 1974) makes it vitally important that ascertainment is complete. I have, therefore, compiled this from several complementary sources.

(a) A central register has been maintained since 1982 at the Leicester Royal Infirmary; for the transfer of all diabetics to U-100 insulin. It was estimated that all existing diabetics would be transferred on to the register by the end of 1984. Subsequent transfers on to U-100 insulin are automatically included in the register. This has been validated by enquiries of hospital consultants, general practitioners, clinical assistants, and diabetic health visitors in Leicester. The register contains name, age, sex, date of diagnosis, name of general practitioner, name of hospital consultant and type and dosage of insulin used.

(b) Independent registers maintained by the three diabetologists (Drs A C Burden, P G F Swift and J R Hearnshaw) caring for the population of Leicester City and County.

(c) Index cards maintained by diabetic health visitors. Specialist health visitors have for the last thirty years

been specifically dealing with any problems encountered in the community by juvenile diabetics (Walker, 1953). They are notified of all diabetics living within the area allocated to them, by hospital clinics, hospital wards after discharge of a diabetic patient, and general practitioners. They also maintain index cards to show the number of diabetic patients within their catchment and these are annotated for each visit.

(d) Three major general hospitals (Leicester Royal Infirmary, Leicester General Hospital and Glenfield Hospital) serve the community of Leicester and Leicestershire for acute medical emergencies. Hospital admissions for one year were scanned specifically for children with diabetic problems.

(e) A recently constructed register by Dr J R Hearnshaw was reviewed. This register was formed with a purpose to analyse the experience of childhood diabetes mellitus in Leicestershire (Hearnshaw, 1986).

Case-notes were then examined to confirm true insulin dependent diabetes mellitus (IDDM) by recording wasting symptoms, hyperglycaemia and ketonuria. The parents of all the Asian children were then confirmed to originate from the Indian subcontinent (India, Pakistan and Bangladesh) in order to eliminate any bias due to racial admixture. Ethnic origin of White Caucasian children was similarly confirmed.

Population Numbers:

Following the 1981 census, which showed that a high proportion of the population belonged to ethnic minority groups, the Leicester City and Leicestershire County Councils felt the need for another survey on a joint basis to examine and amplify the census results as they relate to ethnic populations of the City. The results of this survey have been recently published (Survey of Leicester, 1983) and have been used in this study.

Statistics:

The odds ratio for the age adjusted prevalence of IDDM at the time of the population survey in Asian and White Caucasian children was calculated with 95% confidence intervals (Kahn, 1983). If no difference in the prevalence rates occurred the ratio would be expected to be 1. 95% confidence intervals which include unity would render the observation statistically not significant.

## RESULTS

The overall prevalence per thousand for children aged 0-15 years was 0.54 for Asians and 0.99 for White Caucasians. For children aged 10-15 years, the prevalences were 0.97 and 1.87, and for children 0-9 years 0.31 and 0.38 per thousand for Asians and White Caucasians respectively (Table 2.1). This was not significantly different.

There was only one child, a White Caucasian diabetic girl, below the age of 5 years. An analysis of prevalence in the age group 0-5 years would not be meaningful and therefore I have analysed my results for the ages 0-9 years and 10-15 years.

TABLE 2.1: PREVALENCE OF IDDM IN ASIAN AND WHITE CAUCASIAN CHILDREN

		POPULATION	PREVALENCE PER 1000	RATIO OF PREVALENCES, WHITE CAUCASIAN:ASIAN (95% CONFIDENCE INTERVAL)	SIGNIFICANCE
0-15 YEARS	ASIAN	11 (M= 6 F= 5)	20,267	0.54	
	WHITE CAUCASIAN	44 (M=26 F=18)	44,268	0.99	N.S.
10-15 YEARS	ASIAN	7 (M= 2 F= 5)	7,187	0.97	
	WHITE CAUCASIAN	34 (M=21 F=13)	18,195	1.87	N.S.
0-9 YEARS	ASIAN	4 (M= 4 F= 0)	13,080	0.31	
	WHITE CAUCASIAN	10 (M= 5 F= 5)	26,073	0.38	N.S.

## DISCUSSION

There are no data from the Indian subcontinent on the prevalence of childhood diabetes (Ahuja, 1979; Gupta, Joshi and Dave, 1978). This may be due to widely differing hospital referral patterns, and the high mortality associated with insulin dependent diabetes in developing countries (Bennett, 1983). IDDM has usually been studied in children and young adults as the majority of cases are of this type at least till the age of 14-16 years, and as this is a relatively uncommon condition it is important that ascertainment is complete (Wadsworth and Jarrett, 1974). I feel confident that at the time of writing, I am aware of all children below the age of 15 years, with IDDM, and living within Leicester City boundaries, as I have painstakingly confirmed this from several different sources.

In order for a population study to be successful it is important that accurate information be obtained regarding the concerned population. With regard to the Office of Population Censuses and Surveys (OPCS), information on a subject's ethnic origin is based on the "place of birth of the head of household". As a growing number of "second generation" migrants born in the UK, are now raising their own children, this may give rise to errors in classification for epidemiological work. After a review of the 1981 Census of Population, the Leicester City and

Leicestershire County Councils jointly undertook a survey to amplify the census results as they relate to ethnic minorities in Leicester. As the question of ethnicity is a sensitive one the City and County Councils have taken every precaution in the compilation and handling of their information, at the same time ensuring that it provides a sound data base for epidemiological studies.

The overall prevalence of IDDM of 0.99 per thousand, observed in the population of White Caucasian children is similar to that observed in other studies (Knowleski and Warram, 1985). A prevalence rate of 0.54 per thousand was observed in Asian children. Unfortunately there are no data from the Indian subcontinent to compare this with. However, this appears higher than that observed in other Far and Middle Eastern populations. In Japan and Israel, prevalence rates of IDDM in children were 0.06 and 0.16 per thousand respectively (Knowleski and Warram, 1985). Although the prevalence of IDDM in Asians was lower than that in White Caucasians, this was not statistically significant at the 5% level. This observation suggests that classical childhood IDDM in Asians may occur more frequently than clinically expected. It also questions the hypothesis that there is a large difference in the prevalence of IDDM between Asians and White Caucasians, on the basis that IDDM is regarded primarily as a White Caucasian disease (MacDonald, 1980) (Cudworth and Wolf, 1982).

## B PREVALENCE OF DIABETES IN ASIAN ADULTS

Epidemiological data have show that the prevalence of diabetes mellitus varies with ethnic origin (Mann, Pyorala and Teuscher, 1983) (West, 1978). Studies from the Indian subcontinent have shown a high prevalence of diabetes (Ahuja, 1979) (Gupta, Joshi and Dave, 1978) and a recent survey (Mather and Keen, 1985), has confirmed a high prevalence of known diabetes in immigrant Asians in Southall, London. The overwhelming majority of diabetes in both developing and developed countries is of the non-insulin dependent type (NIDDM) (Mann, Pyorala and Teuscher, 1983). This has been thought to be due to the effects of affluence and overnutrition, and migrant studies of populations moving into developed areas suggest that the prevalence of diabetes may concomitantly increase, as has been shown in the instance of the Pacific Islanders (Prior and Tasman-Jones, 1981) (Taylor and Zimmet, 1981) (Reed et al, 1973).



## METHODS

### Diagnosis of diabetes mellitus:

This was made in the presence of documented evidence of classical symptoms of thirst and profuse urination, and a random venous plasma glucose greater than 11.1 mmol/l (WHO Study Group, 1985).

### Ascertainment from diabetic health visitors:

Specialist health visitors have for the last thirty years been involved in the community care of diabetic patients in Leicester (Walker, 1953). They are informed of all diabetic patients living within their geographical catchment area and visit their patients from time to time. Referral of patients is from hospital consultants of various specialties, hospital nursing staff and general practitioners in Leicester. Health visitors institute first line dietary treatment for new patients, and then refer them to specialist diabetologists. The diabetologist in turn is dependent on the health visitor for the community care of all patients attending the diabetic clinic.

Health visitor records were analysed for diabetic patients living in North East Leicester City. This specific area was chosen because it contained comparable numbers of adult residents belonging to each of the two ethnic groups studied. Patients were taken as "Asian" if they were

confirmed to originate from India, Pakistan or Bangladesh.

Other ethnic groups were excluded from this study as the numbers involved were too small to provide any meaningful information. Patients were then confirmed to be alive, over the age of 16 years, resident at the address listed, and the type of current treatment for diabetes was noted.

Diabetic clinic ascertainment:

Although three general hospitals serve the population of Leicester City the diabetic clinic is situated at The Royal Infirmary. In order to assess the completeness of the above ascertainment a further list of patients living within the defined boundaries was constructed from clinic notes. All those who had not died, and who were still resident within that area had already been included in the previous ascertainment.

Population numbers:

Data was obtained from the Office of Population Census and Surveys, 1981. There were 20,053 Asian and 18,068 White Caucasian above the age of 16 years, living within the area surveyed.

## RESULTS

967 Asian and 1,194 White Caucasian diabetics were ascertained. The precise number of diabetics along with the population base in each age band is shown in Table 2.2.

Unadjusted prevalence rates for Asians and White Caucasians was calculated assuming that the age distributions of the two populations had not changed between the time of the census and the survey. Using this calculation the prevalence of diabetes (both NIDDM and those on insulin) rose sharply in Asians above the age of 45 years.

Age adjusted relative risk (95% confidence limits) for diabetes in Asians aged 45-64 years was 1.6 (1.3-1.8), and for those over the age of 65 years it was 2.7 (2.5-3.2).

The survey was done from late 1984 to early 1986, and diabetics were classified according to the age of entry into the study. Prevalence was estimated as for 1985, that is the midpoint of the survey. A second calculation was performed for age adjusted prevalence rates. This assumed that both populations (Asian and White Caucasian) had aged by 4 years (midpoint of survey since census), and that 26.6% of the population in each 15 year age group had advanced into the next age band. This confirmed the increasing prevalence of diabetes in Asians over 45 years of age, although the rise was not as steep as in the

unadjusted data. The apparent decrease in prevalence by this calculation, in each age band over the age of 30 years appeared greater in Asians because of pronounced differences between the age distributions of the two populations. There were 15,007 Asians and 7,642 White Caucasians below the age of 45 years. Above this age, the ratio was reversed with 5,046 Asians and 10,426 White Caucasians. Using the age adjusted calculation larger numbers of Asians moved in the older age bands, and hence decreased the observed prevalence in Asians over the age of 45 years.

Patients were taken to have NIDDM if they had been on diet and/or tablets and had been diagnosed for at least three years. The exact numbers of patients with NIDDM is shown in Table 2.3. The relative risk of NIDDM with 95% confidence limits is also shown. This was uniformly and significantly higher in Asians in all age bands, being approximately twice that in White Caucasians.

TABLE 2.2: PREVALENCE RATES OF DIABETES MELLITUS IN ADULT ASIANS AND WHITE CAUCASIANS

AGE (YRS)	A S I A N				W H I T E C A U C A S I A N				
	POPULATION	No. OF DIABETIC PATIENTS	PREVALENCE (%) (UNADJUSTED)	PREVALENCE (%) (ADJUSTED)	AGE (YRS)	POPULATION	No. OF DIABETIC PATIENTS	PREVALENCE (%) (UNADJUSTED)	PREVALENCE (%) (ADJUSTED)
16-29	9438	31	0.3	0.3	16-29	4619	69	1.5	1.3
30-44	5569	130	2.3	1.8	30-44	3028	87	2.9	2.5
45-64	3925	527	13.4	10.9	45-64	4102	327	8.0	9.3
≥ 65	1121	279	24.9	13.2	≥ 65	6324	666	10.5	9
OVERALL	20,053	967	4.8	4.3	OVERALL	18,068	1,194	6.6	6.3

**TABLE 2.3: PREVALENCE RATES OF NIDDM IN ADULT ASIANS AND WHITE CAUCASIANS**

AGE (YRS)	RACE	TOTAL POPULATION	No. OF PATIENTS WITH NIDDM	PREVALENCE OF NIDDM (%)	ODDS RATIO, NIDDM ASIAN:WHITE CAUCASIAN (95% CONFIDENCE LIMITS)
16-29	ASIAN	9438	12	0.1	> 2
	WHITE CAUCASIAN	4619	0	-	
30-44	ASIAN	5569	77	1.4	1.9 (1.1 - 2.9)
	WHITE CAUCASIAN	3023	22	0.7	
45- 64	ASIAN	3925	418	10.6	1.8 (1.5 - 2.2)
	WHITE CAUCASIAN	4102	241	5.9	
≥ 65	ASIAN	1121	228	20.3	2.5 (2.1 - 2.9)
	WHITE CAUCASIAN	6324	516	8.2	

## DISCUSSION

The prevalence of NIDDM has been shown to increase with age, and also with the time of the study (Marble et al, 1985). This could be due to a more complete case ascertainment, or broadening of diagnostic criteria. I have shown high prevalence rates of diabetes mellitus in Asian and White Caucasian ethnic groups over all age bands.

I chose as my diagnostic criterion a single point in time when patients had a combination of symptoms attributable to diabetes mellitus, in the presence of a random venous plasma glucose greater than 11.1 mmol/l. This is accepted by the WHO for the clinical diagnosis of diabetes mellitus (WHO Study Group, 1985). As such I may have included patients with "milder" degrees of glucose intolerance, and also those who may have had high glucose concentrations concomitant with an illness or stressful situation. It is debatable whether this glucose intolerance would have persisted after the initiating event subsided, as I did not formally perform an oral glucose tolerance test at a later date. In this respect, this study differs from a previously published report of prevalence of diabetes in Asians in the UK (Mather and Keen, 1985) in that I have ascertained to the best of my ability, those who have "ever had" diabetes, rather than those "known to have diabetes at the time of survey".

What is striking is that using the same diagnostic criteria

for both ethnic groups, Asians had a significantly higher relative risk for NIDDM. This was approximately twice that for White Caucasians and persisted in all age bands above the age of 16 years. The use of insulin in the treatment of "adult onset diabetes" to distinguish insulin dependent diabetes mellitus (IDDM) from NIDDM may be regarded as artificial, as some patients may require insulin in the absence of specific classification criteria for IDDM. However, it is generally agreed that in middle adult life new cases of IDDM are relatively rare compared to NIDDM. By excluding patients taking insulin, newly occurring IDDM and childhood IDDM progressing into adult life would be excluded, and, "true NIDDM" may, if anything, be somewhat underestimated. To the best of my knowledge, insulin therapy in the non-insulin dependent situation is equally acceptable in both the ethnic groups surveyed, and the rate of those failing to be controlled on diet and oral hypoglycaemic therapy in this situation is also about the same in both groups. I do not expect the present results, therefore, to be significantly altered by excluding those currently on insulin.

Studies from the Indian subcontinent have shown a wide variation in the prevalence of adult diabetes mellitus. In a six centre collaborative study in subjects over the age of 15 years, prevalence rates in Gujarat (West India) were marginally higher than in other parts of the country (Ahuja, 1979). Gupta, Joshi and Dave (1978) studied the prevalence in subjects over 15 years in Ahmedabad, Gujarat.



They found an increasing prevalence with age, being 10.3% in those aged 51-60 years, and 16.4% in those over 60 years of age. It has been argued that this study may have overestimated the prevalence of diabetes, as some of the diagnostic criteria may be regarded as too stringent, for example, a fasting blood glucose in excess of 5.5 mmol/l. However, the results of the present survey are very similar particularly in the upper age bands. Over 90% of the subjects surveyed were originally from the Gujerat region of India having come to the UK via East Africa. This leads me to believe that Asians have a truly high prevalence and high risk for diabetes.

Another factor that may be contributory to the prevalence, is the affect of migration. Studies from the Pacific Islands are particularly useful in this respect. Tokelau consists of three coral atolls north of Western Samoa. A number of Tokelauans have migrated to New Zealand. Studies performed on the emigrant population has shown that the prevalence of diabetes is higher in Tokelauans in New Zealand than those in Tokelau (Stanhope and Prior, 1976) (Prior and Tasman-Jones, 1981). Taylor and Zimmet (1981) have shown that diabetes in migrant Wallesians in Noumea is approximately four times higher than those who remained in their home of the Wallis Islands, and was also significantly higher compared to Noumeans even after adjusting for obesity. Similar results of increasing prevalence are seen in Micronesians who have

left their native Rota Island and migrated to California (Reed et al, 1973). Prevalence rates rose from 3% in men and 8% in women on Rota, to 10% in men and 14% in women migrating to California. These studies emphasize the effect of migration into an affluent society, on the development of diabetes.

Several studies have been published on the prevalence of diabetes in expatriate Asians. I have summarized the major ones below. They show considerable variation in the overall crude prevalence rates.

	PLACE	PREV (%)
West and Kalbfleish, 1966	Malaysia	4.2
Poon-King, Henry, Rampersad, 1968	Trinidad	2.4
Jackson, 1978	South Africa	5.0
Zimmet and Sloman, 1980	Fiji	11.8
Cheah and Tan, 1980	Singapore	6.1
Mather and Keen, 1986	Southall, London	2.2

Problems in interpreting these results arise mainly from differences in the methodology and criteria used for the diagnosis of diabetes, as well as the age of the population surveyed. Notwithstanding these difficulties, it would appear that these figures are higher than those reported from India. The overall prevalence of diabetes (all age groups included) have been from just over 2% (Ahuja, 1979) to about 4% (Gupta, Joshi and Dave, 1978). It might be,

therefore, that the observed high prevalence of diabetes in Asians is an effect of migration.

I am aware that the present study has potential sources of error. These may be due to varying attitudes amongst subjects of different ethnic groups in seeking medical advice for symptoms of hyperglycaemia, as well as differing patterns of referral for investigations amongst medical personnel. An analysis of hospital records may underestimate the true prevalence of diabetes as all patients may not attend the hospital clinic. I have, therefore, tried to complement this by analysing health visitor records. Migration into or from the area of the survey might also affect results. From informal discussions with the Leicester City Council, it would appear that the major influx of Asians into Leicester occurred during the late sixties and early seventies, and that over the last five years, there have been no major migratory influences affecting the area of the survey. In my calculation for age adjustment, I have used a relatively simple method by assuming a fixed proportion of the population of each age group moving into the next one, as the whole population ages uniformly. This has not taken into account factors that might affect the "turnover" of the population, such as death for example. As the survey was restricted to a specific area of Leicester City, precise figures for such variables are not readily accessible.

### C. CONCLUSIONS OF THE STUDY OF PREVALENCE OF DIABETES IN ASIANS

Prevalence of diabetes in differing populations have shown considerable variation, and such studies are often beset by several difficulties. These include precise definitions of diagnostic criteria, and accurate case ascertainment as well as assessment of the population base.

In a condition such as childhood diabetes, it has been argued that incidence figures may be of greater value in determining the extent of the disease, especially for comparative epidemiological work. Further, for meaningful information it would be necessary to analyse incidence sequentially and in a longitudinal fashion over several years. A cumulative incidence may again be a useful parameter. (In theory a cumulative incidence would differ from prevalence, and would eliminate bias due to death, and migration either into or out of the survey area). Such a study is a long term objective, and is beyond the scope of work spanning a few years. I have therefore, chosen prevalence of diabetes as the measure of the degree of the disease in Asian children. Owing to the compilation of case ascertainment from different complementary sources, I feel that at the time of writing, this is complete. Another potential source of error would be in misclassification of an ethnic group in the reports of the Office of Population Census and Surveys as this is based on

"place of birth of head of household". The results of the survey by the Leicester City and Leicestershire County Councils aim at deriving precise figures for the ethnic minority populations in Leicester, and I have used these as the denominator for my prevalence study.

On the basis of the above, I have derived an overall prevalence per 1000, of diabetes in the population below 15 years of age in Leicester as 0.54 in Asians and 0.99 in White Caucasians. Although this difference may appear large, the relative risk (White Caucasian:Asian) is 1.83 with 95% confidence intervals of 3.6 to 0.9. This would suggest that the difference between the two ethnic groups is not significant at the 5% level. A further analysis of the data in age bands 10-15 years, and 0-9 years fails to demonstrate statistically significant difference at the 5% level. These results represent an attempt to establish a population based prevalence of diabetes in Asian children. They also suggest that the difference in classical IDDM between Asians and White Caucasians is not as large as would be expected if IDDM were truly a White Caucasian disease (MacDonald, 1980) (Cudworth and Wolf, 1982). Bodansky et al (1987) studying Asian children with IDDM in West Yorkshire, have shown that their 17 subjects had the hallmarks of insulin dependence, proneness to ketosis, significant increase in islet cell antibodies, and increase in HLA-B8, DR3, DR4 and DR3/DR4 markers, all features that would be expected in White Caucasian children.

Despite a large population base of 65,000 children, the rarity of IDDM as a disease provides only a small number of prevalent cases. In order to achieve power of 80% a population of 120,000 is required. I feel that this can best be achieved by collaboration between different centres. If it is then shown that IDDM in Asian children is not as rare as it has been thought, then further investigations would be required to determine why this is so.

In addition to some of the problems mentioned above, a further difficulty in estimating prevalence of diabetes in adults lies in variations in the screening criterion for diabetes. Previous studies have used random glycosuria, early morning glycosuria, 50 gm GTT, 100 gm GTT, questionnaires for known diabetes, reports of self diagnosis. Consequently, the prevalence figures have shown wide variation (West, 1978). The clinical diagnosis of diabetes is made in the presence of symptoms of increased thirst and urine volume and a random venous plasma glucose more than 11.1 mmol/l (WHO Study Group, 1985). This is what I have used for the present study, and it is arguable that this may have resulted in some degree of overestimation. However, recent reports have shown a trend for the prevalence of NIDDM in adults to be on the increase, particularly with age (Marble et al, 1985). A study from the USA in subjects aged 20-74 years and using ascertainment from medical records and the prescription of antidiabetic preparations, or from records of newly

diagnosed diabetics with a venous plasma glucose greater than 11.1 mmol/l two hours after a standard 75 gm GTT showed a prevalence rate of 6.9% (WHO Study Group, 1985). Age adjusted prevalence of diabetes in subjects over 16 years in my study, also shows a trend to increase with age in both ethnic groups. NIDDM, however, appears to be much commoner in Asians, the relative risk being approximately twice that in White Caucasians. This is particularly striking in the group of "young adults" (aged 16-29 years) where 12 Asian patients were ascertained, but not a single White Caucasian.

I have deliberately chosen a specific geographical area of North East Leicester City for my survey. There were several reasons for this. Firstly, this contained very few enumeration districts of the Office of Population Census and Surveys that straddled the geographical boundary of the study. This was a particularly valuable asset in determining accurate population numbers. The OPCS bases its population survey on data from a number of enumeration districts, which is a unit made up of about 20 households. In theory, therefore, the margin of error in estimating the population base, in this area surveyed would be limited to two or three hundred heads, and would be insignificant for a study of this magnitude. The second reason for choosing this area was that I was able to confirm that at the time of survey, all included in the ascertainment were actually living in the area described. This would at least decrease bias due to death and outward migration. Finally, this

area contained the most comparable numbers of Asians and White Caucasians over the age of 16 years, when compared to other areas in Leicester.

I cannot, of course, claim complete ascertainment in this survey as I did with my survey on childhood diabetes. The magnitude of the numbers involved itself makes such a claim exceedingly difficult. Further, most authorities accept that in view of the wider distribution of NIDDM which forms the bulk of diabetes in adults, absolutely accurate ascertainment is not as critical or even practically feasible as in childhood IDDM. I feel that the potential flaws in my survey are not any greater than those that may occur within the limits of chance and the nature of such a study, and I believe that the comparisons that I have made on the prevalence of diabetes in Asians and White Caucasians, are as valid as can be reasonably expected.



## **C H A P T E R    3**

### **CLINICAL FEATURES AND VASCULAR COMPLICATIONS OF DIABETES IN ASIANS**

## INTRODUCTION

The concept of diabetes mellitus as a disorder of failure of glucose metabolism due to inadequate insulin secretion with varying degrees of severity, has now been replaced by one that regards this as an expression of a metabolic state of varying aetologies with a wide spectrum of clinical manifestations and progression (Mann, Pyorala and Teuscher, 1983). In the classical form, studied in the western hemisphere, the clinical features and complications of the disease have been well outlined, at least in the broadest terms (Keen and Jarrett, 1982) (Ellenberg and Rifkin, 1983). Many diabetic variants are seen in developing countries, and the balance between differences in genetic factors and geographical influences are likely to result in differences in the manifestation of the disease (Keen and Ekoe, 1984).

Early reports of ECG changes on diabetic subjects from Hong Kong and Tokyo suggest that this group may be relatively protected against atherosclerosis (Goto, Sato and Matsuda, 1974) (Horiuchi et al, 1971). However, it would appear that this is lost when these subjects move into a "westernised" environment (Kawate et al, 1979). Again it would appear that the Japanese population is perhaps more susceptible to severe proteinuria, retinopathy and retinopathic blindness, and end stage renal disease (Sasaki et al, 1983). These findings are of considerable interest because the Far Eastern population seem to be

relatively protected from macrovascular disease and yet highly susceptible to microvascular complications. Diabetes of relatively long duration in other populations seems to correlate with retinopathy and nephropathy as in Ethiopia (Lester, 1983) and in the Pacific Island (King et al, 1983). Data such as these suggest that geographical and ethnic differences may influence the outcome of diabetes.

Much of the data on the manifestations and complications of diabetes collected over the world, is difficult to interpret on a comparative basis because of lack of agreement on definite criteria and definitions. Because of this, a multinational group under the sponsorship of the WHO agreed on a standard protocol to study the complications of diabetes in patients aged 35-55 years (Jarrett, Keen and Grabauskas, 1979) (Keen and Jarret, 1979) (Jarrett and Keen, 1979). The results of this study have been published in detail recently (Diabetes Drafting Group, 1985) and serve to emphasise the variations that may occur in the clinical manifestations. In the present study I have tried to define the clinical features and complications of diabetes in Asians in Leicester, and to compare them with the indigenous population.

## SUBJECTS, MATERIAL AND METHODS

456 consecutive Asian and 451 consecutive White Caucasian patients attending the diabetic clinic at the Leicester Royal Infirmary for at least one year, were recruited into the study over a period of time. All patients were interviewed at least once in order to verify as accurately as possible, and for completeness of the data points as shown below. The process of data collection spanned a period of two years, from 1984-1986.

(a) Demographic details:- name, age, sex, date of birth and religion were recorded. Duration of stay in the UK, and country of origin was also noted for Asian patients. Social class was recorded according to the Classification of Occupations (1980).

(b) Height was recorded without shoes, and weight while wearing ordinary indoor clothing. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in metres.

(c) Family History: This was noted as no known family history of diabetes; a positive family history in a first degree relative (parents, siblings or children); a positive family history in any other relative (grandparents, uncles, aunts, cousins)

(d) Patients were grouped into cigarette smoking classes

as follows:- Those who had never smoked; those who had ceased smoking; those smoking 1-14 cigarettes a day; 15-24 cigarettes a day; and more than 25 cigarettes a day.

(e) Physical exercise was graded as follows: sedentary (rarely takes exercise, sedentary job); moderate (on feet less than half the day); active (on feet most of the day or some form of exercise at least three times per week); fit (manual worker or vigorous exercise three or more times per week).

(f) Blood pressure was recorded using a standard clinical mercury sphygmomanometer and a 10 x 22 cms cuff after resting in the sitting position for at least 15 minutes. Diastolic pressure was recorded at the time of disappearance of sounds (Korotkov phase 5). Patients were taken as "hypertensive" if systolic blood pressure was more than 160 mm Hg, or diastolic blood pressure more than 95 mm Hg, or if they were receiving treatment with antihypertensive drugs.

(g) Date of onset of diabetes along with plasma glucose and ketonuria at that time were noted by an analysis of case notes. Treatment for diabetes (diet, tablets or insulin), and time after diagnosis for insulin therapy to be initiated, was noted.

(h) Large Vessel Disease. End points of large vessel disease were as shown below.

#### 1. Heart Vascular Disease

End points of heart vascular disease were:

- (i) Clinical angina pectoris exacerbated on exertion with or without an abnormal standard 12-lead ECG. ECG features of Q/QS complexes, ST segment or T wave changes in the presence of angina were taken as abnormal.
- (ii) Clinical myocardial infarction with either definite ECG changes or a temporal rise in cardiac enzymes.

#### 2. Peripheral Vascular Disease

End points of peripheral vascular disease were:

- (i) "Intermittent claudication" which was taken as positive in the presence of a classical history of pain in the leg on walking either on the flat or uphill
- (ii) "Gangrene" or "amputation" was recorded if there was either necrotic or surgical loss of tissue in the toe, foot or leg due to arterial obstruction rather than neuropathic causes, a decision based on clinical judgment.

#### 3. Cerebrovascular Disease

This was recorded if there was documented evidence of neurological deficit lasting more than 24 hours, or a currently persistent neurological deficit, clinically thought to be due to thrombosis in the territory of one or more areas of the cerebral circulation.

(i) Small Vessel Disease

1. Eye Disease

Ocular fundi were examined under full pupillary dilation (except where there may have been a contraindication such as glaucoma) and the following components were noted:- cataracts, microaneurysms, haemorrhages, hard exudates, soft exudates, maculopathy, preproliferative changes (intraretinal microvasculature abnormalities, venous beading, cottonwool spots), proliferative changes with neovascularization, vitreous haemorrhage and retinopathic blindness.

2. Kidney Disease

A freshly passed sample of urine was tested for protein using Albustix. If positive it was re-checked after a period of six weeks. If still positive mid stream urine bacteriology (MSU) and intravenous pyelography (IVP) were performed in sequential order and 24 hour urinary protein assessed.

End points of small vessel disease of the kidney were:

(i) Persistent proteinuria taken as positive on Albustix testing on at least two consecutive occasions separated by a period of at least six weeks, with a 24 hour urinary protein greater than 0.5 gm, in the absence of bacterial infection of the urine, and with a normal intravenous pyelogram.

(ii) Intermittent proteinuria taken as above, but when the episodes of proteinuria were not present on consecutive

testing of urine.

(iii) Raised serum creatininine persistently above 120  $\mu\text{mol/l}$  in the absence of any other identifiable cause.

(j) Random venous blood was sampled for glycosylated haemoglobin (stable fraction, gel electrophoresis).

(k) Relative risk for Asians compared to White Caucasians of developing complications of diabetes, was calculated after adjusting for age, sex, age at diagnosis, duration of diabetes, hypertension and smoking.

Multivariate logistic regression was used to determine the extent of individual contributions from each of the above as well as BMI, physical activity, HbA1 and social class, to the development of complications.

(l) Differences in the frequency of clinical features of the subjects studied, were compared using the Chi-Square Test. Analysis of variance was used to compare means, as appropriate.



## RESULTS

### CLINICAL FEATURES OF SUBJECTS

907 (456 Asian and 451 White Caucasian) subjects were studied. Details of subjects are shown in Table 3.1. There were no significant differences between the number of males and females in each group, or mean age at the time of the study. Mean age at diagnosis of diabetes was significantly higher (46.5 vs 40.6 years) ( $p < 0.01$ ), and mean duration of diabetes significantly less (6.3 vs 11.4 years) ( $p < 0.01$ ) in Asians (Table 3.1).

#### Plasma Glucose at Diagnosis:

Mean plasma glucose was significantly lower at diagnosis in Asians (18.2 vs 19.3 mmol/l) ( $p < 0.01$ ) (Table 3.1). No significant differences were observed between Asians and White Caucasians for those on insulin therapy or those on therapy with diet or tablets.

#### Urine Ketones at Diagnosis:

Overall significant differences in ketonuria at presentation were observed between Asians and White Caucasians ( $p < 0.01$ ) (Table 3.1). 85.3% Asians had absence of ketonuria at presentation compared to 47.8% White Caucasians.

For those on insulin therapy within the first year after

diagnosis, 72.5% Asians and 83.9% White Caucasians had either moderate or severe ketonuria ( $p < 0.05$ ). No significant differences were observed between Asian and White Caucasians for those on insulin after 2 years of diagnosis or those on therapy with diet or tablets.

#### Family History of Diabetes:

Overall significant differences in family history of diabetes were observed between Asians and White Caucasians ( $p < 0.01$ ) (Table 3.1). 29.5% Asians gave a positive history of diabetes in a first degree relative compared to 16% White Caucasians.

For those on insulin therapy within the first year of diagnosis a positive family history of diabetes was obtained in 40% Asians and 29% White Caucasians ( $p < 0.01$ ).

No significant differences were observed between Asians and White Caucasians for those on insulin after 2 years of diagnosis or those on therapy with diet or tablets.

#### Current Treatment for Diabetes:

Significantly greater numbers of Asians were being treated with diet or tablets compared to White Caucasians ( $p < 0.01$ ) (Table 3.1). Current insulin requirement was observed in 31.4% Asians compared to 68.7% White Caucasians.

#### Current Control of Diabetes:

This was judged by a single sample of glycosylated

haemoglobin (HbA1). Mean HbA1, was higher in Asians compared to White Caucasians (9.4 vs 9.1%) ( $p < 0.05$ ) (Table 3.1)

Body Mass Index:

This was significantly higher in Asians compared to White Caucasians (26 vs 25) ( $p < 0.05$ ) (Table 3.1).

Hypertension:

There was no significant difference in the prevalence of hypertension between the two groups.

Social Class:

Overall significant differences were observed between Asians and White Caucasians ( $p < 0.001$ ) (Table 3.1). 75.9% Asians belonged to social classes 4 and 5 compared to 50.9% White Caucasians.

Smoking:

Overall significant differences were observed in smoking habits between Asians and White Caucasians ( $p < 0.001$ ) (Table 3.1). 71.9% Asians had never smoked, compared to 57.8% White Caucasians.

Physical Exercise:

Overall significant differences were observed between Asians and White Caucasians in the amount of daily physical exercise taken ( $p < 0.001$ ) (Table 3.1).

91.7% Asians were classed in groups taking moderate physical exercise , or leading a sedentary existence, compared to 67% White Caucasians.

Duration of stay in the UK for Asian diabetics:

Mean duration of stay in the UK was 16.9 years. 6% of Asians had diabetes prior to migration; 94% developed diabetes subsequent to migration to the UK. Mean duration for development of diabetes was 10.3 years after migration (Table 3.1). 91% had migrated from East Africa (Kenya, Uganda, Tanzania and Zambia), 8% from the Indian subcontinent (India, Pakistan and Bangladesh) and 1% from other countries (Mauritius, Malawi).

Table 3.1CLINICAL FEATURES OF DIABETIC SUBJECTS STUDIED

	<u>Asian</u>	<u>White Caucasian</u>	<u>Statistical Significance</u>
Number	456	451	N.S.
Male	283 (62.1%)	266 (59%)	N.S.
Female	173 (37.9%)	185 (41%)	N.S.
Age (yrs) Mean (SD)	52.7 (12.3)	51.9 (16)	N.S.
Age at diagnosis, yrs.			
Mean (SD)	46.5 (12.8)	40.6 (17.5)	p<0.01 <sup>a</sup>
Duration of diabetes, yrs. Mean (SD)	6.3 (6.0)	11.4 (9.6)	p<0.01 <sup>a</sup>
Plasma glucose (mmol/l) at diagnosis.			
Mean (SD)	18.2 (4.5)	19.3 (4.7)	p<0.01 <sup>a</sup>
Urine ketones at diagnosis			p<0.01 <sup>b</sup>
None	362 (85.3%)	202 (47.8%)	
Mild	25 (5.9%)	39 (9.2%)	
Moderate	16 (3.7%)	82 (19.4%)	
Severe	21 (4.9%)	99 (23.4%)	
Family history of diabetes			p<0.01 <sup>b</sup>
None	309 (67.9%)	335 (74.6%)	
First degree relative	134 (29.5%)	72 (16%)	
Other relative	12 (2.6%)	42 (9.4%)	
Current treatment			p<0.01 <sup>b</sup>
Diet	117 (25.7%)	41 (9.1%)	
Tablets	196 (43%)	100 (22.2%)	
Insulin	143 (31.4%)	310 (68.7%)	
HbA <sub>1c</sub> , %. Mean (SD)	9.4 (2.5)	9.1 (2.3)	p<0.05 <sup>a</sup>
Body mass index.			
Mean (SD)	26 (0.04)	25 (0.04)	p<0.05 <sup>a</sup>
Hypertension	86 (18.5%)	85 (19.5%)	N.S.

Table 3.1 cont

	<u>Asian</u>		<u>White Caucasian</u>		<u>Statistical Significance</u>
<b>Social Class</b>					p<0.001 <sup>a</sup>
1	2	(0.4%)	5	(1.1%)	
2	9	(2%)	38	(8.5%)	
3	98	(21.7%)	176	(39.5%)	
4	295	(65.3%)	178	(39.9%)	
5	48	(10.6%)	49	(11%)	
<b>Smoking</b>					p<0.001 <sup>a</sup>
Never	327	(71.9%)	259	(57.8%)	
Stopped	18	(4%)	67	(15%)	
1-14 cig/day	100	(22%)	107	(23.9%)	
15-24 cig/day	10	(2.2%)	15	(3.3%)	
<b>Physical exercise</b>					p<0.001 <sup>a</sup>
Sedentary	122	(26.9%)	90	(20.1%)	
Moderate	294	(64.8%)	210	(46.9%)	
Active	31	(6.8%)	111	(24.8%)	
Fit	7	(1.5%)	37	(8.3%)	
<b>Religion</b>					
None	0		124	(27.5%)	
Hindu	292	(64.2%)	0		
Sikh	65	(14.3%)	0		
Moslem	92	(20.2%)	0		
Christian	6	(1.3%)	327	(72.5%)	
<b>Duration of stay in UK,</b>					
yrs. Mean (SD)	16.9	(5.9)	-		
<b>Diabetes prior to</b>					
immigration	27	(6%)	-		
<b>Diabetes after</b>					
immigration	424	(94%)	-		
<b>Years after immigration.</b>					
Mean (SD)	10.3	(6)	-		

<sup>a</sup> : Analysis of variance

<sup>b</sup> : Chi-Square test

## LARGE VESSEL DISEASE

### Heart Vascular Disease (HVD):

The overall prevalence of HVD was increased in Asian women being 27.7% compared to 19.5% in White Caucasian women. All three individual components of HVD (angina, angina + abnormal ECG, definite myocardial infarction) were also increased in Asian women (Table 3. 2).

The overall prevalence of HVD in Asian men was 23.8% compared to 24.4% in White Caucasian men. The prevalence of definite myocardial infarction was increased in Asian men, 18.7% compared to 17.2% in White Caucasian men (Table 3.2).

The adjusted relative risk for Asians of developing HVD was 1.15; of angina 1.84; and of definite myocardial infarction 1.12 (Table 3.4).

### Peripheral Vascular disease (PVD):

The overall prevalence of PVD was decreased in both Asian men (3.9%) and women (3.5%), when compared to White Caucasian men (11.7%) and women (5.9%) (Table 3.2).

The prevalence rates of gangrene and amputation taken together, were lower in Asian men (1.5%) and women (2.4%) when compared to White Caucasians of the same sex (men 5.7%, women 3.2%).

The adjusted relative risk for Asians of developing PVD was 0.51 (95% CI 0.27-0.96) (Table 3.4).

Cerebro Vascular Disease (CVD):

The overall prevalence of CVD was decreased in Asian men (2.8%) and women (1.2%) compared to White Caucasian men (4.1%) and women (2.7%). The prevalence of the individual components of CVD was also lower in Asians of both sexes (Table 3.2).

Adjusted relative risk for Asians of developing CVD was 0.61, and of developing neuroplegia lasting more than 24 hours but with significant recovery was 0.48 (Table 3.4).



Table 3.2PREVALENCE OF LARGE VESSEL DISEASE (%)

	<u>Asian</u>		<u>White Caucasian</u>	
	Male	Female	Male	Female
Heart Vascular disease	66(23.8)	48(27.7)	65(24.4)	36(19.5)
Angina	9 (3.2)	9 (5.2)	9 (3.4)	7 (3.8)
Angina + abnormal ECG	32(11.3)	32(18.5)	33(12.4)	23(12.4)
Definite myocardial infarction	53(18.7)	15 (8.6)	46(17.2)	12 (6.4)
Peripheral Vascular Disease	11 (3.9)	6 (3.5)	31(11.7)	11 (5.9)
Intermittent claudication	11 (3.9)	6 (3.5)	31(11.7)	11 (5.9)
Gangrene	3 (1.1)	2 (1.2)	9 (3.4)	5 (2.7)
Amputation	1 (0.4)	2 (1.2)	6 (2.3)	1 (0.5)
Cerebro Vascular Disease	8 (2.8)	2 (1.2)	11 (4.1)	5 (2.7)
Neuroplegia > 24hrs	8 (2.8)	2 (1.2)	11 (4.1)	5 (2.7)
Residual paralysis	6 (2.1)	2 (1.2)	9 (3.4)	3 (1.6)
Large Vessel Disease	71(25.1)	52(30.1)	73(27.4)	42(22.7)

## SMALL VESSEL DISEASE

### Eye Disease:

The overall prevalence of eye disease was lower in Asian men (10.5%) and women (13.3%) compared to White Caucasian men (31.6%) and women (33.5%). The prevalence rates of each of the components of eye disease (background retinopathy, exudative retinopathy, maculopathy, proliferative retinopathy, vitreous haemorrhage, retinopathic blindness) were lower in Asians when compared to White Caucasians of the same sex (Table 3.3).

The adjusted relative risk for Asians of developing eye disease was 0.31 (95% CI 0.19–0.51). The adjusted relative risks for Asians of developing each of the individual components of eye disease was lower (Table 3.4).

The overall prevalence of cataracts was higher in both Asian men (10.6%) and women (8.7%) compared to White Caucasian men (6.4%) and women (3.2%) (Table 3.3). The adjusted relative risk for Asians of developing cataracts was 6.35 (95% CI 1.43–28.16) (Table 3.4).

### Kidney Disease:

The overall prevalence of kidney disease was greater in Asian men (24.4%) and women (19.1%) compared to White Caucasian men (13.2%) and women (11.9%). The prevalence of

persistent proteinuria was also greater in Asians compared to White Caucasians of the same sex (Table 3.3).

The adjusted relative risk for Asians of developing kidney disease was 3.36 (95% CI 1.88-5.99), and of developing proteinuria 2.76 (95% CI 1.66-4.58) (Table 3.4).

Multivariate regression analysis for the individual contributions of duration of diabetes, BMI, physical activity, social class, smoking, HbA1c, towards the complications of diabetes did not show a significant difference between the two ethnic groups.

Table 3.3

PREVALENCE OF SMALL VESSEL DISEASE (%)

	<u>Asian</u>		<u>White Caucasian</u>	
	Male	Female	Male	Female
Eye Disease	30(10.6)	23(13.3)	84(31.6)	62(33.5)
Background retinopathy	13 (4.6)	10 (5.8)	31(11.7)	28(15.1)
Exudative retinopathy	3 (1.1)	1 (0.6)	12 (4.5)	14 (7.6)
Maculopathy	11 (3.9)	8 (4.6)	18 (6.8)	20(10.8)
Proliferative retino-				
pathy	14 (4.9)	6 (3.5)	37(13.9)	10 (5.4)
Vitreous haemorrhage	0 (0)	0 (0)	4 (1.5)	1 (0.5)
Retinopathic blindness	1 (0.4)	2 (1.2)	4 (1.5)	4 (2.2)
Cataracts	30(10.6)	15 (8.7)	17 (6.4)	6 (3.2)
Kidney Disease	69(24.4)	33(19.1)	35(13.2)	22(11.9)
Persistent proteinuria	38(13.4)	21(12.1)	21 (7.9)	13 (7.0)
Intermittent protein-				
uria	20 (1.7)	9 (5.2)	6 (2.3)	4 (2.2)
Raised serum				
creatinine	27 (9.5)	5 (2.9)	13 (4.9)	12 (6.5)

Table 3.4

### RELATIVE RISK FOR ASIANS OF DEVELOPING COMPLICATIONS OF DIABETES

		95% CI
Heart Vascular Disease	1.15	0.84 - 1.57
Angina ± abnormal ECG	1.84	0.97 - 3.49
Definite myocardial infarction	1.12	0.66 - 1.91
Peripheral Vascular Disease	0.51	0.27 - 0.96
Cerebro Vascular Disease	0.61	0.27 - 1.37
Neuroplegia > 24 hours	0.48	0.10 - 2.75
Eye Disease	0.31	0.19 - 0.51
Background retinopathy	0.93	0.56 - 1.54
Exudative retinopathy	0.54	0.22 - 1.33
Maculopathy	0.63	0.42 - 3.03
Proliferative retinopathy	0.75	0.38 - 1.47
Retinopathy blindness	0.36	0.10 - 1.49
Cataracts	6.35	1.43 - 28.16
Kidney Disease	3.36	1.88 - 5.99
Proteinuria (persistent or intermittent)	2.76	1.66 - 4.58
Raised serum creatinine	0.65	0.25 - 1.70

## DISCUSSION

The prevalence of vascular complications in diabetics may show considerable geographic and ethnic differences (West, 1978). There is an urgent need to systematically document such variability. If large differences are persistently noted then these may be due to individual genetic susceptibility or environmental influences. Subsequent identification of specific factors predisposing to diabetic complications may have important regional implications in the trends of administering health care.

Unfortunately, it is not easy to draw valid conclusions from different studies published independently of each other. Many confounding features may be introduced by a multiplicity of interdependent variables, which preclude a direct comparison. Some of the important factors that need to be taken into account in such epidemiological studies are standardized definition of cases, validation of the methods of measurement, accuracy in the repeatability of such measurements, and good quality control (Rose and Blackburn, 1978). It is therefore essential, that for valid conclusions, a degree of uniformity is maintained with respect to the above, in the studies that are being compared. It is no easy task to achieve this especially if the locations of data collection are widely separated geographically. For these reasons, a multinational study was launched under the auspices of the WHO to determine the prevalence of vascular complications using well described

procedures in diabetics from 14 different centres, and representing 13 national groups (Diabetes Drafting Group, 1985). The results of this study show that there is heterogeneity in the prevalence of large vessel disease in diabetics, and it is suggested that heterogeneity in the prevalence of small vessel disease also exists. The study also remarks that "diabetic subjects in this study showed considerable diversity in the vascular disease type . . . clearly, conclusions about diabetic patients drawn from one culture cannot automatically be extrapolated to all diabetic populations".

The implications of the WHO study are manifold, and in one major respect, would suggest the need for studies using standardized methods to achieve comparability of diabetic complications in differing ethnic groups. This is what I have tried to achieve in my present study. I have studied 907 consecutive Asian and White Caucasian subjects attending the diabetic clinic at Leicester, and by applying the same previously determined criteria to them, I have tried to assess the frequency of the vascular complications of diabetes.

There were no significant differences in the numbers and mean age of the diabetic subjects in the two groups. Mean age at diagnosis was significantly higher in Asians being 46.5 years. In my previous chapter I have shown that the prevalence of diabetes rises steeply in Asians above the age of 45 years, and so a greater number of Asians would be

expected to be in the fifth and sixth decades. The duration of diabetes was lower in Asians, as might be expected from the above.

Overall significant differences were observed in the family history of diabetes. 29.5% Asian diabetics gave a history of diabetes in a first degree relative compared to 16% White Caucasians. A recent study, comparing family history of diabetes between Asian and European subjects with non-insulin dependent diabetes has shown Asian diabetics to have a higher prevalence of diabetes amongst first degree relatives (Mohan et al, 1986 a). By an analysis of diabetes in parents of the affected subjects, the study concludes that non insulin dependent diabetes in Asians may be dominantly inherited. Greater numbers of Asian subjects in my study were on treatment with diet with or without tablets. Since the families of many of the Asian patients in this study were not actually living in the U.K., I felt that any further analysis of first degree relatives requiring actual confirmation of diabetes, would not be feasible.

For those starting on insulin therapy within the first year of diagnosis, greater numbers of Asians gave a positive first degree family history and less numbers had moderate/severe ketonuria. However neither of the above features nor plasma glucose at diagnosis had a significant predictive outcome on therapy two or more years after initial diagnosis.



Reports on coronary artery disease in Asian diabetics have been highly variable. Bose (1907) reported high rates of angina in diabetics in Bengal. Yet, De Zoysa (1951) and Ibrahim (1962) found low rates for large vessel disease. However, it would appear that Asians in South Africa have high rates for vascular lesions (Cosnett, 1957 and 1959). In more recent years, reports from India have been difficult to interpret because of differences in criteria and methods of collecting data (West, 1978). To my knowledge, except for the WHO report, which incorporated New Delhi as a centre in its study of vascular complications, there have been no recent standardized data on large vessel disease from India that could be used for comparative purposes.

The prevalence of myocardial infarction was higher in both Asian men and women, and angina was also greater in Asian women. There was a uniformly increased risk in Asians for developing angina or myocardial infarction, although these did not reach statistical significance. Estimates of the individual contributions of duration of diabetes, hypertension, smoking, BMI, physical activity, social class showed no statistically significant difference between the two groups. It is now recognised that Asians have a higher risk of mortality from ischaemic heart disease, (Donaldson and Taylor, 1983) and McKeigue et al (1985) have shown that the high mortality from coronary heart disease in Asians is not fully explained by known risk factors such as total plasma cholesterol, saturated fat in diet, or smoking. It

is, therefore, possible this may be related to the higher prevalence of diabetes in Asians. In the present study, the overall relative risk of heart vascular disease for Asians was 1.15. The major contribution to this would appear to arise from Asian females, in whom the prevalence of all modalities of heart vascular disease was increased.

Although cultural and linguistic differences may confound the comparison of angina, I do not feel that the present figures represent an overestimate, because objective evidence such as an abnormal ECG with angina, or electrocardiographic or biochemical changes of a myocardial infarction were also increased in this group. It is noteworthy that greater numbers of Asians had never smoked, and there was no difference in the prevalence of hypertension in the two groups. The recent WHO study (Diabetes Drafting Group, 1985) has also shown that 'ECG Coronary Probable' rates (Q wave items) in the population studied from Delhi were high and similar to those in Western centres. Jackson (1972) also reported that coronary heart disease in Asian and White diabetics were equally high in South Africa. Unfortunately, I was not able to collect data on serum cholesterol and triglycerides in my study. It is not possible, therefore, to comment on the distribution of serum lipids in these two populations.

There are not many publications addressing the problem of peripheral vascular disease in Asian diabetics. Jackson (1972) found peripheral vascular disease to be less common in Asians compared to White diabetics. The WHO study (Diabetes Drafting Group, 1985) has also shown that the prevalence of vascular disease of the leg was lower in both men and women from the Delhi population, when compared with the same sex from the London population. In my present study the relative risk for Asians of developing peripheral vascular disease was 0.51 compared to White Caucasians. The confidence intervals were narrow and the lower relative risk was statistically significant at the 5% level. Intermittent claudication and gangrene with or without amputation, were considerably less prevalent in both sexes of Asians. In all three instances of Asians who came to amputation, the operations were of toe amputations only, whereas in White Caucasians these were toe, or below knee, or above knee amputations, suggesting that in Asians the peripheral vascular disease may be due to occlusion that occurs more distally rather than proximally. One confounding feature associated with these observations is that a greater overall number of Asians had never smoked. However, estimates of individual risks from smoking, hypertension, degree of control, BMI or physical activity were not significantly different in the two ethnic groups. The assessment of gangrene and amputation in the lower limbs is further confounded by concomitant peripheral neuropathy. It is my impression, that using a standard

tuning fork, the impairment of vibration perception at the ankle, did not seem to be clinically different in the two groups studied. At the start of the study I had anticipated testing this more formally, using a biothesiometer, but unfortunately this was not feasible due to technical problems. However, the prevalence of gangrene/amputation appears to be low in the Asian population, as also estimated from hospital activity analysis in Leicester (Donaldson and Taylor, 1983).

Data on cerebrovascular disease in Asian diabetics are sparse. This may be partly due to difficulties in diagnosing with certainty the occurrence of cerebral thrombosis and due to inadequate reporting of minor degrees of weakness. For these reasons, the end point chosen for the analysis of cerebrovascular disease was a definite neurological deficit lasting for at least 24 hours, and which, therefore, could be judged on clinical grounds to represent a vascular lesion. The overall prevalence in Asian men and women was lower than the corresponding prevalence in White Caucasians of the same sex. The relative risk for Asian diabetics of developing cerebrovascular disease was 0.61. The implications of this are, at this moment difficult to judge, as data on similar events in non-diabetic Asians are currently not available.

Small vessel disease is held to be more specific as a complication of diabetes (Mann, Pyorala and Teuscher, 1983)

and a cross cultural analysis of microvascular complications may reflect subtle ethnic differences. Proteinuria in a diabetic is of major significance as it may suggest the inevitable progression of renal disease (Knowles, 1974). For this reason I felt that it was of extreme importance to establish the existence of proteinuria with reasonable certainty, and this was confirmed on two separate occasions and quantified. Bacteriology of the urine, and radiographic measures were then undertaken to rule out any other cause for the proteinuria. Renal biopsies were not performed as it was felt this was not justifiable at the time of the study. Significantly higher prevalence rates for Asian men and women were observed, when compared with White Caucasians. The relative risks for Asian diabetics of developing proteinuria (2.76) or kidney disease (3.36) were significantly higher. There were no significant differences in hypertension and diabetic control in these two groups. The duration of diabetes in Asians was lower. However, greater numbers of Asians were not on insulin, and in this situation it may be that the precise timing of onset of diabetes was inexact. 9.5% of Asian men compared to 4.9% White Caucasian men had a serum creatinine above the upper limit of normal. However only 2.9% Asian women had an elevated serum creatinine compared to 6.5% White Caucasian women, despite greater numbers of Asian women with proteinuria. One possible explanation for this is that Asian women are predominantly vegetarian (Survey of Leicester, 1983) and a low protein diet is recognised to

slow the progression of renal disease (Williams, Baker and Walls, 1985). A more recent study has shown a high prevalence of microalbuminuria in Asian non-insulin-dependent diabetics, and suggests that nephropathy may emerge as an important clinical problem (Allawi et al, 1988).

The prevalence of retinopathy including each of its modalities was lower in Asians of both sexes when compared to White Caucasians. It has been suggested that there may be a large error rate towards underestimation when retinopathy is assessed by ophthalmoscopy compared to panretinal photography (Sussman, Tsiaras and Soper, 1982). However, as the same method of assessment was used in both groups studied, the proportion of error would remain the same, and so should not greatly influence the difference between the groups. The prevalence of cataracts was increased in Asian men and women. The statistical significance of this difference persisted after adjustment, and the relative risk for Asians of developing cataracts was 6.35. This is not dissimilar to an odds ratio of 5.0, observed by Donaldson and Taylor (1983) in their study on hospital activity analysis. The high risk observed in these two studies of Asians from Leicester might suggest other factors besides diabetes as causal to the development of cataracts in Asians. It is arguable that the presence of cataracts may preclude an adequate assessment of the ocular fundi for retinopathy. This may be true in a small

proportion of patients, and even if they were assumed to have retinal involvement ab initio, the overall numbers of Asians with retinopathy in this study, would still be less than similarly affected White Caucasians. The relative risk for Asians of developing eye disease (excluding cataracts) was 0.31. Background and proliferative retinopathy were less common in Asians. It was difficult to make valid comparisons between vitreous haemorrhage and retinopathic blindness, as the numbers involved were small.

The present study also shows a dissociation between proteinuria and retinopathy. Fewer Asians with proteinuria had retinopathy of any form. This is probably because of the mixed nature of the population studied, containing both insulin dependent and non-insulin dependent diabetics. A study from Oklahoma, also containing a "mixed" population has shown that retinopathy and proteinuria may not always occur concurrently (West, Edreich and Stober, 1980). Paetkau et al (1977) have suggested that cigarette smoking may be implicated in the aetiology of proliferative retinopathy, although the WHO study (Diabetes Drafting Group, 1985) has not revealed any systematic association. Overall fewer Asian diabetics smoked, but numbers were too small to draw any firm conclusions between this and eye disease. The possibility that genetic differences may have a role needs to be borne in mind, and as Dornan et al (1983) have shown, HLA-DR4 and the degree of lack of control of diabetes may interact to prove a substantial risk to the development of retinopathy.

The present study addressed the prevalence of vascular complications in patients attending a hospital diabetic clinic. It was aimed at drawing comparisons between two ethnic groups, rather than being directed towards the complications in a causal fashion. One important aspect to consider is whether patients with severe complications attend more frequently. Ideally, the cases studied should be representative of the totality of such cases in the population at large. However, hospitals provide convenience of accessibility for data collection and is a compelling argument in favour of such studies.

Difficulties may also arise in terms of culture and linguistics, when conducting studies between ethnic groups.

Cultural perceptions of disease may affect the reporting of conditions, beyond the control of the observer. Linguistic barriers were overcome to a large extent in that I could personally communicate with all the Asian patients speaking either English, Hindi, Urdu, Bengali, Gujarati or Punjabi. To my knowledge there are no major differences in the referral patterns of general practitioners of Asian patients.

Comparison of data from different centres has been confounded by the differences in methods of data collection, and in criteria of selection. I had chosen definite end points at the start of the study, and applied



them uniformly to all patients, and so hope to have minimised observer bias.

There were greater numbers of Asians with diabetes of recent onset, and of older age at diagnosis. All results have been expressed after adjusting for age, sex, age at diagnosis and duration of diabetes. Matching for sex, age at diagnosis and duration of diabetes if possible may have provided more refined results. However, this yielded disproportionate figures in "matched cells" with very small numbers in some cells that precluded any meaningful analysis.

Nicholl et al (1986) have shown that the general clinical profile of Asian patients attending a diabetic clinic in this country tends to be different to that seen in indigenous diabetics. The present study extends this to show that Asian diabetics have a significantly higher risk for proteinuria and significantly lower risks for retinopathy and peripheral vascular disease when compared to White Caucasian diabetics. Risks for cerebrovascular disease are lower, and for heart vascular disease higher, but did not reach statistical significance because of wide confidence intervals. These observations would suggest that the vulnerability to complications is different in Asians and White Caucasian diabetics.

C H A P T E R    4

PATHOGENESIS OF NON INSULIN DEPENDENT DIABETES IN ASIANS

## INTRODUCTION

The primary lesion in insulin dependent (Type 1) diabetes is destruction of the pancreatic B-cells. The precise triggering event is still debatable, but once this process of destruction is initiated, there is progressive deterioration of insulin secretory capacity. There is also a component of insulin insensitivity in such patients but this is believed to be a secondary consequence of the insulin deficiency (Nankervis et al, 1984).

The picture in non-insulin dependent (Type 2) diabetes is far from clear. Abnormalities in insulin secretion as well as in insulin sensitivity have been described. This has been observed in established Type 2 diabetes (Weir, 1982) as well as in the earlier or "preclinical" stage of impaired glucose tolerance (Reaven and Miller, 1979). Reaven (1984) has postulated that insulin sensitivity may be primarily at fault, with subsequent hyperglycaemia leading to B-cell decompensation. Cerasi and co-workers (1973) and Kadowaki et al (1984) suggest that impaired insulin secretion is the primary and major feature. In an attempt to clarify the situation Ward and co-workers (1985) studied gestational diabetics in the post pregnancy state, that is, they used a group of subjects who definitely had an abnormality in glucose metabolism, which had subsequently clinically reverted to normal. These subjects would in theory, therefore, continue to harbour the pathophysiology involved, that would be demonstrable by

sophisticated testing methods. These workers showed that in such a group of subjects both impaired insulin secretion as well as decreased insulin sensitivity were involved. In a similar study, I have shown that there is some decrease in insulin sensitivity in gestational diabetics following their period of pregnancy (Samanta et al, 1987).

Why are there such conflicting findings in relation to the pathophysiology of non-insulin dependent diabetes? Part of this is related to the effects that hyperglycaemia may have on insulin secretion and insulin sensitivity. In obese mice, for example, a reduction of hyperinsulinaemia ameliorated insulin resistance (Mahler and Szabo, 1971). Insulin administration may lead to a down regulation of insulin receptors (Kahn, Neville and Roth 1973). The mechanism by which these occur are complex and are probably related to the deleterious effect that hyperglycaemia may have at the receptor and post-receptor levels (Kolterman et al, 1980). In humans, Scarlett and co-workers (1982) have shown that insulin treatment reverses the insulin resistance of non-insulin dependent diabetes, and I have shown that early treatment with insulin in Type 2 diabetes tends to preserve B-cell function (Samanta et al, 1987), whereas insulin treatment in later stages improves hyperglycaemia possibly by ameliorating a post-receptor defect (Samanta et al, 1986).

Another possible reason for these conflicting reports is that perhaps subjects are not being examined early enough

in the evolution of the disease, to discern a primary defect. In this respect, it would be greatly advantageous to examine a group of subjects who are at risk of developing non-insulin dependent diabetes, but who are as yet in the preclinical stage. A strong genetic component to non-insulin dependent diabetes has been recognised. Studies from King's College have shown an almost 100% concordance for this disorder if one of the identical twins is affected (Barnett et al, 1981 a) (Barnett et al, 1981 b). Elegant studies by Simpson (1968) have shown that first degree relatives of patients with non-insulin dependent diabetes have a significantly higher relative risk of developing the disease, and Kobberling et al (1985) have suggested that diabetes may ultimately develop in 40% of such relatives. For these reasons it seems appropriate that a study involving first degree relatives of patients with non-insulin dependent diabetes may be particularly fruitful in an assessment of pathophysiology, and may represent the disease process at its earliest stage of evolution, before clinical manifestations of the disease become apparent.

Interactions between glucose and insulin are complex, and it may, therefore, be difficult to interpret results of these following conventional tests of glucose tolerance. Glucose clamp techniques provide a more refined assessment of insulin secretion and resistance (DeFronzo, Tobin and Andres, 1979). However, these methods are both expensive and labour intensive, and, therefore, difficult to apply on

a large scale. I have studied first degree relatives of patients with non-insulin dependent diabetes using a simple method, continuous infusion of glucose with model assessment, (CIGMA), which allows an estimation of insulin secretion and insulin sensitivity.

## THEORETICAL BASIS OF CIGMA

The interactions between glucose and insulin are sufficiently complex so that single values of plasma glucose and insulin are not easy to interpret in isolation.

The feedback loop between insulin secretion and glucose turnover by the liver is of extreme importance in determining the levels of peripheral plasma glucose and insulin (Turner & Holman, 1976). The B-cell hepatic feedback loop operates in such a way that the basal levels of plasma glucose and insulin are maintained in a careful balance. In a situation where there is decreased B-cell function, hepatic output of glucose would increase to a level whereby a degree of basal hyperglycaemia would be maintained to stimulate the B-cell to achieve a degree of "compensation". Similarly in a situation where there is increased resistance to insulin action at the level of the liver a degree of hyperglycaemia would be achieved to maintain a degree of hyperinsulinaemia. This feedback loop between insulin secretion and hepatic glucose turnover plays a major role in the regulation of fuel supply (Turner and Matthews, 1984) and the pathogenesis of non-insulin dependent diabetes may reflect abnormalities along this axis in varying combinations (Reaven et al, 1976) (Rizza, Maudarino and Gerich, 1981).

Various physiological factors controlling glucose metabolism in man have been defined (Bergman, Phillips and Cobelli, 1981). Using these, as well as control factors derived from animal models, a computer solved mathematical

model can be derived which can define the relative degrees of deficiency in insulin secretion or insulin resistance which may be prevalent in the pathogenesis of non-insulin dependent diabetes (Turner et al, 1979) (Hosker et al, 1985).

The computer model is derived on available physiological data, and aims at a semi-quantitative description of the modalities of insulin secretion and insulin resistance (Turner et al, 1982). Distribution of glucose is regarded as in a unicompartamental model with separate distributions and turnover rates for brain, liver, muscle and adipose tissue. Insulin is physically regarded as distributed in a single compartment. The model considers the delivery of insulin subsequent to its first pass through the liver. Insulin delivery depends upon pancreatic B-cell function as well as plasma glucose profile, and insulin release is regarded in two phases. The 'first phase' is maximal within 2-3 minutes, and subsequently the 'second phase' builds up more gradually upto the maximum of steady state output. B-cell efficiency is a measure of the ability of the pancreas to respond to glucose and is a function of insulin delivery rate. Insulin resistance (or decreased insulin sensitivity) is a defect in the response to insulin and is given as a ratio of the level of insulinaemia in a subject to the expected level of insulinaemia in a standard non-diabetic subject for the same overall effect. These principles are described in greater detail by Hosker et al (1985).



#### PRACTICAL APPLICATION OF CIGMA

Hosker and co-workers (1985) have by meticulous experiments, validated insulin resistance by CIGMA against that derived by the euglycaemic hyperinsulinaemic clamp, and B-cell function by CIGMA against results from the hyperglycaemic clamp techniques (DeFronzo, Tobin and Andres, 1979). They have also shown CIGMA to be highly reproducible with a coefficient of variation of 20%.

In practical terms, therefore, CIGMA represents a non-labour intensive relatively inexpensive convenient and ethically acceptable method for assessing insulin secretion and insulin resistance in man. The results derived from CIGMA are as precise and reproducible as any other method currently available.

## SUBJECTS AND METHODS

Asian patients with non-insulin dependent diabetes were identified and asked if their family members would be prepared to undergo testing with CIGMA. All patients had met standard WHO criteria for diabetes (WHO, 1985) at the time of diagnosis, and all had been on diet and/or oral hypoglycaemic therapy for at least 3 years. All had been attending the diabetic clinic at Leicester Royal Infirmary.

52 (30 male, 22 female) Asian first degree relatives over the age of 15 years (parents, siblings, children) agreed to take part in the study. None of the relatives studied were known to have a history of diabetes or gestational diabetes or were on any medication known to affect glucose tolerance. All tested subjects were on a diet containing at least 200 gm carbohydrate per day.

Following an overnight fast, subjects were tested between 8.30 am - 9.30 am. After informed consent, one cannula was placed in an antecubital vein, and used for glucose infusion. A second cannula was placed in a distal forearm vein, and used for sampling. The hand was warmed to "arterialise" the venous blood sampled.

Glucose solution was infused at a rate of 5 mg/kg ideal body weight/minute for 60 minutes using a volumetric infusion pump. Ideal body weight (IBW) was taken from the Metropolitan Life Insurance table for a medium frame (Metropolitan Life Insurance Company, 1959). Since insulin

secretion is pulsatile and periodic (Lang et al, 1982), three basal samples were taken at 5 minute intervals. Glucose was then infused for 60 minutes, and samples were taken every 5 minutes until 30 minutes after the infusion was stopped. Samples were kept on ice, centrifuged and separated immediately after the test. Plasma was stored at  $-20^{\circ}\text{C}$ . During the test, plasma glucose and insulin levels rise slowly and are dependent upon the reciprocal effect that each has on the other. The mean plasma glucose and insulin achieved at 50, 55 and 60 minutes is called achieved plasma glucose (APG) and achieved plasma insulin (API) respectively, and these values were used in the computer solved model, to assess B-cell function and insulin sensitivity.

Insulin (Albano et al, 1972) and C-Peptide (Holman and Turner, 1977) were measured by charcoal phase-separation radioimmunoassay. Glucose was measured using the glucose-oxidase method (Beckman Autoanalyser).

Fasting plasma glucose (FPG) was calculated as the mean of the fasting samples before starting the insulin infusion taken at -10, -5 and 0 minutes. Achieved plasma glucose (APG) was calculated as the mean of the values attained at 50, 55 and 60 minutes after the glucose infusion.

Fasting plasma insulin (FPI), fasting plasma C-peptide (FPC), achieved plasma insulin (API) and achieved plasma C-peptide (APC) were also calculated from the samples as

above, but values are expressed as the geometric mean (+1SD; -1SD), where indicated.

B-cell function (%B) and insulin sensitivity (% S) were estimated from APG and API with CIGMA (Hosker, 1985). Results are expressed as the geometric mean (+1SD; -1SD). The unpaired t-test was used to compare means.

11 non-diabetic Asians with no family history of diabetes in first degree relatives and 6 Asians with diet controlled diabetes and within 2 years of diagnosis were studied in a similar fashion in order to determine the spectrum of abnormalities identified by CIGMA in the "normal" and "early diabetic" Asian population. First degree Asian relatives were matched for age, sex and ideal body weight with similar White Caucasian relatives studied at the Diabetes Research Laboratories, Oxford.

## RESULTS

The results derived from CIGMA, in non-diabetic and diet controlled diabetic Asians are shown in Table 4.1. In non-diabetic Asians the fasting plasma insulin and C-peptide are slightly higher than the values expected in a normal weight White Caucasian population (5.5  $\mu\text{u/L}$  and 0.35  $\text{nmol/L}$  respectively) as are the achieved values compared with a White Caucasian population (22  $\mu\text{u/L}$  and 1.2  $\text{nmol/L}$  respectively) (Hosker et al, 1985). The %B and %S are similar to the values obtained in a normal White Caucasian population.

Results in diet controlled diabetic Asians are more complex. Both FPG and APG are higher, as would be expected. The FPI and FPC are also higher than in non-diabetic Asians, but this might reflect their slightly greater obesity. Although the APG is raised, the API and APC tend to be lower than in the non-diabetic Asians, and this itself would suggest a diminished B-cell response. The CIGMA derived analysis of %B and %S, are both low, suggesting a combination of decreased insulin secretion and decreased insulin sensitivity, in the pathogenesis of diabetes in this group of subjects studied.

Results in first degree relatives of patients with non-insulin dependent diabetes is shown in Table 4.2. They were matched for age, sex and ideal body weight with

similar White Caucasian relatives, studied in the same manner at the Diabetes Research Laboratories, Oxford. There were no differences in FPG, FPI and FPC in the two groups. However, Asian relatives had a significantly higher API and APC. %B was also significantly higher in the Asians, with a significantly lower %S.

TABLE 4.1

RESPONSES TO CONTINUOUS INFUSION OF GLUCOSE IN NON-DIABETIC  
AND DIET CONTROLLED DIABETIC ASIANS

	NON-DIABETIC ASIANS	DIET CONTROLLED DIABETIC ASIANS
Number	11	6
Male/Female	6/5	4/2
Age (SD), Years	34 (15)	50 (8)
Ideal body weight (SD), %	98 (5)	119 (12)
Fasting plasma glucose (SD) mmol/l	5.0 (0.4)	6.7 (1.6)
Fasting plasma insulin (SD) mu/l	7.4 (4.3)	16.5 (8.5)
Fasting plasma C-peptide (SD) nmol/l	0.6 (0.2)	0.9 (0.3)
Achieved plasma glucose (SD) mmol/l	8.6 (1.0)	11.0 (1.4)
Achieved plasma insulin (SD) mu/l	33.5 (11.4)	30.8 (10)
Achieved plasma C-peptide (SD) nmol/l	1.8 (0.4)	1.3 (0.4)
S%	80 (+35, - 25)	63 (+17, - 10)
B%	102 (+29, - 22)	68 (+32, - 20)

TABLE 4.2RESPONSES TO CONTINUOUS INFUSION OF GLUCOSE IN FIRST  
DEGREE RELATIVES OF NON-INSULIN DEPENDENT DIABETICS

	Asian	White Caucasian	Significance
Number	52	74	
Male / Female	30/22	40/34	NS
Age (SD), Years	31 (11)	30 (7)	NS
Ideal body weight (SD), %	107 (17)	107 (7)	NS
Fasting plasma glucose (SD) mmol/l	4.6 (0.6)	4.7 (0.7)	NS
Fasting plasma insulin* (SD) $\mu$ u/l	6.4 (+4, - 2.7)	5.5 (+4.2, - 2.4)	NS
Fasting plasma C-peptide* (SD) nmol/l	0.5 (+0.2, - 0.19)	0.5 (+0.2 - 0.14)	NS
Achieved plasma glucose (SD) mmol/l	7.6 (1.4)	8.1 (1.2)	p < 0.05
Achieved plasma insulin* (SD) $\mu$ u/l	30.3 (+16.1, - 10.5)	21.8 (+12.4, - 7.9)	p < 0.001
Achieved plasma C-peptide* (SD) nmol/l	1.53 (+0.45, - 0.35)	1.18 (+0.37, - 0.28)	p < 0.001
S%	70 (+52, - 30)	87 (+47, - 20)	p < 0.05
B%	146 (+103, - 60)	88 (+95, - 45)	p < 0.001

\* Insulin and C-peptide values expressed as geometric mean (+ 1SD, - 1SD)



## DISCUSSION

The pathogenesis of non-insulin dependent (type 2) diabetes is complex, and may involve both insulin resistance, and impaired insulin secretion to varying degrees. The aim of the present analysis was to try and determine the relative contributions of these two major pathogenetic mechanisms in the development of non-insulin dependent diabetes in Asians.

The results of these studies show in non-diabetic Asians, a moderately raised fasting plasma insulin and C-peptide, which suggest that they have impaired insulin sensitivity (Matthews et al, 1985). This is in concordance to the CIGMA results with a raised %B (an estimate of beta cell function and hence insulin secretion) and a low %S (an estimate of insulin resistance). The degree of insulinaemia may be appropriate for the slightly higher achieved plasma glucose, compared to the normal under 7.8 mmol/L in non diabetic White Caucasians.

Results in non-diabetic first degree relatives of patients with non-insulin dependent diabetes depict a similar but more exaggerated trend. When formally compared with age, sex and body weight matched White Caucasian first degree relatives, they show a significantly higher API and APC. This is further confirmed by significant differences in %B and %S. There is a "higher" state of beta cell function and lowered insulin sensitivity. Therefore, in first degree

relatives, and in non-diabetic Asians there is a tendency for hyperinsulinaemia with insulin resistance.

The concept of insulin resistance has undergone much change over the last few years (Kahn, 1986). In physiological terms, insulin resistance is a state in which a certain amount of insulin produces a less than expected response (Kahn 1978). A more subtle form of insulin resistance is one that may occur in persons not taking insulin. In such circumstances, this is defined by the finding of higher (than normal) levels of insulin, that is, hyperinsulinaemia in the presence of normal or elevated levels of plasma glucose (Kahn 1978). This concept has been shown to play an important role in understanding the pathogenesis of diabetes, as well as in understanding the altered physiological processes at work in the non diabetic person at risk for the disease (Amiel et al, 1986), (Yki-Järvinen and Koivisto, 1986), (Schade and Duckworth, 1986).

Of particular interest is the observation by Haffner et al (1986a) of hyperinsulinaemia in a population of Hispanic Mexican Americans who are at a high risk for non-insulin dependent diabetes mellitus. Peripheral resistance to insulin action may occur due to obesity (Olefsky and Kolterman, 1981). In addition, the distribution of body fat may also influence resistance to insulin (Haffner et al 1986b) (Krotkiewski et al, 1983). Hispanic Mexican Indians have a greater overall and more centralised obesity when compared to non-Hispanic whites (Stern et al, 1983).

Haffner and colleagues (1986a) have shown that after adjusting for features such as body mass index, and regional body fat distribution, non-diabetic Hispanic Mexican Americans have a significantly greater degree of hyperinsulinaemia, and that at any given level of adiposity they are more insulin resistant than non-Hispanic Whites, following an oral glucose tolerance test. These data would suggest that in addition to obesity, ethnic differences may have a role in determining insulin resistance. This may be particularly true in those populations at high risk for developing non insulin dependent diabetes mellitus and this has been shown in Navajo Indians (Rimoin and Sdiki, 1968), Seneca Indians (Frohman, Doeblin and Emerling, 1969), and the Pima Indians (Aranoff et al, 1977) (Nagulesparan et al, 1982).

Asians in the U.K. have been shown to have a high prevalence of diabetes mellitus, and this has been discussed in detail in Chapter 2 of this thesis. In theory, therefore, they may have a degree of insulin resistance that predisposes them to this. In a more recent study, Mohan et al (1986 b) have shown that Asians have a higher insulin response to an oral glucose load when compared to White European subjects. This was observed in healthy non-diabetic subjects, as well as diet controled diabetics within the first year of diagnosis. Basal insulin levels were also higher in Asians. These data would suggest that hyperinsulinaemia may exist as a "pre-diabetic" state in Asians.

The present study addresses the question of the underlying pathogenetic mechanisms in a population known to have a high prevalence of diabetes. This study, however, addresses this question with two further degrees of sophistication. In the past, the studies as quoted above, have incorporated subjects either randomly, or those with impaired glucose tolerance, and hence, may have constituted a heterogeneous group. The subjects in the present study have been identified through their family history of diabetes, and are likely, therefore to represent a different and more homogeneous group. By specifically studying first degree relatives of individuals known to have non insulin dependent diabetes, I had hoped to have a population at high risk for developing diabetes - on account of ethnicity and on account of the positive family history. It was felt studying such a population might be of particular advantage in that preclinical pathophysiological derangement might be noted.

The second distinguishing feature of the present study is the method that has been used. Continuous infusion of glucose with model assessment is a novel method of assessing insulin resistance, as well as B-cell function, and can estimate these parameters in quantitative terms. Many studies above have used the oral glucose tolerance test and concomitant levels of insulin in their assessment of the underlying pathophysiology. The interpretation of the oral glucose tolerance test may be confounded by

factors such as variable glucose absorption, glucose load relative to the weight of the subject, and neural and gastrointestinal effects on insulin secretion. Consequently, the interpretation of "point" plasma insulin levels may also be difficult because of the rapidly altering plasma glucose levels. The present technique attempts to overcome these particular problems by using a constant intravenous infusion of glucose that is related to the body weight. The final model of analysis, further incorporates known physiological data concerning the metabolism of glucose in relation to insulin, and therefore provides the best overall assessment of the complex glucose-insulin interaction that may exist at any given moment in time. The technique has been validated against the glucose clamp, and is relatively less labour intensive, as well as practically applicable in the clinical setting.

The results of the present analysis in first degree relatives of Asians with non-insulin dependent diabetes when compared to similar White Caucasian relatives show a significantly higher API and APC. Fasting values were not significantly different. This is interpreted as evidence for a degree of insulin resistance in these subjects that becomes manifest when the insulin-glucose homeostasis is stressed. Under these circumstances, the plasma insulin, and plasma C-peptide were relatively higher compared to the degree of glycaemia, and were also higher when compared to the levels achieved in White Caucasian subjects. %S was lower in Asian subjects, again indicating a degree of

insulin resistance, and %B, an estimate of B-cell function was higher suggesting a state of "hyperactivity" of the pancreatic B-cells. All comparisons were made after matching the subjects in the two groups for age and sex. Overall obesity was taken into account by matching subjects for ideal body weight, but body distribution of fat was not assessed independently. Although Asian subjects may have a smaller body build than their White Caucasian counterparts, ideal body weight was determined using Metropolitan Life Insurance tables as these are widely accepted, and studies on the basis of this have the advantage of being repeatable, and reproducible. Ideal body weight charts for individual ethnic groups are not easily available nor are they universally accepted.

Detailed studies with CIGMA in first degree relatives of White Caucasian non-insulin dependent diabetics suggest that the primary defect is beta-cell dysfunction (O'Rahilly et al, 1986). In Asians, however, the situation may be different. From the above observations it would appear that in Asians a possible mechanism for the development of diabetes would be chronic insulin resistance that leads to a compensatory hypersecretion of insulin eventually leading to islet cell decompensation and clinical non-insulin dependent diabetes mellitus. Hyper-insulinaemia (Reaven et al, 1976) as well as insulin deficiency (Cerasi, Efendic and Luft, 1973) have been suggested as antecedents of non insulin dependant diabetes.

Studies in different populations have yielded varying results. In Pima Indians, a population known to have a high prevalence of non-insulin dependent diabetes, hyperinsulinaemia has been found to predict the conversion from normal glucose tolerance to the diabetic state (Knowler and Bennet, 1983). Similar findings have been observed by Balkau et al (1985) in Micronesians.

In an attempt to delineate the time sequence of events in this altered pathophysiological state, I have studied a few normal Asians (that is non-diabetic, and with no family history of diabetes) and a few diet controlled Asian diabetics. The diet controlled diabetics were within two years of diagnosis, and therefore, represented a relatively early stage of clinical conversion from normal glucose tolerance. In diet controlled diabetics FPI and FPC are higher than in non-diabetic Asians, and yet, API and APC are lower. Two hypotheses are feasible. The first is a "compensatory" hyperinsulinaemia in the fasting state fails to respond adequately because of B-cell "exhaustion" when the insulin-glucose axis is stressed, and hence the lower achieved values. A possible postulate for the development of pathophysiological processes leading to non-insulin dependent diabetes in Asians may initially begin with insulin resistance and compensated hyperinsulinaemia, leading to exhaustion and islet cell decompensation, and clinical diabetes mellitus. The second hypothesis is that Asians who develop diabetes are those who have an impaired

B-cell capacity in addition to the ethnic impairment of insulin resistance. In the Japanese population, however, a low plasma insulin response, rather than a high response, seemed to predict this conversion of impaired glucose tolerance to diabetes (Kadowaki et al, 1984). It thus seems that hyperinsulinaemia can be associated with glucose intolerance but only those with either "islet cell decompensation", or with low responses of insulin become diabetic. This issue can only be resolved by prospective studies in which a high risk population is evaluated at intervals in time from the non-diabetic state until conversion from normal glucose tolerance occurs. Such serial studies for insulin secretion and insulin resistance might reveal important insights into the pathophysiological mechanisms of non-insulin dependent diabetes. Such studies are, however, time costly and labour intensive and the practicalities are exceedingly complex.

It is currently difficult to answer with any degree of certainty as to what the primary precipitating event might be. Obesity is a common accompaniment of non-insulin dependent diabetes. Neither first degree Asian relatives nor non-diabetic Asians studied were particularly obese. Further studies addressing the question of body fat distribution and insulin secretion may be of value in this respect.



Another possible mechanism might be related to diet. In Chapter 6 of this thesis, I have shown that in normal volunteers, a standard Asian meal produces an exaggerated insulinaemic and glycaemic response when compared to an equicaloric European meal. Although these findings are preliminary, and relate only to the acute metabolic effects of the meal, they are of interest, in that they suggest that in the long term such a diet may possibly lead to a state of "chronic hyperinsulinaemia", with its subsequent effects as already discussed.

It is also possible that B-cell dysfunction and/or insulin resistance is genetically influenced. Non-insulin dependent diabetes is known to have nearly complete concordance in twins (Barnett, 1981 b), and an abnormal glucose tolerance has been observed in the clinically unaffected twin (Barnett et al, 1981 a),. O'Rahilly et al (1987) have very elegantly studied insulin secretion in families with non-insulin dependent diabetes, and have shown 69% of glucose intolerance in siblings of diabetics with early onset of disease. Assuming homozygosity of inheritance in this group, this figure is close to what would be expected (75%) by mendelian calculations. It is, therefore, possible that within the Asian ethnic group B-cell dysfunction may be genetically determined as in White Caucasians, and combined with ethnic or environmental factors (diet, obesity) leading to impaired insulin sensitivity, may be responsible for the high degree of glucose intolerance that has been noted.

## CHAPTER 5

### GLUCOSE TOLERANCE DURING PREGNANCY IN ASIAN WOMEN

## INTRODUCTION

Complications in pregnancy both to the mother and the foetus are recognised when the mother has insulin dependent diabetes prior to pregnancy (Pederson, 1977) (Drury, Green and Stronge, 1977). Increased perinatal and neonatal morbidity (Kitzmilller et al, 1978) and abnormalities of foetal development (Chez, 1980) are amongst the predominant complications of these pregnancies. Careful control of maternal diabetes in recent years has done much to reduce the incidence of these (Gabbe et al, 1978) (Jovanovic and Peterson, 1982). There is now evidence that abnormalities in glucose tolerance occurring for the first time during pregnancy, that is gestational diabetes mellitus, may be associated with an increase of these complications (O'Sullivan et al, 1974) (Forest et al, 1983). The need to define levels of glycaemia that may be associated with complications of pregnancy, and to screen pregnant women for abnormalities of glucose metabolism, therefore, is a matter of immediate practical relevance (Beard and Hoet, 1982).

Much of the literature on gestational diabetes has been confounded by lack of uniform diagnostic criteria. The Workshop-Conference on Gestational Diabetes (1980) as well as the National Diabetes Data Group (1979) recommend that the criteria of O'Sullivan and Mahan (1964) should be used for the diagnosis. These workers have done much to standardise the glucose tolerance test (GTT) and to

relate results to the outcome of pregnancy. However, their criteria are based on 100 gm oral GTT, and they were developed retrospectively on their ability to predict that diabetes would develop in subsequent years. The Expert Committee of the World Health Organisation (WHO, 1985) recommends that the criteria for diagnosing diabetes in pregnancy should be the same as those in non-pregnant adults. Thus many of the subjects diagnosed as diabetic on O'Sullivan and Mahan's criteria might not be regarded as definitely diabetic on the WHO criteria. The 100 gm oral GTT used by O'Sullivan has had only limited acceptability in Europe. These discrepancies, therefore, may make any direct comparison of results from different groups of workers exceedingly difficult (Jarrett, 1981).

Hadden (1985) in his review of the subject points out that there is considerable variation in the racial and ethnic prevalence of gestational diabetes. He also points out that data from developing countries in this respect are sparse. In a study from Chandigarh, India, Agarwal and Gupta (1982) found a prevalence rate of 1.88% for gestational diabetes, over a period of three years. In a smaller study, Tandon et al (1983) found gestational diabetes in 6 (28.5%) of 21 patients who had a GTT for classical indications during pregnancy, and in 2 (22.2%) of 9 "controls". These varying results suggest the need for a standardised study to establish the prevalence of gestational diabetes in Asians.

In a review on the subject, Beard and Hoet (1982) state

that currently the weight of evidence points clearly to maternal hyperglycaemia adversely affecting foetal development. Karlsson and Kjellmer (1972) have shown that maternal hyperglycaemia may lead to foetal malformations in the early stage of pregnancy, whereas in the later stages there is an increase in perinatal morbidity and mortality, which may directly correlate with the severity of the hyperglycaemia. A controlled trial of therapy in gestational diabetes suggests that there may be a considerable reduction in the birth weights of infants in the treated group (O'Sullivan, Charles, Dandrow, 1971). Jovanovic and Peterson (1981) have, therefore, strongly argued in favour of treating even minor degrees of hyperglycaemia during pregnancy. In an interesting study by Abell and Beischer (1975) the authors performed 50 gm oral GTT on 2000 women between 32-34 weeks of pregnancy, and subsequently calculated the 5th and 95th percentiles. Women were classified as hypo- or hyperglycaemic if their blood glucose level was at any time beyond these limits. Perinatal mortality in both these groups was significantly higher than in the "normoglycaemic" group. These results suggest that the precise degrees of glycaemia associated with an increased frequency of complications is poorly defined currently, and a recent study suggests that even limited hyperglycaemia during pregnancy (which may be regarded as within the "normal range") may have a deleterious effect on the outcome of pregnancy (Tallarigo et al, 1986).

On the basis of the literature as reviewed above, I planned my study on glucose tolerance during pregnancy in Asian women along the following lines:

(A) The first part consists of establishing figures for the prevalence of abnormal glucose tolerance in pregnant Asian women, and comparing these with a similar group of White Caucasian women.

(B) The second part consists of examining the outcome of pregnancy in terms of maternal and foetal complications in relation to the degree of maternal glucose tolerance. The purpose of this was to examine the levels of glycaemia that may predispose to complications.

(A) PREVALENCE OF ABNORMAL GLUCOSE TOLERANCE DURING PREGNANCY

METHODS

All 75 gm oral glucose tolerance tests (OGTT) performed in the third trimester of pregnancy, over a three year period, were retrospectively analysed. Indications for performing an OGTT included a family history of diabetes, history of previous abortions or still-births, large for date babies, congenital malformations in a previous pregnancy, and glycosuria either currently or in the past.

Based on current WHO criteria (WHO, 1985), abnormal glucose tolerance (AGT) was taken as a 2 hr venous plasma glucose  $>7.8$  mmol/L which reverted to normal ( $< 7.8$  mmol/L at 2 hours) when formally tested during puerperium. This was further divided into impaired glucose tolerance (IGT) (2 hr venous plasma glucose between 7.8 and 11.1 mmol/L) and gestational diabetes mellitus (GDM) (2 hr venous plasma glucose  $> 11.1$  mmol/L).

Statistical analysis was by the Chi-Square Test. Two tailed p values of  $< 0.05$  were taken as significant.

## RESULTS

Of a total of 12,005 pregnancies (4561 Asian and 7444 White Caucasian), 314 (6.8%) Asian and 504 (6.7%) White Caucasian women had an OGTT. AGT was found in 1.38% of Asian and in 0.87% of White Caucasian pregnancies ( $p < 0.01$ ). IGT was found in 1.2% Asian and 0.84% White Caucasian pregnancies ( $p < 0.01$ ), and GDM in 0.18% and 0.02% respectively ( $p < 0.01$ ) (Table 5.1).



**TABLE 5.1****GLUCOSE TOLERANCE DURING PREGNANCY**

	<u>Total Deliveries</u>	<u>Total No. Tested</u>	<u>AGT (%)</u>	<u>IGT (%)</u>	<u>GDM (%)</u>
Asian	4561	314	63 (1.38) *	55 (1.2) *	8 (0.18) *
White Caucasian	7444	504	65 (0.87)	63 (0.84)	2 (0.02)

\* P &lt; 0.01

## DISCUSSION

There is now evidence that the prevalence of gestational diabetes may vary with ethnic groups. The classical studies on Pima Indians who have a remarkably high prevalence of non-insulin dependent diabetes, has shown that gestational diabetes is also considerably higher in this ethnic group (Pettit et al, 1980). Pettit and co-workers showed a prevalence that was approximately 40 times higher compared to the group studied by O'Sullivan and Mahan (1964). Although O'Sullivan's group contained about 60% White and 40% non-white subjects, there was no apparent ethnic difference. Merkatz et al (1980) in a population in Cleveland showed that white women tended to have glucose tolerance levels at the upper end of the range. However, they were older and studied later in gestation than non-white women.

On reviewing the literature in gestational diabetes it is striking to observe the wide differences in the represented prevalence. A prevalence of as low as .15% has been reported by Lind (1983) from Newcastle, UK, and as high as 12.3% by Mestman (1980) from Los Angeles, USA. This wide variation illustrates the difficulty that might be experienced while trying to make international comparisons because of differences in the testing method (that is 100 gm, 75 gm or 50 gm oral GTT), and also differences in the cut-off points. It is also particularly difficult to judge even approximately the prevalence in developing

populations because of the paucity of data. Hadden (1985) has drawn attention to this pointing out that in the Excerpta Medica database from 1975 to 1984, of 165 references on gestational diabetes and glucose tolerance tests in pregnancy, there was only 1 from India, compared to 44 from the USA and 24 from the UK.

The current study attempts to establish prevalence figures for gestational diabetes in the Asian ethnic group. Of a total of 12,005 pregnancies, 6.8% of Asian and 6.7% of White Caucasian mothers had an OGTT. The similarity in the overall proportions of each group that had an OGTT, would obviate any bias due to ethnic selection. The GTT was performed between 28-32 weeks of gestation when glucose tolerance is supposed to deteriorate (Pederson, 1977). Following a 75 gm oral glucose load a 2 hr venous plasma cut-off point of 7.8 mmol/L was used to identify IGT and 11.1 mmol/L to identify GDM. As the same method and criteria were used uniformly in both groups, the results are more accessible to direct comparison. Further, this study addressed the problem of "true" gestational diabetes in that a postpartum GTT was performed to establish that normal glucose tolerance was achieved after delivery.

Using the criteria as described above, the present study shows that AGT occurs in 0.87% of White Caucasian pregnancies, and is significantly higher at 1.38% of Asian pregnancies. I think that it is important to include

impaired glucose tolerance as well as frank diabetes as defined by the WHO in a study on gestational diabetes because many of the "diabetics" by the American criteria would probably be deemed to have impaired glucose tolerance by the more recent WHO criteria (Jarrett, 1981), and if at all any comparisons are to be drawn between these studies and the current one, then impaired glucose tolerance would have to be included. On the basis of the available literature, Hadden (1985) feels that  $< 1\%$  of all pregnancies would be found to have gestational diabetes. The data in White Caucasian women would seem to concur with this. However, Asian women, have a significantly higher prevalence using the same criteria.

Unfortunately, due to the paucity of literature from the Third World, it is difficult to compare the current results with what might be occurring in this respect in the Indian subcontinent. However, the study from Chandigarh in India (Agarwal and Gupta, 1982) found a prevalence of 1.88% over 6465 deliveries using the criteria of O'Sullivan and Mahan (1964). The present results are not dissimilar and therefore lead me to believe that the prevalence rates that I have shown are probably true.

It is known from the Pima Indian Study (Pettit et al, 1980) and from the follow-up of O'Sullivan and Mahan's subjects, (O'Sullivan and Mahan, 1980) that in later years the subsequent development of diabetes in women who may have had gestational diabetes is high. The high prevalence of

gestational diabetes in Asian women may to some extent be contributory to the subsequent overall high prevalence of diabetes, particularly after middle age, in this ethnic group.

Perhaps the most valuable method of comparing ethnic differences would be to do so against the background of the true annual incidence of diabetes in women in the childbearing age in each group. Unfortunately this is available for only very few populations, and the difficulties in accurately collecting this data for women in Leicester along with accurate yearly population figures, precluded drawing such a comparison. Other variables may ostensibly affect prevalence rates, and these are maternal age and weight in particular. Differences in the time of booking for maternal weight have introduced too complex a confounding effect in the present study to allow for any valid comparisons. Further stratification into age bands decreases the total number of subjects in each group, and lowers the power of the observations.

A further question that arises is the validity of using diagnostic criteria for non-pregnant adults for the diagnosis of gestational diabetes, and whether the same criteria can be used in all populations. Fraser (1981) in a study in Nairobi in Kenya has shown that for age matched women, 2 hour capillary blood glucose following a 50 gm oral GTT was about 5.55 mmol/L in both pregnant and non pregnant women, and allowing for corrections, this was not significantly different from a venous plasma glucose of

5.83 mmol/L found by O'Sullivan and Mahan (1964). Although only a single study, this would seem to suggest that uniform diagnostic criteria should probably be used for all countries and populations (Hadden, 1985). Jarrett (1981) has also suggested that as matters currently stand, for clinical purposes at least the view of the WHO Expert Committee that diagnostic criteria for diabetes should be the same in pregnancy as in all adults, should be accepted.

For these reasons, I feel that using WHO criteria for both Asian and White Caucasian pregnant women is a reasonable method of assessing diabetes in this context.

It is also possible that environmental influences following migration may influence the prevalence of gestational diabetes. This is further complicated by the degree to which migrants may retain their traditional culture, or take on the culture of the host country. The majority of the Asian women in the current study migrated from East Africa towards the end of the sixties and early seventies. In order to determine the affect of environmental influences, one would have to ascertain the development of gestational diabetes prospectively in the long term. This is beyond the scope of the present work.

The importance of gestational diabetes lies in the possible risk that it might impose on the outcome of pregnancy. There is evidence that maternal hyperglycaemia may have a deleterious affect on the foetus (Beard and Hoet, 1982), (O'Sullivan et al 1973), (Forest et al, 1983) although the Belfast experience suggests that this may be small (Hadden,

1980). It is yet debatable whether hyperglycaemia is directly causal, or acts as a marker for other factors (Jarrett, 1981). Work from Leicester has shown that perinatal mortality is still higher in Asian women (Dhariwal, 1982) when compared to White Caucasians and it may be that hyperglycaemia is responsible for this to some extent. Current screening procedures in most maternity units in the UK are haphazard (Beard and Hoet, 1982) and the present study argues the need for possibly a uniform policy especially in a high risk group.

In conclusion, therefore, I have determined the crude prevalence rate of gestational diabetes in Asian women attending a single maternity unit. My results show that when compared to a White Caucasian population attending at the same time, the prevalence of gestational diabetes in Asians seems to be higher than expected. Despite limitations of this study, which I have discussed, I feel that the results I have shown are of importance as they suggest that a genuine difference in prevalence occurs in these two ethnic groups, and this may have clinical relevance.

(B) LEVELS OF GLYCAEMIA IN RELATION TO COMPLICATIONS OF PREGNANCY

METHODS

Screening:

All women attending the maternity unit at the Leicester General Hospital, were screened for the following:

glycosuria; family history of diabetes; history of previous abortions; stillbirths; large for date babies or congenital abnormalities; maternal obesity; hydramnios; a history of altered glucose tolerance during a previous pregnancy. If any of the above was positive, they were referred for an oral GTT.

Subjects:

198 Asian, and 356 White Caucasian women had an OGTT between 28 and 32 weeks of pregnancy. These subjects were then followed through pregnancy to determine maternal and foetal outcome in relation to third trimester glucose tolerance.

OGTT:

After the standard advice of consuming more than 200 gms carbohydrate per day for at least three days, subjects were tested following a 12 hr fast. 75 gms glucose was administered, and venous blood drawn after two hours. Venous plasma glucose was measured by the glucose-oxidase method (Beckman Autoanalyser).



Glycaemic levels:

On the basis of a 2 hr venous plasma glucose following a 75 gm OGTT, women were classified into the following groups:

## (a) Normal Range

- (i)  $< 4.0$  mmol/L
- (ii) 4.1 - 5.0 mmol/L
- (iii) 5.1 - 5.5 mmol/L
- (iv) 5.5 - 6.6 mmol/L
- (v) 6.7 - 7.7 mmol/L

## (b) Abnormal Range

- (i) 7.8 - 11.0 mmol/L
- (ii)  $> 11.1$  mmol/L

A venous plasma glucose  $> 7.8$  mmol/L following a 75 gm OGTT was taken as abnormal according to WHO criteria (WHO, 1985). Levels above this were further divided into two groups, 7.8 - 11.0 mmol/L and over 11.0 mmol/L corresponding to the WHO classification of impaired glucose tolerance and frank diabetes mellitus.

Factors relating to the mother and foetus:

(i) Maternal age was calculated from the date of birth as given at the time of the first visit to the maternity unit.

(ii) Height and weight of the mother was determined at the

time of booking, that is in the first trimester of pregnancy. This was used to calculate ideal body weight (IBW) from the Metropolitan Life Insurance Tables.

(iii) Toxaemia of pregnancy was diagnosed in the presence of any two of the following:- proteinuria, hypertension, oedema or convulsions.

(iv) Microsomia for the present analysis was taken as a birth weight < 2500 gms.

(v) Congenital anomalies was defined as specified by Bennett, Weber and Miller, (1979).

(vi) Perinatal mortality was taken if death occurred between 28 weeks of gestation and 1 week of birth.

(vii) A birth was regarded as premature if it occurred at <37 weeks of gestation (Beard and Lowy, 1982).

#### Statistics:

Statistical Analysis was carried out by a test for linear trend in proportions (Snedecor and Cochran, 1976). The Chi-square test was used to compare the frequencies of maternal and foetal complications. Two tailed p values of <0.05 were taken as significant.

## RESULTS

Details of maternal and foetal complications for Asians are shown in Tables 5.2-5.5 and for White Caucasians in Tables 5.6-5.9. Further, specific details of congenital anomalies and perinatal mortality is shown in Table 5.10.

There were only 5 White Caucasian and 10 Asian women with a 2 hr venous plasma glucose on OGTT  $> 11.1$  mmol/L. As these numbers were too small to provide any meaningful information the glycaemic groups 7.8 - 11 mmol/L and  $> 11.1$  mmol/L were amalgamated for statistical analysis.

Maternal complications and foetal complications were analysed as two broad groups. Maternal complications included toxæmia, caesarean section and both these together.

Foetal complications included macrosomia, microsomia, prematurity, congenital abnormalities and perinatal mortality.

The components of these two groups were not analysed separately as the individual prevalences of the separate components were too small to preclude their occurrence by chance alone. Therefore, total maternal complications, and total foetal complications were analysed.

### Asians

#### Maternal features:

There was no significant difference in maternal age or maternal body weight between the group of women with normal glucose tolerance. There was a trend for those with an abnormal GTT to be older and heavier.

There was a significant linear trend in the proportions of maternal complications across the GTT groups ( $p < 0.05$ ). Total maternal complications occurred in 16.6% (OGTT plasma glucose 4.1–5.0 mmol/L), 19.2% (OGTT plasma glucose 5.1–5.5 mmol/L), 21.2% (OGTT plasma glucose 5.6–6.6 mmol/L), 10.7% (OGTT plasma glucose 6.7–7.7 mmol/L) and 37.5% (OGTT plasma glucose  $> 7.8$  mmol/L) (Tables 5.2 and 5.3).

#### Foetal features:

There was no significant difference in gestational age or birth weight of infants born to mothers between the groups.

There was a significant overall difference in foetal complications between the GTT groups ( $p < 0.01$ ). Total foetal complications occurred in 33.3% (OGTT plasma glucose  $< 4$  mmol/L), 10.4% (OGTT plasma glucose 4.1–5 mmol/L), 23.1% (OGTT plasma glucose 5.1–5.5 mmol/L), 11% (OGTT plasma glucose 5.6–6.6 mmol/L), 3.5% (OGTT plasma glucose 6.7–7.7 mmol/L) and 37.5% (OGTT plasma glucose  $> 7.8$  mol/L) (Tables 5.4 and 5.5). This did not appear to be influenced by a linear trend, but subjects at the extreme ends of values for the OGTT seemed to have a higher prevalence of foetal complications.

TABLE 5.2

MATERNAL COMPLICATIONS IN ASIAN WOMEN WITH NORMAL GLUCOSE TOLERANCE (n=166)					
2 hr venous plasma glucose on 75 gm OGTT (mmol/L)	≤4.0	4.1 - 5.0	5.1 - 5.5	5.6 - 6.6	6.7 - 7.7
No. of women	12	48	26	52	28
Age (yrs) Mean (SD)	26 (3.5)	28.9 (4.3)	29.6 (4.7)	28.7 (3.2)	28.6 (3.8)
Maternal Weight Mean (SD) IBW %	97.2 (6.4)	105.3 (11.1)	110.1 (8.8)	116.4 (8.7)	103.7 (11.7)
Toxaemia or Caesarean Section (%) (or both)	0 (0) 0 (0) 0	3 (6.3) 5 (10.4) 0	3 (11.5) 2 (7.7) 0	1 (1.9) 10 (19.2) 0	1 (3.6) 2 (7.1) 0
Total No. of Maternal Complications (%)	0 (0)	8 (16.6)	5 (19.2)	11 (21.2)	3 (10.7)

TABLE 5.3

MATERNAL COMPLICATIONS IN ASIAN WOMEN WITH ABNORMAL GLUCOSE TOLERANCE (n = 32)

2 hr venous plasma glucose on 75 gm OGTT (MMOL/L)	7.8 - 11.0	≥ 11.1
No. of Women	22	10
Age (yrs) Mean (SD)	31.8 (5.0)	32.7 (5.7)
Maternal Wt. Mean (SD) IBW%	114.2 (20.1)	120.3 (20.1)
Toxaemia or Caesarean Section or both (%)	1 (4.5) 9 (40.9) 0 (0)	0 (0) 2 (20) 0 (0)
Total No. of maternal complications (%)	10 (45.5)	2 (20)

TABLE 5.4

## FOETAL COMPLICATIONS OF ASIAN MOTHERS WITH NORMAL GLUCOSE TOLERANCE (n = 166)

	< 4.0	4.1 - 5.0	5.1 - 5.5	5.6 - 6.6	6.7 - 7.7
Maternal 2 hr venous plasma glucose on 75 gm OGTT (MMOL/L)					
No. of pregnancies	12	48	26	52	28
Gest age (wks) Mean (SD)	38.1 (2.4)	39 (13)	39.3 (1.0)	33.7 (1.5)	39.3 (0.8)
Birth wt (gms) Mean (SD)	3055 (833)	3159 (335)	3182 (458)	3288 (269)	3110 (872)
Macrosomia (%)	0 (0)	1 (2.1)	0 (0)	2 (3.8)	1 (3.6)
Microsomia (%)	2 (16.7)	3 (6.3)	3 (11.5)	2 (3.8)	0 (0)
Prematurity (%)	2 (16.7)	1 (2.1)	1 (3.8)	2 (3.8)	0 (0)
Congenital abnormalities (%)	0 (0)	0 (0)	1 (3.8) <sup>a</sup>	0 (0)	0 (0)
Perinatal mortality (%)	0 (0)	0 (0)	1 (3.8) <sup>b</sup>	0 (0)	0 (0)
Total No. of foetal complications (%)	4 (33.3)	5 (10.4)	6 (23.1)	6 (11)	1 (3.5)

a, b: Refer Table 5.10

TABLE 5.5

FOETAL COMPLICATIONS OF ASIAN MOTHERS WITH ABNORMAL  
GLUCOSE TOLERANCE (n = 32)

Maternal 2 hr venous plasma glucose on 75 gm OGTT (MMOL/L)	7.8 - 11.0	> 11.1
No. of Pregnancies	22	10
Gest age (wks) Mean ( SD)	37.6 (1.8)	38 (1.5)
Birth wt (gms) Mean ( SD)	2875 (581)	3372 (391)
Macrosomia (%)	1 (4.5)	1 (10)
Microsomia (%)	5 (22.7)	0 (0)
Prematurity (%)	4 (18.2)	0 (0)
Congenital abnormalities (%)	0 (0)	0 (0)
Perinatal mortality (%)	1 (4.5) <sup>c</sup>	0 (0)
Total No. of foetal complications (%)	11 (50)	1 (10)

c: Refer Table 5.10



White CaucasiansMaternal features:

There was no significant difference in maternal age or maternal body weight between the groups. Although there was a trend for those with an abnormal GTT to be slightly older and have a higher body weight.

Total maternal complications occurred in 13% (OGTT plasma glucose < 4 mmol/L), 12% (OGTT plasma glucose 4.1-5.0 mmol/L), 6.8% (OGTT plasma glucose 5.1-5.5 mmol/L), 11.9% (OGTT Plasma glucose 5.6-6.6 mmol/L), 13.9% (OGTT plasma glucose 6.7-7.7 mmol/L), and 25% (OGTT plasma glucose > 7.8 mmol/L). There was no significant difference in the proportions of maternal complications between the GTT groups, nor was there a significant trend in the proportions across the groups.

Foetal features:

There was no significant difference in gestational age or birth weight of infants born to mothers, between the groups. Total foetal complications occurred in 32.5% (OGTT plasma glucose < 4 mmol/L), 18.6% (OGTT plasma glucose 4.1-5 mmol/L), 20.5% (OGTT plasma glucose 5.1-5.5 mmol/L), 19.8% (OGTT plasma glucose 5.6-6.6 mmol/L), 27.9% (OGTT plasma glucose 6.7-7.7 mmol/L) and 25% (OGTT plasma glucose > 7.8 mmol/L). Although subjects at the extreme ends of glucose tolerance appeared to have a higher prevalence of foetal complications, this was not statistically significant, nor was there a significant trend in the proportions across the groups.

TABLE 5.6

## MATERNAL COMPLICATIONS IN WHITE CAUCASIAN WOMEN WITH NORMAL GLUCOSE TOLERANCE (n = 324)

2 hr venous plasma glucose on 75 gm OGTT (MMOL/L)	≤ 4.0	4.1 - 5.0	5.1 - 5.5	5.6 - 6.6	6.7 - 7.7
No. of women	40	86	44	111	43
Age (yrs) Mean ( SD)	25.6 (4.1)	26.7 (5.6)	26.7 (4.9)	28.6 (6)	28.2 (4.8)
Maternal weight Mean ( SD) IBW %	109.2 (7.1)	113.3 (10.9)	112.1 (12.9)	112.3 (11.3)	111.1 (12.6)
Toxaemia or	3 (7.5)	2 (2.3)	0 (0)	2 (18)	1 (2.3)
Caesarean Section (%)	2 (5)	7 (8.1)	3 (6.8)	10 (9)	5 (11.6)
or both		1 (1.2)	0 (0)	1 (0.9)	0 (0)
Total No. of maternal complications (%)	5 (13)	10 (12)	3 (6.8)	13 (11.9)	6 (13.9)

TABLE 5.7

## MATERNAL COMPLICATIONS IN WHITE CAUCASIAN WOMEN WITH ABNORMAL GLUCOSE TOLERANCE (n=32)

2hr venous plasma glucose on 75 gm OGTT (MMOL/L)	7.8 - 11.0	≥11.1
No. of women	27	5
Age (yrs) Mean (SD)	32.1 (5.2)	32.4 (6.1)
Maternal Wt. Mean (SD) IBW%	116.2 (20.3)	113.2 (27.2)
Toxaemia or Caesarean Section both (%)	1 (3.1) 5 (18.5) 0 (0)	0 (0) 2 (40) 0 (0)
Total No. of maternal complications <sup>(%)</sup>	6 (22.2)	2 (40)

TABLE 5.8

## FOETAL COMPLICATIONS OF WHITE CAUCASIAN MOTHERS WITH NORMAL GLUCOSE TOLERANCE (n = 324)

Maternal 2 hr venous plasma glucose on 75 gm OGTT (mmol/l)	< 4.0	4.1 - 5.0	5.1 - 5.5	5.6 - 6.6	6.7 - 7.7
No. of pregnancies	40	86	44	111	43
Gest age (wks) Mean	39.6 (1.4)	39.7 (1.4)	39.3 (1.4)	39.2 (3.2)	39.3 (1)
Birth Wt (gms) Mean	3638 (510)	3468 (525)	3530 (501)	3529 (525)	3373 (588)
Macrosomia (%)	8 (20)	13 (15.1)	8 (18.2)	21 (18.9)	6 (14)
Microsomia (%)	2 (5)	1 (1.1)	1 (2.25)	0 (0)	5 (11.6)
Prematurity (%)	1 (2.5)	1 (1.1)	0 (0)	0 (0)	0 (0)
Congenital abnormalities (%)	1 (2.5) <sup>d</sup>	1 (1.1) <sup>e</sup>	0 (0)	1 (0.9) <sup>f</sup>	1 (2.3) <sup>g</sup>
Perinatal mortality (%)	1 (2.5) <sup>h</sup>	0 (0)	0 (0)	1 (0.9) <sup>f</sup>	0 (0)
Total no. of foetal complications (%)	13 (32.5)	16 (18.6)	9 (20.5)	22 (19.8)	12 (27.9)

d, e, f, g, h: Refer Table 5.10

TABLE 5.9

FOETAL COMPLICATIONS OF WHITE CAUCASIAN MOTHERS  
WITH ABNORMAL GLUCOSE TOLERANCE (n=32)

Maternal 2 hr venous plasma glucose on 75 gm OGTT (MMOL/L)	7.8 - 11.0	≥ 11.1
No. of pregnancies	27	5
Gest age (wks) Mean	38.9 (1.4)	37.2 (0.8)
Birth wt (gms) Mean	3447 (466)	3588 (285)
Macrosomia (%)	3 (10.7)	0 (0)
Microsomia (%)	1 (3.6)	0 (0)
Prematurity (%)	1 (36)	1 (20)
Congenital abnorm (%)	0 (0)	0
Perinatal mortality	1 (36) <sup>j</sup>	1 (20) <sup>k</sup>
Total no. of foetal complications (%)	6 (22.2)	2 (40)

j,k: Refer Table 5.10

TABLE 5.10

CONGENITAL ANOMALIES AND PERINATAL MORTALITY

<u>Congenital Anomalies</u>	<u>Perinatal Mortality</u>
a. Epispadias	b. Respiratory distress
d. Single ventricle	c. Cause unclear
e. Cleft palate	
f. As adjacent	f. Abnormal penis with hypospadias
g. Leber's anaurosis	Ventricular hypertrophy
	Hydrocephalus
	h. Respiratory distress syndrome
	j. Intracranial haemorrhage
	k. Respiratory distress syndrome

## DISCUSSION

From my review at the beginning of this chapter, it would appear that there is good evidence to suggest a higher prevalence of complications affecting both the mother and the foetus, if the mother has established insulin dependent diabetes prior to the pregnancy. The situation in gestational diabetes, however, is not so clear, and is further confounded by differences in the diagnostic criteria employed. As maternal hyperglycaemia during pregnancy is eminently correctable, it would seem to be of value to determine the levels at which this may have detrimental effects and whether early detection and treatment of this may confer some practical benefit. Jarrett (1981) has pointed out that currently it is difficult to be certain whether hyperglycaemia per se during pregnancy is causal for any added risk to the pregnancy or whether it merely acts as a marker for other factors that may confer this risk (such as increasing maternal age or weight). Further, due to differences in the diagnostic criteria of the WHO, and those of O'Sullivan and Mahan (which form the basis of the recommendations of the Workshop-Conference and the National Diabetes Data Group) it is unclear as to the level beyond which glycaemia may confer an added risk to the pregnancy. For these reasons, I felt that in the present study I would examine maternal and foetal complications through a range of glycaemic levels, to assess the impact of the degree of glucose tolerance on the outcome of pregnancy.

Several studies have shown retrospectively that women recognised to have diabetes subsequent to their pregnancy, have had an excess of stillbirths, neonatal deaths, prematurity, macrosomia, congenital abnormalities and maternal obesity and toxaemia (Pettit et al, 1980). O'Sullivan et al (1973) have shown an increased perinatal mortality rate associated with gestational diabetes as determined by an OGTT during pregnancy. None of these studies, however, have tried to differentiate between complications in different ethnic groups. Pettit et al (1980) have also shown that in a study involving Pima Indians, perinatal mortality, macrosomia, toxaemia and Caesarean section varied directly with glucose concentration, but congenital abnormalities and prematurity rates did not. However, the rates for all these complications were higher in known diabetic women than in the rest of the population.

In the present study I have presented data from two different ethnic populations. No significant effect of either maternal body weight or age was found on glucose tolerance although there was a trend for glucose tolerance to worsen with increasing age and weight. In previous studies (Tallarigo et al, 1986) (Pettit et al, 1980) maternal body weight was determined postpartum, and used to calculate ideal body weight. In the present study the weight used was a "booking weight" within the first trimester. It is possible that this may act as an additional confounding factor. Both maternal weight and



age are expected to exert greater effects towards the upper end of the glycaemic levels. Unfortunately, due to small numbers of subjects, this particular group (2 hr venous plasma glucose  $>11.1$  mmol/L on OGTT) had to be amalgamated with the one below. This may possibly again mask the effect of these variables on glucose tolerance.

Pettit et al (1980) in the Pima Indian study have shown that perinatal mortality was related to infant birth weight. Their findings suggested that in large for gestational age infants, the perinatal mortality rate was 4-5 times greater, and the stillbirth rate was 6 times greater. I have not been able to demonstrate any relation of perinatal mortality with glucose tolerance. The overall perinatal mortality rate was 10/1000 (10/1000 in Asians and 8/1000 in White Caucasians). This is not different from the rate that might be expected in general population in this country (House of Commons Social Services Committee, 1979-1980). In the Pima Indian study the rate was higher at 27/1000. Tallarigo and colleagues (1986) were also unable to demonstrate an affect of glucose tolerance on perinatal mortality. They observed four deaths in the group in which the 2 hr plasma glucose level was  $< 5.6$  mmol/L and none in the groups with greater degrees of glucose intolerance.

I was not able to demonstrate a relationship with infant birth weight and the degree of maternal glucose tolerance.

The Pima Indian study suggested that birth weight in terms of large for gestational age was higher in the group with increasing glucose concentration. However, after multiple regression analysis allowing for maternal weight and age (which can influence glucose tolerance), this relation was lost. The Italian study (Tallarigo, 1986) also suggested a similar correlation, but an analysis of the data on birth weight shows considerable scatter. This, and data from the present study, would seem to suggest that in the normoglycaemic range at least, infant birth weight may be determined by factors other than glucose tolerance alone.

The congenital malformation rate did not vary with third trimester maternal glucose concentration. Five congenital abnormalities were observed, and the details are shown in Table 5.10. The overall rate was 0.9%, being 1.1% in White Caucasians and 0.5% in Asians. This is similar to the results of the Pima Indian study. Although Tallarigo et al (1986) showed a significant increase in congenital malformation with higher 2 hr plasma glucose levels the actual numbers of malformations in each of the three glycaemic groups studied were very small. A chance occurrence of a single extra malformation in the lower glycaemic group would have considerable weight in altering the statistical significance.

It is possible that the method of selecting subjects for the study may influence the outcome. The subjects in this study were those who had a recognised indication for an

oral GTT. As such, one might have expected to possibly err on the side of overestimating those with higher degrees of glucose intolerance and in theory, therefore, find a higher prevalence of complications with increasing glycaemia. This, however, does not appear to be the case.

In the Asian mothers, there was a trend for higher maternal complications with higher degrees of glycaemia. In the major part, this has been due to the high number of Caesarean sections. It is difficult to clearly interpret the implications of this. The rate of Caesarean sections may be because of a "true maternal complication", or alternatively may simply be a reflection of medical practice in a particular centre. Foetal complications were also higher in the Asian group. Unfortunately due to the small numbers of complications in each of the areas examined it was not possible to determine precisely which specific complication(s) were responsible for this. It would appear, however, that in the majority this may have been due to "microsomia", which was taken as a birth weight below 2500 gms. A particular difficulty in this respect is the lack of standard and uniformly accepted birth weight charts for Asian infants. It is an impression that Asian infants are not as heavy as White Caucasian infants of the same gestational age. Whereas 2500 gms may be definitely small for a White Caucasian term infant, it is not clear as to how far from the mean Asian birth weight this value may lie.

Glucose tolerance during pregnancy may be useful in predicting the subsequent development of diabetes in the mother. O'Sullivan (1961) has shown that women with glucose intolerance during pregnancy have a high incidence of overt diabetes in later life. In the Pima Indian study, during a 4-8 year follow up, subsequent overt diabetes occurred in 4.5% of women with third trimester glucose concentration less than 5.6 mmol/L. This rose with increasing glucose concentrations, being tenfold higher than with women with values between 8.8 and 10 mmol/L. The potential benefit that may arise from such information lies in the observations of O'Sullivan and Mahan (1980) that insulin treatment during gestational diabetes resulted in a significantly lower incidence of overt diabetes 16 years later. This aspect has not been addressed in the present study and would require a prospective analysis spanning a number of years.

Does a degree of glucose intolerance in pregnancy then impose a risk on the outcome? The literature is divided in this respect, Beard and Hoet (1982) feel that gestational diabetes as a clinical entity is of importance as there is an increase in foetal and neonatal morbidity in this group.

Hadden (1980) in his careful analysis of the Belfast experience from 1966-1977 feels that in mothers with glucose tolerance between one and three standard deviations from the mean, the pregnancy complications were only slightly more than those with a normal GTT. Hadden (1980) also suggests that no particular management of these

mothers is necessary. More recently interest has been focused on the "normal range of glycaemia" with evidence suggesting that even in this range complications of pregnancy are related to the level of glycaemia (Tallarigo et al, 1986), (Pettit et al 1980). In the present study I was unable to show a difference in complications in the normal range of glycaemia in White Caucasians. No differences were found in the hyperglycaemic range either, but this may have been due to small numbers at this end of the spectrum, and also because for purposes of analysis, all subjects in this range had to be amalgamated into a broad group with a 2hr venous plasma glucose  $7.8 \text{ mmol/L}$ . Perhaps what is necessary is a more detailed analysis of subjects who have 2 hr venous plasma glucose in excess of  $7.8 \text{ mmol/L}$  in pregnancy. Such an analysis would need to substratify this group, as well as incorporate the maximum numbers of subjects to attain meaningful information.

In Asians, there was a linear trend for increasing maternal complications with increasing degrees of glycaemia, as well as differences in foetal complications between the glycaemic groups. I have drawn attention to some of the difficulties in interpreting this within the constraints of the present study. However, I feel that the results I have presented have a relevant bearing on gestational diabetes. It would suggest the need for examining different ethnic populations in greater depth, as there may be considerable heterogeneity in the clinical patterns of gestational diabetes and its outcome. Until more information is

forthcoming, it would seem clinically prudent to keep a closer surveillance during pregnancy on groups known to have a high risk for diabetes.

## **C H A P T E R    6**

### **DIET AND ITS IMPLICATIONS IN DIABETES IN ASIANS**

## INTRODUCTION

Diet has major implications in everyday life. Eating regularly and at particular times of the day, shows how important this is. Eating habits can be very deeply ingrained and to a great extent depend upon the influences prevalent in formative years, as well as in one's immediate environment. Sociologists are only too aware of the differences in eating habits, and the divergent eating patterns that one may come across within the spectrum of ethnic groups. In addition to being an intrinsic part of individual human function, it also forms part of one's sociocultural environment. For human beings, eating together forms an important part in the interaction and relationship that one person may have with another. Realising this, Shakespeare remarked that at a banquet "the sauce to meat is ceremony".

For a diabetic, diet is particularly important. Firstly, it forms the cornerstone of treatment, and is used either alone or in conjunction with oral hypoglycaemic agents or insulin. The ancient Egyptians realised the benefits of diet in diabetes, and the Papyrus Ebers which dates back to around 1500 BC contains many such dietary prescriptions (Major, 1945). Successive centuries have witnessed several changes in diabetic dietary concepts. These have ranged from rotten meat and rancid fat in the eighteenth



century, to carbohydrate modification in the nineteenth century (Thomas, 1983). Since the discovery of insulin in 1921, the major emphasis on diet has been one of carbohydrate restriction (Truswell, Thomas and Brown, 1975). It is only in recent years that the pendulum has swung in the other direction, suggesting that the major portion of energy intake should be from unrefined carbohydrates with a reduction of energy intake from fats, especially saturated fats and proteins, and an increase in dietary fibre (British Diabetic Association, 1982). Secondly, since a diabetic has to follow a particular diet, this may in some respects be "restricting" especially as eating is a fundamental part of life. This may have secondary effects on the diabetic's perceptions towards treatment.

Another relevant aspect of diet lies in its postulated aetiology in non-insulin dependent diabetes. Sucrose and highly processed carbohydrates have been implicated in the aetiology. Evidence for this is conflicting, and West (1978) in summarizing the evidence quotes 21 major studies for and 22 studies against the possible role that sucrose may have to play. Trowell (1975, 1978) has been a firm protagonist of the theory that a diet low in starchy food and dietary fibre may predispose to diabetes. His observations are based on the fact that some decades ago diabetes was very uncommon in East Africa. The low glucose, low insulin profile after a glucose load in primitive people following a hunter-gatherer life style,

may be altered by changes in dietary habits and results in a subsequent emergence of diabetes in these populations. Himsworth (1935 a) and Himsworth and Marshall (1935) showed that newly diagnosed diabetics seemed to take less carbohydrate than non-diabetics, and that glucose tolerance in healthy adults could be improved by increasing the proportion of carbohydrate in the diet. These observations have formed the basis of the argument that dietary factors may have a role in the emergence of diabetes.

The Asian diabetic in the UK presents several unusual problems. Firstly, due to linguistic barriers it is possible that dietary advice may not be as effectively instituted as planned. Secondly, the Asian diet contains specific food items that may not be common to a European diet. Diabetic dietary advice for those used to European diets may therefore be inappropriate to one consuming an Asian diet, as specific daily items may be different. Finally, there is a marked paucity in the current medical literature concerning data on the glycaemic effects of Asian foods. This information would be of value in offering practical advice to Asian diabetics.

For the reasons given above, I have divided my study into two parts. The first part is concerned with the effectiveness of dietary advice offered in terms of assessing subsequent dietary practices in Asian diabetics. The second part examines the glycaemic effects of a standard Asian meal.

#### (A) DIETARY PRACTICES OF ASIAN DIABETICS

##### METHODS

In 1982, a diabetic clinic was started in the Westbourne Street Surgery, Leicester, by a principal in general practice. Of a total catchment of approximately 5000, about sixty percent are Asians. They are mainly Gujarati speaking Hindus who have migrated from East Africa. The clinic is held monthly, and 59 Asian diabetics attend regularly, on an average once every 2 or 3 months. This particular clinic was chosen for the purpose of the present study because of several unique features. The clinic is one of two established diabetic clinics run by general practitioners in Leicester. The surgery has a large catchment area, mainly of Asian patients. Most importantly, in an attempt to overcome linguistic barriers and in order to specifically tailor dietary advice according to Asian patients needs, the help of a dietitian speaking Asian languages was enlisted when initially offering dietetic advice (Shah, 1984). Each patient was initially interviewed by the dietitian in either Gujarati or Hindi, and then dietary advice was given according to the principles recommended by the British Diabetic Association (1982). This was modified by the dietitian to suit an Asian diet, with reference to foods consumed by Asians. Patients were then given a diet sheet in the appropriate language, to take home with them. At subsequent visits dietetic advice was verbally reinforced in Asian languages by the two general practitioners. The

purpose of this was to try and improve both communication and compliance.

All 59 diabetics were invited by post to attend for a dietetic interview. Each patient was asked to attend once, and complete a dietary questionnaire. Interviews were conducted in the presence of a dietitian and myself in order to help with the completion of the questionnaire where necessary, and to confirm the responses given. If patients experienced language problems in responding to the questionnaire, then the questions were translated either by me or one of the two general practitioners. Each interview lasted between 15 and 30 minutes.

The questionnaire was designed to directly ascertain whether a particular item was used, and if so the number of times per week. Any item used less than once weekly was regarded as being used only rarely; occasional use was taken as between 1-3 times per week; regular use implied four or more times per week. Specific food items covered were sugar, "gur", cakes, biscuits, diabetic foods, artificial sweeteners, sweets, chocolates, Asian sweets, Asian snacks, brown bread, white bread, type of flour for chappaties (number 1 white, number 2 brown), fresh fruit, "fizzy" drinks (coke, lemonade, lucozade), pulses, "dahls", meat, fish and herbal remedies for diabetes.

The amount of "ghee", butter, margarine and cooking oil used per month per household was ascertained, along with

the number of persons per household. An estimate of fat consumption was made by dividing the amount of cooking oil/fat bought over a period of time, by the number of heads regularly living within a household. This was expressed as an amount per person per month.

Case notes were scrutinised to record demographic features such as height, weight, age, sex, duration of diabetes, type of treatment, and the degree of glycaemic control at the time of the dietetic interview. As all patients did not agree to attend for interview, I retrospectively analysed case notes of the non-responders, and determined from visits within the last three months, demographic features as above, in order to eliminate the possibility of bias occurring due to potential differences, particularly in weight and diabetic control, in these two groups.

## RESULTS

40 out of 59 patients aged 30-70 years, responded by attending for a dietetic interview. There were 26 men and 14 women. 28 (70%) were on oral hypoglycaemic agents; 10 (25%) were on diet alone and 2 (5%) were taking insulin. 24 (60%) were over 120% of their ideal body weight (Royal College of Physicians of London, 1983), and 16 (40%) had a glycosylated haemoglobin (HbA1) over 9% (normal range 5-9%). There was no significant difference (Chi Square Test) in terms of the type of therapy for diabetes, obesity or elevated HbA1 between the responders and non-responders (Table 6.1).

All patients admitted to taking sweeteners in the form of sugar or "gur" at least occasionally. 18 (45%) had Asian sweets at least occasionally and 32 (80%) had Asian snacks regularly. 36 (90%) had "Indian tea" regularly. 34 (85%) tried herbal remedies for diabetes, mainly in the form of "karela" at least occasionally. Interestingly, diabetic foods, artificial sweeteners, cakes, biscuits, sweets, chocolates and fizzy drinks were consumed only rarely or never by the whole group. There was some confusion about diabetic foods and artificial sweeteners, and about two thirds had no knowledge of these items. Two thirds used No.2 flour (brown) regularly, but wholemeal bread was never used. The frequency with which specific foods were used is shown in Table 6.2.

Individual intake of fat and oil was estimated on the basis of household consumption per month. This appeared to be high. 32 patients (80%) took about 3 lbs of hard fat ("ghee") and 20 (65%) also took between 1-3 litres of cooking oil per person per month.

TABLE 6.1

DEMOGRAPHIC FEATURES OF RESPONDERS AND NON-RESPONDERS  
TO DIET QUESTIONNAIRE

	<u>RESPONDERS</u>	<u>NON-RESPONDERS</u>
	(n=40) (%)	(n=19) (%)
Male	26 (65%)	10 (53%)
Female	14 (35%)	9 (47%)
Diet therapy alone	10 (25%)	7 (37%)
Oral hypoglycaemic agents	28 (70%)	12 (63%)
Insulin	2 (5%)	0 (0%)
Overweight *	24 (60%)	10 (53%)
HbA <sub>1</sub> > 9% **	16 (40%)	8 (42%)

\* Overweight : Above the upper limit of weight range  
for height (Royal College of Physicians  
of London, 1983)

\*\* Normal range : 5 - 9%



TABLE 6.2

FREQUENCY OF SPECIFIC FOOD ITEMS USED BY ASIAN DIABETICS (n = 40)

	REGULAR ( > 4 TIMES/WK ) Number (%)	OCCASIONAL (1-3 TIMES/WK) Number (%)	RARE ( < 1 TIME/WK ) Number (%)	NEVER Number (%)
Sugar /"Gur" <sup>a</sup>	20 (50%)	20 (50%)	-	-
"Indian Tea" <sup>b</sup>	36 (90%)	4 (10%)	-	-
Asian sweets <sup>c</sup>	2 ( 5%)	16 (40%)	22 (55%)	-
Asian snacks <sup>d</sup>	32 (80%)	8 (20%)	-	-
Fruit juice, unsweetened	-	16 (40%)	16 (40%)	8 (20%)
Fresh fruit (1 - 2 pieces)	17 (42.5%)	20 (50%)	3 (7.5%)	-
Tinned fruit	-	-	-	40 (100%)
"Karela" <sup>e</sup>	24 (60%)	10 (25%)	6 (15%)	-
Diabetic Foods <sup>f</sup>	-	-	6 (15%)	-
Artificial sweeteners <sup>g</sup>	-	-	14 (35%)	-
Cakes / Biscuits	-	-	40 (100%)	-
Sweets / Chocolates	-	-	26 (65%)	14 (35%)

TABLE 6.2 (continued)

	REGULAR ( > 4 TIMES/WK ) Number (%)	OCCASIONAL ( 1-3 TIMES/WK ) Number (%)	RARE ( < 1 TIME/WK ) Number (%)	NEVER Number (%)
White bread	-	15 (37.5%)	11 (52.5%)	4 (10%)
Wholemeal bread	-	-	-	40 (100%)
No 1 Flour (white)	14 (35%) <sup>a</sup>	-	-	-
No 2 Flour (brown) <sup>h</sup>	26 (65%)	-	-	-
Fizzy drinks	-	-	5 (12.5%)	35 (87.5%)
Pulses / "Dahl"	6 (15%)	29 (72.5%)	5 (12.5%)	-
Meat / Fish	4 (10%)	7 (17.5%)	16 (40%)	13 (32.5%)

a.	Brown sugar made from palm sap (Tan et al. 1985)	b.	Made by boiling tea leaves and sugar in equal amounts of milk and water (Tan et al. 1985)
c.	Mainly Burfi, Gulab Jaman	e.	Mormodica Charantia which has a hypoglycamic effect and used as a herbal remedy (Pitchumoni, 1979)
d.	Mainly samosas, pakoras, chevda, ganthia		
f.g.	85% and 65% respectively of patients had no knowledge that these items existed		
h.	Extraction rate approximately 70%		

## DISCUSSION

Diet is most important in the management of the diabetic patient, and current recommendations focus on the importance of a total energy intake individualised according to the patients needs, a reduction in energy from fat sources, an increase in unrefined carbohydrate and dietary fibre, and the elimination of simple sugars (British Diabetic Association, 1982). From the present survey, it would appear that at least in this sample of Asian diabetic patients, these objectives have not been achieved. Patients continue to take simple sugars in the form of "gur" (jaggery) and sweets such as gulab jamans and burfi, which contain between 17-50% of carbohydrate mainly in the form of sugar (Tan et al, 1985). The intake of "ghee" and cooking oil was also very high. Further, Asian snacks such as chevda, ganthia and samosa contain between 25-50% of fat (Tan et al, 1985), and these were eaten not infrequently. Another interesting feature that emerged was that 90% of patients drank "Indian tea" daily, and many of them several times per day. As the recipe indicates, this contains half milk and half water (Tan et al, 1985), and so the amount of milk consumed per person per day was high, and estimated between 1-2 pints in many patients.

Previous studies from India seem to suggest that the diet followed by Asian diabetics is fairly close to what has been recommended (Patel et al, 1969). However, a study on Asian diabetics in Brent found that most seemed to consume

a diet low in carbohydrate, high in fats especially saturated fats, and that subjects ate sugar and refined carbohydrates regularly (Peterson et al, 1986). The authors postulate that one possible reason for this failure is a lack of basic knowledge about Asian diets, as well as a lack of culturally acceptable educational aids with which practical advice may be given. Whilst this may be true to some extent, the present study would indicate that the reasons for failure are possibly more complex and may reflect certain cultural attitudes. One of the reasons for choosing this particular group of Asian diabetics (as opposed to a group attending only a hospital clinic) was that dietary advice was given, as well as reinforced by professionals who had a knowledge of Asian diets and Asian languages. If the management of an illness is viewed in sociocultural terms as in the models of Balint (Balint, 1957), then ethnic differences in perception of the interactions between the individual and the environment take on a very major significance. This is particularly true with respect to the views held by the ethnic group concerned. When asked as to why so much fat and oil was used in the diet, patients responded by saying that they felt this was essential to Indian cooking, as most ingredients, especially spices, had to be well fried for the "correct taste". It is also not too surprising that 60% of them were over-weight and not particularly motivated to lose weight, as they regarded this as a sign of affluence and well being. From personal knowledge, I can say that in Bengal (East India) the word for describing

a thin person shares a common etymological root with "disease", and in Delhi it is not uncommon to describe a plump person as "healthy". Being somewhat over-weight would, therefore, seem to be culturally desirable.

Another important aspect that emerged from casual questioning was that most patients visited other households - family and friends - very frequently and on an informal basis. They felt that hospitality demanded that the host provides a full meal or at least tea and snacks, and that the guests partake of this. Most Asian snacks (gulab jaman, samosa) contain a high proportion of either sugar or fat (Tan et al, 1985).

Interestingly, seven patients volunteered that they felt the dietary advice they had received was inappropriate to their dietary habits. This was because emphasis had been laid on the reduction of sugar, butter and margarine, with inadequate mention of jaggery, ghee or oil, chevda, ganthia, samosas and pakoras which are eaten widely and regularly. Cakes, biscuits, sweets, chocolates and "fizzy drinks" were not popular with the group as a whole reflecting that these items were not considered as important components of their diet.

The fact that 85% of subjects tried Karela occasionally (ie at least once a week) emphasises the role of culture and health beliefs in the management of disease. Research on

"Asiatic Medicine" has drawn attention to the use of Ayurvedic or Unani medical practice (Hakims and Vaid) as an important aspect in Asian communities (Johnson, 1984). Ayurvedic physicians (Vaid) were aware of diabetes for over 2500 years, and used three broad groups of "drugs" for treatment: minerals, drugs from herbal or vegetable sources and drugs from animal sources (Ajgaonkar, 1969). Amongst these, Karela (*Momordica Charantia*) or "bitter gourd" is very commonly used, and its hypoglycaemic effect has been documented in the Indian medical literature for many years (Ram, 1950). It is only recently that its property as a hypoglycaemic agent and its possible role in diabetes has been highlighted in the West (Pitchumoni, 1979) (Leatherdale et al, 1981). All the patients interviewed had tried Karela at least once, and the majority were still using it.

The present study, though small, gives an indication of dietary practices in Asian diabetics. The study was aimed at examining the frequency with which specific food items particularly applicable to this group were eaten, after they had received intensified dietetic advice. It was not designed to examine caloric intake or the proportions of fat, carbohydrate, protein and fibre. As such the estimate of fat consumption may be regarded as not wholly accurate. However, it does serve as an approximation of the amount of fat consumed per person, and allowing for a margin of error, this would seem unduly high. "Indian ghee" contains

a high proportion of cholesterol oxides (Jacobson, 1987), and this may be a possible cause for the observed high risk of ischaemic heart disease in Asians (McKeigue et al, 1985). The questionnaire did not examine patients' knowledge of current dietary recommendations nor did it include a section on alcohol. It was not possible to compare Asian diabetics with White Caucasian diabetics as there is no other general practice clinic dealing with similar numbers of white diabetics for the same duration of time. However, a study involving diabetics in Islington, North London seems to suggest that there is a time lag between offering dietary advice, to actually implementing this, and that possibly such advice is not as effective in practice as one might imagine (Sheard, 1984). A comparison with Asian diabetics attending the hospital clinic would also not be quite valid as they would not have had dietary instruction in the mother tongue, and it is also possible that the hospital environment might have induced a bias towards giving more "approved" responses.

The present study is important in several respects. Firstly it suggests the need for detailed evaluation of dietary habits to judge the effect that dietary advice has on diabetics in ethnic minority groups. Secondly, it would appear that overcoming linguistic barriers and simply covering aspects of an "Asian diet" in broad terms is probably insufficient. What is required is emphasis on specific food items, and an understanding of the differences that may occur because of sociocultural

implications of cooking and eating habits. If one holds the view that the success of dietary advice lies in appropriate dietetic education of patients, then ethnic cultural beliefs and practices assume a major role. This is what I have tried to highlight as applied to diabetes in Asians.



(B) A COMPARISON OF THE GLYCAEMIC AND INSULINAEMIC EFFECTS  
OF A STANDARD EQUICALORIC ASIAN AND EUROPEAN MEAL

The importance of diet in the overall management of diabetes has been stressed by both the British Diabetic Association (1982) and the American Diabetes Association (1979). The aims of diet therapy are to produce a minimal degree of postprandial hyperglycaemia as well as to reduce wide swings in plasma glucose levels. The recommendations suggest that 50-60% of total energy be derived from carbohydrate sources, with a restriction of refined sugars. Studies have been performed on individual food items, to determine their glycaemic effects (Crapo, Reaven and Olefsky, 1976), (Crapo et al, 1980), (Ionescu-Tirgoviste et al, 1983). However, it has been argued that whilst these studies provide valuable information in terms of the degree of hyperglycaemia that specific foods may produce, they are not "physiological" in that it is unusual to consume test items in isolation. A "true" test that might provide useful practical information would be to test the glycaemic effects of whole meals. Two such studies have shown that sucrose, when taken as part of a whole meal did not significantly aggravate postprandial hyperglycaemia (Bantle et al, 1983), (Slama et al, 1984). This finding is of particular importance as it emphasises the value of testing foods in a more "physiological" form, and shows that when this is done the observed effects may be different from what might be expected by testing individual items separately. A second potential value of

examining a standard whole meal in terms of its glycaemic effect, lies in the possibility that dietary factors may have a role in the aetiology of non-insulin dependent diabetes. It is possible that different meals may have varying effects on plasma glucose and insulin secretion, and if a particular type of meal is consumed regularly then it may have a degree of significance in the subsequent development of diabetes. Current knowledge regarding the glycaemic effect of carbohydrate foods is based almost entirely on foods commonly consumed in the West (Jenkins et al, 1984), and there is a marked paucity of data concerning Asian foods. For these reason, I have chosen to examine the glycaemic and insulinaemic effects of a standard Asian meal and compare this with a standard equicaloric European meal.

## METHODS

A large proportion of Asians in Leicester live in the Belgrave area. This area also has The Belgrave Asian Community Centre, which serves as a centre for social meetings, as well as a local "citizens advice bureau" for Asians. The Centre is responsible for cooking "meals on wheels" for elderly Asians, and takes great care in ensuring that these meals are fairly "typical" in terms of content and taste. In conjunction with the centre a menu for a standard Asian lunch was devised. This was deliberately kept as vegetarian, as it was the Centre's experience that the majority of their clientelle preferred this to a non-vegetarian meal. Subsequently, a trained dietitian observed this meal being prepared, and noted the amount of each specific ingredient that was employed as per the recipe of the cooks of the centre. A cook was then engaged to prepare the "standard" meal using the same ingredients in the same amounts each time. Meals were prepared for five people at a time as this was a convenient number to test simultaneously. Similarly a menu for a standard European meal was devised so that it would be equal (as far as possible) in terms of calories, to the Asian meal. The individual components and quantities were noted, and the same amounts used subsequently to ensure uniformity of the meals.

The menu for the Asian meal was rice, chapatis, potatoes and cabbage, chick pea curry, urad dahl, and yoghurt. The

menu for the European meal was roast beef and Yorkshire pudding, gravy, roast potatoes, boiled carrots peas and potatoes, cheese and biscuits. Each Asian meal was 1439 calories and each European meal 1370 calories. The individual constituents of the meals are shown in Table 6.3 and Table 6.4 respectively.

Nine male and 6 female healthy volunteers were recruited into the study. None had any known illness, nor any known diabetes in a first degree relative. None were on any medication (including the contraceptive pill). They were aged 23-36 years (mean 25.3 years) and body weight ranged from 95-115% (mean 105.2%) ideal body weight (Metropolitan Life Insurance Tables). All subjects were consuming a diet containing at least 200 gms carbohydrate daily, and were instructed to continue doing so. None were taking more than 4 units of alcohol per week.

A full explanation of the trial was given to each subject, and they were required to report at midday after an overnight fast of 12 hours. An intravenous cannula was inserted into a forearm vein, and they were required to rest for half an hour. Each subject was tested twice, once with the Asian meal and once with the European meal, in random order on consecutive days, and so served as his own control. The test meal was administered as "lunch" between 1230-1300 hours. The test was regarded to commence with the first bite of food, and subjects were instructed to complete the meal within 15-20 minutes of commencement.

They were allowed upto 400 mls of plain water, with each meal. Venous blood was sampled from just before commencement of the study and then every hour for 3 hours, collected in lithium heparin bottles and stored on ice at 4 °C. Plasma was separated immediately after completion of the study and stored at -20 °C till assay. During the study subjects were required to remain seated and resting, and were not allowed to smoke.

Plasma glucose was measured by the glucose-oxidase method (Beckman Autoanalyser). Plasma insulin was measured by radio-immunoassay (Serono Insulin Kit).

Statistical analysis was done by Students paired t-test.

TABLE 6.3  
COMPONENTS OF THE ASIAN MEAL

	Wt (gms)	Kcal	Prot (gms)	CHO (gms)	Fat (gms)	Fibre (gms)
Chick peas (dry wt)	200	640	40.4	100	11.4	30
Lentils (split urad, dry wt)	200	608	47.6	106.4	2.0	23.4
Flour (wheat- meal)	550	1821	63.3	402	6.6	63
Basmati rice (raw)	220	790	16.3	159.6	1.1	5.3
Yogurt (full fat)	400	260	13.2	18.8	15.2	0
Potatoes (peeled, raw)	290	252	6.1	60.3	0.3	6.1
Cabbage (white)	250	55	4.8	9.5	Tr	6.8
Onions (peeled)	166	38	1.5	8.6	Tr	2.2
Tomatoes (tinned)	232	28	2.5	4.6	Tr	2.1
Butter	62	459	0.2	Tr	50.8	-
Oil (240 gms)	8 Fl oz	2158	Tr	0	240	0
Ginger (peeled)	17	7.8	0.3	1.3	0.1	0
Coriander	9	25	2.0	3.8	0.4	0
Turmeric	3	10.6	0.2	1.7	0.3	0
Chilli	4	12.6	0.5	0.4	0.7	0
Cumin seeds	5	18.9	0.9	1.7	1.1	0
Garam masala	3	9.8	0.4	1.3	0.4	0
Bicarbonate of Soda	0.5	-	-	-	-	-
Parsley	15	3.1	0.8	Tr	Tr	1.4
Salt	30	-	-	-	-	-
Total for 5 meals		7197	256	880	330	140
Amount per meal		1439	51	176	66	28
(%)			(14.2)	(45.9)	(41.3)	

TABLE 6.4COMPONENTS OF THE EUROPEAN MEAL

	Wt (gms)	Kcal	Prot (gms)	CHO (gms)	Fat (gms)	Fibre (gms)
Roast Beef (cooked lean and fat)	625	1338	166	-	75	-
Potatoes (roast cooked)	300	471	8.4	82.0	14.4	3
Potatoes Boiled (cooked)	750	600	10.5	148	0.8	7.5
Butter (for mashed potato)	75	555	0.3	Tr	61.5	-
Milk (fresh, whole)	45ml	29	1.5	2.1	1.7	-
Peas (frozen, boiled)	250	103	13.5	11.0	1.0	30
Carrots (boiled)	250	50	2.2	11.3	Tr	7.8
Yorkshire Pudding	375	806	25.5	96.8	37.9	3.8
Cheddar Cheese	250	1015	65	Tr	83.8	-
Cream Crackers	120	528	11.4	82	19.6	3.6
Butter (for crackers)	75	555	0.3	Tr	61.5	-
Flour Plain (white)	25	88	2.5	20.0	0.3	0.9
Fat (oil juices from meat)	80	713	Tr	-	79.2	-
Total for 5 meals		6851	307	453	437	57
Amount per meal		1370	61	91.0	87	11
(%)			(17.8)	(24.9)	(57.2)	

## RESULTS

At fasting, there was no difference in plasma glucose between the Asian and European meal, Mean (SEM) plasma glucose (mmol/L) was 4.3 (0.23) before the Asian meal, and 4.2 (0.13) before the European meal. Plasma insulin values, mean (SEM) (mU/L) were 1.81 (0.89) and 2.67 (0.48) respectively. The difference was not statistically significant.

At 1 hr, plasma glucose was 4.93 (0.38) and 4.15 (0.21) mmol/L following the Asian and European meal, and plasma insulin was 28.67 (4.28) and 28.17 (5.34) mU/L respectively. The difference was not statistically significant.

At 2 hr, plasma glucose and plasma insulin were significantly higher following the Asian meal. Plasma glucose was 5.29 (0.35) mmol/L compared to 4.32 (0.09) mmol/L ( $p < 0.02$ ), and plasma insulin was 28.17 (6.87) mU/L compared to 8.06 (1.54) mU/L ( $p < 0.02$ ).

At 3 hr, plasma glucose and plasma insulin remained significantly higher following the Asian meal. Plasma glucose was 5.12 (0.25) mmol/L compared to 4.24 (0.17) mmol/L ( $p < 0.01$ ) and plasma insulin was 24.11 (4.36) mU/L compared to 9.84 (2.46) mU/L ( $p < 0.02$ ).



Mean (SEM) plasma glucose and plasma insulin responses to the meals are shown in Figure 1 and Figure 2 respectively.

Peak achieved plasma glucose and plasma insulin were calculated from the highest observed individual values of glucose and insulin.

Peak achieved plasma glucose was mean (SEM) 6.16 (0.27) mmol/L following the Asian meal, and 5.43 (0.17) following the European meal ( $p < 0.01$ ). Mean (SEM) time for this was 68.4 (9.6) minutes and 36 (3) minutes following the Asian and European meals respectively ( $p < 0.01$ ).

Peak achieved plasma insulin was mean (SEM) 39.37 (5.11) mU/L after the Asian meal, and 38.35 (6.05) mU/L after the European meal. This difference was not statistically significant. Mean (SEM) time for this was 86 (10.5) minutes and 40 (3.8) minutes following the Asian and European meals respectively ( $p < 0.01$ ).

Figure 1

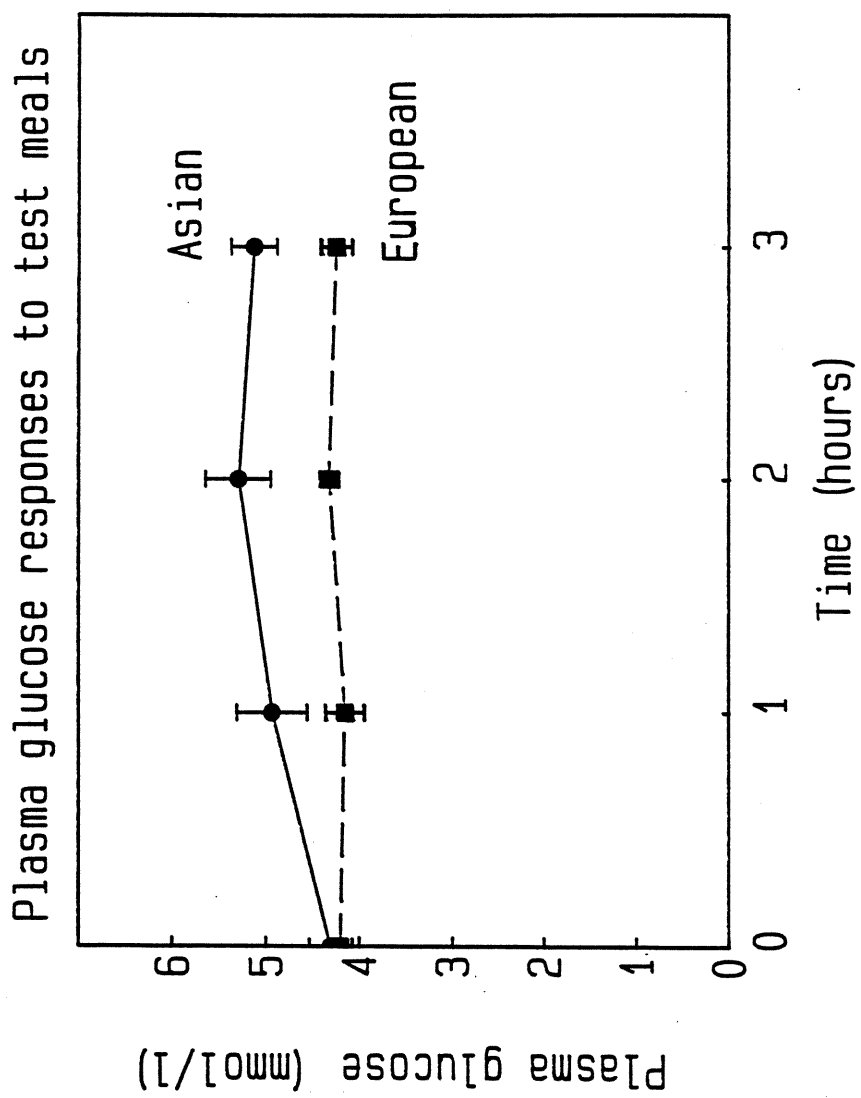
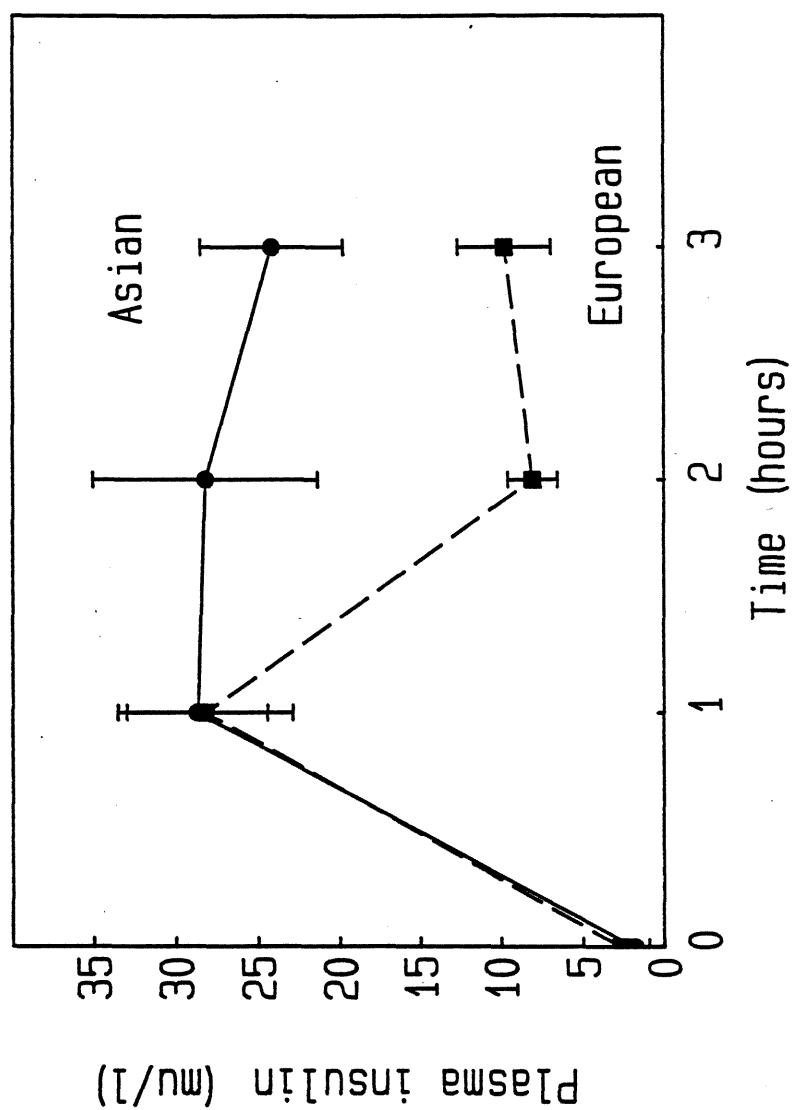


Figure 2

Plasma insulin responses to test meals



## DISCUSSION

The present study was designed to examine the glycaemic and insulinaemic effect of a standard Asian meal, compared to a European meal. It would appear that the time taken to achieve a peak plasma glucose and peak plasma insulin response is greater following the Asian meal. A significantly higher peak plasma glucose, and significantly greater degrees of hyperglycaemia and hyperinsulinaemia, occur at 2 hours and 3 hours after the Asian meal.

In the present study the two test meals were as equicaloric as could practically be attained. The Asian meal contained 1439 calories and the European meal 1370 calories. It would seem unlikely that a difference of only 70 calories in a single meal could account for the difference in the observed responses.

It is also unlikely that variability in subjects would account for this difference. All subjects were healthy volunteers with no known predisposing factors that might adversely affect glucose tolerance. As each subject was tested twice, each person served as his or her own control.

An analysis of individual responses also shows a trend for subjects to have a greater glycaemic and insulinaemic response following the Asian meal. Only one subject was Asian, and his response also followed the above pattern.

In order to ensure that each test meal was started from comparable levels of plasma glucose and insulin, all subjects were tested after a 12 hr fast and venous sampling was begun after a half hour rest. Fasting plasma glucose and insulin levels showed no significant difference prior to either test meal. Time taken to eat the meal might influence the time of the peak response, but this was uniformly kept between 15-20 minutes. The total volume of each meal was not measured and a confounding variable that might occur is the amount of liquid ingested with the food.

Liquids leave the stomach more rapidly than solids (Cooke, 1975), and it is known that carbohydrate in liquid form induces a greater rise in plasma glucose levels than carbohydrate in solid form (Schusdziarra, 1981). In the present study, subjects were given two glasses of plain water (400 mls) with each meal. Although the exact volume (both solid and liquid) ingested is not known, it would not appear to be vastly different between the two meals. Following ingestion of the meal subjects were requested to remain seated, resting and not to smoke until venous sampling was completed at 3 hours, in order to standardise the postprandial environment. The meals were given in random order as to obviate any "carry on" effect that might possibly occur.

A feature peculiar to the European meal was that it contained 57% fat, which is relatively high. Fat inhibits gastric emptying (Cooke, 1975) (Welch et al, 1986) and so may have an effect in delaying digestion and absorption of

carbohydrate and so reducing plasma glucose concentrations. However, in the present study the peak achieved plasma glucose concentration was earlier after the European meal, rather than later. This might be due to the confounding effect that other nutrients may have when comparing two meals made up of differing individual components. The problem inherent in comparing meals of unequal fat content have to some extent been minimised by administering different carbohydrates with a constant amount of protein and fat (Crapo, Reaven and Olefsky, 1976). However, this would alter the structure of the meal in terms of the proportions of its components and so would vitiate a comparison of "standard" meals that are actually eaten.

The Asian meal contained a greater amount of dietary fibre and a higher proportion of energy in the form of carbohydrate. The higher fibre content may account for the later peak achieved plasma glucose concentration. Himsworth (1935 b) first suggested that a high carbohydrate diet can improve glucose tolerance in normal subjects. A diet very high in carbohydrate, with over 70% of total energy from carbohydrate sources, and 65 gm daily dietary fibre, can very dramatically improve glycaemic control in patients with non-insulin dependent diabetes, sometimes resulting in complete elimination of oral hypoglycaemic agents or insulin (Anderson and Ward, 1979). Similarly a high carbohydrate diet considerably improves twenty four hour blood glucose profiles in insulin dependent diabetics, when compared to a "low carbohydrate" diet (Simpson et al, 1981).

The evidence, therefore, points to a high carbohydrate and fibre being advantageous in terms of minimising postprandial hyperglycaemia. The mechanisms by which the Asian meal resulted in higher plasma glucose and insulin levels at 2 hours and 3 hours are not fully clear as yet. A possible explanation for the results of the present study may be due to the spices present in the Asian meal. The effect that spices may have on plasma glucose regulation and insulin secretion, either directly, or via intermediaries such as the gut hormones (in particular GIP) is not known. GIP is regarded as the major enteric mediator of insulin release (Dupre et al, 1973), (Cataland et al, 1974). GIP is also known in humans to stimulate insulin release in the presence of hyperglycaemia (Anderson et al, 1978), and some of the present observations could be mediated through GIP release. It is possible that the cumulative action of the meal may be to produce initial hyperglycaemia, followed by a "rebound" relative hyperinsulinaemia.

The present study presents very preliminary work on the glycaemic effects of a standard Asian meal. It would be interesting to examine what effects might accrue from meals of equal energy content representing "standard" meals from different parts of the Indian subcontinent. It would also be of value to know for how long the accentuated glycaemic and insulinaemic responses persist, and whether these responses vary with ethnic origin or dietary life style of subjects tested. A possible value of the present

observations might lie in analysing the hypothesis that specific dietary factors lead to postprandial hyperglycaemia. This in turn may result in compensatory relatively high plasma insulin levels. If this state is maintained for a prolonged period of time, then it might be a possible mechanism leading to B-cell "exhaustion" and subsequent clinical diabetes.



## **C H A P T E R    7**

### **SUMMARY AND CONCLUSIONS**

In the present thesis I have studied several aspects of diabetes in Asians. The studies on prevalence show high rates of diabetes in adult Asians, rising sharply above the age of 45 years. The risk for developing non-insulin dependent diabetes is also higher for Asians and is about twice that in White Caucasians.

The prevalence of true insulin-dependent diabetes in Asian children is lower than in White Caucasian children, but this difference fails to reach statistical significance. This would suggest that insulin-dependent diabetes in Asians is not as rare as has been previously thought, and that the individual roles of genetic and environmental factors need to be explored.

Asian diabetics attending a hospital clinic have been studied for clinical features and vascular complications of diabetes. The mean age of onset of diabetes and a positive family history in first-degree relatives is higher in Asians. Asians also have less ketonuria and a lower tendency for treatment with insulin. The risk for Asians of developing kidney disease and cataracts is significantly higher, and significantly lower for eye disease and peripheral vascular disease. The risk for heart vascular disease is higher in Asians, and the risk for cerebrovascular disease is lower. These features illustrate the heterogeneity that may exist in the complications of diabetes amongst different ethnic groups.

The prevalence of gestational diabetes is significantly higher in Asian women. On the basis of a 2 hour plasma glucose value following a 75gm oral glucose tolerance test in the third trimester, women were classified into "glycaemic bands" from the normoglycaemic to the hyperglycaemic range. Asian women had a significant linear trend in the proportions of maternal complications across the glycaemic range. Foetal complications were also higher in Asian mothers at the extreme ends of the maternal glycaemic range.

I have studied patterns of insulin secretion and insulin sensitivity using the method of continuous infusion of glucose with model assessment. Non-diabetic Asians (first degree relatives of patients with non-insulin dependent diabetes and those without such a family history) have a lowered insulin sensitivity and hyperinsulinaemia. A hypothesis is proposed that insulin sensitivity may be ethnically determined. When this is compounded by B-cell dysfunction (which may be a primary or a secondary event) then this may lead to overt diabetes.

The acute metabolic effects of a standard Asian meal in normal volunteers resulted in a prolonged and greater degree of glycaemia and insulinaemia. Although preliminary, these findings suggest that dietary factors may in the long term exacerbate the cycle of hyperinsulinaemia - insulin sensitivity as described above.

Eating habits in Asian diabetics attending a clinic in general practice showed a high consumption of snacks, and sweets. I have shown that in the main this is due to the sociocultural customs prevalent in the Asian community, and I suggest that these need to be borne in mind when advising such patients.

In conclusion, Asians have a high prevalence of diabetes, with differences in the spectrum of clinical features when compared to White Caucasians. These studies indicate that both genetic and environmental factors may influence the development and outcome of diabetes in Asians, and suggest avenues for future work.

**PUBLICATIONS BASED ON THIS THESIS**

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