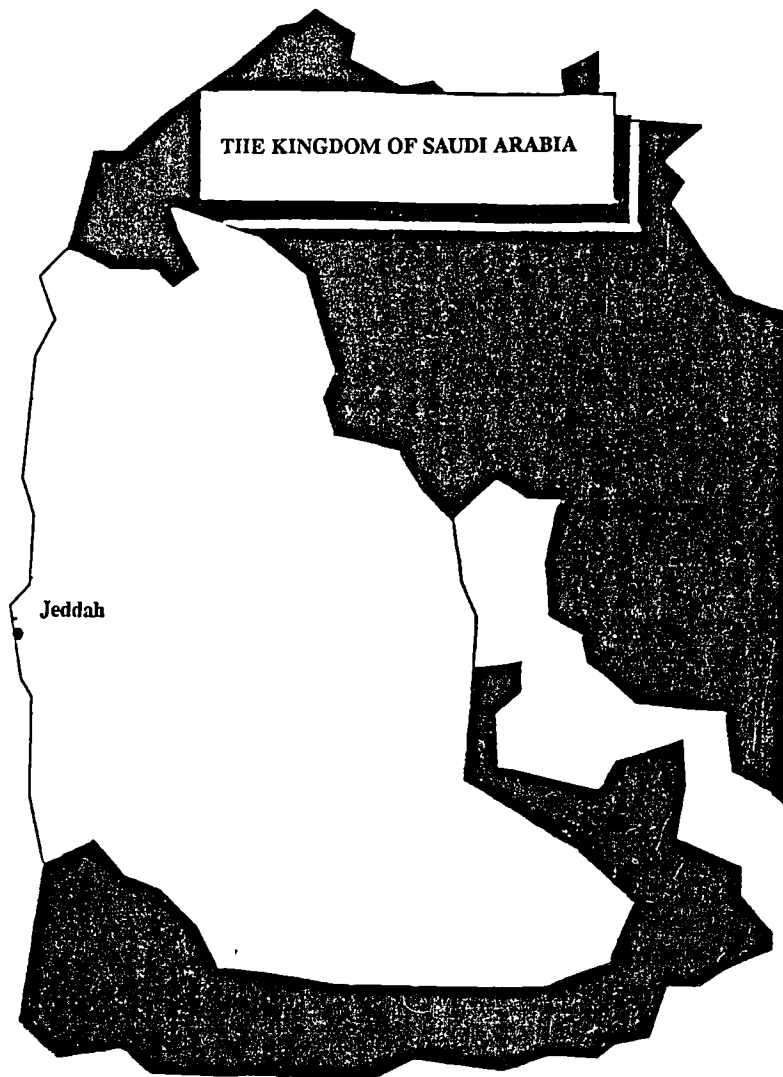

PhD THESIS

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GLUCOSE INTOLERANCE

IN AN URBAN MALE COMMUNITY IN SAUDI ARABIA



B

ABSTRACT

Most chronic non-communicable diseases result from a complex interaction between heredity and environmental factors. With better living conditions and adoption of western lifestyles in developing countries, there is an increased incidence of these diseases, the most common of which is diabetes. This study documents the prevalence of NIDDM, IGT, hypertension, obesity and hyperlipidaemia in an urban male community [n=125] in Jeddah, Saudi Arabia. It also examines OGTT reproducibility [n=35]; the influence of diet and physical activity; the differences in these aspects between nationals and non-nationals and the metabolic responses following the OGTT between the glucose tolerance groups [n=43].

Glucose intolerance, NIDDM [14%] and IGT [27%], were very common. Overall, CVD risk factors such as smoking [43%], obesity [29%], hypertension [5%], hypercholesterolaemia [7%], hypertriglyceridaemia [14%], occurring in association with diabetes were high. Clustering of other risk factors such as abdominal obesity, hyperinsulinaemia and hyperproinsulinaemia were also shown. The OGTT is a poorly reproducible test in this community and a further confirmatory test is always required to establish the diagnosis of glucose intolerance. The dietary habit and food item record identified recognizable features characteristic of this community, which were affected by both the cultural and the social background. However, no differences were found between the glucose tolerance groups. Physical inactivity was a major lifestyle problem and the inactive group tended to have increased risk factors, although differences were not significant. These environmental factors could not, however, be excluded as possible causative factors in the high prevalence of glucose intolerance and CVD risk factors in this community as the sample was small. Subjects with IGT tended to have intermediate levels of risk factors and this study favours identifying IGT as an independent category which lies between normal and NIDDM. Ethnic differences should be considered whenever possible particularly in this multinational community, since 40 % of this community were non-nationals. Nationals differed in certain dietary aspects and they tended to be inactive, otherwise no other significant differences existed between the groups.

As shown in different populations, those identified as IGT or NIDDM in this community, were characterised by hyperfunction of the β -cell in IGT, hypofunction of the β -cell in NIDDM and associated with immature secretion of proinsulin. The insulin resistance which was profound in NIDDM and intermediate in IGT was characterised by high glycerol and NEFA which were suggestive of insulin insensitivity at the level of adipose tissue. Large-scale and prospective studies are strongly recommended. Meanwhile, primary prevention measures are urgently required as these findings pose a significant public health problem.

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DEDICATION

[1] : To those who donated their blood for this research: without them this project would not have been possible.

[2] : To the people most dear to me Father, Mother, Wife and Arwa my lovely daughter.

DECLARATION

All field and analytical experiments reported in this thesis were performed by myself in both Jeddah, Saudi Arabia and Newcastle upon Tyne, UK. Considerable support and help was gratefully received from many members in the departments of medicine as shown in the acknowledgment. I declare that the whole of this work has not been submitted for a degree in any other university

ETHICAL COMMITTEE APPROVAL

The protocol for each study was approved by both the supervisor Professor KGMM Alberti and the local Regional Health Authority at Jeddah, Saudi Arabia. The purpose, nature and potential benefits and adverse effects of each test were fully explained both verbally and in written form to each subject prior to participation in each study.

PRESENTATION ARISING FROM THIS STUDY

1. ZJA Gazzaz and KGMM Alberti: The prevalence of glucose intolerance and cardiovascular risk factors in male in Jeddah, Saudi Arabia. Presented before the 5th World Congress on diabetes in the Tropics and developing countries, December 14-17, 1990; Karachi, Pakistan.

2. ZJA Gazzaz and KGMM Alberti: Relationship of sex hormone binding globulin (SHBG) to glucose intolerance, overall adiposity, body fat distribution, and lipids in Arab men. Presented before the 14th International Diabetes Federation Congress, June 23-28, 1991; Washington, DC, USA.

**'NIDDM, to a large extent, is due to an unhealthy lifestyle.
The prevention of diabetes mellitus and its devastating complications
is the ultimate dream.
The prevention of NIDDM is closer to reality.
The WHO program 'Health for All by the year 2000' may well be a reality
for those people at risk of NIDDM'.
Paul Zimmet, 1992.**

INTRODUCTION

CHAPTER ONE

DIABETES MELLITUS IN WORLD CONTEXT

CHAPTER CONTENT :

- Summary.
 - 1.1 History of diabetes.
 - 1.2 Definition.
 - 1.3 Classification and types.
 - 1.4 Diagnosis.
 - 1.5 Prevalence.
 - 1.6 Incidence.
 - 1.7 Mortality.
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 - 1.9.7 Insulin sensitivity.
 - 1.9.8 Insulin secretion.
 - 1.10 Conclusion.
-

SUMMARY

This chapter examines some aspects of diabetes with particular reference to some epidemiological features in a world context. It will emphasise those areas most relevant to the material discussed in this thesis.

1.1 HISTORY OF DIABETES

Knowledge of diabetes dates back to centuries before Christ. The Egyptian Ebers Papyrus [ca. 1500 B.C.] described an illness associated with the passage of much urine. Celsus [30 B.C. to 50 A.D.] recognised the disease but it was not until two centuries later that another Greek physician, the renowned Aretaeus of Cappadocia, gave the name diabetes [a siphon]. He made the first complete clinical description, describing it as "a melting down of the flesh and limbs into urine". In the 3rd to 6th centuries A.D., scholars in China, Japan and India wrote of a condition with polyuria in which the urine was sweet and sticky. However, although it had been known for centuries that diabetic urine tasted sweet, it remained for Willis in 1674 to add the observation "as if imbued with honey and sugar". The name diabetes mellitus [mellitus = honey] was thus established. A century after Willis, Dobson demonstrated that the sweetness was, indeed, due to sugar. From the time of the earliest recorded history of diabetes, progress in the understanding of the disorder came slowly until the middle of the 19th century (MacFarland, 1991).

However, over these centuries gradually the course and complications of the disease were recognised. Gangrene had been described by Avicenna, an Arab physician, in about 1000 A.D. Its hereditary tendency was described ["Passed with the seed"] as well as two general varieties, one with the classic acute symptoms noted above [Type I or IDDM in today's terminology] and the other with "torpor, indolence and corpulence" [Type II or NIDDM]. Within the past century an association was established with a disturbance in the beta cells. These islets were first noted in fish by Brockman early in the 19th century, but they bear the name of Langerhans who described them in mammals in 1869. Soon after, the German scientists, von Mering and Minkowski, found that surgical removal of the

pancreas produced diabetes in the dog. At the turn of the century, an American, Opie, noted the beta cells in the islets to be damaged in humans dying of the disease. Finally in 1921 Banting and Best, Canadians, prepared active extracts of pancreas which lowered the elevated glucose levels of diabetic dogs (*Engelhardt, 1989*).

1.2 DEFINITION

What is diabetes mellitus?. In generalisation, it is a grouping of anatomic and chemical problems resulting from a number of factors in which an absolute or relative deficiency of insulin and/or its function is present. It tends to run in families; is associated with accelerated atherosclerosis, and predisposes to certain specific microvascular abnormalities including retinopathy, nephropathy and neuropathy. It doubles the risk of stroke, increases the risk for heart attacks 2- to 3-fold, and for peripheral vascular problems, particularly in the feet, 50-fold. There are other problems, such as the lessening of resistance to infection, especially if the diabetes is poorly controlled (*Marble et al, 1985*).

1.3 CLASSIFICATION AND TYPES

In the mid-sixties a set of diagnostic criteria for diabetes was published among others with wide variation both between and within countries (*WHO, 1965*). Since then and before 1978, a variety of descriptive terms were used to classify diabetes, some based on the age of onset and others, the stage or the degree of severity of the disease. Substantial differences in the diagnosis criteria used by diabetes experts were also found (*West, 1975*). This leads to confusion which hindered the assessment of data from studies of the natural history of the disease and its complications. The NDDG [USA] then created a new classification based on clinical or descriptive observations from epidemiologic studies of large populations to provide uniform designations and a framework for collecting investigative and epidemiological data on diabetes (*NDDG, 1979*). A similar but more inclusive classification adopted by the WHO Expert Committee on Diabetes Mellitus in 1980 (*WHO, 1980*) and modified in 1985 (*WHO, 1985*)

has received general acceptance. Diabetes is subclassified as: Type I, insulin-dependent diabetes mellitus [IDDM]; Type II, non-insulin dependent diabetes mellitus [NIDDM]; malnutrition-related diabetes mellitus [MRDM]; and other types of diabetes. Each category is described briefly below (*Kareen et al. 1982*).

IDDM or type I diabetes mellitus, which involves about 15 % of the diabetic population, occurs primarily in young patients, but may be seen at any age. It is usually characterised by an abrupt onset of symptoms, although present evidence suggests that its evolution may involve an antecedent period of slowly developing autoimmune damage to the pancreatic B cells (*Leslie et al, 1989*).

NIDDM or type II diabetes mellitus, which occurs in 80 to 85 % of the diabetic population, is usually encountered in adults, but may occur in young patients. NIDDM is recognised as having a strong genetic basis, as evidenced by studies of identical twins and by familial transmission of diabetes in an autosomal dominant inheritance pattern (*Taylor, 1989*).

Malnutrition-related diabetes mellitus is a clinical subgroup that included in the WHO classification but not in that of the NDDG. It occurs predominantly among young adults in tropical, developing countries. Distinctive clinical features and course, and the great number of cases in certain regions, led to the creation of this new major class of diabetes. Clinical studies have suggested the existence of at least two subclasses: FCPD and PDPD (*Abu-Bakare, 1986*).

There were other types of diabetes mellitus which was formerly termed secondary diabetes. This is a heterogeneous subclass that includes many specific disorders that induce diabetes including pancreatic disease, hormones, drugs or chemicals, certain genetic syndromes and insulin receptor abnormalities (*Keen et al, 1982*).

The designation of impaired glucose tolerance [IGT] applies to individuals whose plasma glucose concentrations after an oral glucose load lie between normal and values diagnostic of diabetes (*Alberti, 1980*). The term IGT avoids the social, economic, and psychologic disadvantages associated with such

formerly used designations as chemical, latent or subclinical diabetes. A detailed account of IGT is found in Chapter two below.

Gestational diabetes mellitus occurs in approximately 2 % of pregnancies. It is a consequence of the diabetogenicity of the gravid state in women with marginal insulinogenic capacity; it generally reverts to normal following parturition. If unrecognised or untreated, gestational diabetes may increase the risk of perinatal morbidity and mortality (*Hadden, 1986*).

To identify the statistical risk classes for glucose intolerance, two additional terms are used. These are not part of the diagnostic identifications for patient records but are useful in research studies.

The term previous abnormality of glucose tolerance refers to individuals with previous diabetes or IGT who regained normal glucose tolerance (*NDDG, 1979*). Most frequently, individuals in this class include patients with former gestational diabetes or acute hyperglycemia whose metabolic status has returned to normal following appropriate treatment. These individuals are at increased risk for developing diabetes with stress or weight gain.

The potential abnormality of glucose tolerance was formerly termed prediabetes or potential diabetes and applies to individuals at substantially greater risk for diabetes than the general population (*WHO, 1980*). The category includes first-degree relatives of patients with diabetes, an identical co-twin of a patient with IDDM or NIDDM, HLA-identical siblings, or islet-cell antibody positive individuals. Also included are obese individuals and individuals who have delivered a large infant.

1.4 *DIAGNOSIS*

Classic symptoms, fasting plasma glucose, elevated postprandial or postglucose values and OGTT are the four diagnostic areas that will be considered here. Criteria for the diagnosis of diabetes mellitus have been developed by both the NDDG and the World Health Organisation based on data from epidemiologic surveys in different parts of the world. These diagnostic

standards provide a basis for uniformity in research and data collection. Further, the plasma glucose concentrations now considered diagnostic of diabetes provide better prediction for subsequent development of the specific complications of diabetes than those in the previously recommended criteria (*Shuman, 1988*).

In clinical practice, suspicion of diabetes is gleaned from history and physical findings. Symptoms such as fatigue, thirst, polyuria, weight loss, and recurrent infection are frequent clues. A family history of diabetes, obesity, unfavourable obstetrical experiences, premature atherosclerosis, neuropathic disorders are indicators of probable diabetes mellitus. Urine glucose testing is frequently performed as a screening test, but is not acceptable for diagnostic purposes. A positive urine test can be a helpful indicator, but may give misleading results during pregnancy because of increased renal blood flow or in the presence of renal glycosuria. Patients with high renal glucose thresholds or elderly patients with decreased renal blood flow may not have glycosuria in spite of elevated blood glucose concentrations (*Shuman, 1988*).

In normal subjects, the upper normal limit of fasting plasma glucose is 6.4 mmol/l 115 mg/dl. Diabetes can be diagnosed reliably when fasting plasma glucose concentrations are 7.8 mmol/l [≥ 140 mg/dl]. Immediate confirmation of the diagnosis can be obtained by determining the glycated haemoglobin concentrations simultaneously. If the glycated haemoglobin concentration is greater than normal, the diagnosis is confirmed by an elevated ambient glucose concentration preceding the fasting plasma glucose determination. Otherwise, a second diagnostic plasma/blood glucose is required on a second occasion in asymptomatic subjects. With few exceptions, fasting plasma glucose values correlate well with the rise in plasma glucose concentrations observed after a meal or glucose load, although it is less sensitive and less specific for the diagnosis of diabetes than the post-glucose load glucose (*Shuman, 1988*).

A two-hour postprandial plasma glucose concentration of ≥ 11.1 mmol/l [≥ 200 mg/dl] or 10 mmol/l [≥ 180 mg/dl] for whole blood may be indicative of

diabetes if certain precautions have been observed. Because glucose utilisation is impaired in persons consuming low-carbohydrate or weight-reduction diets, the postprandial glucose test should be performed in those consuming unrestricted diets providing greater than 150 g of carbohydrate daily for at least 3 days. Additional precautionary measures include eliminating drugs that reduce glucose tolerance, having individuals maintain normal physical activity, and avoiding the test in ill or stressed persons. The test is most reliably performed using a standard oral glucose load. In patients with liver or kidney disease, partial gastrectomy, or thyrotoxicosis, an elevated postprandial plasma glucose may also be observed. Diabetes can also be found in subjects with normal fasting values, although this is unusual in clinical practice (*Shuman, 1988*).

The oral glucose tolerance test [OGTT] is the most sensitive test for the diagnosis of diabetes. Without scrupulous care in standardising the test and preparing the patient, however, the OGTT can be misleading since some factors can interfere with normal glucose tolerance and result in a hyperglycemic curve. This test is not required for diagnostic purposes when the fasting plasma glucose is unequivocally elevated. The OGTT as adopted by the WHO requires two plasma glucose values; fasting and 2-h after a 75 g glucose load. The intervening samples at ½ , 1, and 1½ hours are not used. The scheme provides a simple and accurate method for obtaining a diagnosis criteria. There is insufficient evidence from the available studies to justify the use of the more complicated NDDG criteria. Both sets of diagnostic criteria specify that a fasting plasma glucose ≥ 7.8 mmol/l [≥ 140 mg/dl] and/or a 2-h of 11.1 mmol/l [≥ 200 mg/dl] are diagnostic of diabetes mellitus in the nonpregnant adult (*WHO, 1985; Harris et al, 1985*). If only the 2-h value is elevated, then a second test is required for confirmation. The latter value represents the concentration observed in the bimodal distribution of two-hour plasma glucose in epidemiological studies, and is the glucose concentration at which characteristic microvascular lesions such as diabetic retinopathy appeared in such studies (*Shuman, 1988*).

1.5 PREVALENCE

The prevalence of NIDDM varies greatly between population and it is 6.6 in the USA in persons aged 18 ys and over which increases with age, and the frequency in females slightly exceeds that in men(*Harris et al. 1987*). The highest prevalence (and incidence) of NIDDM in the world has been described among the Pima Indians of Arizona where the age-adjusted prevalence rate is at least 10 times as high as in the general US population . In contrast, other Native Americans, such as Eskimos were reported to have the lowest prevalence rates in the world (*Bennett, 1990*).

Large variations in the prevalence of NIDDM are also found in other countries (*Zimmet, 1982*). Very low rates occur among Melanesians from Papua New Guinea and in Australia rates of 3.4% are reported among Caucasians aged 25 years and over. In a series of studies among Pacific Islanders using WHO criteria, Zimmet and his colleagues have shown that the prevalence of NIDDM in persons aged 20years or over varies from 2.9% in Polynesians living in a very traditional manner on the island of Wallis, to 12% in persons who had migrated from Wallis to New Caledonia . Among Micronesians in the same age range, rates vary from 3.6% among those living in a relatively traditional manner in the Island of Kiribati to 9% in those living in the most urbanised island of that country (*King et al, 1984*). Immigrants from the India sub-continent show a prevalence of 5 to 15% world-wide (*Ekoe, 1988*).

1.6 INCIDENCE OF NIDDM

Only a few studies of the incidence of NIDDM using standardised and comparable methodology have been performed (*Bennett, 1990*). The most satisfactory method to determine the incidence of NIDDM is to study a specific population by testing glucose tolerance at two separate points in time and then estimating the cumulative incidence within the period between the examinations. Such studies have been performed in the Pima Indians of Arizona and among Micronesians in the central Pacific Island of Nauru . The incidence of NIDDM in

the Pima was compared to that of the predominantly Caucasian American population in Rochester, Minnesota, 19 times that of the Caucasian population. A high incidence of NIDDM has also been found in the population of Nauru. A less desirable, but less difficult method of estimating the changes in the incidence of NIDDM was used to examine whether there has been a secular increase in the disease in the general population. The incidence of diabetes has risen considerably in the USA and there are also indications that the prevalence of NIDDM has increased in England during the last 20 years (*Bennett, 1990*).

1.7 MORTALITY

Many studies of mortality in diabetes have made no distinction between the major forms of the disease. Furthermore, underreporting makes accurate assessment of the impact of diabetes on mortality and life expectancy impossible if only death certificates are available. In spite of underreporting, diabetes ranks as the seventh leading cause of death in USA (*Finch et al, 1988*).

Several prospective studies have documented excessive risks of cardiovascular death among diabetics compared to nondiabetic. In each instance the incidence of cardiovascular death was increased among the diabetics, and in each the relative risk for women exceeded that of men, but the absolute risk of ischemic heart disease mortality among diabetic men was greater in several of them. Overall mortality and cause-specific mortality were determined from a 9-year follow-up of men and women aged 44-77 in U.S.A survey. All cause age-adjusted mortality rates were more than twice as high in diabetic men and women than in the corresponding nondiabetic groups, with most of the increase attributable to cardiovascular disease. Ischemic heart disease was 2.8 times as frequent in men and 2.5 times as frequent in women. Ischemic heart disease counted for approximately one-half of the deaths among diabetic men and one-third of those among diabetic women. Other cardiovascular disease (including renal disease) deaths were 2.34 and 1.93 times as frequent in diabetic men and women, respectively. Noncardiovascular causes accounted for 26% of the excess

of deaths among diabetic men and 22% among women. The risk of death increased with increasing duration of diabetes. Thus, each additional 10 years of diabetes was associated with a 24% increase in risk for cardiovascular disease death.

Excessive mortality among diabetics has also been found among the Pima Indians among whom diabetic nephropathy accounted for about 25% of the deaths among diabetics, whereas ischemic heart disease, while much more common among the diabetics, accounted for a much lower proportion of the diabetic deaths. In Nauru the age-standardised mortality among diabetic men and women was increased approximately four-fold over that of the population with normal glucose tolerance (*Finch et al, 1988*). Large variations in mortality among diabetics from different countries have been found, with much higher mortality rates in Western Europe (predominantly cardiovascular disease) than in Hong Kong and Japan (primarily renal disease). This study is notable insofar as hypertension emerged as one of the most predictive factors for increased mortality among diabetics after adjustment for age, sex, and duration of diabetes. Proteinuria is a strong predictor of mortality in NIDDM. It was shown that abnormal albumin excretion at levels below those normally detected by dipstick predict higher mortality rates including higher rates of cardiovascular and renal disease. Among the Pima Indians proteinuria is associated with virtually all of the excess risk of mortality that is attributable to NIDDM (*Finch et al, 1988*).

1.8 MORBIDITY

Macroangiopathy:

Atherosclerosis is more severe and starts earlier than in non-diabetics. Due to this accelerated atherosclerosis diabetics have a markedly increased risk of myocardial infarction, cerebral stroke and gangrene of the legs. Taken together, the various macrovascular complications account for about 75% of all deaths in diabetes. How diabetes contributes to the complex process of atherogenesis is unclear. Factors that may play a role are hypertension [one of every two adult

diabetics is hypertensive], hyperlipidaemia and hypercholesterolaemia, sorbitol accumulation in cells of the vessel walls and altered platelet aggregation (*Marble, 1985*).

Microangiopathy:

The most powerful risk factor for diabetic microangiopathy is degree and duration of hyperglycaemia. Ethnic differences seem to play no role. Although the exact biochemical mechanism linking sustained hyperglycemia, basement membrane thickening and disturbed vascular function are not yet fully understood, there is good evidence that an increased nonenzymatic glycation of proteins induces diabetic microangiopathy (*Marble, 1985*).

Diabetic microangiopathy affects the glomerular and retinal capillaries in particular, resulting in glomerular sclerosis and retinopathy. About 90% of all adult diabetics show minor signs of diffuse and/or nodular (*Kimmelstiel-Wilson*) glomerulosclerosis after 15-20 years duration of the disease without any significant clinical symptoms, except slight proteinuria. In about 10% of the adult diabetics and 50% of the juvenile diabetics an accelerated course of glomerulosclerosis occurs, usually associated with hypertension, proteinuria and renal insufficiency. Forty to 50% of Type I diabetics with an onset of their disease before 15 years of age die of renal insufficiency. Among all diabetics nephropathy accounts for about 9% of deaths and is thus the second leading cause of death after myocardial infarction (*Marble, 1985*).

As with diabetic glomerulosclerosis the rate of diabetic retinopathy is closely related to the severity and the duration of diabetes. Retinopathy starts with the development of microaneurysms, macular oedema, periodic acid-Schiff (PAS)-positive lipid exudates (hard waxy exudates), haemorrhages, and gray-white microinfarcts (cotton wool spots). The nonproliferative stage is followed by proliferation of new small vessels and fibrous tissue, probably due to retinal anoxia, within and on the inner side of the retina. In the end stage of proliferative retinopathy adhesions between the newly developed fibrovascular tissue on the

retina and the vitreous body induce traction, retinal detachment, and ultimately blindness. A similar process may concomitantly affect the iris resulting in glaucoma. Cataract formation, on the other hand, is directly related to the disturbed glucose metabolism in the lens that leads to sorbitol accumulation.

Diabetic polyneuropathy appears in different forms, the most common being the bilateral distal sensorimotor syndrome (Symmetric peripheral polyneuropathy) affecting symmetrically the nerves of the lower extremities. Other forms of diabetic neuropathy include mononeuropathy, amyotrophy, and dysfunction of the autonomic nervous system (*Marble, 1985*).

Infections, which in the preinsulin era played a significant role in the natural course of diabetes, are nowadays of minor significance for the diabetic. Infections most often affect the skin [*candida albicans*], the urinary tract and the kidney [*pyelonephritis* with and without necrotizing renal papillitis]. *Necrobiosis lipoidica* is a rare skin disease closely related to diabetes. It usually develops after diabetes has been present for years, but in some patients it may precede clinical diabetes (*Marble, 1985*).

1.9 NIDDM

NIDDM is one of the most important non-communicable diseases in the world, with a prevalence ranging from less than 2% in rural India to as much as 30% in certain American Indian and Pacific Island populations (*Zimmet, 1982*). The disease generally presents in middle life and is diagnosed either as an incidental finding or following presentation with thirst, polyuria and recurrent infections. It is a cause of substantial morbidity and mortality, frequently due to atherosclerotic complications, and in certain developing countries is assuming equal importance to infectious diseases. It is widely assumed that NIDDM has a multifactorial aetiology in which the role of environmental factors is to hasten the progression of NIDDM in a genetically predisposed individual (*Zimmet, 1982*). The next few paragraphs discuss these factors briefly.

1.9.1 Role of genetics:

The genetics of diabetes is perhaps no longer a nightmare but still a headache (*Keen, 1987*). The importance of the genetic contribution to NIDDM has been established by the study of certain inbred populations, the almost 100% concordance of disease in monozygotic twins and by familial clustering. The study of inbred populations has suggested that the genetic component of NIDDM is due to a single gene inherited in an autosomal dominant fashion (*Hitman et al, 1991*). Progress in identifying specific genetic factors involved in NIDDM has been slow and no consistent evidence has emerged supporting a major aetiological role for any of the genes so far studied. This may be due in part to methodological problems encountered in the identification of such disease susceptibility genes. Less well known is the mode of inheritance of NIDDM genes, how many genes may contribute to the disease, and the way in which they may interact. Further, not one of the genes that contributes to NIDDM has been identified. This lack of knowledge is largely attributable to the nature of NIDDM. Family studies suggest a strong genetic component in the aetiology of NIDDM, with evidence for a major gene of co-dominant effect. A gene-dosage effect, whereby diabetes develops earlier in people with two susceptibility genes than in those with one susceptibility gene is likely (*Serjeantson et al, 1991*). The search for the diabetes gene has led to the cloning and characterisation of many genes involved in controlling glucose homeostasis. These include the insulin, insulin receptor, glucose transporter, amylin and glucokinase genes. Molecular techniques have permitted rapid screening of these genes in NIDDM patients and controls. Finally, there is now a rather contradictory genetic literature for NIDDM, with weak disease associations reported and refuted for most candidate genes (*Serjeantson et al, 1991*).

1.9.2 Environment:

Environment has been described epidemiologically as 'all that which is external to the individual human host' (*Last, 1983*). This definition encompasses

not only such concepts as physical and biological agents but also less measurable and direct-acting influences such as social and cultural forces and the behavioural tendencies of individuals. It has also been traditional to consider certain characteristics of the host, such as anthropometric indices, and also immutable factors, most particularly subject's age, under the broad heading of environmental influences (*West, 1978; Zimmet, 1982*). The following factors are those which are currently suspected of being precipitants of NIDDM.

1.9.3 Ethnicity:

The prevalence and incidence of NIDDM varies widely among different ethnic groups (*Bennett, 1990*). American Indians are at particularly high risk, although the rates vary widely according to tribe. Mexican Americans have rates of NIDDM that are two to three times greater than those of USA population, an increase that has been attributed in part to their heritage of American Indian genes. In the USA the rates are also high in persons of Pacific Island origin, particularly among Polynesians. Also in USA, persons of Japanese heritage have rates of NIDDM that are appreciably greater than in the Caucasian population. In many parts of the world Asiatic Indians have rates of NIDDM that exceed those of the native population. High prevalence rates in Indians relative to those of the majority population of the country have been described in Mauritius, Tanzania, South Africa, the Caribbean [Trinidad], Fiji, and the United Kingdom (*Taylor et al, 1983*). Furthermore, diabetes appears to be relatively frequent in Polynesians, who now live in more westernised surroundings and the Australian aborigines living in urban environments also have much higher rates of NIDDM than the remainder of the Australian population (*Bennett, 1990*).

1.9.4 Obesity:

The association between obesity and NIDDM has long been recognised, and while NIDDM is more frequent among obese persons, it is also clear that not all the obese, even the very obese, develop NIDDM. Obesity may, therefore, be a frequent precipitant of NIDDM among those who are otherwise susceptible to its

development, and NIDDM may develop among persons who are not obese. Many studies of the incidence of NIDDM have demonstrated a relation with obesity and the risk is related to the duration, degree and distribution of obesity (*Horton, 1990*).

The risk of developing NIDDM in relation to obesity is a function of the underlying susceptibility to the disease and the evidence of the interaction of genetic susceptibility and obesity first came from one of the earliest follow-up studies of diabetes epidemiology conducted in Oxford, Massachusetts (*O'Sullivan et al, 1965*). They found that the appearance of NIDDM was more frequent among the obese when there was a history of diabetes in a parent than when there was no parental history. In addition, among Pima Indians who have at least one parent with NIDDM the incidence is much more strongly related to obesity than among persons of similar degrees of obesity in whom neither parent has NIDDM (*Zimmet, 1982*). In support to this observation, a recent report showed that the duration of obesity increases the incidence of NIDDM in Pima Indians (*Everhart et al, 1992*).

The late Dr Kelly West suggested that the maximum attained body weight at age 25 years was one of the strongest predictors of the occurrence of NIDDM in later years and those who became obese only in late middle age had a much lower risk of developing the disease than those who had been of a similar degree of obesity throughout their adult years (*West, 1978*). Thus, the risk of developing diabetes appears to be a function of both the extent and duration of obesity.

Not only the presence of obesity, but its distribution within the body, central or truncal, determines the incidence of diabetes. Data from Gothenberg, Sweden, have shown among males that there is a striking relation between BMI and the risk of developing diabetes. However, when BMI is subdivided according to the ratio of WHC, those with larger WHR for a given BMI have a much higher risk of NIDDM (*Vague, 1988*). Thus, there is no question that obesity is a major risk factor and perhaps, the most important factor that is amenable to change.

1.9.5 Diet

Diet has long been believed to play a role in the development of diabetes and the idea that excessive caloric intake could increase the frequency of the disease and conversely that caloric deprivation could reduce it was reinforced several times (*West, 1978*). Diabetes mortality rates decreased in countries that experienced food shortages during World War I and World War II, whereas the rates were relatively unchanged in countries where the food supply was unaffected. However, cross-sectional or case-control studies have failed to document any convincing relation between dietary intake and NIDDM (*Ekoe, 1988*). Based on studies of diabetes prevalence in several populations, West showed that obesity was closely correlated with the prevalence of diabetes, but he was unable to find any evidence that calorie intake or individual components of the diet, independent of obesity, were implicated in its pathogenesis (*West, 1978*).

Studies of migrant populations suggest that diet may play a role in the development of the disease. Most of the studied populations, as in the Pacific, that have migrated from a traditional environment who now have higher prevalences of diabetes than are found in their countries of origin, consume diets that are at least as high in calorie content and that contain much higher quantities of refined carbohydrates, e.g., rice, flour, and sugar, than in the traditional environment. Such populations, however, develop obesity and their level of physical activity is usually decreased (*Taylor et al, 1983*). Similarly, among the Japanese subjects residing in Hawaii, for example, the prevalence of NIDDM is twice that found in Hiroshima, but the caloric consumption was no different, yet the Hawaiian Japanese consume approximately twice as much fat, one-third less complex carbohydrate, and almost three times as much simple carbohydrate as their counterparts in Hiroshima.

Of the few attempts to perform prospective studies on the relationship between the risk of developing NIDDM and dietary intake, in one there was no effect of diet or its components on the incidence of men with diabetes. By

contrast, a significantly increased carbohydrate and starch consumption was found among 87 subjects who subsequently developed the disease and only total and complex carbohydrates showed a significant relation to the incidence of the disease (*Ekoe, 1988*). Total calorie intake is greater among persons who subsequently develop diabetes, but whether the effect of dietary intake on the incidence of diabetes are the result of obesity or diet is unknown. Although sucrose intake has been suggested as a factor in the development of NIDDM, based on the observation of higher sucrose intakes in some populations with high rates of diabetes, there is no convincing epidemiological evidence at this time that sucrose per se is a risk factor for the disease (*Mann, 1987*).

The effects of dietary intervention [reduction of total caloric and carbohydrate intake] on the incidence of NIDDM among subjects with IGT (*Sartor et al, 1980*), suggest that advice to moderate the diet may have an effect on the incidence of diabetes. In view of this, additional prospective studies of dietary intervention among groups of subjects at risk of developing NIDDM are required.

1.9.6 Physical activity

Physical activity influences glucose metabolism, since well-trained athletes, have less glycaemia after a glucose load and insulin responses are diminished compared to untrained persons of similar weight. Conversely, profound physical inactivity, eg, bedrest, is associated with the development of abnormal glucose tolerance and higher insulin levels. These observations suggest that physical activity influences insulin resistance (*Horton et al, 1988*).

There are few epidemiological studies of the relation of NIDDM to physical activity. The prevalence of diabetes, in Fiji, was twice as high in those with the lower degrees of physical activity and, while suggestive of a protective effect, the amount and degree of physical activity needed to achieve protection from NIDDM is unknown (*Taylor et al, 1984*). Similar results have been found recently in the cross-sectional study from Mauritius (*Dowse et al, 1991*) and in the

prospective study from Malta (*Schranz et al, 1991*).

PATHOGENESIS

From the foregoing discussion it is clear that little can be stated definitely about the aetiology of NIDDM except that it has a strong genetic basis. It is therefore appropriate to consider the pathogenesis of the syndrome in order to trace back the individual processes or mechanisms which must be initiated by aetiological factors as yet unrecognised. It is clear that both impaired β -cell functions and insulin insensitivity are consistent features of NIDDM but the question of which defect is primary in the aetiology of NIDDM has caused much controversy (*Feldman, 1988*).

1.9.7 Insulin sensitivity:

NIDDM subjects increase glucose utilisation, during insulin infusion, by only 30% compared with 300% in normal subjects, since, subjects in the earliest detectable phases of NIDDM show, similar but less marked changes and restoration of normoglycaemia has only a minor effect in ameliorating the insulin insensitivity. Moreover, the insulin insensitivity is marked in muscle and adipose tissue but is also present in liver (*Taylor, 1989*).

The mechanism of the insulin insensitivity has been intensively investigated largely on insulin receptor number and affinity using blood cells and careful study of a more appropriate cell type (adipocytes) from NIDDM subjects has shown insulin receptor binding to be normal despite subnormal insulin sensitivity. It is not appropriate to extrapolate findings from one cell type to another such as muscle which plays a much greater role in vivo in the uptake of glucose after an insulin stimulus, but these experimental data along with others, are important in demonstrating that minor changes in insulin receptor number or affinity are neither necessary nor sufficient to produce cellular insulin insensitivity.

Transmission of the insulin signal across the insulin receptor, which is a transmembrane glycoprotein approximately 80-fold larger than the insulin

molecule, involves a series of unidentified steps. Similarly, transmission of the message to the enzymes which mediate the actions of insulin is not yet understood. The discovery of tyrosine kinase moieties on the intra-cellular portion of the insulin receptor has raised hopes that this may represent a link in the chain of events in signal transmission which could be subject to regulation, control of kinase activity thus underlying changes in cellular insulin sensitivity. Although there is a considerable evidence for this, anti-receptor antibodies may initiate insulin action without affecting the kinase and, in some experimental models of insulin resistance, insulin receptor kinase activity is unaltered. The observation that insensitivity to insulin action is not exhibited by all insulin responsive pathways within one cell type or by all metabolic effects of insulin in vivo suggests that the insulin signal is transmitted via branching pathways after insulin binds to its receptor (*Taylor, 1989*).

NIDDM is not merely a disorder of carbohydrate metabolism, since there are prominent associated disorders of lipid metabolism. Several studies have demonstrated that a part of the measured insulin insensitivity in NIDDM with respect to glucose disposal results from metabolic competition between nonesterified fatty acids and glucose. This increases the number of ways in which insulin insensitivity may be influenced by genetic regulation, the used polygenic effects being mediated not only by aspects of islet and insulin receptor function but also by aspects of lipid metabolism (*Erkelens, 1988*).

1.9.8 Insulin secretion:

The normal human pancreas contains approximately 200 units of insulin, and in patients with NIDDM diabetes, the pancreas has variable reductions in insulin. Generally, postprandial insulin responses are decrease relative to circulating glucose concentration, but absolute plasma insulin concentrations may be decreased, normal, or even increased. Commonly, in patients with only moderate or severe diabetes, sluggish insulin release immediately after a meal leads to rapid increases in plasma glucose concentrations; later, with intense

stimulation of insulin secretion from marked hyperglycaemia, circulating insulin concentrations may be greater than normal. In general, however, patients with advanced hyperglycaemia [fasting plasma glucose >300 mg/dl (16.6 mmol/l)] have reduced postprandial insulin secretion (*Feldman, 1988*).

The major feature of insulin secretion which characterises NIDDM is the impaired or absent first phase insulin response. This appears to be closely related to the loss of normal basal pulsatile insulin release, which may be produced in normal subjects by infusing somatostatin. These abnormalities of dynamics of stimulated insulin release must be distinguished from the day-long hyperinsulinaemia that is seen in many NIDDM subjects. This may be a response to the ambient hyperglycaemia or to insulin insensitivity or to both of these factors. However, lowering of blood glucose by whatever means shows a partial recovery in the ability of pancreas to respond to stimuli. Some sub-types of NIDDM may never exhibit hyperinsulinaemia as evidenced by the observation of low insulin response in the non-diabetic co-twin of identical twins discordant at the time for diabetes. NIDDM, also characterised by a slow time course of progression, insulin insensitivity and response to sulphonylureas for a period of time, is not produced by a simple decrease in beta cell numbers alone.

The notion of 'pancreatic exhaustion' has been evoked in an attempt to explain how insulin resistance may lead to secondary failure of insulin secretion. There is no evidence that subjects without a genetic disposition to islet malfunction ever exhibit such a phenomenon, and examination of subjects with extreme insulin resistance due to insulin receptor blocking antibodies demonstrates that the normal pancreas can sustain enormously elevated rates of insulin production over many years (*Taylor, 1989*).

The pancreas may be smaller than normal in NIDDM and decreased exocrine function is associated with fibrosis of the exocrine tissue. Within the normal islet, cells producing insulin, glucagon, somatostatin and pancreatic polypeptide are in close proximity and defined spatial relationships. This allows

effective paracrine control of one cell type by another. In this respect the approximate doubling of alpha cell numbers of NIDDM is of interest. The histological finding is corroborated by hyperglucagonaemia in both established NIDDM subjects and their offspring. The role of somatostatin within the islet is unclear but changes in the relative proportions of the cell types or their position within the islet could affect insulin secretion profoundly. Beta cell numbers are only moderately decreased, perhaps up to 50 %, and this contrasts with the requirement for a 90 % pancreatectomy in animals or man to produce hyperglycaemia (*Taylor, 1989*).

Amyloid deposition in the islets occurs in at least 50% of NIDDM subjects and in some accounts for 90% of the islet volume. A novel peptide, islet amyloid polypeptide has recently been identified which appears to be produced by beta cells of normal and NIDDM subjects, but is incorporated into amyloid almost entirely in the latter. This form of localised amyloidosis which occurs only in relation to insulin producing cells may reflect a cellular dysfunction in NIDDM.

1.10 CONCLUSION

NIDDM has a strong genetic basis, autosomal dominant in some isolated populations but more usually polygenic in nature. The major environmental factors involved in the aetiology of NIDDM remain uncertain, and at the present time, these cannot be regarded as primary factors. Disturbance of insulin secretion and insulin action are necessary in the genesis of the syndrome, and NIDDM cannot occur in the absence of β -cell dysfunction. There is no evidence that insulin insensitivity per se can initiate β -cell damage although it is uniformly present from very early in the development of the syndrome and is important in its pathogenesis.

INTRODUCTION

CHAPTER TWO

IMPAIRED GLUCOSE TOLERANCE

CHAPTER CONTENT :

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 - 2.1 Historical background.
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SUMMARY

After almost 2000 years we are beginning to have some biochemical understanding of diabetes and over the past 15 years it has become evident that diabetes is a heterogenous chronic disease and both IDDM and NIDDM are real and increasing problems worldwide. Emerging from this heterogeneity is the recently recognised Impaired Glucose Tolerance [IGT] class, which lies between normality and abnormality of the diabetic syndrome spectrum. This brief account discusses IGT category from two main aspects; namely epidemiology and metabolism as far as possible. The literature since 1980 usually refers to this group as IGT while before that it was chemical, latent or borderline diabetes.

2.1 HISTORICAL BACKGROUND

Over 100 years ago it was recognised that at least two forms of diabetes existed, clinically, in man, one characterised by obesity and the other occurring usually in younger persons of even subnormal weight. Later on, attempts were made to classify diabetes as either primary or secondary. Primary diabetes was then subclassified according to the age of onset of the disease; to the therapeutic response; to the stage in natural history of the disease; to insulin secretory status or therapeutic requirement; to the predisposition to develop ketosis; or according to the degree of glucose intolerance (*Bennett, 1983*). All of these are alternative approaches that have been taken, but the most logical approach to classification of the group of disorders which constitute diabetes mellitus would be a classification based on the pathogenesis of the disease and, in most instances, however, this is not known, and no classification until now is completely satisfactory (*Ellenberg et al, 1983*). Accordingly, wide disagreement and a confusing literature failed to give rise to a single classification scheme or definition of terms.

To narrow this gap and to lessen this confusion the WHO Expert Committee in their first report (*WHO, 1965*) introduced a classification of patients according to age of recognised onset. Asymptomatic, sub-clinical or chemical diabetes also appeared to define a person with a diabetic response to the OGTT whose fasting capillary blood sugar was below 130 mg/100 ml. Since then, a considerable growth in knowledge about the various forms of diabetes has occurred, research had brought to light several pathogenic mechanisms leading to diabetes and long-term follow up studies had provided evidence of differing courses and outcomes.

This new information has led several international groups of EASD (*Keen et al, 1979*), NDDG (*NDDG, 1979*) and WHO (*WHO, 1980*), to review the

classification of the disease and introduce valuable comments and suggestions. The rationale for this new categorization was that there was a substantial group of individuals who showed 'abnormal glucose tolerance' at a level that was considered insufficient to classify them as diabetic. Even so, they were at high risk of developing macrovascular disease and of progression to diabetes. This category, also satisfied a need for defining a level of glucose intolerance that was not clearly normal but that was also not sufficiently severe to predict microvascular disease, particularly retinopathy, in prospective studies. In December 1979 the NDDG declared the birthday of the term IGT as an independent category which shortly thereafter was adopted by WHO.

Further justification for the consideration of IGT as a discrete entity has come from the second US national Health and Nutrition Examination Survey (*Harris, 1989*). Here individuals with IGT had rates of risk factors for NIDDM [age, plasma glucose, past obesity, family history of diabetes, physical inactivity] that were intermediate between those with NGT and those with diabetes, although current obesity levels were similar for IGT and diabetes.

2.2 DEFINITION and TERMINOLOGY

The state of IGT is defined as "a glycaemic response to a standard glucose challenge intermediate between normal and diabetic" (*WHO, 1985*). The introduction of IGT class in 1980 replaced the confusing terms of asymptomatic diabetes, borderline diabetes, chemical diabetes, glucose tolerance test diabetics, latent diabetes and subclinical diabetes; that had been used previously in the literature to describe mild degrees of glucose intolerance. Moreover, this term, unless a less ambiguous term found, would be strongly retained for the time being to define the post 75g glucose levels, as in the WHO recommendations (*Alberti, 1980*). Glucose intolerance implies both classes of abnormal glucose tolerance, diabetes mellitus and IGT.

Recently, some studies however, have cast doubt on the concept of IGT, both because of its ephemeral nature (*Riccardi et al, 1985; Glatthaar et al, 1985;*

Forrest et al, 1988) and as a consequence of doubts about whether it warrants categorisation as a separate entity (*Jarrett, 1987*).

2.3 CLASSIFICATION and HETEROGENICITY of IGT

The IGT subclass remained in the most recent version of the WHO classification (*WHO, 1985*), since its appearance, and formed with diabetes mellitus and gestational diabetes the clinical class. The IGT category, similar to diabetes mellitus, is further subdivided into primary, whether obese or non-obese, and secondary, which is associated with certain conditions and syndromes. The class of IGT is also heterogeneous because of both the distribution of patterns of glucose intolerance in populations and the variability of the test employed to characterise glucose intolerance in individual people.

Recently, the new concepts of IGT which was based on the phenomenon of bimodality of plasma glucose distribution, suggests that IGT category consists of three entities (*Stern et al, 1985*). (i) 'IGT Normals' are subjects classified as IGT but are normoglycaemic situated in the upper distribution of the normal range; (ii) 'False Negative' are the subjects having diabetes but their OGTT values do not exceed the currently accepted NDDG or WHO cut-off points because of the overlap between the normal and abnormal range; and (iii) 'IGT in Transition' are the subjects who are truly in transition from normal to diabetic. When a population is examined cross-sectionally, only a minority of IGT subjects belong to the third category while in longitudinal studies, the cumulative percentage of individuals passing through this stage would be much larger. These three categories of IGT cannot be distinguished on the basis of their OGTT values and such a differentiation, however, will have to await the development of a definitive marker(s) for the prediabetic state. Moreover, even "transient" IGT is associated with an increased risk of deterioration to diabetes (*Saad et al, 1988*).

Bimodality implies that the transition state between normal and diabetic is relatively short. Decompensation occurs relatively rapidly over a period of two years or less in Pima Indians (*Knowler et al, 1978*) while other studies have

reported lower cumulative decompensation rates (*King et al, 1984; Keen et al, 1982; O'Sullivan et al, 1968*). As seen in Fiji (*Coventry et al, 1986*) and Kiribati (*Collins et al, 1984*), the cut-off point defining diabetes in the distribution of plasma glucose concentration may vary between populations of different ethnic origins further supporting the theory of IGT heterogeneity. It is therefore likely that the IGT subjects who later develop cardiovascular disease are from the 'False Negative' and 'IGT in Transition' categories and not from the ;IGT Normals; (*Stern et al, 1985*).

2.4 BIMODALITY PHENOMENON

Bimodality of plasma glucose distributions has been reported in Pima Indians (*Bennett et al, 1976*), Micronesians (*Zimmet et al, 1978*) and Polynesians (*Raper et al, 1984*) who are relatively isolated genetically and have a high prevalence of diabetes. Bimodality has also been reported in Mexican Americans (*Rosenthal et al, 1985*), a population which is more than 50% Caucasian, much larger and genetically less isolated. These findings therefore suggest that bimodality may be much more generalised to include other populations such as Caucasians and Blacks (*Motala et al, 1987*) but difficult to detect because of much lower prevalence of diabetes and the second mode (*Stern et al, 1985*).

Rushforth et al estimated that a prevalence of at least 10% was necessary to see bimodal distribution (*Rushforth et al, 1971*), though it has been found in a population with a prevalence of diabetes of 6.7% (*Raper et al, 1984*). It was also suggested that in the populations displaying bimodality the nadir between the two modes may be higher than 11.1 mmol/l, the two hour blood glucose concentration used to define diabetes mellitus (*Stern et al, 1988*). Whether this is also the case for the threshold for microangiopathy is not clear.

2.5 DIAGNOSIS and CRITERIA

The United States Public Health Service (USPHS), the Fajans and Conn criteria, and the Rosenthal and Barry criteria were the three commonly accepted diagnostic criteria by the year 1965. Since then, agreement and discrepancy in the

evaluation of normal and diabetic OGTT has been hotly discussed. Subsequently 15 years later, another three sets of criteria were proposed, EASD, NDDG and WHO in order to achieve a standardization in classification, methodology and diagnostic criteria for the diagnosis of glucose intolerance. However there are certain differences between the NDDG and the WHO recommendations. The NDDG criteria for diabetes and for IGT require that the ½ hr, 1 hr or 1 ½ hr plasma glucose value exceed 200 mg/dl. This is not a requirement of the WHO criteria. This requirement creates a group of subjects with "nondiagnostic" OGTTs, many of whom would be classified as IGT by the WHO criteria. The WHO recommendations pointed out specifically against the overuse of the OGTT and state that a fasting venous plasma glucose values of less than 100 mg/dl or random glucose values of less than 140 mg/dl are sufficient to exclude the diagnosis.

Afterward, imprecision of these criteria for the OGTT had been questioned when these were compared with 7 other previous sets (*Massari et al, 1983*). They found a major redistribution of a symptomatic subject in the 3 categories of glucose tolerance with a lower percentage of "diabetes" and "normal" subjects and a higher percentage of "IGT" subjects. A third of their population (33%) could not be classified into the three categories of glucose tolerance using NDDG criteria; 20% were "Nondiagnostic" and 13% could not be classified. However, this does not occur when using the WHO criteria. Later, it was shown that the omission of the mid-test value only makes a small difference and of the 3.6% of persons who were diagnosed as having diabetes by WHO criteria; 9.4% also had diabetes according to NDDG criteria (*Harris et al, 1985*). However, the NDDG requirement for the mid-test value resulted in 11.3% of the OGTTs being non-diagnostic, whereas all were classified according to WHO criteria. This study supports the use of WHO criteria.

The NDDG/WHO difference have more relevance with respect to the diagnosis and prevalence of IGT. The prevalence is generally lower with the NDDG criteria due to a substantial proportion being non-diagnostic due to the

lack of an elevated mid-test value. In the US population, if the intervening value between 0 and 2-h is not imposed, the number of people with IGT is more than doubled (*Harris et al, 1987*). Also the proportion of Nisei men with IGT is increased by only 40% with the WHO criteria and the NDDG criteria led to a very high prevalence of non-diagnostic class (*Fujimoto et al, 1987*). Thus, the WHO protocol is the most internationally accepted one (*WHO, 1980*)).

IGT category can only be defined by using the OGTT which is principally used, nowadays for diagnosis when blood glucose levels are equivocal, during pregnancy, or in an epidemiological setting to screen for diabetes and IGT. At present IGT is rarely diagnosed in the clinical setting, perhaps because of its recent introduction as a glucose tolerance class and lack of knowledge of its clinical significance (*Bennett, 1983*). Moreover, both short-term (*Riccardi et al, 1985; Ganda et al, 1978*) and long-term (*King et al, 1984; Keen et al, 1982*) studies have shown that IGT is an acutely unstable state and the OGTT is a test with very poor reproducibility. In one of these studies (*Riccardi et al, 1985*) only 56 % of the subjects with IGT at the start of the study showed persistent intolerance 2-4 months later.

The values for diagnosis of IGT include a fasting blood glucose below a cut-off level and two-hour post glucose blood values within a defined range. The upper end of this range is defined by the lower level of the range for diabetes. It is worth noting that the fasting glucose cut-off value was arbitrarily chosen and recent work suggested that it was set too high (*Saad et al, 1988; Finch et al, 1990*). For epidemiological studies, it is recommended that diagnosis be based on the results of blood glucose 2-h after a 75g OGTT, since it is not possible to ensure the fasting state in all subjects and the diagnosis of IGT cannot be made without the glucose load (*WHO, 1985*). In addition the fasting value used to date lacks sensitivity.

In epidemiological studies where the prevalence of IGT and diabetes are to be assessed, WHO considers that a single elevated 2-h post OGTT blood glucose

is sufficient for the diagnosis of diabetes (*WHO, 1985*). In cross-sectional studies, misclassification of people does not matter provided it occurs equally in both directions so that the resulting prevalence is not changed (*Fletcher et al, 1982*). However, this has to be considered with caution. In longitudinal studies, the different rates of progression from IGT to diabetes may, in part, be due to different spectra of blood glucose distribution within the IGT category (*Jarrett, 1987*).

For diagnostic screening, only the full diagnostic criteria i.e. two abnormal tests in the absence of symptoms should apply. At least one of these values should not be a fasting blood glucose level, given the possibility of abuse of the fasting state. Even with the 2-h post OGTT blood glucose values, there was a within subject coefficient variation of 32.4% when a single 2-h post OGTT capillary blood glucose level (*WHO, 1985*) was compared with a fully supervised OGTT (*Forrest et al, 1988*). The unsupervised drink and the timing of 2-hr sample did not contribute substantially to the variability thus implying that the diagnosis of diabetes should not be based in an asymptomatic subjects on the basis of a single OGTT. With the risk of developing diabetes being directly related to the degree of glucose intolerance and cardiovascular disease morbidity/mortality being associated with the upper 5% of the blood glucose distribution, IGT is not a clinical entity by itself. It is clearly impracticable to repeat an OGTT several times to define the severity of glucose intolerance, so other methods are necessary to distinguish the three subgroups of IGT.

On the basis of studies in Bedford (*Keen et al, 1982*) and in Pima Indians (*Bennett et al, 1976*); Jarrett et al (*1976*) suggested that a capillary blood glucose concentration of 11.1 mmol/l (200 mg/dl) two hours after a 50g OGTT was a reasonable cut-off point to divide those at risk of microvascular disease. A two-hour post-glucose capillary whole blood glucose concentration of 7.5 mmol/l (135 mg/dl) had also been shown to be the value above which the risk of progression to diabetes rose significantly (*Jarrett et al, 1979*), while below the value of 11

mmol/l (199 mg/dl) spontaneous remission to normal glucose tolerance occurred in some subjects (*BDSWP, 1976*).

At first glance, in view of this, assays of glycated haemoglobin or glycated protein might offer potential advantages in classifying disorders of glucose tolerance, their biological variability and dependence on nutritional state being far lower than those for blood glucose concentrations (*Pecoraro et al, 1986*). These benefits must, however, be set against the narrower biological range for these variables. Glycated haemoglobin concentrations are not raised in people defined as having IGT in the OGTT (*Forrest et al, 1988; Albutt et al, 1985*). In preliminary studies it was found that the values of 2-h blood glucose are better able to discriminate the presence of vascular disease in a diabetes screening study than the results of any of four assays of glycated haemoglobin (*Yudkin et al, 1988*).

2.6 OGTT VARIABILITY

The implication of the biological variability of the OGTT is likely to be much smaller for people classified as normal or diabetic than for those categorised as having IGT, because the IGT category has a range of 2-h blood glucose concentration of only 3.3 mmol/l, the two margins are only 0.5 SD away from the midpoint (*Yudkin et al, 1990*). Thus, if a population is selected as having IGT on the basis of a single test result only a small proportion would be expected still to have IGT on repeat resting - whether the test is repeated at one week or five years.

In some published studies in which OGTTs were repeated in people with IGT after an interval of < 1 year the rate of reversion to normal tolerance was 28-67% and that of "deterioration to diabetes" 4-9% (*Riccardi et al, 1985; Forrest et al, 1988*). The fact that people discovered to have IGT in the first test are reclassified on repeat testing begs the question where they really belong. Someone with a two hour blood glucose concentration of 9.5 mmol/l in the first test and of 6.5 mmol/l in the second could be in the category of "IGT normal" and returning to the biological set point or in the category of "IGT in transition" and testing low on the day of the second test. A recent study has looked at

electrocardiographic evidence of CHD in 52 people classified as having IGT on the basis of the results of a single OGTT and found that the prevalence of these changes increases with increasing degrees of intolerance on the second test (*Yudkin et al, 1988*). This supports the hypothesis that these 52 people comprised a mixture of "IGT normals" with a low prevalence of CHD, "false negative diabetics" with a higher prevalence of CHD, and some patients with true IGT, perhaps in transition.

There is some recent evidence of another factor that may contribute to the changing of category among people shown by a single test to have IGT. A study recently performed in six villages in rural Tanzania in which a 75g OGTT was given to 6299 people (*Swai et al, 1988*). In some 8% of these a repeat OGTT was performed within seven days. On the second occasion only one quarter of the people with a two hour blood glucose exceeding 10 mmol/l on first testing were still "diabetic", while over three quarters of those with initial IGT had reverted to normal and 3% had diabetes. That this was not simply regression to the mean was shown by the fact that when the population levels of 2-h blood glucose were reconstructed from this sample there was a highly significant decrease of 0.4 mmol/l between values at screening and those at recall and the estimated population prevalence of IGT fell from 7.6% to 3.3% on repeat testing (*Yudkin et al, 1990*). If the phenomenon is widespread it would imply that the epidemiological survey of glucose intolerance in a population may appreciably overestimate the prevalence of both IGT and diabetes.

2.7 THE PREVALENCE of IGT

The prevalence is the number of cases in a population at a specific time while the incidence is the number of new cases occurring in a population during a specified period of time, often one year. Knowledge of the prevalence of diabetes and IGT in the population provide important information on the definition and classification of the disease, its early detection, its genetic and environmental background, its social and economic impact, and the effect of the disease on

health and the quality of life. The prevalence may need to be known, as well, for public health or research reasons. Recent epidemiological studies using similar OGTTs showed higher prevalence of IGT than NIDDM. The prevalence of IGT varies widely between different populations in the same country and between different countries.

A health examination survey carried out in Italy showed that 3% were diabetic and 6% have IGT according to the EASD diagnostic criteria (*Riccardi et al, 1985*). In the USA population aged 20-70 years, OGTT data showed a total diabetes prevalence of 6.8% by NDDG and WHO criteria and the prevalence of undiagnosed diabetes by both criteria [NDDG=3.2%] and [WHO=3.4%] were almost equal to that of previously diagnosed diabetes [3.4%] (*Harris et al, 1987*). However the rate of IGT [11.2%] by WHO criteria was more than twice the NDDG estimate [4.6%]. It has also been shown that both obesity and parental history of diabetes were associated with significantly higher rates of diabetes and IGT. On the other hand among second-generation Japanese American men, in Nisei, such prevalence, estimated to be 20%, have diabetes (both previously diagnosed and undiagnosed) and 36% have IGT (*Fujimoto et al, 1987*).

Migrant Asians from the Indian subcontinent tend to have an increased prevalence of IGT as compared with other ethnic groups in the same country. There have been very few studies from India (*Ramachandran et al, 1988*) reporting prevalence rates of IGT using WHO criteria and the rates are much lower when compared with those in migrant Indians elsewhere (*Zimmet et al, 1983; Omar et al, 1985; Beckles et al, 1986; Ramachandran et al, 1988; Dowse et al 1990; Swai et al, 1990*). The low prevalence rates of IGT reported in migrant Indians in Coventry, UK (*Simmons et al, 1989*) are presumably due to initial screening values being set too high.

There were no significant differences in the prevalence rates of IGT between Melanesians and Indians in Fiji irrespective of gender and rural/urban environment (*Zimmet et al, 1983*). In Trinidad (*Beckles et al, 1986*), in men,

prevalence rates of IGT were highest in Indians, intermediate in Africa and mixed and lowest in white populations. This was in contrast to that found in females of all groups, where the rates were similar. In Mauritius, the age standardised prevalence of IGT was significantly greater in women than men in all ethnic groups (*Dowse et al, 1990*). In Tanzania, both the Muslim and Hindu Indians had significantly higher prevalence of IGT compared with ethnic Africans (*Swai et al, 1990; McLarty et al, 1989*). The prevalence rate was significantly higher in Muslim Indians than in Hindu Indians. There were no gender differences amongst Hindu Indians while, in Muslim Indians, women had an increased frequency of IGT as compared with men.

There is a wide variation in the ratio of the prevalence of NIDDM to the prevalence of IGT in different societies and, IGT is more weakly related to age than is diabetes mellitus, even in people of different ages within the same population (*Yudkin et al, 1990*). This may be because some populations (such as those with a high prevalence of IGT compared with the prevalence of diabetes) have a skewed unimodal distribution and others (with a higher prevalence of diabetes) a bimodal one; the diabetic 2-h blood glucose concentration mode differs in different populations; the degree of skew of a single curve differs; or the number of people with IGT or its rate of transition differs.

Finally one question might be asked; should we screen for those IGT individuals to advise therapy? A widespread and costly screening programme to detect IGT seems unjustified at present (*Editorial, 1980*). Another opinion (*Tuomilehto et al, 1987*) stressed that high risk groups should be screened for IGT and the screening should probably be repeated at regular 5 to 10 year intervals. Subjects with IGT should be given individual health education counselling and treatment to improve the metabolic state.

2.8 SIGNIFICANCE of IGT

The clinical relevance of the finding of IGT has been reviewed and debated extensively (*NDDG, 1979; Stern et al, 1985; Bennett, 1985*). It has

become clear from prospective studies that this category of glucose intolerance has unique attributes not shared by subjects with normal glucose tolerance or overt diabetes. The presumed significance of IGT (*Stern et al, 1985*) is threefold: firstly it is commonly believed that it represents a transitional state between normality and diabetes, thus it emphasizes that mild degrees of glucose intolerance have a different prognostic significance than the diagnosis of diabetes. Secondly, IGT is also believed to be a risk factor for cardiovascular disease, either in its own right, or as a consequence of its presumed precursor relationship to diabetes. However IGT is not predisposed to microvascular disease. Thirdly, the use of the term "IGT" avoids many of the psychosocial and economic implications that a diagnosis of diabetes carries, and as such alleviates many problems for physician and the patient, particularly if the impaired tolerance can be corrected (*Bennett, 1983 ; Fantus, 1987*). A discussion on these aspects are given below.

2.9 DETERIORATION to DIABETES in IGT

Stages. The natural history of diabetes can be defined in general as a number of stages relating to the course and development of diabetes and which apply to both common types of the disease and, therefore, several stages were proposed (*Bennett, 1984*). The first stage is genetic susceptibility. The second is the state of potential abnormality of glucose tolerance, a statistical risk class including subjects who have normal glucose tolerance but who by virtue of other characteristics have substantially increased risk for the development of diabetes. Thirdly is IGT, a phase in the development of type II diabetes, and as only recently recognised, in type I also. The fourth is diabetes without complications, a stage in which chronic hyperglycaemia is present and symptoms attributable to hyperglycaemia may or may not be present. The fifth is diabetes with vascular complications, but without associated symptomatology or disability. Lastly is diabetes with disability, when complications of diabetes lead to functional impairment. However, progression through these stages is not inevitable; many

people with characteristics which are risk factors for abnormal glucose tolerance never progress, and many people with IGT remain nondiabetic after many years of follow up. On the other hand, The natural history and consequences of IGT differ in many respects from those of diabetes mellitus and do not justify the expectations inevitably associated with the diagnosis of "diabetes mellitus" (Zimmet, 1985).

Rates, course and prognosis Our ability to predict metabolic deterioration in subjects with IGT is limited. Early reports (O'Sullivan *et al*, 1966) demonstrate frequent remissions among persons diagnosed as having chemical diabetes, 54 % of whom exhibit an unexplained return to normal levels over the next two years. Others suggest that in at least 20% of persons with IGT, diabetes mellitus eventually develops (Davidson, 1985). While this group carries a greater than normal risk of ultimately developing diabetes, several population-based follow-up studies have shown that the risk of decompensation is in the range of 1.0 - 4.5 per year (Anger *et al*, 1982) over a 5 or 10 year time span. Depending on criteria used, at least 8.9% and at worst 52.5% of a group of female chemical diabetes patients (IGT) were calculated to deteriorate over a 10 year period and the cumulative rate of developing diabetes was found to be 32% when the (USPHS) criteria were applied (O'Sullivan *et al*, 1968). In the Birmingham survey (BDSWP, 1962; BDSWP, 1970; BDSWP, 1976) 21.4% of "glucose tolerance test diabetics" (1-h > 10.0 and 2-h > 7.5 mmol/l) in capillary blood changed to "florid diabetes" (fasting glucose > 7.2 mmol/l over 5 years) (BDSWP, 1970) and subsequently 45.2% of GTT diabetes became florid diabetes over a 10 year period (BDSWP, 1976). In the Whitehall survey, 27 of 204 men [13.2%] with IGT were found to worsen to diabetes during a 5 year follow-up period (Jarrett *et al*, 1979). In the Bedford study, 8.5% deteriorated over 8.5 years, 15% deteriorate to diabetes in 10 years but if obese at baseline, this rises to 19.5% (Keen *et al*, 1982). In the Swedish study, 29% of untreated male patients with IGT developed diabetes over 10 years (Sartor *et al*, 1980). However, in the Osaka study, the rate

of worsening to diabetes after 7 years was 38.5% [5.5%/year] for those with IGT and 22.9% [3.3%/year] for those with 2-h blood glucose values between 6.1-11.1 mmol/l (*Sasaki et al, 1982*). In Nauru, IGT carries an unpredictable prognosis, and the relative risk for NIDDM for subjects with IGT at baseline was 3.6 over a 6.2-year period (*King et al, 1984*). In the Pima Indians with IGT [n=384] who were followed over a median period of 3.3 years, NIDDM developed in 31%, IGT remained in 26%, and 43% reverted to NGT (*Saad et al, 1988*). Thus, in Pima Indians, a 6-fold increased risk has been demonstrated, like, the 7-fold increased risk shown in Malta (*Schranz, 1989*). Up to one half of subjects with IGT may not have a progressive condition, while in 29%-59% IGT does appear to equate with "early diabetes" (*Mutch et al, 1982*).

Therefore, these population studies, demonstrated a trend in the natural history of IGT over 5-10 year period and showed approximately one third of individuals reverting spontaneously to normal, one third remaining IGT and one third deteriorating further to NIDDM. These studies confirm, also, the heterogeneity of IGT category.

Predictors. There are many factors which can result in the final resultant of IGT and each is likely to show natural evolution, in some cases towards worsening, in others towards normalization. In addition to such factors as the presence of genetic susceptibility to diabetes and the taking of diabetogenic drugs, there are the effects of obesity per se [and of weight change], of emotional factors and their neuro-endocrine-metabolic consequences, of insulin resistance and unknown contributions to the outcome in respect of glucose tolerance. Thus, a critical, yet still unresolved issue concerns who will progress to overt diabetes ?.

Several longitudinal studies of IGT have appeared in the literature all of which examine "determinants" of future diabetes and all of those examined different ethnic groups, e.g Pima Indian, Caucasoid, Japanese and Micronesian.

An old study showed that, diabetes occurred 5 times more frequently in people with initial post OGTT blood glucose from 7.8-9.4 mmol/l [140-169

mg/dl], and 15 times more frequent in those with blood glucose of more than 9.4 mmol/l [169 mg/dl] (*O'Sullivan et al, 1965*). This study also showed that diabetes occurred very much more frequently in people 20% above IBW, and as shown subsequently, those above 150% of IBW at the time of diagnosis were at increased likelihood of deterioration (*O'Sullivan et al, 1968*).

Subsequently, more recent longitudinal studies conducted in several populations show that, the strongest and consistent independent risk factor for deterioration to NIDDM, either for all subjects or for those with IGT alone, is the baseline blood glucose itself -either the fasting and/or the post-load level (*Daumerie et al, 1989; Sicree et al, 1987; Balkue et al, 1985; King et al, 1984; Kadowaki et al, 1984; Sasaki et al, 1982; Jarrett et al, 1979*). Even after taking into account the other risk factors such as obesity or family history of diabetes mellitus, the risk increased significantly as a function of the degree of glucose intolerance (*Bennett, 1985*).

Another possible significant predictive factor is the degree of obesity. In studies from Japan (*Sasaki et al, 1982; Kadowaki et al, 1984*) obesity has been found to be an independent predictor, in contrast to studies from UK (*Keen et al, 1982; Jarrett et al, 1979*) and Nauru (*King et al, 1984*) where it was inconsistent in its effect. In the Bedford Study (*Keen et al, 1982*), BMI became a significant factor only during the later five years of the ten-year follow-up, thus, obesity revealed a "delayed diabetogenic effect". Thus, obese subjects had a 2.9-fold increase in incidence of NIDDM compared with non-obese persons. However, after adjustment for plasma glucose and serum insulin levels, obesity was no longer predictive of progression to NIDDM (*Yadkin et al, 1990*).

An old prospective study showed that a family history of diabetes did not influence the frequency of worsening to diabetes (*O'Sullivan et al, 1968*). A Japanese study revealed that, sex was also significant, indicating that risk of worsening to diabetes was greater in males than in females (*Sasaki et al, 1982*). Systolic blood pressure was negatively associated with subsequent diabetes, in the

Whitehall study (*Jarrett et al, 1979*) and in Nauru (*King et al, 1984*).

When IVGTTs were performed yearly on 116 middle-aged non-obese subjects for 6 yrs, it was found that age, fasting plasma glucose and the increment index at presentation were significant predictors of the behaviour of IGTT, whereas, sex, treatment and family history were not significant predictors; and other factors such as islet cell antibodies play an additional role (*Stowers et al, 1981*).

A critical, yet still unresolved issue concerns whether those who will progress to overt diabetes with fasting hyperglycaemia respond to OGTT primarily with hypoinsulinaemia or hyperinsulinaemia. In definite diabetes, it has been known that the insulin response to glucose is increased, but heterogeneity of plasma immunoreactive insulin responses in subjects with IGT is still a matter of discussion and the predictive value of a low insulin response for the development of diabetes remained controversial (*Kosaka et al, 1980; Keen, 1980; Fajans, 1980*). Subsequently, a low insulin response was regarded as a significant independent risk factor for the development of diabetes in subjects with IGT, even when one takes other risk factors into account (*Kadowaki et al, 1984; Knowler et al, 1986*). Data from Nauru have shown that subjects with higher post-load serum insulin levels [presumably indicative of insulin resistance at base-line were more likely to progress to either IGT or diabetes over a 6-year period (*Sicree et al, 1987*). Conversely, amongst subjects with IGT, progression to NIDDM was predicted by lower base-line insulin responsiveness. Similar results for subjects with IGT have, also been described in Pima Indians and Mexican Americans (*Saad et al, 1988; Haffner et al, 1988*).

The presence of hyperinsulinaemia and hypertriglyceridaemia in young, lean Australian Aborigines [from the desert] with IGT was recently reported (*O'Dea et al, 1988*), and this suggested that the hyperinsulinaemia and hypertriglyceridaemia form part of the metabolic adaptation of the 'thrifty' gene (*Neel, 1962*). Also, the tendency to hyperinsulinaemia/insulin resistance may be

the modern expression of this 'thrifty' genotype.

Thus, these findings of these various studies suggest a teleological sequence in the development of NIDDM leading from compensated hyperinsulinaemia and insulin resistance, through moderate hyperglycaemia and hyperinsulinaemia, to increasing hyperglycaemia and decreasing insulin response, and ultimately to β -cell decompensation and diabetes (*Zimmet et al, 1989*).

The longitudinal and cross-sectional studies in Pima Indians have shown that IGT in obese subjects is primarily due to a reduction in insulin action with normal pancreatic β -cell secretory function (*Lillioja et al, 1988*). Later, persistent hyperglycaemia increases the pancreatic secretory function culminating in β -cell failure and diabetes. Both insulin resistance and impaired insulin responsiveness lead to subsequent development of diabetes in subjects with IGT (*Saad et al, 1988; Knowler, 1986*).

There are, therefore, many problems in defining a true change in glucose tolerance category, particularly in people with IGT. If the variability of a test can result in the recategorisation of people as "deteriorating to diabetes" and thereby exclude them from further study the frequency of such "deterioration" will be substantially over-estimated. To show a true change in a variable that has a poor biological or assay reproducibility the change in the level of the variable should exceed 2 SD of the intraindividual variation (*Yudkin et al, 1990*). This criterion will, however, merely define 2.5% of the population as having deteriorated in the second test. The method employed in the Bedford and Whitehall surveys to define deterioration to diabetes was the requirement for two consecutive or three non-consecutive 2-h capillary blood glucose values [50g OGTT] to be equal to or more than 11.1 mmol/l [or symptoms and signs of hyperglycaemia] (*Jarrett et al, 1979; Keen et al, 1982; Jarrett et al, 1984*).

Because the OGTT used to define IGT was performed only once, however, those so defined might include people with IGT who were "false negative diabetics" re-establishing their biological set point (*Yudkin et al, 1990*).

A more satisfactory approach would be to repeat the OGTT on at least three occasions each time in order to reduce the CV to less than 20%, but this is unacceptably demanding for both subjects and investigators.

The value of the study in Pima Indians is that knowledge of the previous degree of glucose tolerance in people with IGT allows exclusion of these "false negative" diabetics from investigation (*Saad et al, 1988*). Nevertheless, the high rate of deterioration to diabetes of these people was probably found because only one 2-h blood glucose concentration of 11.1 mmol/l or more was necessary to define diabetes, and this may have occurred frequently in people with true set IGT or even, on occasions, in those with concentrations at the upper end of the normal range.

The observation that rates of "deterioration to diabetes" increase when criteria are less rigorous was noted in the Whitehall Study (*Jarrett et al, 1979; Jarrett et al, 1984*). Several studies have looked at factors that may improve the ability to predict deterioration to diabetes in people with IGT. In Pima Indians (*Saad et al, 1988*), as well as in Japanese (*Kadowaki et al, 1984*) and Nauruans (*Sicree et al, 1987*), a poor insulin response to a glucose load predicts deterioration. Nevertheless, cross-sectional studies of glucose intolerance may misclassify diabetic patients as having IGT, and these patients may show an impaired insulin response to a glucose load as a consequence of diabetes (*Lillioja et al, 1988; Reaven et al, 1968; Modan et al, 1986*).

If a later OGTT were to show deterioration to diabetes in these people the poor insulin response might falsely be interpreted as a predictor, rather than a consequence of diabetes. The Pima Indians study is unique as longitudinal data make it improbable that those with IGT were false negative diabetics. The ability, shown in other studies, of using either fasting or 2-h plasma glucose concentrations to predict deterioration to diabetes (*Keen et al, 1982; Ito et al, 1983; King et al, 1984; Kadowaki et al, 1984, Jarrett et al, 1984A; Saad et al, 1988 ; Sicree et al, 1987*) could again reflect the possibilities of an initial false

negative OGTT result.

Therefore when the concept of deterioration to diabetes and the instability of the IGT class in the light of data on the variability of the biological response to a glucose load was analysed an additional criterion were suggested to categorise people with IGT and that measures of insulin and of proinsulin like molecules are possible candidates for this task (*Yadkin et al, 1990*).

In conclusion all these studies showed that baseline blood glucose concentration was the most powerful and consistent predictor. Obesity was a further independent predictor in the two Japanese studies (*Sasaki et al, 1982; Kadowaki et al, 1984*) but was inconsistent in its effect in the United Kingdom (*BDSWP, 1976; Jarrett et al, 1979; Keen et al, 1982*) and Nauru (*King et al, 1984*) studies. An early insulin response in the OGTT have been found to be additional independent predictor in some studies.

Thus, although the incidence may be low, the eventual prevalence of diabetes may be high. These people will have considerable influence upon the use of expensive health care facilities and their early recognition may allow successful intervention.

2.10 CARDIOVASCULAR RISK in IGT

Several epidemiological studies carried out in the last few years have shown an increased frequency of clinically significant atherosclerotic events and have suggested that IGT might be associated with a high risk for CVD (*Jarrett et al, 1982; Fuller et al, 1980*). While studying the lack of association between CHD mortality and diabetes duration it has been pointed out that subjects with IGT but not diabetes have an increased risk of CVD relative to non-diabetics (*Jarrett et al, 1984A*). Moreover, he concluded that the supposition that in some way hyperglycaemia or its associations causes the increased prevalence of macroangiopathy in terms of atherosclerosis/CHD can be challenged (*Jarrett, 1984B, Jarrett, 1984C*). He pointed out that macroangiopathy seems to be independent of diabetes duration among NIDDM patients. Also the level of

glycaemia seems to play a minor role since NIDDM and IGT appears to have a similar risk for CHD, but a totally dissimilar risk for microangiopathy. Furthermore, NIDDM seems to arise from groups of patients within the general population having higher than average frequency of risk factors for CHD.

The association between IGT and hypertension had been repeatedly found in several clinical and epidemiological studies. Hence, when several risk factors were examined, blood pressure (systolic and diastolic) was the only one significantly associated with IGT despite the fact that treated hypertensives were excluded (*Vaccaro et al, 1984*).

Uncertainties about the relationship between IGT and serum lipoproteins still exist . . . When the plasma lipoprotein composition was evaluated in individuals with IGT [n=65], it was found that they have significantly higher total triglyceride values but total cholesterol levels were similar in IGT and each of the control groups (*Capaldo et al, 1983*). However, no significant correlations were found between serum lipoproteins and blood glucose levels either fasting or after OGTT. Another study found that elevated mean levels of total cholesterol, LDL-cholesterol and triglycerides in women rather than in men with IGT (*Ganda et al, 1985*). The mean HDL-cholesterol levels were 20% lower and LDL/HDL cholesterol ratios were 60% greater in women than in men with IGT. These observations indicate that IGT can be associated with significant alterations in lipid metabolism, particularly in women. The Paris Prospective Study of 943 individuals with glucose intolerance [GI] found that hypertriglyceridaemia emerged as the major risk factor of coronary artery death in subjects with IGT (*Fontbonne et al, 1989*). In addition, plasma cholesterol and plasma insulin levels [fasting and 2-h] were significantly higher in those who died from CHD compared to those that did not.

The prevalence of ECG abnormalities was nearly doubled in both the IGT and diabetic groups in the Whitehall Study. Despite inconsistencies regarding an excess CHD mortality at the upper extreme of blood sugar distribution, nearly all

the International Collaborative Group Studies showed an increased prevalence of defined ECG abnormalities in the IGT range (*Stamler et al, 1979*). In the Whitehall IGT group there was a significantly increased prevalence of certain specific ECG findings - ST depression, T-wave inversion and left bundle branch block - all of which have been shown to be associated with a significantly increased CHD risk in another analysis of the whole Whitehall population. The mortality rate was about 3 times higher than that in the NGT group for IGT individuals with small Q-waves, frequent premature beats and sinus tachycardia. Abnormalities of the resting ECG may, therefore, define at-risk groups of subjects with IGT who are particularly suitable for dietary or drug intervention.

It is currently unclear as to whether hyperglycaemia increases CHD mortality except among those with extremely high post-challenge hyperglycaemia (*Fuller et al, 1983*). An excess in mortality in IGT, as compared with normal subjects was confirmed by the Bedford (*Jarrett et al, 1982*) and the Danish (*Anger et al, 1982*) studies. This is also found in the bi-ethnic population of Fiji (*Sicree et al, 1985*), and Nauruans with IGT had a higher relative risk than those with NIDDM of mortality, although this was not significantly in excess of that of individuals with NGT (*Zimmet et al, 1988*). The 9 year follow-up data from the Chicago Heart Association Project in Industry found that asymptomatic hyperglycaemia was associated with an increased risk of death from CHD with greater relative significance in women than in men (*Wen-harn et al, 1986*). Individuals with IGT have also been studied by Jarrett and co-workers (*Jarrett et al, 1984A*) in a 10 year follow-up of men in the Whitehall Study. It was found that baseline blood glucose significantly predicted both all-cause and CHD mortality in this group of men and that all-cause mortality rates were higher in the less obese. Age and blood pressure were the two factors most strongly related to subsequent death from CHD in the glucose intolerant and diabetic groups. This study confirmed the importance of hypertension as an associated risk factor in these types of diabetic subjects. A recent evidence showed subjects with IGT had

mortality rates nearly identical to those of newly diagnosed diabetics, 2.7/1000 per year and 2.9/1000 year respectively (*Fontbonne et al, 1989*). This study also produced evidence that the increased risk of death from CHD in subjects with glucose intolerance [GI; IGT or NIDDM] may be a consequence of the clustering of CVD risk factors with insulin resistance. In general, these studies clarify whether individuals with IGT are more prone to atherosclerosis of the coronary vessels than the general population.

On the other hand, IGT is of little or no importance as a risk factor for atherosclerotic PVD (*Vaccaro et al, 1985*). In the Micronesian population of Nauru, where NIDDM is present in 24% of the population and 80% of those over 55 years have IGT (*Zimmet et al, 1984*), retinopathy occurs in 24% of all diabetic subjects (*Zimmet et al, 1984*). In those with IGT it was only 2.5% and in newly diagnosed diabetics 6%. The majority of patients had background retinopathy of varying severity, only 1.2% of males and 2% of females having proliferative lesions.

On the basis of these epidemiological studies a blood glucose level of 200 mg/dl measured 2-h after a 50g OGTT has been suggested as a practical criterion which distinguished between those 'at risk' of diabetic complications and those with IGT but without significant risk (*Jarrett et al, 1978*). Thus, it is conceivable that NIDDM and/or IGT and atherosclerosis share a number of antecedent metabolic risk factors, possibly on a genetic basis, which predisposes the individual to either diabetes, atherosclerosis or both of these clinical outcomes. Furthermore, the levels of cardiovascular risk factors in subjects with IGT were more like those in the diabetics than in those with NGT.

2.11 INTERVENTION IN IGT

As described above patients with IGT are at risk to develop overt NIDDM (1%-5%/year), and in many populations they have an increased incidence of macrovascular disease (*NDDG, 1979*). Thus, intervention at any of the previously mentioned stages may prevent progression to a later stage and IGT may be a

critical stage in the development of diabetes because it is the earliest recognizable stage in this process, and there is some evidence that its progression to diabetes can be prevented (*Bennett et al, 1984*). There have been a few attempts to determine the effect of intervention on IGT and a number of possibilities were examined, namely drug treatment, dietary intervention, weight loss, exercise, or multiple intervention.

A borderline diabetic state was improved by short-term energy restriction or weight loss, and successful results of dietary advice and physical training were reported in 48 middle-aged IGT males (*Cederholm et al, 1985*). In this study, OGTT was restored to normal in 25 IGT subjects who were given dietary advice and two weekly exercise sessions during a period of 6-12 months, and it improved in 12 IGT males given dietary advice alone and in 11 IGT males participating in an exercise group for 3 months. The mean body weight was decreased and the working capacity improved, even in the diet-treated group.

In another two studies diet and tolbutamide or phenformin showed no discernible effect on the subsequent incidence of diabetes (*Jarrett et al, 1979; Keen et al, 1982*). Moreover the size of the samples in these trials is so small that their results are compatible with an effect as great as a 50% reduction in the incidence of diabetes. In the "glipizide trial", 23 IGT subjects were treated with 2.5 mg daily (*Camarini et al, 1983*) At follow up after three years, the mean width of the muscle capillary basement membrane had decreased to a level similar to that in normal subjects, whereas the width in 18 untreated IGT subjects was increased at follow up. In the 10 year follow-up study a significant difference in the rate of development of diabetes was found between subjects randomised to treatment and a "no therapy" group (*Saltin et al, 1980*). While there was no overall difference in those randomised to tolbutamide (500 mg t.i.d), placebo or diet only, it was notable that of 23 subjects who continued to take tolbutamide throughout the trial, none developed diabetes. None of the tolbutamide treated subjects had developed manifest diabetes, compared with 13% of the diet-treated

and 29% of the untreated subjects. These subjects represented only half of those randomised to this group, and whether this represents a true therapeutic effect, or whether those who elected to continue tolbutamide were a self-selected group who for other reasons had a lower risk of development of disease, is unknown. No case of myocardial infarction or intermittent claudication had occurred in the tolbutamide treated IGT subjects and the rate of pathological ECG changes was close to that in the normoglycaemic control group.

Therefore, these studies, utilising a variety of sulphonylureas for treatment of patients with IGT, have failed to show any effect of two to eight and one-half years of treatment on glucose tolerance or progression to overt diabetes (*Lebovitz et al, 1986*), although one of these claims that ten years of treatment with tolbutamide (1.5 g/d) markedly improves glucose tolerance, reduces progression to overt diabetes, and decreases the development of cardiovascular disease (*Sartor et al, 1980*). In light of the large number of studies showing no effect of sulphonylureas in patients with IGT (*Lebovitz et al, 1986*) this latter study will need to be amply confirmed before there can be any consideration of the use of sulphonylureas in patients with IGT.

Thus, because of the uncertainties in these studies it seems unwise to recommend wide-spread detection and treatment of IGT at this time except on an experimental basis. Debatably, if treatment of IGT with drugs, diet, or exercise will indeed delay or prevent diabetes, the detection and treatment of persons at this stage could reduce the incidence of NIDD. In the view of the magnitude of the problem and the evidence that the progression of the disease at this stage is not inevitable, further investigations should be given high priority as this may be the most opportune stage to prevent NIDDM and its complications.

2.12 SPECIAL GROUPS with IGT

The potential significance of IGT in pregnancy has become more widely recognized and both the WHO and the NDDG draw attention to the special significance of glucose intolerance in pregnancy. This was emphasized at the

Second International Workshop Conference on GDM (*Metzger et al, 1985*).

IGT in childhood was also reported. A ten-year prognosis of IGT in 140 siblings of 67 children with IDDM concluded that the 2-h OGTT identified a subset of the sibling cohort at increased risk for the development of IDDM (*Rosenbloom et al, 1981; Rosenbloom et al, 1982*).

Glucose tolerance is known to decrease with advancing age (*DeFronzo, 1989*). This decline begins in the third or fourth decade of life and is progressive throughout the entire adult life span. Mean fasting plasma glucose concentration changes only slightly with increasing age whereas average 2-h plasma glucose in an OGTT rises about 0.5 mmol/l per decade after 50 years of age (*Keen et al, 1982*). There has been much debate whether this IGT is physiological and hence whether diagnostic criteria ought to be age-related as in the nomogram of Andres (*Chen et al, 1985; Andres, 1971*). This will remain unresolved until prospective studies are available in the elderly, but for the time being the criteria of the WHO and NDDG are to be applied uniformly irrespective of age. However, IGT in pregnancy, childhood or elderly are beyond the scope of this thesis.

2.13 SECONDARY IGT

IGT, likewise diabetes mellitus, can be associated with pancreatic diseases, disease of hormonal aetiology, drug induced or chemical induced conditions, abnormalities of insulin or its receptors and certain genetic syndromes (*WHO, 1985*). These, also, will not be discussed further here.

2.14 PATHOGENESIS OF IGT

As shown before, NIDDM and IGT are common and are responsible for a great deal of morbidity and mortality in adults. Current treatment is imperfect, reflecting our ignorance of the pathogenesis of these disorders. The pathogenesis of IGT and NIDDM would seem to be either impaired insulin secretion, impaired insulin action or possibly some combination of the two. The current status of IGT and NIDDM pathogenesis was described elegantly recently (*Davidson, 1985*).

Glucose intolerance in diabetes results from a lack of glucose utilization.

As a consequence, glucose remains in the circulation and is responsible for hyperglycaemia. Impaired glucose oxidation in human diabetes has been demonstrated. However, glucose intolerance in diabetes cannot be entirely explained by a lack of glucose oxidation. Glucose storage, principally in the liver plays an essential role in glucose homeostasis. A defect in glucose storage is certainly one of the main causes of glucose intolerance in diabetes, mostly because this phenomenon is directly under the control of insulin. Since different mechanisms regulate glucose storage and oxidation the study of these two parameters was expected to a better understanding of the pathophysiology. The results suggest that in IDDM complete insulin deficiency seriously impairs two major mechanisms regulating glucose homeostasis, i.e. glucose storage which is a high rapid phenomenon, and peripheral glucose oxidation, which is a slower and delayed one. Whereas in NIDDM, where a weak insulin response is present, the defect in glucose oxidation is markedly attenuated. As a consequence, glucose storage deficiency, although less important than in IDDM, remains the major cause of glucose intolerance.

Like NIDDM, insulin resistance is a characteristic feature of patients with IGT (*Olefsky, 1981; Olefsky et al, 1977; Reaven et al, 1976*). Patients with IGT have relatively mild insulin resistance, whereas patients with NIDDM have more severe insulin resistance (*Olefsky, 1981*). Furthermore, as the degree of carbohydrate intolerance worsens, the frequency of insulin resistance increases (*Olefsky et al, 1977*). Thus, many, but not all patients with IGT are insulin resistant, while essentially every NIDDM patient with significant fasting hyperglycaemia displays this abnormality. Using the glucose clamp techniques (*Bergman et al, 1985*) significant insulin resistance has been demonstrated in the overwhelming majority of NIDDM patients studied, while the presence of insulin resistance has been variable in subjects with IGT.

It was also shown that people with IGT, as a group, have raised concentrations of insulin both when fasting and after a glucose load (*Modan et al,*

1985; Lillioja *et al*, 1988; Saad *et al*, 1989) and show insulin resistance when investigated with glucose clamp techniques (Lillioja *et al*, 1988; Reaven *et al*, 1989). Patients with IGT (n=5) have insulin resistance in NEFA and glucose metabolism but not in ketone body metabolism (Singh *et al*, 1987).

People with IGT show hyperinsulinaemia and insulin resistance, both in cross-sectional (Lillioja *et al*, 1988; Reaven *et al*, 1989) and in longitudinal (Saad *et al*, 1989) studies. As a group their mean concentrations of insulin when fasting and two hours after a glucose load are increased by roughly 50% and 250% respectively (Lillioja *et al*, 1988; Saad *et al*, 1989), while their insulin stimulated glucose disposal is reduced by some 70% (Reaven *et al*, 1989).

Though a true deterioration from normal to IGT is associated with an increase in fasting and post-load insulin concentrations and in insulin resistance, it is not clear whether a person classified as "IGT normal" would also show hyperinsulinaemia during the abnormal OGTT. Possibly, therefore, measures of insulin, employed as surrogates for those of insulin resistance, might help define patients with true IGT (Saad *et al*, 1989; Reaven *et al*, 1989). Not all people with IGT progress to diabetes; those who do seem to show a deterioration in insulin response to glucose, suggesting that insulin deficiency, super-imposed on insulin resistance, is the cause of the further deterioration in glucose tolerance (Saad *et al*, 1989). If this is so measures of insulin might distinguish two subgroups of patients with true IGT: those in transition (who deteriorate to diabetes) showing failing β -Cell function and those with persistent hyperinsulinaemia who remain glucose intolerant. Hyperinsulinaemia in the presence of raised fasting concentrations of glucose is taken to imply insulin resistance (Turner *et al*, 1982). Though insulin resistance has been shown in people with IGT and diabetes by using infusions of exogenous insulin (Reaven *et al*, 1989), "hyperinsulinaemia" in diabetic patients may be in part a manifestation of raised concentrations of intact and split proinsulin (Temple *et al*, 1989), which seem to be detected by standard radioimmunoassays for insulin.

The implication of these findings is that insulin deficiency may be a more important contributor to the aetiology of diabetes than has been suspected, but it remains to be seen whether "IGT normals" and "false negative diabetics" might be distinguished from patients with true IGT by the use of more sensitive and specific assays for insulin-like molecules. Preliminary findings have suggested that raised concentrations of these molecules - rather than of insulin per se - are associated with the excess cardiovascular risk in diabetic patients (*Nagi et al, 1989*), and it is an intriguing possibility that both the hyperinsulinaemia and the cardiovascular risk associated with IGT may also represent the consequences of raised concentrations of these molecules.

Thus, from the information which is currently available, the following was concluded (*Davidson, 1986*). For unknown reasons, in persons destined to have IGT and NIDDM, insulin resistance develops. Those whose pancreatic β -cells can meet this challenge by secreting increased amounts of insulin continue to have normal glucose concentration or IGT at the expense of hyperinsulinaemia. Only those with a genetic predisposition will develop NIDDM. This predisposition involves a limited ability of the β -cells to continue to synthesize and secrete the extra insulin demanded of them. Thus, NIDDM ensues when the β -cells can no longer respond well enough to prevent fasting hyperglycaemia.

2.15 CONCLUSION and FUTURE

In my thesis work, I have discussed IGT, a term which was coined by NDDG and accepted by WHO in 1980, to describe a state intermediate between diabetes mellitus and normality. People with IGT who have high glucose levels and low insulin responses early in the glucose tolerance test, appear to be more likely to progress with time from IGT to diabetes mellitus. This group of subjects is also at a high risk of developing macrovascular disease. I have also enumerated various preventive measures for NIDDM and IGT. Insight on pathogenesis was also given.

Further studies are therefore required to determine its natural history and its clinical relevance in progression of diabetes and macrovascular disease. In clinical terms it is probably worth searching for IGT in high risk populations eg. Saudi Arabia, but not in, for example, UK, where rates are not particularly high and the risk of underlying CVD is negligible. Finally, IGT is an interesting phenomenon and its relationship with NIDDM and cardiovascular disease, particularly in the contest of preventive medicine, are worthy subjects for research.

INTRODUCTION

CHAPTER THREE

DIABETES MELLITUS IN SAUDI ARABIA

CHAPTER CONTENT :

- Summary.
 - 3.1 Introduction.
 - 3.2 Epidemiology.
 - 3.2.1 Diagnosis.
 - 3.2.2 Prevalence.
 - 3.2.3 Risk factors.
 - 3.3 Types and features of diabetes.
 - 3.4 Acute complications.
 - 3.5 Chronic complications.
 - 3.5.1 Microvascular.
 - 3.5.2 Macrovascular.
 - 3.6 Lipids.
 - 3.7 Management and care.
 - 3.8 Monitoring.
 - 3.9 Special topics in diabetes.
 - 3.10 Conclusion.
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SUMMARY

Diabetes in Saudi Arabia is very common. This chapter elaborates on this problem with particular emphasis on epidemiology and associated risk factors. Some aspects of diabetic complications have also been included. In addition a short comparison of the characteristic(s) of diabetes was included.

3.1 *INTRODUCTION*

Saudi Arabia is the largest country [land area : 2,240,000 sq km] in the Arabian Gulf. The estimated total population is about 12 million, including 28 % non-nationals (*James et al, 1990*). The population growth rate of 6.5 % per annum is due both to an increase in immigrants and a rise in the national population. Improved standards of living and health services have contributed to a longer life expectancy which is now 62 years. The rapid economic growth of Saudi Arabia has led to drastic change in life-style of the people with effects on health, nutritional status and the expression of disease patterns. Diabetes is emerging as a major health problem ((*Bancroft, 1984; Sebai, 1987; Sebai, 1987; Abdella, 1988; Ekoè, 1988; El-Hazmi, 1990*)). This chapter summarizes the available present knowledge on diabetes mellitus in Saudi Arabia.

3.2 EPIDEMIOLOGY :

3.2.1 Diagnosis

3.2.1.1 OGTT

The OGTT remains the gold standard test for the diagnosis of diabetes in Saudi Arabia (*Ismail, 1987*). Using WHO criteria, the fasting plasma glucose was found to be normal in many non-pregnant Saudi subjects with diabetes which led Bell and colleagues (*1984a*) to conclude that the WHO recommendations are not entirely suitable for interpretation of glucose values in Saudi Arabia. They found that on the basis of post-OGTT values [75 g], 6 % of those classified as diabetics had a fasting value of < 5.0 mmol/l which, according to WHO criteria, if taken on its own would exclude diabetes. On the other hand, many normals [59%] as well as subjects with diabetes [42%] had fasting glucose levels of $\geq 5.0 - < 6.7$ mmol/l. There is, therefore, a large overlap in the fasting values of diabetics and normals and the 2-h post glucose value is essential for diabetic screening. This is

indeed recommended by WHO. The unsuitability of the present WHO fasting glucose criteria has recently been shown for other populations (*Finch et al, 1990*).

3.2.1.2 Glycosuria

The correlation between plasma and urine glucose was even poorer than elsewhere since Saudi diabetic subjects were found to have a mean renal threshold for glucose higher than in American and European population (*Bell et al, 1982*). Many of those with serum glucose values ≥ 10.0 mmol/l did not exhibit glycosuria [men 50%, women 48%] and when the serum glucose levels were between 12.1 and 14.3 mmol/l many men and women [62% vs 75%] did not have glycosuria. Therefore, not only is glycosuria unsatisfactory for diagnosis but self-testing urine for glucose is an unsatisfactory method of diabetic control in Saudi diabetic patients.

3.2.1.3 Symptoms on diagnosis

A notable feature of the cases detected in one survey was the denial of classical symptoms despite glucose levels as high as 26.2 mmol/l (*Bacchus et al, 1982*). Nocturia was absent in approximately 50 % (*Ahmed et al, 1987*) and polyuria was mild (*Kingstone et al, 1986*) or rare (*Ahmed, 1989*).

3.2.2 Prevalence :

Little was known of the prevalence of diabetes mellitus in Saudi Arabia before 1975. One of the earliest observations stated that "maturity onset diabetes mellitus and impaired glucose tolerance are common in Arabs in Riyadh; they are not usually associated with obesity" (*Cook, 1976*). Seven years later a further report suggested a high rate of diabetes amongst other diseases (*Dodd, 1983*). Several reports have now described the high prevalence of diabetes mellitus in Saudi Arabia. Some of these reported from the central region (*Abu-Aisha et al, 1980; Bacchus et al, 1982; Bell et al, 1984A; Bell et al, 1984B*), Some reported from the western region (*Mira et al, 1983; Fatani et al, 1983; Fatani et al, 1985A; Fatani et al, 1985B; Fatani et al, 1987; Fatani et al, 1987*) while one was conducted in different regions (*El-Hazmi et al, 1989*). Two of the studies were

hospital-based and five were community-based. Urban and rural comparisons were also carried out (*Fatani et al, 1985A; Fatani et al 1987*). In population based studies the prevalence in the total population ranged from 2.5 % to 5 % with rates higher in the elderly and in the obese. Recently, a prevalence of 6 % was observed for fasting blood glucose > 7.8 mmol/l in 14 % of university community males in Riyadh (*Anokute, 1990*). Details of these studies are shown in Table 3.1.

3.2.3 Risk factors

Studies of diabetes mellitus in Saudi Arabia have clearly demonstrated correlations of diabetes mellitus with some risk factors such as gender, age, obesity, social class and family history.

One population based study showed a prevalence of 2.5 % in males and 4.7 % in females (*Bell et al,1984*). The prevalence in women was also twice that for men [5.9 % vs 2.9%] in a rural area (*Fatani et al,1987*). However, the opposite was found in an urban survey [males 5.6 %; females 4.2 %] (*Fatani et al, 1985*). The higher prevalence of diabetes in general in females in Saudi Arabia may be related to a greater tendency for obesity in the female than in the male population and could also be related to parity, although this was not investigated (*Bell et al, 1984*).

Diabetes is also related to increasing age in Saudi Arabia as in other countries. The prevalence was 11% in subjects over the age of 40 years [yr] (*Abu-Aisha et al, 1980*). Although, no diabetic subjects were under the age of 25 yr and only one male diabetic subject [1 %] was discovered up to the age of 34 yr, an overall prevalence of 6.5 % - 11 % was found in the age group [55-64 ys] and 23 % in those above 65 ys (*Bacchus et al,1982*). In Bell's study there was no diabetes in females less than 35 yr of age, with the peak [29 %] at age group 45-54 yr although no females of greater than 65 yr were surveyed (Bell et al, 1984). This is also confirmed by the comparative study of hyperglycaemia where the prevalence was low in persons under 20 yr old and the majority of cases were 40 yr and above (*El-Hazmi et al, 1989*). In general, rates were approximately 20 %

in the over 55 yr [Table 3.1]; higher than in Caucasian populations (*Ekoè, 1988*).

Overweight was reported in a few studies in Saudi Arabia. It was found more in diabetics [65 %] than in non-diabetics [26 %] (*Bacchus et al, 1982*). All the females were overweight, 66 % being between 35 and 55 % above their ideal body weight (*Bell et al, 1984*). In urban dwellers, obesity was two-fold commoner in women than in men. Diabetic men [35 %] were more obese compared to non-diabetic men [19 %] and, similarly, diabetic women were obese [79 %] compared to non-diabetic women [52 %] (*Fatani et al, 1985*). In rural dwellers, the rate of obesity in adult [≥ 15 ys] diabetics [41 %] was significantly higher than in non-diabetics [29%] (*Fatani et al, 1987*).

Social class had a strong positive correlation with diabetes in Saudi Arabia. In urban dwellers, social class status (British Registrar-General classification) revealed a higher proportion of diabetics among subjects of social class 1 and 2 than social classes 3,4 and 5 (*Fatani et al, 1985*). Similar rates were seen in rural areas (Saudi Arabian Civil Service Bureau Scheme) (*Fatani et al, 1987*). This could have been related to overnutrition. First degree family history of diabetes was found more in the new and untreated referred adult diabetics [21 %] compared to the overall positive family history [28%] (*Laajam et al; 1987*).

3.3 TYPES AND FEATURES OF DIABETES

3.3.1 Primary Diabetes

The Saudi diabetic population is composed of 85 % NIDDM and 15 % IDDM (*Ahmed, 1989*). The prevalence of IDDM was found to be 0.3 % in the age group 0-14 ys (*Fatani et al, 1985*). Three cases of maturity onset diabetes of youth [MODY] have also been described in Saudi in the western region (*Kassimi, 1981*). Circulating immune complexes [14 %, 9 % and 8 %] and islet cell antibodies [31 %, 9 % and none] were detected in Saudi subjects with IDDM [n=73], NIDDM [n=35] and control [n=24] respectively; and when ethnic comparisons were carried out, immunopathological mechanisms might be involved more in Egyptian IDDM than in Saudi IDDM (*Ibrahim et al, 1983*).

Recently, the frequencies of ICA, CF-ICA and organ specific antibodies have been evaluated among Saudi Arab diabetic children [n=86] (*Abdullah et al, 1990*) and newly diagnosed adult diabetic subjects [n-138] (*Al-Attas et al, 1990A*). The results of the former suggested that Arab diabetic children have a lower prevalence of thyroid antibodies than European or American Caucasian diabetic subjects and thus the regular screening for these antibodies was not justified. The latter study showed that ,in relation to age at onset above 35 yr, only 13 % of Saudi adult diabetic subjects are characterized by ICA. Moreover, recent findings indicated that there was no relationship between endogenous insulin secretion and the presence of ICA in newly diagnosed adult Saudi diabetic subjects suggesting further that these subjects have only mild insulin deficiency (*Al-Attas et al, 1991*). These findings seem to fall halfway between those reported in Caucasians and the few reports on non-Caucasian populations (*Al-Attas et al, 1991*). Furthermore, Saudi IDDM had a slow acetylator phenotype which might be relatively ineffective in detoxifying a proposed toxic natural substrate that can precipitate type I diabetes (*Price Evans et al, 1985*).

Little is known of pancreatic function in subjects with diabetes in Saudi Arabia. El Attas et al (*1990*) found recently that the newly diagnosed diabetic-patients in Saudi Arabia is characterized by high basal C-peptide and insulin levels which increase significantly with stimulation, suggesting diminished but present endogenous B-cell function. Moreover, they also suggested in a different study that a varying degree of obesity influences the rate of both beta cell secretion, insulin resistance and impaired lipid metabolism (*Al Attas et al, 1990C*) Recently, the population gene frequencies of restriction fragment length polymorphisms of the human insulin gene, which is located on the short arm of chromosome 11, were studied in Saudi Arabians [n=148] blood donors (*Johansen et al, 1990*). They found that the Class 3 allele frequency were four times higher in Arabs than in Philipinos, but they did not examine whether or not low or high allelic Class 3 was associated with low or high prevalence of atherosclerosis,

hypertriglyceridaemia or NIDDM.

Finally, Saudi Arabian diabetics display different HLA markers from both European and Asian populations. In a single reported study there was an increased frequency of HLA BW 35 in IDDM, with an apparent increase of HLA B8 and unlike IDDM of Caucasian origin, there was no increase in HLA B15 and B18 (*Fatani et al, 1986*). The frequency of HLA B52 was reduced in both IDDM and NIDDM reaching statistical significance in the latter. There have been no reports of so-called "malnutrition related diabetes mellitus".

3.3.2 Secondary diabetes

Pancreatic disease, diseases of hormonal aetiology, drug-induced or chemical-induced conditions, abnormalities of insulin or its receptors, and certain genetic syndromes are the main five groups that can lead to secondary diabetes (*WHO, 1980*). A few reports from Saudi Arabia has demonstrated such an association with respect to liver diseases, insulin receptors defects or genetic syndromes. Diabetes [fasting values > 7.8 mmol/l] was present in patients with chronic active hepatitis [8 %], cirrhosis [40 %], and hepatoma [15 %], compared with of all other patients aged 35 ys or over, undergoing liver biopsy (*Kingston et al, 1984*). Compared to this high prevalence of diabetes in liver disease, only 3% of the diabetic patients had chronic hepatitis or cirrhosis. This high prevalence of diabetes in chronic active hepatitis and cirrhosis in Saudi Arabia may due to the insulin insensitivity of chronic liver disease acting over many years in a population with a high genetic predisposition to diabetes. Patients with bilharzial liver disease show impairment of liver function as well as diminished insulin secretion as evidenced by insulin:glucose [I/G] ratios (*Saeed et al, 1983*). It is possible that liver function may not be entirely responsible for the disturbance in insulin status and glucose tolerance and factors related to the haemodynamic changes due to portal hypertension and portosystemic shunts may have a more significant role than previously accepted (*Saeed et al, 1983*). Moreover, insulin receptor antibodies causing steroid responsive diabetes mellitus was

reported (*Fonseca, 1984*) and a distinct autosomal recessive hereditary syndrome associated with glucose intolerance has been observed, as well, in six Saudi Arabian patients from two highly inbred families (*Woodhouse et al, 1983*).

3.3.3 Features of diabetes

There are both clinical similarities and differences between NIDDM in Saudi Arabians and in Europe and North America (*Bacchus et al, 1985*). The distinctive biochemical features of Saudi NIDDM include moderately severe hyperglycaemia; relative insulin deficiency but sufficient insulin present to prevent ketoacidosis; normal serum cholesterol; hypovolaemia; and hyperosmolarity (*Ahmed; 1989*). Saudi diabetics were similar to NIDDM reported from the west in being overweight and middle age of onset, having a positive family history and resistance to ketoacidosis (*Kingston et al, 1986*).

3.4 ACUTE COMPLICATIONS [Diabetic ketoacidosis]

Diabetic non-ketosis in young non-obese (*Fonseca et al; 1985*) and diabetic ketoacidosis were reported in Saudi Arabia (*Kingston et al, 1982; Jan, 1982; Fatani et al, 1983; Mira et al, 1987; Mira et al, 1988*). Adult diabetic subjects were characterized by well-tolerated hyperglycaemia and resistance to ketoacidosis (*Kingston et al, 1982*). Both IDDM [55%] and NIDDM [45%] were predisposed to admission [Hospital stay 2-3 weeks] due mainly to poor compliance [66%] with mean blood glucose and pH of 26 mmol/l and 7.2 respectively and they require a mean of 3 L total fluid replacement in the first 5h (*Mira et al, 1987*). The use of continuous low dose intravenous insulin infusion were recommended (*Jan, 1982*) and insulin oedema particularly in children was found (*Abdullah et al, 1989*). Reported mortality was 3% (*Fatani et al, 1983*) and 4.3% (*Mira et al, 1987*).

3.5 CHRONIC COMPLICATIONS

NIDDM patients show the full range of microvascular and macrovascular complications (*Ahmed, 1989*). However, coronary artery disease [CAD], large vessel peripheral vascular disease [PVD], retinopathy and proteinuria were less

common than in Caucasians (*Kingston et al, 1986*). It is postulated that normal blood pressure and cholesterol values probably explain the lower incidence of macrovascular complications (*Ahmed, 1989*).

3.5.1 Microvascular

Retinopathy is a common complication of diabetes in Saudi Arabia (*Bashi et al, 1987; Wafai, 1987*). In a cross-sectional study it was found in 24 % [n=64], four of whom had proliferative retinopathy ; 31 % were insulin-dependent. Diabetes duration [11 vs 6 ys], smoking [31 % vs 6 %] and presence of proteinuria [31 % vs 11 %] between those with and those without retinopathy were significantly different but the prevalence of hypertension did not differ. Photocoagulation is the present mainstay of treatment in diabetic retinopathy (*Khatib, 1987*). Nephropathy, defined as macroproteinuria, > 550 mg/24 h with a positive reagent strip-test, was found in 13 % of IDDM within 5 years of onset and 18% after 5 years of diabetes (*Fatani et al, 1985; Fatani et al, 1989*). No reports of microalbuminuria have appeared, however, in screening for nephropathy. The diagnosis of neuropathy was based on the presence of persistent symptoms or signs of peripheral neuropathy in the presence of peripheral pulses, mononeuropathy, or autonomic neuropathy. It was observed in 17 % of newly diagnosed diabetic adults (*Laajam et al, 1987*) and occurred with the highest frequency of the specific complications with no significant differences between IDDM [28 %] and NIDDM [24 %] subjects (*Fatani et al, 1989*). The correlation between duration of diabetes mellitus and neuropathy was significant in NIDDM but not in IDDM (*Fatani et al, 1989*). Also reported were neurovascular complications, including diabetic foot disease, which was frequent in all diabetic groups (*Hagroo et al, 1987*). In Saudi Arabia, diabetic foot gangrene is usually due to factors other than macrovascular occlusion because peripheral pedal vessels are easily palpable in the majority of cases (*Kingston et al, 1986*).

3.5.2 Macrovascular complications :

Macrovascular complications [CAD; cerebrovascular accident, CVA; and

PVD] were found to be impressively low in Saudi diabetics (*Kingston et al, 1986; Hagroo et al, 1987; Fatani et al, 1989*). The prevalence, in one report, of CAD and of large vessel PVD were 1.3 % and 4.0 % respectively (*Ahmed, 1987*). CAD [7 % vs 10 %], CVA [1 % vs 2 %] and PVD [5 % vs 3 %] showed no significant differences between IDDM and NIDDM subjects but there was a significant positive correlation between duration of diabetes mellitus and macrovascular complications in NIDDM [4.5 ± 0.3 ys] but not in IDDM subjects [7.4 ± 0.5 ys] (*Fatani et al, 1989*). Systolic time intervals, which were simple non-invasive tests, may be of value in selecting diabetic subjects at high risk of cardiovascular complications (*Tongia et al, 1984*). Normal blood pressure, low cholesterol and low insulin levels may individually, or in combination, may account for the low frequency of atherosclerotic complications (*Kingston et al, 1986; Ahmed, 1989*).

The majority of IDDM [80 %] and NIDDM [71 %] had one or more complication (*Fatani et al, 1989*). There were no significant differences between the frequencies of complications in IDDM vs NIDDM subjects except in the case of nephropathy where IDDM [18 %] had a significantly higher frequency than NIDDM [11 %] (*Fatani et al, 1989*). The prevalence of micro- and macrovascular complications of Saudi IDDM vs NIDDM were neuropathy [28 % vs 24 %], nephropathy [18 % vs 11 %], retinopathy [13 % vs 8 %], coronary heart disease [7 % vs 10 %], peripheral vascular disease [5 % vs 3 %] and cerebrovascular accident [1 % vs 2 %] respectively (*Fatani et al, 1989*). In IDDM [age 32 ys], there was a positive correlation between duration of diabetes mellitus [7.4 ys] and nephropathy, but this correlation was not significant in the case of nephropathy, retinopathy and macrovascular disease (*Fatani et al, 1989*). In NIDDM [age 46.5 ys] a significant positive correlation was found between duration of diabetes [4 ys] and nephropathy, retinopathy, and macrovascular complications, but there was no correlation between duration and nephropathy (*Fatani et al, 1989*). However, there were no previous single epidemiological study that reported on hypertension in Saudi Arabia.

3.6 LIPIDS

The established normal reference ranges for serum cholesterol in healthy adult Saudi Arabs were [males 3.2 - 6.2 ; females 3.5 - 5.5 mmol/l] (*El-Hazmi et al, 1982; Bacchus et al, 1982; El-Hazmi, 1991*), and these levels are generally normal or low in Saudi Arabians compared with Northern Europeans (*Cook: 1976; Bacchus et al: 1982*). However, In diabetic patients, levels were slightly higher than normal for Saudi Arabians, but lower than those reported for normal subjects from Europe and America (*Kingston et al: 1986*). These levels had a low correlation with serum glucose and thus, hyperglycaemia per se was not an important variable influencing serum cholesterol levels (*Kingston et al: 1986*). No reports on lipids in conjunction with diabetes.

3.79 MANAGEMENT AND CARE :

Modification of diet and increase of activity reduced weight in 83 % after 3-4 months and decreased serum glucose values in 72 % and thereafter should be the first and principal mode of treatment particularly for Saudi NIDDM subjects, even though, dietary advice was not usually given and oral hypoglycaemic drugs were prescribed for the majority of referred diabetic subjects (*Kingston, 1985*).

Education of diabetic subjects in Saudi Arabia should be greatly emphasised into the nature and self-management of their disease (*Larson, 1982*), since problems might be encountered in caring for Arabic origin subjects which either be due to their failure in receiving the maximum benefit from even the most rudimentary treatment resources (*De Senarclens et al, 1983*), or encountered when non-Arabic speaking diabetic health care providers challenged with the problem of instructing non-English speaking Saudi Arabian diabetic subjects (*Weiss, 1984*).

3.8 MONITORING

Self-testing urine for glucose is an unsatisfactory method of control in majority of Saudi diabetic subjects since they exhibit a high renal threshold and day-to-day control should be assessed by blood glucose measurements if possible

or with medium- or long- term glycated proteins. Several of the latter have been examined in Saudi Arabia.

Glycated haemoglobin values, *in line with other studies; correlated with* fasting blood glucose (*Mira et al, 1985*) but not with age (*Al-Aayash et al, 1987*) or duration of diabetes (*Ajabnoor et al, 1987*), were not different between men and women (*Kilshaw et al, 1983*) and the values in IDDM were higher than NIDDM (*Mira et al, 1985*). It is also a valid measure of monitoring diabetic control in the presence of both normal and abnormal haemoglobins as in sickle cell anaemia subjects particularly in the eastern provinces where these predominated (*Al-Torki et al, 1987*). Alternatively, serum fructosamine is useful in monitoring medium-term glycaemic control (*Ajabnoor et al, 1988; Ajabnoor et al, 1990*) and glycated fibrinogen which is more sensitive in reflecting mean blood glucose changes over a shorter period of observation [2-3 days] (*Ardawi et al, 1990*).

3.9 SPECIAL TOPICS IN DIABETES :

When the effects and safety of Ramadan fasting [May/June 1985] on diabetic subjects [32 NIDDM and 20 IDDM] have been evaluated, it is suggested that diabetic Muslims in Saudi Arabia could observe fasting provided that proper attention is given to the state of control (*Khogheer et al, 1987*).

3.10 CONCLUSION :

This chapter demonstrated that diabetes mellitus is an emerging problem in Saudi Arabia, particularly in urban areas. Further studies are needed to determine the prevalence, incidence, types, genetics, aetiology, complications, treatment and prognosis, in order to plan services and to minimize the future risks of this health problem in Saudi Arabia. Hence the study objectives were perceived and shown with the methods and results in the next few chapters.

GENERAL OBJECTIVES

Most studies that attempt to measure the prevalence of diabetes in Saudi Arabia [*Chapter 3*] have a priori notion that environmental factors play the major role in the high prevalence of diabetes in this community but no one has actually assessed any of these factors. Moreover, no data were available on the associated risk factors. The need to conduct a survey among the urban subpopulation was thus perceived. Therefore, the main objectives of this study can be stated broadly as follows :

1. To describe the prevalence rates of glucose intolerance (diabetes and impaired glucose tolerance) and the associated cardiovascular risk factors in a cross-sectional pilot urban community and to compare these with respect to different glucose tolerance groups and nationalities. In addition, establishing in statistical terms, the relative importance of factors considered necessary to foster the development of diabetes in this community [*Chapter 5*].
 2. To test the reproducibility of OGTT in sub-sample [*Chapter 6*].
 3. To describe the dietary pattern and to investigate any differences between glucose intolerance or nationality groups [*Chapter 7*].
 4. To describe the physical activity pattern and to investigate any differences between glucose intolerance or nationality groups [*Chapter 8*].
 5. To examine the effect of nationality on different metabolic, dietary and physical activity variables [*Chapter 9*].
 6. To describe the hormonal and the metabolic responses between the glucose intolerance groups and to elucidate whether defects in insulin secretion and/or insulin action are responsible for the glucose intolerance [*Chapter 10*].
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GENERAL METHODS

CHAPTER FOUR

GENERAL METHODS

CHAPTER CONTENT :

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- 4.4 **GENERAL STATISTICAL APPROACH.**
- 4.5 **COMPUTING METHODS.**

SUMMARY

This chapter outlined briefly the general methods used in this study. This required three visits, an interviewer-administered questionnaires, and involved an anthropometric and blood pressure measurements, OGTT, blood sampling and assaying for hormones and metabolites and involved using certain machines and instrument. Specific methods are presented in the appropriate chapter.

4.1 PLAN and ASSESSMENT

Many of the factors that might affect the study design should be identified before conducting any survey, (*Abramson, 1990*). The methods of ascertaining such factors are described below.

4.1.1 First visit (Official approval and evaluation) :

Before designing the study, acquiring research materials and formulating the questionnaire, site visits, interviews, discussions and examination of published studies and government reports were carried out to identify the different factors and problem areas thought to affect either the conduct and/or the anticipated objectives or results of the study. The preliminary interviews, with managerial personnel responsible for the Health Service or other study-related official government authorities in the Jeddah region, showed the difficulty encountered in arranging and conducting these personal interviews, especially if no previous contact with the managers existed. Despite this, it was felt that a lot of the background information and facilities required could be attained. Familiarity with the services provided in the majority of the primary health centres and some hospitals was also acquired. The author, being an employee of the Ministry of Health, requested the issuing of official letters from the M.O.H to support him in conducting personal interviews with a number of government officials for the purpose of collecting more supplementary data and information. Accompanying the letters, was a brief summary describing the author's research objectives and the purpose of conducting this study. It is fair to mention at this point that the author experienced encouraging as well as frustrating times during the course of conducting these official surveys.

4.1.2 Second visit (Pilot study) :

The aims of this visit were to examine the feasibility, arrange the requirements, assess the difficulties and perform a pilot study. This involved piloting the field methods discussed below as well as using a preliminary questionnaire with 30 subjects in a primary health clinic. This showed that the questionnaire needed to be refined, adjusted and most importantly conducted by interview, since mailing the questionnaire was found impractical. Further evaluation of the difficulties of taking a biological or informative sample in Jeddah to the final stage of analysis at Newcastle Upon Tyne was assessed. Furthermore, additional interviews with officials were carried out. The information obtained and the basic data collected led to refinement and adjustment of the final plan of the major study. This was done between November 2nd, Wednesday 1988 and January 10th, Tuesday 1989.

4.1.3 Third visit (Main studies) :

Based on the previously stated objectives and the insight gained from the pilot study, a final set up of the samples and format of the questionnaire was designed for the Jeddah Cardiovascular Diseases [CVD] study [n=95]. In this study the full range of the field methods were employed. The basic general data, and all physical and biological variables that were obtained for the pilot study [n=30] were added to that obtained from the main study [n=95] and the results of both [n=125] presented later [*chapter 5*]. However, the data obtained from dietary and physical activities questionnaires in the pilot study were mainly investigatory, proved unreliable and have therefore been excluded. Hence, only the dietary [*Chapter 7*] and the physical activity [*Chapter 8*] responses from the main study are presented. Efforts were made to ensure that the data were collected under the same condition. Simultaneously, two other studies were conducted [*Chapter 6, 10*]. This visit was between June-November 1989. During both visits, volunteers were tested and interviewed in one day between 08:00 till 13:00 and if necessary requested to return to the afternoon between 16:00 - 19:00 to complete their

sheets. The period for each visit was selected because most, if not all, people were settled as it precedes the mid-year holiday.

4.1.4 Study city, JEDDAH :

Knowing in brief the background of the city is of great importance in understanding its urban nature, in explaining the relevant features of the whole subpopulation living in this city and in interpreting the pattern of risk factors found in this urban community. This section is intended to provide the reader with general information about Jeddah (*Al-Harbi, 1988; Al-Ansari, 1982*). The name Jeddah, 'Grandmother', and the legendary tomb of Eve, located near the city, give a strong indication of the ancient character of the city. At present, Jeddah is the largest city in the western region of Saudi Arabia and the principal sea port on the Red Sea. Over the last three or four decades the growth of the city has been truly spectacular, and has transformed it from a homogeneous to a heterogeneous urban environment. The city can be divided spatially into three zones; the old town area, the transitional area and the contemporary area. Historically, the city's role was, and still is, as a port and gateway to the Holy City of Makkah. Presently, Jeddah is of prime importance, both socially and economically, to the kingdom since in 1980, 80% of the food stuff imported to the country arrived through the port of Jeddah and 30% of the government's project expenditure was invested in the city during the second five year plan. It is situated on a coastal plain, called "Tuhama" and located in the arid zone between the mild climate of the Mediterranean Basin and the monsoon climate of the Indian Ocean. This gives the city an average monthly temperature of 25-30 °C. The lowest (14 °C) is during December and January and the highest (47°C) is during June. High relative humidity is the characteristic, rain is very rare (40 mm annually) and the most prevailing winds are from the north and north-west.

Throughout the centuries, a large number of Jeddah's population has consisted of Muslims of different national origin, who came for Hajj and later on settled in Jeddah. In addition, there have been a few non-muslims who came for

trade, business, work or diplomacy. Since 1978 Jeddah population has shown a steady increase until it reached 1,234,200 inhabitants in 1985, with foreigners constituting about 53 %. The population age structure since 1978 is similar to the Third World Countries and has remained relatively stable recently. Of the total population 41 % is less than 15 years old, 58 % is in the adult group (15-64) years and 1 % is those aged 65 years and over. Government and private Health Services are provided through major referral hospitals as well as primary health care centres distributed to serve most of the districts in the city. It is homogeneous with respect to the environment but not to the lifestyle. However, generally, each district is homogeneous in both environment and lifestyle, which in the proposed area, is affluent and non-traditional.

4.1.5 Study area :

The recruitment of this study was carried out in three different places and in two periods of time. Al-Salama Primary Health Care Centre (PHC) was selected from amongst six PHC centres which serve the North West region of Jeddah. Availability of facilities, central location and familiarity with the investigator were the reasons for its selection. Al-Shaty Teaching Hospital was the second place for this study. In this hospital, a recruiting clinic was established on arrival by the investigator. It is called the Screening Clinic for Diabetes and Hypertension. Two months later, the investigator moved to the newly opened Diabetic and Hypertension Centre where he established the same screening clinic with the name of the Well-Adult Clinic [WAC].

4.1.6 Publicity :

An invitation to a "FREE TEST" for diabetes, hypertension and lipids was offered using different means. Invitation posters were attached to notice boards at the place of the study and a descriptive sheet in Arabic was distributed to everyone attending the place of the study. The governmental hospitals and PHC centres were also informed by through the dissemination an official circular. Special explanatory and invited visits were carried out by the investigator to some

of these centres. On the second visit more than 3,000 sheets were distributed to some medically related places such as chemists shops in addition to non-medical places such as supermarkets and some governmental departments. The invitation was to attend on any day except Friday and pre-registration was requested as late as one day prior to the day of investigation. An official permission letter was arranged for the working subjects. The response rate [50 %] was estimated by dividing the numbers of those registered initially and those who came for the test. Women were asked in the pilot visit to attend this free test, but they were unreliable attenders as they depended on others for transport. Furthermore, the unavailability of a nurse during the study period made exclusion of women from the study inevitable.

4.2 FIELD METHODS :

4.2.1 Subjects :

A representative group for either the whole city population or a district community was conceived impossible during the first visit, due to many limitations including time, cost and personnel (*Lameshow et al, 1990*). Any subject who was male, age between 20 - 65 and living in Jeddah with any nationality was welcomed for the study. Those known by simple question to have diabetes or hypertension were excluded from the study even if they registered for investigation. Pre-registration was requested or needed to ensure understanding of the instruction required for this study, which was explained by the investigator who also provided the subject with an appointment slip which indicated the day and time of the test. Thus sampling bias can not be excluded and extrapolation for the whole community should be treated cautiously.

4.2.2 The Health Questionnaire :

The WHO oriented health questionnaire (*Laparasky et al, 1987; Rose, 1982*) contained questions on five main aspects namely: general, personal and medical history, cardiovascular; social habits; dietary and physical activity [Appendix 1-5] . On arrival, each subject was given this questionnaire to look

through before it was administered and completed individually by the investigator using the direct questioning technique on the same day of attendance. The questionnaire initially written in English was translated into Arabic but the English version was included. The time required to complete the whole questionnaire varied between 45 to 75 minutes per subject, utilizing the waiting time for the physical measurements and blood samples. Biases during the interview could have arisen from the interviewers or the respondents. Interviewer biases may be caused by incorrect questions, incorrect recording of responses, intentional omissions, biases associated with interview setting, distractions, confidentiality and anonymity of the respondent, and the degree of rapport between the interviewer and the respondent (*Lydeard, 1991*). Respondent biases arise because the respondent may misunderstand what the interviewer has requested, receive nonverbal clues to the 'right answers' from the interviewer; or have a need to give 'socially desirable' answers. Respondent biases may lead respondents to overestimate facts such as income and age. In order to minimize interviewer and respondent biases, the interviewer during the pilot study trained himself to anticipate and recognize potential sources of distortion and bias in addition to avoidance of value judgments by the interviewer. Nonresponse rate was also minimized when the interviewer conveyed warmth, understanding and trust.

4.2.3 Body fat estimation :

There were two techniques for estimating body fat. The direct techniques include densitometry, total body water, total body potassium and uptake of lipid-soluble inert gases. The indirect techniques include skin-fold measurements, weight : height ratios and waist-hip circumferences (*Gibson et al, 1990*). Of the later techniques only the last two were used in this study. Anthropometric measurements can be derived directly from a single or combination of raw measurement(s) and are of two types : growth and body composition measurements. The most widely used anthropometric measurements of growth are

height [Stature] and weight. They are employed in epidemiological studies as indirect measures of obesity, because measurements of weight and height are easy, quick, relatively noninvasive, and are precise and accurate with care and training (*Lohman et al, 1988*). However, obesity indices cannot be used to distinguish between excessive weight produced by adiposity, muscularity, or oedema. Standing height was measured once using a stadiometer, to the nearest 0.5 cm, without shoes and head cover, the back square against the wall tape, eyes looking straight ahead, with a set square resting on the scalp and against the wall. Weight was measured once with a beam balance to the nearest 0.1 kg without shoes, in light dress and undergarments. The 'Quetelet's index' or body mass index [BMI] was then calculated [$\text{Weight}(\text{kg})/\text{Height}(\text{cm})^2$] since, it was considered to be the least biased by height and easily calculated for most adult population (*Garrow et al, 1985*). However, it is not a valid index for those under twenty or over sixty-five years of age, or for those who are pregnant or lactating and should not be used as an index of body fatness in individuals with a grossly abnormal relationship between leg and trunk length. (*Gibson et al, 1990*).

Most anthropometric methods used to assess body composition are based on a model in which the body consists of two chemically distinct compartments: fat and fat-free mass. The latter consists of the skeletal muscle, nonskeletal muscle and soft lean tissues, and the skeleton. Anthropometric techniques can indirectly assess these two body compartments. Subjects should fast overnight prior to the measurement and wear little clothing to ensure that the tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs.

To perform the waist circumference [WC] measurement, the lowest rib margin is first located and marked with a felt tip pen. The iliac crest is then palpated in the midaxillary line, and also marked. An elastic tape is then applied horizontally midway between the lowest rib margin and the iliac crest, and tied firmly so that it stays in position around the abdomen about the level of the

umbilicus. The elastic tape thus defines the level of the WC, which can then be measured by positioning a fibreglass tape over the elastic tape (*Jones et al, 1986*). Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. The reading is taken to the nearest millimetre. For the hip circumference [HC] measurement, the subject should stand erect with arms at the side and feet together. The measurement should be taken at the point yielding the maximum circumference over the buttocks (*Jones et al, 1986*), with the tape held in a horizontal plane, touching the skin but not indenting the soft tissue (*Lohman et al, 1988*).

The waist-hip circumference ratio [WHR] can be measured more precisely and provides an index of both subcutaneous and intra-abdominal adipose tissue. It is a simple method for describing the distribution of both subcutaneous and intra-abdominal adipose tissue (*Larsson et al, 1984; Jones et al, 1986*). Results of computer tomography scans in twenty-eight women showed a high degree of correlation between the WHR and the proportion of fat situated intra-abdominally at the umbilical level (*Ashwell et al, 1985*). It was suggested that WHR greater than 1.0 for men and 0.8 for women were indicative of increased risk of cardiovascular complications and related deaths, although more research is needed before specific recommendations for classifying waist-hip ratios can be made (*Björntorp, 1987*). In a semi-random, age-stratified sample of 4349 British Caucasian adult men, it was found that 4% had a WHR > 1.0, the cut-off point associated with increased risk of mortality and morbidity, and 12 % had values between 0.95 and 0.99. Moreover, the WHR increased with age and excessive weight, both separately and in combination.

4.2.4 Blood pressure measurements :

Blood pressure was measured twice on each participant during the waiting time for the two hour OGTT. Once was on arrival and the second was anytime between the 1-h and 2-h blood samples. Each measurement was preceded by at

least a three minute resting period. All were made on the right arm (unless injured or otherwise unsuitable) with subjects seated and the arm supported at heart level (*Petrie et al, 1986; O'Brien et al, 1990*). In this study, the Copal UA-231 automatic sphygmomanometer was used (*Meyer-Sabellek et al, 1990*). This machine was evaluated in the field against the ordinary standard mercury sphygmomanometer, and found to be a useful instrument for epidemiological survey work by removing some of the observer variation in the measurement of blood pressure (*Rogers et al, 1988*). The standard adult-size (12x23 cm) cuff provided with instrument was used, irrespective of the arm circumference. The instrument was demonstrated to the participants before BP measurement. A peak inflation pressure at 180 mmHg was used and this was increased to 220 mmHg if the first pressure proved inadequate. The machine recorded the diastolic pressure at phase 5. The means of the two readings was taken and the results interpreted according to the WHO Criteria (*WHO, 1978*).

4.2.5 The oral glucose tolerance test (OGTT):

Solution :

Bottles of 300 ml solution degassed, with an orange flavour, containing 100 g of dextrose were used (*Sun-Dex-Trade*)*. In order to get 75 g (WHO), 75 ml of solution was withdrawn and discarded and the bottle was refilled to 300 ml mark using canned water.

*The Sun-dex-Trade 100, an oral carbonated GTT beverage, 10 g glucose/fluid oz (29.57 ml) USA by customs laboratories. Ingredient: 100 grams dextrose (D-glucose), citric acid, orange flavour extract, artificial colouring and sodium benzoate.

Protocol :

The WHO, 1980 protocol was followed which involved the following. The OGTT was administered in the morning after at least three days of unrestricted diet (greater than 150 g of carbohydrate daily) and usual physical activity. The test was preceded by an overnight fast of 10-16 hours, during which water was allowed. Smoking was not permitted during the test. The presence of

factors that influence interpretation of the results of the test was recorded (eg. medications, inactivity, infection etc). After collection of the fasting blood sample between 0800 and 0900 hours, the subject was given 75 g of glucose as above over the course of 5 minutes. Blood samples were collected 1 hour and 2 hours after the test load.

4.2.6 Sampling scheme and tubes preparation :

In the morning of the study, each subject was asked to confirm the overnight fast of 10-14 h, otherwise he was given another appointment. Three venepunctures were used in the community study. Indwelling cannulae (Branula) were inserted into the subjects' right and left antecubital veins unless inconvenience or failure prevented this. Local anaesthesia was used for the study described in chapter 10. Informed consent (in writing) was obtained for both tests. Blood was collected into tubes containing fluoride oxalate for glucose, lithium heparin for NEFA, 5 ml perchloric acid for metabolites, trasylol for glucagon and plain for other estimations. In the pilot study fasting samples were taken for glucose, insulin, cholesterol, triglycerides, uric acid and fructosamine. Additional 1-h and 2-h samples for glucose and insulin were taken. In multiple samples OGTT study [chapter 10] two fasting samples were taken; for hormones [insulin, C-peptide, proinsulin and glucagon]; for intermediary metabolites [glucose, lactate, alanine, glycerol, pyruvate, 3-hydroxybutyrate and NEFA]; for lipids [cholesterol and triglycerides] and for fructosamine. Further samples were taken for hormones and metabolites at 30,60,90 and 120 minutes. For insulin, C-peptide and proinsulin an additional sample at 10 and 20 minutes was also taken. The samples was obtained on the specified time plus or minus 5 minutes. Once collected these samples were centrifuged immediately at 4°C and the serum or plasma kept at -40 °C for later analysis at Newcastle. Since no bedside measurement of blood glucose was available, all the samples were analysed at Newcastle. However, to inform subjects about their results an aliquot was taken for routine analysis for glucose and lipids by local methods.

4.2.7 Packing, storage and transportation :

The samples were prepared in groups in plastic bags and kept in a -40°C freezer. They were packed in the morning with dry ice in an icebox, sealed with an adhesive tape around the brim and left at room temperature until the departure time at night. On arriving at the department in Newcastle (within 24h) the samples were moved to the appropriate freezers until assayed. All were still frozen on arrival.

4.3 LABORATORY METHODS :

INSTRUMENTS :

4.3.1 The Yellow Spring Instrument [YSI]:

The Yellow Spring Glucose Analyser instrument, Model 23AM, is a quantitative device for measuring glucose in blood plasma and blood serum for in vitro diagnostic purposes using a sample of 25 μ l. It is based on the glucose oxidase enzyme hydrogen peroxide sensor which is highly specific for glucose.

4.3.2 The Cobas Bio Centrifugal Analyser :

Many of the spectrophometric and fluorometric assays in this thesis were performed using a Cobas Bio centrifugal analyser model 8326 (Roche, Basle, Switzerland). The instrument can measure up to 24 samples and 3 standards for any particular assay. The sequence of events may be summarised as follows: the instrument pipettes into separate disposable cuvettes, a water blank (used for internal standard) and 3 standards and 24 samples either without or with the main reagent. The contents of the cuvette are mixed at approximately 2000 rpm and then the start reagent is pipetted in. The Cobas can be programmed to read changes in absorbance or fluorescence from either the first (main reagent) or second addition (start reagent). The result is calculated from the change in absorbance or fluorescence, by first subtracting the end reading from the internal blank and extrapolating this result from the standards. Details of the individual assays are described below.

ASSAYING PROCEDURES :

PROTEIN HORMONES

4.3.3 - Insulin :

Serum insulin was assayed in the department laboratory by a double antibody radioimmunoassay technique (*Soeldner and Slone, 1965*). Five hundred and fifty microlitres of insulin standards (Wellcome Reagents Ltd, UK) or sample and 50 μ l anti-insulin serum (raised locally in guinea pigs) in borate buffer pH 8.0, were incubated at 4°C for 48 hrs. 50 μ l of 125 I insulin (CMD, Bournemouth, UK) was added to each tube, the tubes were further incubated at 4°C for another 48 hrs. Separation of bound from free insulin was achieved by adding 1 ml of anti-guinea pig insulin (Wellcome, UK) to each tube. The tubes were left to stand at room temperature for 30 minutes, spun at 1850 g for 30 minutes, the tubes decanted, and the precipitate counted using a gamma counter. The normal adult fasting range was 2.8-13.5 mU/l with intra-assay coefficient of variation (CV) of 4.2% and inter-assay CV of 4.8 % .

4.3.4 - C-peptide :

Serum C-peptide was assayed after extraction of proinsulin and insulin with Sepharose bound, anti-insulin antibodies (*Heding, 1975*). C-peptide was measured by ethanol precipitation radioimmunoassay (*Heding, 1975*) using the M1221 antibody and a synthetic standard (Novo Research Institute, Denmark) with delayed addition of labelled C-peptide (Novo Research Institute, Denmark). One hundred microlitres of standard or sample was incubated with 100 μ l of antiserum (1:25000) for 24 hours at 4°C. To this mixture at 4°C was added 100 μ l of 125 I-Tyr-C-peptide. The mixture was further incubated for 24 hrs at 4°C. After this period 1.60 ml of 96% (v/v) ethanol was added to each assay tube, vortexed and centrifuged at 2000g for 10 minutes. After discarding the supernatant, the precipitate was washed with 2.0 ml of a solution composed of 960 ml 96% (v/v) ethanol, 18 ml assay buffer, and centrifuged at 3000 g for 10 minutes. The supernatant was discarded, and 0.5 ml of 0.05 M NaOH added to each precipitate

and counted. The adult reference range was between 0.18 and 0.52 nmol/l. The intra- and inter-assay coefficients of variation were between 5.9 and 7.2 and 7.9 and 10.1% respectively.

4.3.5 - Proinsulin :

Proinsulin was measured by immunoradiometric assay (*Dhahir, Cook and Self, in press*). 220 μ l polyclonal quinea-pig antibody to human proinsulin [Eli Lilly], equivalent to 2.2 μ g protein, partially purified from serum by ammonium sulphate precipitation, was coated to the wells of Immulon Immunostrips^m [Dynatech] by incubating at 4°C for 24h. The plastic was then treated by incubation with a solution of 1 % bovine serum albumin for 30 min to reduce non-specific binding of protein and the wells washed three times with a 0.02 % solution of Tween 20 in 0.1 M phosphate buffer, pH 7.4 . 200 μ l serum sample or standard in bovine serum were incubated in the wells for 24 h at 4°C after which the wells were washed 4 times with the Tween solution. 200 μ l of 125-iodine labelled monoclonal antibody to C-peptide [PEP-001], a gift from [Novo Laboratories, Bagsvard, Denmark] containing about 200,000 counts per minute were then added to the wells and incubated for a further 24h at 4°C. Finally the wells were again washed 4 times with the Tween solution and the wells broken part from the strips for counting of radioactivity. Typically, a sensitivity of 0.4 pmol/l [zero + 2.5 sd] intact proinsulin was obtained with this procedure. Cross-reactivity observed with 32/33 split proinsulin and 65/66 split proinsulin was 77.9% and 61.0% respectively with respect to intact human proinsulin.

4.3.6 - Glucagon :

Glucagon samples were sent to Denmark for assay. There, glucagon was measured by double antibody radioimmunoassay using small, vertical, dry paper wicks. Free and antibody bound radioactive hormone are located at opposite site ends of the paper strips. The wicks are cut through the middle and the two halves are placed vertically into counting tubes. The percentage activity of bound hormone or the bound/free ratio is calculated for serum and standard samples

(Orskov *et al*, 1968). The interassay CV was 9 % .

STEROID HORMONES

4.3.7 - Sex hormone binding globulin (SHBG) :

The sex hormone binding globulin was determined using the Farnos diagnostic immunoradiometric assay kit [Farnos SHBG-IRMA]. The procedure is based on the principles of a "sandwich type" non competitive "liquid phase" immunoradiometric assay (Hammond *et al*, 1985). Serum samples, controls and standards were diluted in assay buffer. A mixture of ¹²⁵I labelled monoclonal SHBG antibody and anti SHBG antiserum is then added to aliquots of samples, controls and standards. The mixture is incubated for 1 hr. Solid phase donkey anti-rabbit IgG antiserum is then added, followed 15 minutes later by 2 ml 0.9% NaCl. After centrifugation the supernatant is decanted to waste. The radioactivity of the solid-phase matrix pellets are counted in a gamma counter. The normal adult fasting range was 2.8-13.5 mU/l with intra-assay CV of 4.2% and inter-assay CV of 4.8% .

METABOLITES :

Whole blood [0.5 ml] was added volumetrically to 2 ml 0.77 mol/l perchloric acid and thus weighing omitted in the field. After mixing, the tube was centrifuged at 2500 g for 5 min and the protein-free supernatant removed. The supernatant was placed in plain tubes and stored at - 40 °C for later analysis at Newcastle. Glucose, lactate, pyruvate, alanine, glycerol, acetoacetate and 3-hydroxybutyrate were determined in the unneutralised perchlorate extracts by fluorometric enzymatic methods (Burrin *et al*, 1987; Harrison *et al*, 1988) on the Cobas Bio. The assay cocktails and reaction sequences are given below briefly.

4.3.8 - Glucose :

Two aliquots of plasma were used, one for immediate analysis to inform the subjects and the other to be kept stored in deep freezers for assaying at Newcastle. For the former purpose, the SKD glucose test kit method, based on O-toluidine reaction, was used which was subsequently substituted by an enzymatic

method using a Beckman Astra System. At Newcastle, plasma glucose was measured in the department using the YSI. The principal reactions were three (Burrin *et al*, 1990). The glucose assay in YSI is dependent upon the glucose oxidase which results in the formation of D-gluconic acid and hydrogen peroxide as follows:

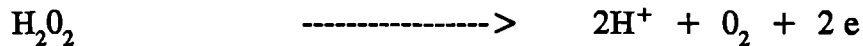
Reaction I:



The hydrogen peroxide produced is measured by electrode.

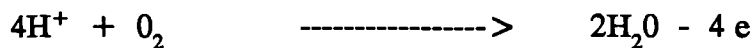
The probe, then oxidises a constant portion of the hydrogen peroxide at the platinum anode (Reaction II).

Reaction II:



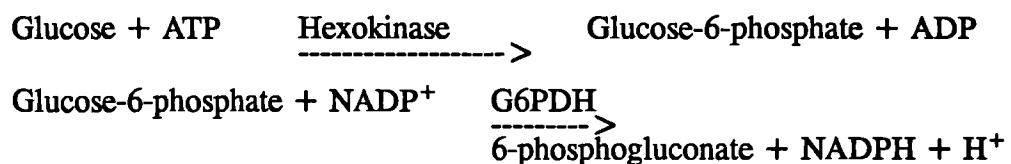
The current thus created is directly proportional to the glucose level in the diluted sample. The circuit is completed by a silver cathode at which oxygen is reduced to water (Reaction III).

Reaction III:



Although a great amount of oxygen is present in this process, note that the 23AM does not measure oxygen. Nor does it respond measurably to normal changes in atmospheric pressure. The plasma glucose samples taken for classification or confirmation purposes were based on this method.

Glucose samples taken for glucose with the other metabolites during the metabolic responses following OGTT study [Chapter, 10], were analysed using the Cobas Bio Centrifugal analyser. The reaction sequence for the assay is:



Main reagent: 0.7 ml glucose buffer, 0.7 ml pyruvate buffer, 2.25 mg NADP and 2.6 mg ATP.

Start reagent: 7.0 uL hexokinase and 7.0 U1 G6PDH.

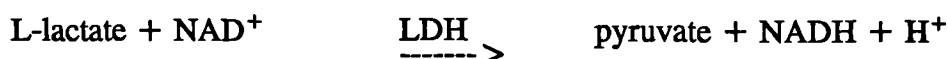
The coefficients of variation of the assay were 1.2, 1.1 and <1% for mean plasma glucose levels of 3.8, 9.3 and 15.4 mmol/L.

4.3.9 L-lactate :

Main Reagent: 0.1 M Tris-HCl, 1% (v/v) hydrazine hydrate and 1 mM NAD⁺ pH

9.3. Start Reagent: 30 U/ml lactate dehydrogenase.

The assay CVs was 7.2% for low and 4.4% for high values. The reaction sequence for the assay is:



4.3.10 Pyruvate :

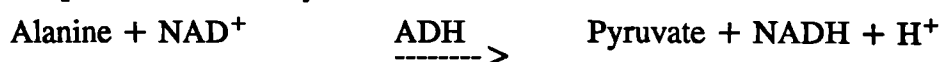
Main Reagent: 0.4 M K⁺ phosphate and 40 uM NADH, pH 7.0;

Start Reagent: 2 U/ml lactate dehydrogenase. The assay CVs were 5.0% for low and 4.7% for high values. The reaction sequence for the assay is:



4.3.11 Alanine:

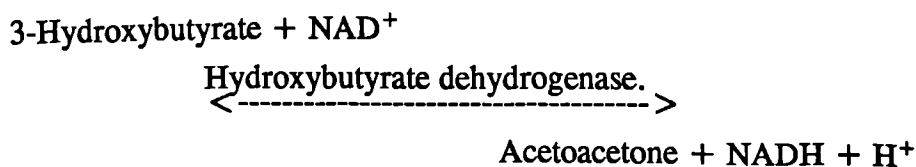
Reagent: 40 mol/L tris (hydroxymethyl) methyl-amine buffer, pH 10. The enzyme-co-enzyme stock were 2 mg NAD, 10 uL in 1ml phosphate buffer plus 0.7 ml alanine dehydrogenase. The assay CVs were 6.5% for low and 6.4% for high values. The reaction sequence for the assay is :



4.3.12 3-Hydroxybutyrate :

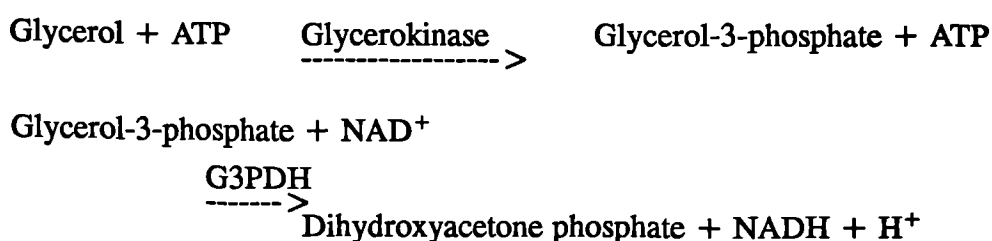
Buffer : 0.1 mol/l TRIS, 1 mol/l hydrazine hydrate, 2.7 mmol/l EDTA [disodium salt] adjusted to pH 8.5 with 10 mol/ hydrochloric acid.

Enzyme reagent : 10 mg NAD and 350 μl 3-hydroxybutyrate dehydrogenase [7.5 U] in 5 ml 0.1 mol/l phosphate buffer, pH 7.4. The working reagent is prepared by adding 0.7 ml of this solution to 8.8 ml of the buffer. Top standard [120 μmol/l] was used to set up PM voltage. The assay CVs were 5.6% for low and 6% for high values. The reaction sequence for the assay is:



4.3.13 Glycerol :

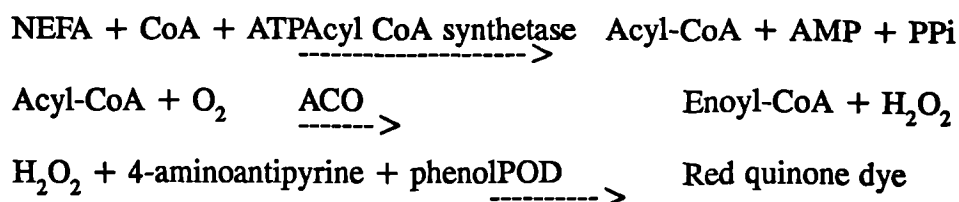
Reagent : Glycerol buffer of 0.2 mol/L glycine buffer containing 1 mol of hydrazine and 0.01 mol of magnesium chloride per litre. The enzyme-co-enzyme stock were: 2 mg of NAD, 2 mg of ATP and 5 μ l of glycerol-3-phosphodehydrogenase [G3PDH]. The assay CVs were 7.0% for low and 4.3 % for high values. The reaction sequence for the assay is:



LIPIDS

4.3.14 NEFA:

Fatty acid concentration was determined using a NEFA Wako commercial kit on the Cobas Bio Centrifugal Analyser (*Knox and Jones, 1984*). The reaction depends on the conversion of fatty acid to acyl-CoA by acyl CoA synthetase [ACS]. Coupling of this synthetase with acyl-CoA oxidase [which oxidises acyl CoA to enoyl CoA and generates H_2O_2], has made it possible to quantify non-esterified fatty acid. The H_2O_2 generated by the oxidase is determined by the oxidative coupling of the H_2O_2 with 4-aminoantipyrine and phenol by peroxidase [POD], which produces a coloured quinone dye that can be determined by measuring the increase in absorbance at 500 nM. The assay CVs were 2.7% for low and 2% for high values. The reaction sequence for the assay is:



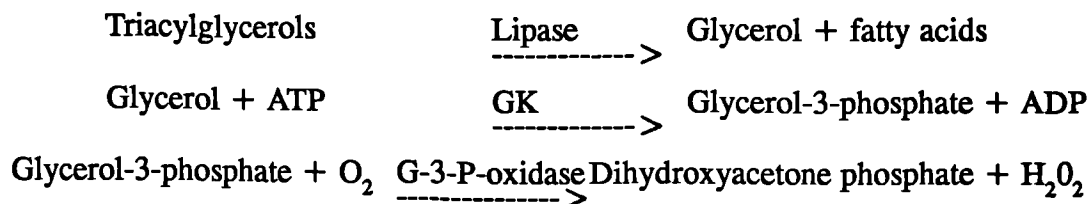
4.3.15 Cholesterol :

Total serum cholesterol was measured enzymatically by the in Cobas Bio analyser after hydrolysis of cholesterol esters by cholesterol esterase and oxidation of cholesterol by cholesterol oxidase. This method is based on Deeg et al (*Deeg et al, 1982*). The assay CVs were 3% for low and 2% for high values. The reaction sequence for the assay is :



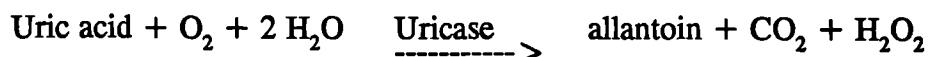
4.3.16 Triacylglycerols (Triglycerides) :

Serum acylglycerols were measured in the Cobas Bio analyser using an enzymatic method (*Megram et al, 1982*). They are measured as glycerol using glycerol kinase after hydrolysis of the triacylglycerols by lipase to glycerol. The assay CVs were 2.4% for low and 2.3% for high values. The reaction sequence for the assay is:



4.3.17 Uric acid :

Serum uric acid concentration was determined by an enzymatic colorimetric method (*Fossati et al, 1980*) with uricase and 4-aminophenazone [PAP] using Cobas bio [4.3.2]. The principle of the reaction is :



The quinoneimine formed is proportional to the uric acid concentration and it is determined by measuring the absorbance in the range of 480 - 550 nm. The CV for serum uric acid levels of 5.9 mmol/l was 1.8 % .

4.3.18 Fructosamine :

Serum fructosamine was measured using a Cobas Bio Centrifugal analyser (Roche, Diagnostics, UK). The method employed is similar to that described by

Hindle et al (1985). In this method serum is mixed with 0.1 mmol/l carbonate buffer, pH 10.35, containing 0.25 mmol/l nitroblue tetrazolium (NBT) at 37°C; the absorbance at 530 nm was measured at 11 and 15 minutes after mixing. Quantitation was by comparison with standards of 1 deoxy-1-morpholinofructose (DMF) in albumin (40 g/l) similarly treated.

4.3.19 HOMA assessment of β -cell function and insulin resistance:

The fasting plasma glucose and insulin concentrations in each normal subject or NIDDM patient are set at a level characteristic for that individual for a given state of nutrition (*Turner et al, 1979*). The fasting plasma insulin concentration is largely determined by the glucose concentration and the basal hyperglycaemia in diabetes appears to arise from the feedback loop between the liver and β -cell, thereby maintaining an effective insulin action in the liver and at the periphery. The degree of basal hyperglycaemia is thus determined by a combination of β -cell deficiency and insulin resistance. The interpretation of the 'set' of a feedback loop termed "homeostasis model assessment" [HOMA] (*Matthews et al, 1985*). Thus, HOMA was based on estimation of fasting glucose and insulin concentration. Assuming that normal-weight normal subjects aged < 35 years have 100 % β -cell function, and an insulin resistance of one, the values for a patient can be assessed from the insulin and glucose concentrations by the formulae : β -cell function [%] = $20 \times \text{insulin} / [\text{glucose} - 3.5]$, and [near approximation] resistance = $\text{insulin} / [22.5 e^{-\ln \text{glucose}}]$ (*Matthews et al, 1985*). It should be noted that these data are based on Caucasian subjects.

4.4 GENERAL STATISTICAL APPROACH

In order to interpret and make sense (*Abramson, 1988*) in using these data further analysis and computing should be carried out. Statistics furnishes ways and means to define objectively and introduce order to the steps and procedures used for forming conclusions from a sample of data. Statistics is mainly concerned with describing of the population characteristics and analysis or testing hypotheses (*Daniel, 1991*). The categorical qualitative data, nominal and ordinal as well as

the numerical quantitative data, discrete or continuous were the main types of data used in this thesis mainly from a survey. The tests that apply to draw inferences from ordinal information are not suitable to be applied to categorical information but can still be applied to cardinal information with a loss of efficiency. The tests that apply draw inferences from cardinal information are not suitable to be applied to categorical or to ordinal information. For this thesis, there were four sets of samples of different sizes that were intended to examine different aspects including the OGTT reproducibility [n=35 subjects, chapter 6], dietary [Chapter 7] and physical activity assessment [Chapter 8] [n=95 subjects] and the metabolic and hormonal responses [n=43 subjects, Chapter 9] but all were drawn from one main subpopulation [n=125 subjects, Chapter 5]. While it is felt that it is not important to get a proportional representation of the different types for study purposes, it was shown that a reasonably unbiased sample representation with respect to the various types of areas of interest was achieved. Also it is generally recognised that in developing countries this type of survey is not common and that awareness of people towards responding to such exercise is still relatively low. When the responses were by ranking as in dietary assessment, it is to be noted that rank one signifies the highest degree of importance, in relative terms, given to the respective parameter and so on, in an ascending order, for the rest of the ranks. There are two interpretations for explaining no rank occurrence; the first is that a respondent does not have enough information to acknowledge and rank the particular parameter, the second is that the respondent does not consider the particular parameter to be important enough to be included for ranking. In some questions, the first interpretation seems to apply to a number of respondents and the second interpretation applies to the rest. In this study the second interpretation is considered to be more plausible. This is mainly due to the high number of the no rank occurrences for specific factors/parameters that are originally expected to have a low level of importance from insights gained from the field study.

The data were carefully prepared and examined before proceeding to the substantive analysis in particular with respect to extreme values [outliers] or the distribution of observations. Data were described numerically in means with standard deviations [SD], standard error of the mean [SEM] or range as measures of central tendency or dispersion (*Swinscow, 1983*). At the same time a histogram was produced to see the shape of the distribution and two quantities were examined, the skewness, which is a measure of asymmetry, and kurtosis, which is a measure of flatness or peakedness.

Furthermore, all data were tested for normality by using the Kolmogorov-Smirnov one sample test [K-S] (*Armitage, 1987*). This non-parametric test was used to determine how well a random sample of data fits a particular distribution [Uniform, normal, or Poisson] and it is based on comparison of the sample cumulative distribution function to the hypothesized cumulative distribution function. The K-S one sample test takes explicit account of ordering and deals with each of the observations on a separate basis and so no information is being lost because of grouping. The K-S output might show an observed significance level of 0.05, small enough to cast doubt on the assumption of normality. This revealed normally distributed variables like age, BMI and glucose and thus parametric tests were applied and skewed variables like insulin and SHBG. The latter were non-linearly transformed by using \log^{10} . It has the unique property that it is possible to get a confidence interval for the difference between the groups that relates to the original data and fortunately, taking logs is very often successful in removing skewness and also making variances more equal. This approximated a normal distribution but when this cannot be achieved the rank distribution-free [non-parametric] methods were used (*Siegel et al, 1988*).

Throughout the thesis except chapter 6, testing the null hypothesis in responses between three groups [glucose intolerance groups namely; NGT, IGT, NIDDM], or between two groups [nationality wise groups namely; Nationals and non-nationals] was carried out. To assess whether a factor had a significant effect

over all groups, the analysis of variance for a normally distributed or transformed variables or alternatively the Kruskal-Wallis one-way analysis of variance were used.

When comparing between the two groups of nationality or between any two groups of glucose intolerance categories, the unpaired t test or the non-parametric comparison of two groups, Mann-Whitney test were applied appropriately. A crosstabulation or frequency tables [contingency tables] procedure with the Chi squared statistics for large cells samples or the Fisher's exact test for small samples were also considered when comparing two or more categorical data. Descriptive data, both continuous [Mean, SD, SEM or Range] and categorical [No (Percentages)] were presented in tables and some were illustrated diagrammatically using linear or bar graphs. A p value of < 0.05 was considered statistically significant and indicated accordingly by abbreviations namely ; a ($p < 0.05$), b ($p < 0.01$), or c ($p < 0.001$).

4.5 COMPUTING METHODS :

A single-user configuration of the microcomputer systems (*IBM, 1987*) and (*Amstrad, 1989*); were used to facilitate the layout of this thesis (*Wordstar 60, 1989*). These run the Micro Soft Disk Operating Systems (*MSDOS, version 3.01*) and thereby MSDOS computer applications softwares packages. The investigator handled the data collected using the following software for: management (*dBase III Plus, 1990*) ; statistical analysis (*SPSS/PC+, 1989*) (*Brown, 1990*) graphical presentations (*Micrografx, 1988; and/or Fig P, 1990*) in addition to some of the *utility* programmes (*Davis, 1989*).

RESULTS

CHAPTER FIVE

POPULATION FEATURES, RISK FACTORS and PATHOGENESIS.

CHAPTER CONTENT :

- Summary.**
 - 5.1 Introduction.**
 - 5.2 Subjects and methods.**
 - 5.3 Results.**
 - 5.4 Discussion.**
-

SUMMARY

This chapter includes an overall description and analysis of the examined population including socioeconomic and environmental factors. The prevalences of NIDDM, IGT, hypertension and some related cardiovascular risk factors; insights into the pathogenesis of glucose intolerance and finally, comparisons based on glucose tolerance groups are shown and discussed.

CHAPTER FIVE :

POPULATION FEATURES, RISK FACTORS and PATHOGENESIS.

5.1 INTRODUCTION

Case finding for diabetes mellitus with or without the postulated causal factors had become almost a traditional activity worldwide (*Jarrett, 1986*). The OGTT is the best screening test at present (*Home, 1988*) but if glucose loading is not possible the use of a fasting plasma glucose has been recommended (*Finch et al, 1990*). Others have, however, found that both fasting blood glucose and serum fructosamine are poor screening and diagnostic tests for diabetes, and glucose loading is required (*Swai et al, 1988*). IGT cannot be diagnosed at all without glucose loading, as its definition depends on the 2-h post-load value.

A major objective of a community screening programme should be to identify individuals with \geq one diabetes risk factors (*Position- Statement, 1989*). The major risk factors or high-risk groups for NIDDM include : 1) a family history of diabetes; 2) Obesity; 3) Ethnicity; 4) age > 40 years; 5) previously identified IGT; and 6) hypertension or significant hyperlipidaemia. Identifying the magnitude and the spread of these clusters of risk factors within a community or between communities is also a common epidemiological practice. Symptoms of diabetes included excessive thirst and hunger, frequent urination and weight loss may be useful in the diagnosis but should be confirmed by glucose testing. The effect of socioeconomic and environmental factors on diabetes were known and described before [Chapter 1]. An increased frequency of hypertension in diabetes is well-known (*Jarrett et al, 1975*) and, although half of diabetic subjects might have hypertension the true association between hypertension and diabetes once all confounding factors are considered is still controversial (*Drury, 1990*). Diabetes mellitus is also characterised by a lack of insulin secretion and/or increased

cellular resistance to insulin resulting in hyperglycaemia and other metabolic disturbances (*Rossini et al, 1988*).

NIDDM is common in Saudi Arabia with a prevalence of 4.5 - 6 % in adult middle-aged males [Chapter 3]. All surveys to date were, however, carried out using a single fasting sample [either whole, capillary blood or plasma] with or without urine collection as a first screening procedure. This will underestimate the true prevalence rate and does not allow estimation of the prevalence of IGT. Moreover, no study has examined the occurrence in diabetes of hypertension , central obesity or metabolic-endocrine groups of risk factors. Earlier studies, also did not differentiate between nationals and non-nationals with respect to these aspects [Chapter 9]. Thus, the prevalence rate of diabetes in Saudi Arabia is probably much higher than the rates reported previously [Chapter 3] and this hypothesis needs to be investigated (*Ekòè, 1988*). Hence, the aims would be :

- 1). To describe socioeconomic and environmental aspects that might be related to glucose intolerance.
- 2). To find out the prevalence of glucose intolerance (NIDDM and IGT) using the WHO recommended OGTT.
- 3). To assess the prevalence of hypertension, obesity whether gross or abdominal, and some metabolic and endocrine risk factors.
- 4). To compare these aspects and risk factors in the glucose tolerance groups.

5.2 SUBJECTS and METHODS

Jeddah city is homogeneous in environment but not in lifestyle. However, the samples collected from two areas were, in general, homogenous in lifestyle and were mainly middle-class. Initially, there were 250 subjects who recorded their names and agreed to participate in the study. However, the total number who actually turned up and were examined fully was 125 giving a response rate of 50%. It should be emphasized that the results presented in this chapter were obtained from the continuous variables that were available for the whole

examined group (n=125) and from the questionnaire data (categorical) that were available only for 80% of the subjects (n=95), since the questionnaire data that were obtained from the pilot group (n=30) were basically investigatory and found to be unreliable and thus excluded. The strategy in describing the results and the discussion section will follow the following scheme. Firstly, a general description for the population features will be given. Secondly, comparisons in relation to glucose intolerance groups will be discussed.

Chapter four provided a detailed description of what will be briefly summarized here. The study was conducted over a period of 12 weeks and in two different places but under comparable conditions. Male subjects of 20 years and above were included and subjects who at the time of study had already been diagnosed as having diabetes or hypertension were excluded. A detailed description of the study was given a day or more in advance to each subject who signed an informed consent and came on appointment. To maximize attendance an official off-work sheet was provided if necessary and the weekends were utilized when appropriate. The investigation utilized the whole morning and maximum of three subjects a day were handled by the investigator. Subjects attended at 8:30 am having fasted from 11:00 pm the night before. On arrival, each subject was guided to their place to wait for approximately 15 minutes during which the study description and instructions were reiterated to them. Once overnight fasting was confirmed the participants were subjected to further examination. Anthropometric measurements were performed including weight [kg] and height [cm] to deduce BMI [kg/m^2]; and waist [cm] and hip [cm] circumferences to calculate WHR. Fasting venous samples were taken for glucose, fructosamine, cholesterol, triglycerides, uric acid, insulin, proinsulin and SHBG.

OGTTs were then performed. Beforehand, subjects ate their normal diet which contained a minimum 300g of carbohydrate. No instruction was given regarding physical activity, since the pilot study at visit two [section 4.1.2] had

indicated that the subjects were generally inactive. Smoking was not permitted and no-one drank alcohol. Glucose [75g in 300ml] was consumed over five min and the time after the first sip of solution was recorded. Post load samples at 1-h and 2-h were also taken for glucose and insulin. The waiting time between samples were occupied with filling up the set of questionnaires, blood pressure recording and health education or entertainment. Sitting blood pressure was measured twice on the same arm using an automatic sphygmomanometer. The questionnaire which was completed by the investigator by interview with each participant, was written in English [Appendix 1-5] but translated by the investigator on the same sheet into the language spoken by the participants [Arabic]. A feedback questionnaire about the study were requested from the last half of the subjects.

Blood was separated using a refrigerated centrifuge and stored at -40°C for subsequent analysis in Newcastle. There, each metabolic or endocrine variable was assayed appropriately [section 4.3]. All measurements and subsequent analyses were performed by the author.

Most cut-off points for biological and non-biological variables are often based on recommended classifications, while the minority were selected arbitrarily by the investigator. The concept of likelihood or risk of a particular parameter can be used in which the two intervals are designated high-risk and low-risk group. This approach is used for all measured parameters in this study including dietary [Chapter, 7] and physical activity [Chapter, 8] assessment.

Dichotomous grouping was carried out for some socioeconomic factors. Hence, residence duration in Saudi Arabia was defined by a cut-off point at > 15 years; high education level was considered for university or above responses and high income [social class] by earning a salary of 4500 SR [\$1200] or above per month. A family history of diabetes or hypertension was recorded when any first degree relative [either father, mother, brother or sister] had these disorders. Smoking cigarettes was considered only for analysis and as the number of ex-

smokers was small, they were counted with non-smokers.

Criteria, definitions or cut-off points for the various variables are shown in Table 5.1. Diabetes and IGT were defined according to the 1985 WHO criteria for epidemiological studies using venous plasma - that is, a fasting venous plasma concentration ≥ 7.8 mmol/l or a venous plasma glucose concentration two hours after OGTT ≥ 11.1 , or both, for diabetes; and a fasting plasma glucose concentration ≤ 7.8 mmol/l with a venous plasma glucose concentration two hours after OGTT of 7.8-10.9 mmol/l for IGT. Body mass index was calculated as weight/height² (kg/m²). Overweight was defined as a BMI ≥ 27 and obesity as a BMI of ≥ 30 . WHR greater than one which divided the number of subjects into two halves is considered high. Since, all subjects were found above the cut-off points of 0.93 which was suggested by Larsson et al (1984) for Swedish men, or 0.92 which was suggested by Jones et al (1986) for British men.

Hypertension was defined based on WHO criteria (WHO, 1978) - that is, systolic blood pressure ≥ 160 mmHg or diastolic pressure ≥ 95 mmHg, or both. Mild hypercholesterolaemia was defined as a serum total cholesterol concentration of ≥ 5.2 mmol/l. Hypercholesterolaemia, was defined as a serum total cholesterol concentration ≥ 6.5 mmol/l. Hypertriglyceridaemia was defined as a serum triglyceride concentration ≥ 1.7 mmol/l. Hyperuricaemia was defined as a serum uric acid concentration ≥ 0.42 mmol/l.

Data were handled with dBase+III and analysed by means of SPSSC+, and was based on glucose tolerance groups (discrete explanatory variable). The data have also tested for normality using K-S test. Differences between the three groups were examined by means of ANOVA for normally distributed variables [age, BMI] or by means of the Kruskal-Wallis test. Similarly, the comparison between any two groups were by unpaired t test or Mann-Whitney test. A p value <0.05 was taken to be significant.

5.3 RESULTS

Total study group:.

An endogenous place of origin was found in 56 %, unlike the duration of residence of > 15 years in Saudi Arabia which was found in 43 % of the total study group. The majority of subjects [92%] had their basic primary school or above while 1% were illiterate. The majority of subjects are working [96%] either with Government [47%], a private firm [42%] or were self employed [7%] and none were unemployed. Only 1% were retired and 3% were students. The monthly income was used as an index for social class and an arbitrarily income of 4500 RS (\$1200) is used as a cut-off point. Thus, "low" social class subjects (56%) slightly exceeded "high" social class subjects (44%). Marriage was found in 93% and consanguinity with wife is shown in 31 %. This population had 398 children of whom 5% had died, and none of their children were known to have diabetes mellitus.

Social habits covered different activities. Smoking presently or in the past was found for cigarettes [46%], shisha [Hookah, Hubble-bubble pipe] [34%], both [8%], cigars [2%] and none were pipe smokers. Regularity in smoking was found for cigarettes (77%) vs shisha (63%). Smoking of more than 10 cigarettes a day was found in 59% and 55% smoked for ≥ 10 yrs. Smoking of shisha 5 times per week was found in 47% and smoking for ≥ 10 years was found in 37%. Shisha smokers usually used 1-4 boxes per week [weight 0.5 to 1 kg per box of tunbac (old fermented fruits)]. 41% never smoked either cigarettes or shisha. Past and short experiences of drinking alcohol or eating Qat [Plant from Yemen] were also found in 17% and 5% respectively. The experience in drinking alcohol extended sometimes between 1 to 22 years whilst for Qat the most recent experience was 1 year prior to the questionnaire. All Qat-eaters are from Yemen.

The historical background revealed several aspects. At least a fifth of the subjects gave a history of one or more of the classical symptoms of diabetes. Excessive urination was found in 27%, thirst in 18%, hunger in 20%, unchanged

weight during the preceding three months in 58% and impotence in 8%. Although known subjects with diabetes or hypertension were excluded from the study, a few subjects still responded positively and had been told by a doctor, at one stage of their life, that they had diabetes (7%), high blood pressure (7%) and high lipids (2%). Almost a quarter (23%) of them gave a history of receiving off-counter medicines for short-term illnesses which they were asked to stop on the day of investigation. They gave, also, a history of having pain or discomfort, pressure or heaviness in their chest (7%), had a history of severe pain across the front of their chest lasting for half an hour or more (2%), had a history of having pain in either leg on walking (24%), while none had weakness or loss of strength in an arm or leg lasting for 24 hours.

A family history of diabetes was found in 24% of fathers, 25% in mothers, , and both parents in 6.3% and in both parents plus either brother or sister in [1%]. A history of diabetes in any first-degree relative was found in 48.4%. Similarly, family history of hypertension was found in fathers [16%], mothers in 20% and in 2% in both parents. A history of hypertension in any first-degree relative was found in 39%. A family history of both diabetes and hypertension was found in 23%. There were a total number of 593 siblings of whom 20% were already dead; 18% gave a history of diabetes and 11% hypertension.

The prevalence rates of glucose intolerance and risk factors in the whole population are shown in Table 5.1. Glucose intolerance according to WHO criteria was found in 41% with 14% diabetes and 27% IGT. Also shown, are high rates of gross obesity [29%], abdominal obesity [50%], hypertension [5%], mild hypercholesterolaemia [29%], hypertriglyceridaemia [27%], hyperuricaemia [40%], first-degree history of diabetes [48.4%] and smoking in [43%].

Glucose tolerance groups :

The classification of subjects according to glucose tolerance groups and compared by two criteria [WHO and NIDDM] is shown in Table 5.2. Those classified as NGT and NIDDM showed no differences. The rates for IGT by

WHO was double the rate of those found by NDDG, but with the creation of 14 % in a non-diagnostic group in the latter criteria.

Age structure by glucose tolerance groups is shown in Table 5.3. A normally distributed age structure is clearly observed. Half of the subjects [47%] were between 35-44 years. The prevalence of NIDDM increased with age and those above 35 years had double rates than those before 35 years.

Data related to glucose tolerance groups are presented in tables [5.4 - 5.8]. The general socio-economic characteristics of these subjects by glucose tolerance groups showed no significant differences in various aspects including education and social class [income].

The glucose tolerance status in relation to risk factors [Table 5.5] showed that subjects with NIDDM and IGT had significant [$p < 0.0001$] and higher rates of family history of diabetes only compared to NGT. Smoking was higher in NIDDM, lower in IGT, but that was not significant. Also, subjects with NIDDM had a two-fold increased rate, but not significant because of small numbers, of obesity and a two-fold increase in abdominal obesity whereas IGT subjects had intermediate values and WHR was only significant [$p=0.03$]. The rates of hypercholesterolaemia [≥ 6.5 mmol/l] in NIDDM and IGT subjects were the same and three times higher than in people with NGT, and there was a three-fold increase in hypertriglyceridaemia in NIDDM whereas IGT subjects had intermediate values [≥ 1.7 mmol/l] [$p=0.02$]. However, there was no significant relationship between hypertension and glucose tolerance status, nor with hyperuricaemia.

General and clinical characteristics by glucose tolerance groups are shown in Table [5.6]. Age is comparable, although it tended to be higher, but not significantly as so the glucose intolerance worsens. Also, subjects with IGT and NIDDM were slightly shorter than normal [ns]. BMI was similar for both IGT and NIDDM [IGT vs NGT, $p < 0.05$]. WHR was significantly [$p < 0.01$] higher in NIDDM versus NGT. Systolic and diastolic blood pressure were slightly higher in

the glucose intolerance groups compared to those with NGT, but these differences were not significant.

Glucose, insulin, fructosamine values and β -cell function and insulin resistance as assessed by the HOMA model were all shown in Table 5.7. Obviously and not surprisingly, the glucose AUC was significantly higher in subjects with NIDDM, intermediate in IGT and lowest in NGT. The same trends were also found for fructosamine. Also, fasting insulin was higher in NIDDM, intermediate in IGT and lowest in NGT, but this was not significant. However, the insulin AUC was significantly higher in IGT vs NGT [$p = 0.00001$] and NIDDM [$p = 0.006$] and both NGT and NIDDM had comparable values. HOMA assessment of β -cell function showed that subjects with IGT had significantly higher values than NGT [$p < 0.05$] and NIDDM [$p < 0.05$] subjects, and those with NIDDM had the lowest values as compared to NGT [$p < 0.05$] and IGT [$p < 0.05$] subjects. Insulin resistance evaluated also by HOMA revealed higher values for NIDDM [$p < 0.01$] and intermediate for IGT [$p < 0.05$] when compared to those with NGT.

The metabolic-endocrine group of risk factors including cholesterol, triglyceride, uric acid, fasting insulin and proinsulin, proinsulin:insulin molar ratio and SHBG are shown in Table 5.8. Fasting insulin was discussed earlier. Proinsulin values were significantly higher in NIDDM, intermediate in IGT and lowest in those with NGT, [NIDDM vs IGT, $p = 0.001$; NIDDM vs NGT, $p = 0.00001$; IGT vs NGT, $p = 0.003$]. The proinsulin:insulin molar ratio differed significantly in subjects with NIDDM compared with those with IGT [$p 0.02$] and with NGT [$p = 0.002$]. SHBG values were comparable and not different between the three glucose tolerance groups.

5.4 DISCUSSION

A cross-sectional epidemiological study provides estimates of the prevalence of diabetes or other diseases together with information on the general characteristics of the studied population at the time when the study is conducted

(West, 1978). A high prevalence of diabetes mellitus in Saudi Arabia have been recorded in few studies (Fatani et al, 1987; Bacchus et al, 1982; see Chapter 3). Although, their samples were large, these studies lack the initial screening using an OGTT which allows identification of subjects with IGT. These studies were, also, deficient in determining several confounding factors known to contribute to the increased prevalence of diabetes such as socio-economic, environmental or physical measurements. This study is the first which has used the OGTT in initial screening and reported cases of IGT. It was also, originally planned to examine several anthropometric and metabolic-endocrine group of risk factors and has demonstrated for the first time several features which were not reported before in Saudi Arabia, although mentioned in the literature worldwide.

High rates of both NIDDM [14%] and IGT [27%] were shown in this study compared to previous prevalence estimate for diabetes of 5%. These prevalence might be too high due, perhaps, to selection bias, yet the figures are alarming. Similarly, we have reported risk factors prevalence not reported before in conjunction with diabetes in Saudi Arabia, such as smoking [43%], gross obesity [29%], abdominal obesity [50%], hypertension [5%] and lipids [Cholesterol, 7%; Triglyceride, 14%]. This has emphasized the importance of screening such factors in any community programme. Both genetic and environmental factors are of importance in the aetiology of diabetes mellitus (West, 1978) and can contribute to this high prevalence.

Prevalence differs with gender. NIDDM is commoner in females than in males in the USA, whereas the reverse is true in England (Rifkin et al, 1990). In addition, urban-rural differences are known but none of these aspects were compared in this study and are obvious topics for future work. Only males were studied which accords with some major studies carried out in western societies (Jarrett et al, 1979; Keen et al, 1982).

The prevalence of NIDDM, in this study, increased with age a finding consistent with previous reports (Davidson, 1979; Defronzo, 1981) and act as

independent determinant of glucose tolerance (*Shimokata et al, 1991*). Also, there was an increased prevalence of NIDDM and IGT in those who had a positive family history of diabetes and this may, at least, reflect that many of the subjects were aware about the disease in their family.

The WHO and NDDG recommendations have been the most widely used diagnostic criteria since 1980. They were similar since, 1) both permit the diagnosis of diabetes in asymptomatic individuals with unequivocally elevated plasma glucose concentrations and, 2) both recommend that in asymptomatic individuals, a 2-h 75 g OGTT be performed to establish a diagnosis of diabetes or IGT. They also differ in two major aspects which has lead to discrepancies in classification of individuals based on OGTT results. 1) To class an OGTT as normal, WHO does not stipulate an upper limit of normal, and implies that FBG may not be ≥ 6.7 mmol/l, since such levels constitute diabetes, whereas NDDG requires a FBG < 6.4 mmol/l. 2) To classify an individual using WHO criteria, mid-test glucose values are not considered, and need not be obtained. Moreover, NDDG recommends 5 PG values, whereas WHO requires only two. Both, however, require fasting and 2-hour post load glucose values, but NDDG also recommends that glucose values at mid-test levels [$\frac{1}{2}$ hr, 1 hr or $1 \frac{1}{2}$ hr post load] be used in order to determine an individual's diagnostic class. If the glucose level of one of these mid-test samples does not meet certain specific criteria, the OGTT is considered "Non-diagnostic" in the NDDG classification. Thus in this study, it is inappropriate to use NDDG criteria since it gave 14 % as non-diagnostic, although the rate of IGT reduced to half.

The 2-h value after 75 g OGTT may be used alone or with the fasting value for epidemiological or population screening purposes. The fasting value alone is considered less reliable since true fasting cannot be assured and spurious diagnosis of diabetes may more readily occur.

Fructosamine, along with glycated haemoglobin, is a poor screening and diagnostic test for diabetes and IGT (*Swai et al, 1988*). In this study the diagnosis

was not based on fructosamine but the differences that were found in the glucose tolerance groups agreed with the report which showed that fructosamine seems unsuitable for the diagnosis of mild abnormalities in glucose tolerance (Guillausseau *et al*, 1990).

Diabetes has been suggested to be a disease of the rich, and rich people living in poor countries are known to have a higher prevalence than the poor of these countries (West, 1978). Although, the prevalence for the whole population agrees with this concept, the social class as indicated by income among other socio-economic and environmental factors did not suggest an important role in determining the prevalence of IGT and NIDDM. However, family history of diabetes is a major known determinant for high rates of glucose tolerance as evidenced again in this study where NIDDM and IGT were found more frequent in those with a family history of diabetes. Smoking habits, unlike alcohol was a major problem in this community. Rarity of diabetes among children of this population might be an indirect estimate and indicator that type I diabetes was rare.

The overall prevalence of hypertension in a community will vary according to the age range of the population included in the survey and the demographic characteristics of the community studied. This is the first to report on hypertension in a community screening which was shown to be high but the association of hypertension with glucose intolerance was not clearly found.

Several prospective studies have supported the definition of the category of IGT, intermediate between normality and diabetes [Chapter, 2]. As an intermediate category of glucose tolerance, it could be expected that people in the IGT group should differ from both normal and diabetic subjects in some respects, if this category is a true entity. This study has examined certain variables comparing the IGT group with both normals and NIDDM. The results indicate that means or proportions for some of the variables are indeed intermediate between those for normal and NIDDM groups and in some showed significance.

As IGT is defined using plasma glucose concentration, therefore it is expected that the mean glucose levels between three groups [NGT, IGT and NIDDM] will differ. As high plasma glucose concentration, gross obesity, abdominal obesity, serum cholesterol and triglyceride concentrations, hyperinsulinaemia and hyperproinsulinaemia are risk factors for atherosclerosis, the observed differences in the means and prevalence of these variables could help to explain why IGT subjects are at a higher risk for CVD than those with NGT.

Generalised and abdominal obesity have previously been found to be strong risk factors for the development of diabetes (*Gaal et al, 1988*). Obesity alone is said to carry a 3.2 fold diabetic risk but when the fat distribution predominated in the upper body segment this risk increased to 10.3 (*Emara et al, 1988*). More importantly, as shown in this study, abdominal localization of adipose tissue, irrespective of the degree of obesity was associated with NIDDM or glucose intolerance (*Bjorntorp, 1991*).

This study reported low rates of hypercholesterolaemia compared with a previous report from Riyadh of larger sample [$n=8291$] (*Inam et al, 1991*). The rates at ≥ 5.2 mmol/l were 29% vs 38% and 7.2% vs 11% at ≥ 6.5 mmol/l. Cholesterol values tended to be higher in the glucose intolerance groups as shown in previous reports. Hypertriglyceridaemia is a prominent feature in this community and not surprisingly was significantly higher in those with NIDDM. In addition to hypertriglyceridaemia, upper-body obesity, glucose intolerance and hypertension forms in this community what is called "the deadly quartet" (*Kaplan, 1989*).

Uric acid levels, in the 'pre-diabetic state', are often high. Later the values come down to normal or even below the control values once clinical diabetes supervenes (*Herman et al, 1982*). In addition, hyperuricaemia may be part of a constellation of abnormalities found in the pre-diabetic state namely an obesity-hypertension-hypercholesterolaemia-hyperuricaemia syndrome (*Alberti et al, 1986*). My study demonstrated that hyperuricaemia is part of the risk factor constellation but uric acid was unchanged in those with NIDDM or IGT.

One of the pathophysiological schemes of classifying insulin resistance include circulating pre-receptor antagonists of insulin action and one of these is hyperandrogenaemia. Low SHBG values are a sign of hyperandrogenicity and can predict the development of NIDDM (*Lindstedt et al, 1991*). However in my study, subjects with NIDDM did not have low SHBG as compared with those with NGT. Thus, SHBG would not be considered as a predictive factor for NIDDM in men as shown here and appears therefore to play no role in the high rates of diabetes and obesity seen in this high risk population.

HOMA model assessment revealed that NIDDM had hypofunction of the β -cell which was reduced by 6%, in contrast to the 13% hyperfunction in those with IGT. Similarly, insulin resistance was a prominent feature in both NIDDM where it was severe and IGT which was mild. It seems that subjects with IGT characterized by mild degree of insulin resistance and hyperfunction of β -cell, but once β -cell function deteriorates and insulin resistance becomes the prominent feature, hyperglycaemia and NIDDM develop. The findings of proinsulin support that found in Pima Indians with NIDDM who have a disproportionate elevation of proinsulin consistent with the hypothesis that β -cell dysfunction associated with hyperglycaemia leads to the release of proinsulin-rich immature granules (*Saad et al, 1990*).

In conclusion, this population of urban men showed high rates of glucose intolerance and CVD risk factors including smoking; obesity, gross and abdominal; hypertension and hyperlipidaemia. Screening with proper intervention for diabetes and IGT is recommended in Saudi Arabia using WHO criteria, providing that the high rates described here are confirmed in a full study. Other cardiovascular risk factors such as hypertension, obesity and lipids should not be ignored in the screening programmes with special consideration for abdominal adiposity. Finally, environmental factors presumably have a role in the high prevalence of glucose intolerance found in these populations in Saudi Arabia. These will be discussed in the future chapters.

It must be emphasised, however, that this is a pilot study and bias cannot be excluded and therefore, a full study will be of great interest. Moreover, with the limitations of a cross-sectional study, there was no possibility of discriminating between the variables which are predictive of subsequent diabetes and those which are not. Hence, equally interesting would be a prospective longitudinal study on the same group [n=125] sometime during late 1993 and early 1994 as a three year follow-up study.

Table 5.1
Prevalence of glucose intolerance and risk factors in the whole population [n=125]

	Criteria/ Definition/ Cut-off point.	n	%
NIDDM	(WHO, 1980)	17	13.6
IGT	(WHO, 1980)	34	27.2
All glucose intolerance		51	40.8
Overweight	(≥ 27)	68	54
Obesity	(≥ 30)	36	28.8
High WHR	(> 1.0)	63	50
Hypertension	(WHO, 1978)		
-Definite	(160/95)	6	4.8
-Borderline	(140/90)	12	10
Hypercholesterolaemia	(≥ 6.5)	9	7.2
Hypercholesterolaemia/ mild	(≥ 5.2)	36	29
Hypertriglyceridaemia	(≥ 2.2)	18	14.4
Hypertriglyceridaemia/ mild	(≥ 1.7)	34	27
Hyperuricaemia	(≥ 4.2)	50	40
Family history of diabetes	any first-degree relative	46	48.4
Smoking	Cigarettes only	45	43
Nationality	ID identity [n=125]	76	61
	[n=95]	48	51

Table 5.2
Classification of glucose tolerance groups [WHO vs NDDG].

CRITERIA		NGT	IGT	NIDDM	Non- -diagnostic	Total
WHO	n (%)	74 (59)	34 (27)	17 (14)	- -	125 (100)
NDDG	n (%)	74 (59)	16 (13)	17** (14)	18 (14)	125 (100)

All values for classification are based on venous plasma concentration.

**The National Diabetes Date Group (NDDG) requires an intermediate time point of ≥ 11.1 mmol (2.0 g/l) for these categories.

Table 5.3 :
Age structure by glucose tolerance groups no (%)

Age Group (years)	n	%	Glucose tolerance groups (%)		
			NGT	IGT	NIDDM
<25	4	3	75	25	0
25 - 34	38	31	74	18	8
35 - 44	59	47	53	30	17
45 - 54	21	17	52	33	15
≥ 55	3	2	33	33	33
All	125	100			

Table 5.4
Environmental and socio-economic by glucose tolerance groups (n = 95).

	NGT	IGT	NIDDM
n	55	25	15
(%)	(58)	(26)	(16)
Nationality:			
Saudis	45	58	62
Non-Saudis	55	42	38
Place of origin:			
Saudi Arabia	51	61	63
Elsewhere (Mediterranean Indian, South East Asian and Africa)	49	39	37
Residence duration in Saudi Arabia :			
up to 15 yrs	60	42	69
> 15 yrs	40	58	31
Education level:			
Up to secondary school	61	65	44
University or above	39	35	56
Income (SR):			
Up to 4500	63	38	56
> 4500	37	62	44
Symptoms of CVD:			
The response to the questions:			
"Have you ever had.... ?"			
-Pain or discomfort in chest	3	15	6
-Severe pain across the front of chest lasting for half an hour or more	2	4	0
-Pain in either leg on walking	25	12	38
-Weakness or loss of strength in an arm or leg lasting for 24 hrs	0	0	0

Table 5.5
Risk factors prevalences by glucose tolerance status.

	Glucose tolerance groups (%)			<i>P</i> value
	NGT	IGT	NIDDM	
Family history of diabetes	33	84	47	0.0001
Smoking	46	37	53	ns
Obesity [≥ 30]	26	35	47	ns
WHR [> 1]	42	56	77	0.03
Hypertension [160/95 mmHg]	7	3	0	ns
Hypercholesterolaemia [≥ 6.5 mmol/l]	4	12	12	ns
Hypercholesterolaemia [≥ 5.2 mmol/l]	27	29	35	ns
Hypertriglyceridaemia [≥ 2.2 mmol/l]	11	15	29	ns
Hypertriglyceridaemia [≥ 1.7 mmol/l]	20	29	53	0.02
Hyperuricaemia [≥ 4.2 mmol/l]	39	38	47	ns

Table 5.6 :
Clinical characteristics by glucose tolerance groups in mean \pm SEM or range[n=125].

	NGT	IGT	NIDDM
n (%)	74 (59)	34 (27)	17 (14)
Age [yrs]	37 \pm 7 (20-55)	39 \pm 8 (20-60)	41 \pm 9 (30-64)
Weight [kg]	78 \pm 15	83 \pm 13	82 \pm 15
Height [m]	1.70 \pm 0.1	1.69 \pm 0.1	1.68 \pm 0.1
¹ BMI [W/H ²]	27 \pm 5	29 \pm 4	29 \pm 5
Waist [cm]	95.3 \pm 11.5	99.5 \pm 9.6	101.5 \pm 11.7
Hip [cm]	95.1 \pm 11.0	98.5 \pm 9.1	99.2 \pm 11.5
² WHR	1.00 \pm 0.02	1.01 \pm 0.02	1.02 \pm 0.04
Systolic BP (mmHg)	119 \pm 16	120 \pm 12	120 \pm 11
Diastolic BP (mmHg)	74 \pm 11	76 \pm 10	77 \pm 10

1, NGT vs IGT, p=0.03

2, NGT vs NIDDM, p=0.01

Table 5.7 :
Glucose and insulin during OGTT (75g); fructosamine and the calculated area under the response curve [AUC] for glucose and insulin in mean \pm SEM [n=125].

	NGT	IGT	NIDDM
Glucose mmol/l :			
Fasting	5.3 \pm 0.1	5.5 \pm 0.1	8.6 \pm 0.8
1-h	8.8 \pm 0.3	11.3 \pm 0.4	16.1 \pm 1.2
2-h	5.8 \pm 0.2	8.9 \pm 0.2	16.5 \pm 1.4
Glucose AUC mmol l ⁻¹ h	13.3 \pm 0.2	17.2 \pm 0.4	27.5 \pm 2.2
^{1,2,3}Fructosamine mmol/l			
	2.4 \pm 0.03	2.5 \pm 0.05	2.8 \pm 0.1
Insulin mU/l.			
Fasting	13.3 \pm 1.4	16.9 \pm 1.2	24.3 \pm 3.8
1-h	111.2 \pm 5.4	135.2 \pm 8.2	76.2 \pm 15.1
2-h	76.6 \pm 5.3	151.6 \pm 12.1	96.9 \pm 18.6
^{4,5,6} Insulin AUC mU l ⁻¹ h	134.1 \pm 6.5	202.4 \pm 13.1	131.6 \pm 24.1
HOMA model assessment of :			
^{7,8,9} β -cell function	157 \pm 19	179 \pm 16	148 \pm 35
^{10,11,12} Insulin resistance	3.2 \pm 0.3	4.2 \pm 0.3	8.4 \pm 1.1

1, NGT vs NIDDM, p=0.001
3, IGT vs NIDDM, p=0.03

2, NGT vs IGT, p=0.06

4, NGT vs NIDDM, p=ns
6, IGT vs NIDDM, p=0.006

5, NGT vs IGT, p=0.00001

7, NGT vs NIDDM, p=ns
9, IGT vs NIDDM, p=ns

8, NGT vs IGT, p=0.02

10, NGT vs NIDDM, p=0.00001
12, IGT vs NIDDM, p=0.0005

11, NGT vs IGT, p=0.0004

Table 5.8 :
Metabolic-endocrine group of risk factors in mean \pm SEM [n=125].

	NGT	IGT	NIDDM
Cholesterol [mmol/l]	4.7 \pm 0.1	4.9 \pm 0.2	4.9 \pm 0.3
¹ Triglyceride [mmol/l]	1.3 \pm 0.1	1.4 \pm 0.1	1.9 \pm 0.2
Uric acid [mmol/l]	3.8 \pm 0.1	4.0 \pm 0.2	4.0 \pm 0.3
^{2,3} Fasting insulin (pmol/l)	79.7 \pm 8.2	101.2 \pm 6.9	146.5 \pm 22.9
^{4,5,6} Proinsulin (pmol/l)	8.6 \pm 0.6	14.7 \pm 1.6	27.0 \pm 3.3
^{7,8,9} Proinsulin/ insulin molar ratio	0.14 \pm 0.01	0.15 \pm 0.01	0.22 \pm 0.03
SHBG (nmol/l)	35.2 \pm 1.9	35.6 \pm 4.9	34.4 \pm 5.5

1, NIDDM vs IGT and NGT, p=0.005

2, NGT vs NIDDM, p=0.0003

3, NGT vs IGT, p=0.0005

4, NGT vs NIDDM, p=0.00001

5, NGT vs IGT, p=0.003

6, IGT vs NIDDM, p=0.001

7, NGT vs NIDDM, p=0.002

8, NGT vs IGT, p=ns

9, IGT vs NIDDM, p=0.02

RESULTS

CHAPTER SIX

OGTT REPRODUCIBILITY

CHAPTER CONTENT :

- Summary.
 - 6.1 Introduction.
 - 6.2 Subjects and methods.
 - 6.3 Results.
 - 6.4 Discussion.
-

SUMMARY

The reliability of the OGTT was examined in 35 urban middle-aged male subjects in Saudi Arabia with varying degrees of glucose intolerance. Subjects were recruited as part of a screening programme for diabetes, IGT and cardiovascular risk factors performed during the summer of 1989 at Jeddah. Two identical OGTTs of 75 g anhydrous glucose in 300 ml water were performed within a period of 8 weeks and interpreted according to WHO 1985 criteria. Glucose and insulin were measured fasting and at 1 and 2 h. The first test suggested that eight of the 35 had diabetes and 12 Impaired Glucose Tolerance [IGT]. On repeat testing three with IGT became 'normal', and two with diabetes became IGT, with one 'worsening' to IGT. For the whole group, glucose AUC (Mean \pm SEM) was lower on retesting (24.0 ± 2.0 mmol/l/h, $p < 0.05$), a trend evident in each subgroup. Similar changes were found in insulin AUC (Mean \pm SEM) (174 ± 17 mU/l/h, $p < 0.05$). The fasting insulin:glucose ratio (Mean \pm SEM) were consistently lower (2.0 ± 0.2 , $p < 0.001$) on repeat testing. Our results suggest that in this community the standard OGTT [75 g] may have poor reproducibility, and that labelling subjects on the basis of a single OGTT during a screening program or in a clinical sitting should be carefully interpreted.

6.1 INTRODUCTION

It is known that the OGTT is a test with poor reproducibility with a coefficient variation of the 2-h blood glucose concentration of up to 40 % (*MacDonald et al, 1965; Kosaka et al, 1966*). Poor reproducibility of the OGTT for the diagnosis of IGT has also been described, with only 56 % of subjects with IGT at the first test showing glucose intolerance on a second OGTT (*Riccardi et al, 1985*). More recently a study in which the OGTT was repeated within a week suggested that a single 2-h postload measurement may be inadequate for the accurate assessment of IGT and diabetes prevalence, particularly in those unused to blood sampling (*Swai et al, 1991*).

Similar information concerning the intra-individual variability of glucose and insulin responses to OGTT is not available for individuals living in Saudi Arabia. Therefore, we have measured the plasma glucose and insulin responses during two identical OGTT's in a cohort of male individuals with different degrees of glucose intolerance during a screening programme.

6.2 SUBJECTS AND METHODS

The study group consisted of 35 adult men with an age range of 20-65 yr. The first OGTT was performed during a screening programme for detection of glucose intolerance and CVD risk factors during the summer of 1989 at Jeddah, Saudi Arabia, while the second was carried out 1-60 days later [mean 13 days]. All subjects were approached and invited to participate in repeat testing without informing them of the initial diagnosis.

The studies were conducted at the recently constructed diabetes and hypertension centre by permission of the Ministry of Health [MOH]. Subjects were asked to present themselves at 08:30 h having fasted from 23:00 h the

previous evening. They were asked to follow their normal diet which contained a minimum of 300 g of carbohydrate. Subjects were generally inactive, none had any known disease, or were ingesting any drug, and none drank alcohol. Height was measured without shoes, and weight in light clothes was measured using a beam balance. Two identical OGTT's were performed by the administration of 75 g anhydrous glucose as an orange-flavoured dextrose solution in a volume of 300 ml, consumed over 4-5 min. Venous blood was drawn for measurement of plasma glucose and insulin before (fasting), 60, and 120 min after taking the glucose load.

All samples for plasma glucose, serum insulin and serum fructosamine estimation were deep frozen (-40°) and subsequently assayed in Newcastle upon Tyne. Assays for samples from the two OGTTs samples were performed under identical conditions. Plasma glucose was measured by a Yellow Springs Instrument analyser (Yellow Springs, OH, USA) using a glucose oxidase method (*Chua et al, 1978*) with an intr-assay CV of 1.1 %. Plasma insulin was determined by a radioimmunoassay technique (*Soeldner and Slone, 1965*) with intra-assay CV of 4.2 % and inter-assay CV of 4.8 %, and serum fructosamine using a centrifugal analyser (*Hindle et al, 1985*) with a CV of 1.5 % .

Area under the curve (AUC) was calculated by the trapezoidal rule (*Matthews et al, 1990; Le Floch et al, 1990*) . All comparisons were based on the diagnostic outcome of the first test judged according to a recommended criteria for epidemiological screening (*WHO, 1985*). Thus, diabetes was defined as plasma glucose at 2 h \geq 11.1 mmol/l, and IGT as fasting $<$ 7.8 mmol/l and 2-h between 7.8 - 10.9 mmol/l. Results were expressed as mean \pm SD or range, and were analysed using SPSSPC+ packages (*Norusis, 1986*) with Student's paired t test for the whole group and for the subgroups separately.

6.3 RESULTS

Thirty five subjects [28 %] of those attending for a first OGTT [n=125] agreed to come again for the second OGTT. Subject characteristics are given in Table 6.1. At the first test 15 of the 35 subjects [43%] had 'normal' glucose

tolerance, 12 [34%] had Impaired Glucose Tolerance and 8 [23%] had diabetes. Fructosamine levels were unchanged between the first and the repeat test.

The changes that occurred in glucose tolerance on repeat testing are shown in Table 6.2. Although the total prevalence of IGT remained the same [34 %] on the first and the second OGTT, three subjects [25 %] returned to normal glucose tolerance but were replaced with two previously classified as diabetic and one previously 'normal'. No 'normal' subject was reclassified as diabetic. Thus, the apparent prevalence of diabetes fell to 18 %, and all glucose intolerance to 52%. Glucose area under curve (mean \pm SEM) was lower on retesting for the whole group (24.0 ± 2.0 mmol/l/h, $p < 0.05$), a trend evident in each subgroup (Table 6.3). Similar changes were found for 1-h plasma glucose concentration (Mean \pm SEM) (9.7 ± 1.0 , $p < 0.05$), although differences were not significantly different at fasting or at 2-h (Table 6.3), and also in insulin area under the curve (mean \pm SEM) [174 ± 17 , $p < 0.05$] and for fasting insulin concentration [11.4 ± 1.1 , $p < 0.001$] (Table 6.3).

The fasting insulin:glucose ratio differed between tests [$p < 0.001$], and between IGT and diabetes subgroups [$p < 0.05$] (Table 6.4). Only the fasting insulin:glucose ratio was consistently lower on repeat testing (Table 4).

6.4 DISCUSSION

The reproducibility of a measurement is one criterion for judging the value of a test. If test-retest measurements performed within a short time relative to the evolution of the disease vary appreciably, the reliability of the test in individual subjects is reduced. Reproducibility inevitably affects the sensitivity and specificity of the test, and interpretation of OGTT's should take this into account (*Rushforth et al, 1975*).

Prevalence estimates of diabetes and IGT within communities are now quoted on the basis of a single OGTT after a 75 g glucose load. However, a number of studies have shown an up to 50 % variability in blood glucose values within individuals after a glucose load (*Home P, 1988*). Therefore, a single 2 h

glucose may result in the misclassification of individuals. For this reason, WHO and others have recommended that, for clinical purposes and during screening programs when the primary purpose is to identify asymptomatic diabetic individuals, no one should be labeled as having diabetes on the basis of a single abnormal blood glucose value. However, in epidemiological studies where the primary purpose is assessment of the prevalence of diabetes and IGT within communities, WHO considers a single elevated 2 h blood glucose sufficient for the diagnosis of diabetes (*WHO, 1985*).

Misclassification of a few individuals may occur, but on repeat testing, a similar degree of misclassification should occur, and an overall prevalence estimates should be unchanged. In the present study, although the total prevalence estimate of IGT remained the same on repeat testing, 25 % of people were misclassified with diabetes on the first test compared with the second test, although numbers were very small. Hence, the study suggests that it is incorrect to assume that if an entire population were to be rescreened within a short interval the results of the second survey would be similar. A more marked change has been reported for a Tanzanian population (*Swai et al, 1991*).

The downward trend in plasma glucose values raises several queries. The reduction in plasma glucose values might reflect methodological problems or changes in the circumstances of the second test. However, to minimize bias, the methods were carefully standardized and all the field and laboratory work were performed by a single investigator. In addition, retesting of subjects was carried out while the screening programme was proceeding so that the circumstances of the repeat OGTT were similar to those of the first OGTT. Therefore, technical reasons are unlikely to account for the downward trend.

Another possibility could be changes in diet or life-style between the first and second tests. Prolonged intervals between tests make comparisons with the initial test difficult because many factors could in the meantime have changed an individual's glucose tolerance. In the present study, repeat testing occurred on

average within 2 weeks to avoid changes in the life-style of the subjects. Moreover, the subjects were also unaware of the diagnosis from the first OGTT. Thus, it is unlikely that any consistent bias was introduced by differences in preparation between the first and second tests or by the possible action that might have taken place if they were aware of the abnormality. In addition fructosamine was unaltered (and indeed tended to rise) suggesting no consistent lifestyle changes. It is more likely that ill-defined and nonquantifiable physiological and psychological factors might influence gastrointestinal motility, glucose absorption, and the release of gut factors, which have a major impact on insulin secretion during the OGTT (*Ganda et al, 1978*). Anxiety could well have the most important factor in this study, since most of the study participants were unused to blood sampling.

This is the first study of this kind in this community and thus the results cannot be compared with others, although the blood sampling in rural Tanzanians could be considered similar. If our observations are confirmed, they raise several questions. How accurately does reported prevalence of diabetes and IGT in this community or in different communities, usually based on a single OGTT, reflect the true prevalence of glucose intolerance? Doubts must also exist as to the precision of diabetes prevalence estimates based on a single OGTT in field studies. Hence, in the present study, the prevalence estimate of diabetes in the retested sample were 25 % lower than the estimate of the first test, although the estimates for IGT remained the same. There has been a general trend in recent years to broaden the range of values considered normal or borderline. People with IGT form an identifiable risk group, but, it is not possible to identify people at risk of developing diabetes with acceptable specificity.

The plasma glucose differences between the two tests were not great for each glucose tolerance category, but intraindividual OGTT differences in 1-h and 2-h levels as great as 2.2 mmol/l of glucose are not uncommon, and differences greater than 1.1 mmol/l almost usual (*West et al, 1964*). These data confirm

previous reports (*McDonald et al, 1965; Kosaka et al, 1966; Harding et al, 1973; Olefsky et al, 1974; Riccardi, 1985; Le Floch et al, 1991*) which suggested that the plasma glucose response to serial OGTT's is not very reproducible within any individual.

It was suggested that part of the variation in response is attributable to a considerable variation in levels of insulin secretion when duplicate tests are performed (*Olefsky et al, 1974*). In the present study, the results also demonstrate that the plasma insulin response varies considerably when an OGTT is performed twice on the same individual within 60 days. Indeed, the plasma insulin response between OGTT's was even more variable than the plasma glucose response. Because of the known influences of the autonomic nervous system on insulin secretion (*Porte et al, 1973*), one might anticipate that a subject's emotional reaction to his first OGTT will be different from his reaction to a second OGTT, and this could produce a consistent difference in the insulin response to the two tests.

Certain straightforward conclusions follow from these results. The lack of reproducibility of the glucose response to the OGTT emphasizes the danger of diagnosing diabetes mellitus and IGT on the basis of a single abnormal OGTT, as discussed in detail by others (*MacDonald et al, 1965 ; Kosaka et al, 1966*). A further conclusion concerns the insulin : glucose ratio. In an effort to define the relationship between insulin response and diabetes, several authors have proposed the concept of an "insulinogenic index" (*Seltzer et al, 1967 ; Perley et al, 1966*) in which the insulin response during an OGTT is related to the coexisting glucose response. This is most commonly done by dividing the two responses and determining the I/G ratio. It is obvious that the I/G ratio should be a reasonably consistent characteristic of an individual if it is to provide any biological insights. Given the lack of reproducibility of both glucose and insulin responses to an OGTT, one might predict that there would be considerable variability in any individual's I/G ratio. On the other hand, it might also be that if the direction and

magnitude of change in insulin response followed the direction and magnitude of change in glucose response, then the I/G ratio would be a more reproducible physiological measurement than either value alone. In the present study, fasting insulin:glucose ratios were significantly different between tests, although fasting glucose concentrations alone did not differ significantly. This might imply that the glucose values were more reproducible than IGR values, although the IGR was more indicative of poor reproducibility of the OGTT.

Our study was designed to analyse the reproducibility of glucose and insulin responses to OGTT in a small cohort of glucose tolerance groups. For the whole group, basal glucose and insulin levels were not reproducible and glucose responses to OGTT showed significant bias was not shown for each diagnostic category separately, perhaps due to a type 2 statistical error, which might be resolved by a larger sample size. Although conditions of reproducibility seem to be optimized, changes in digestion or absorption, and uncontrolled environmental factors cannot be ruled out.

The detection of glucose intolerance, in presence of fasting normoglycaemia, is rarely of benefit to the patient in the absence of obesity or other risk factors and may prove a hardship for psychological reasons. Thus, the clinician should carefully evaluate the medical indications and the potential benefits derived prior to ordering an OGTT. Caution should be used in making a diagnosis of diabetes mellitus based on this test when results are marginal. Unfortunately no other diagnostic test for diabetes is available, and it is not recommended that the use of the OGTT be curtailed as a result of our data until a more definitive, more reproducible, and more practical test, is available. It is hoped however that these results will provide greater insight into the meaning of individual test results, and will also increase the responsibility which the clinicians assume for the continued observation of suspects.

Finally, a specific recommendation for public diabetes detection programs is that those persons classified as suspect on the basis of a screening test or other

selected characteristics be retested periodically when the initial retest does not indicate immediate referral to a physician. Values selected for referral should be determined at the community level with the cooperation of local physician and official agencies.

ADDENDUM TO DISCUSSION

Table : 6.2 A

**Change in glucose tolerance category between the first and repeat OGTT in number [%].
Test 2 in the whole group [n=125] was extrapolated.**

Category	NGT	IGT	Diabetes	All
Repeated OGTT actual results [n=35] :				
Age	37	39	44	39
BMI	29	29	27	29
[test 1]	15 (43)	12 (34)	8 (23)	35 (100)
[test 2]	17 (49)	12 (34)	6 (17)	35 (100)
Results extrapolated to whole group [n=125] :				
Age	37	39	41	38
BMI	27	29	29	28
[test 1]	74 (59)	34 (27)	17 (14)	125 (100)
[test 2]	84 (67)	34 (27)	13 (10)	125 (100)

DISCUSSION :

The above table [6.2A] demonstrates the effect of extrapolating the results of the repeated OGTT's to the whole group. This is necessary and desirable because the repeat OGTT group contains a higher proportion of patients with IGT or diabetes than the whole group, and the results in table 6.2 may therefore be biased by the phenomenon of regression to mean. The first test showed that 17 of the 125 subjects had diabetes and 34 IGT [chapter 5]. On repeat testing, extrapolated to all subjects, ten subjects would move down to normal glucose tolerance and 4 to IGT from diabetes. However 5 subjects would show 'worsening' to IGT from normal, so the total number with IGT remain unchanged. However the small decrease in numbers of subjects with diabetes and increase in subjects with normal glucose tolerance does still suggest some bias between first and second tests.

Table : 6.1**Characteristics of the subjects who had a repeat OGTT.**

	<u>Glucose Tolerance Category</u>			All
	Normal	IGT	Diabetes	
n	15	12	8	35
Age (yr)	37 (29-51)	39 (33-50)	44 (30-55)	39 (29-55)
BMI (kg/m ²)	28.7 ± 5.1	29.4 ± 3.2	27.2 ± 4.7	28.6 ± 4.4
Fructosamine (mmol/l) :				
First test	2.3 ± 0.1	2.4 ± 0.1	2.8 ± 0.3	2.5 ± 0.1
Second test	2.3 ± 0.1	2.4 ± 0.1	3.3 ± 0.4	2.6 ± 0.1

Number, or mean (range), or mean ± SD

Table : 6.2**Change in glucose tolerance category between the first and repeat OGTT.**

	<u>First test category</u>			Total (Test 2)
	Normal	IGT	Diabetes	
<u>Second test category</u>				
Normal	14 (93)	3 (25)	0 (0)	17 (49)
IGT	1 (7)	9 (75)	2 (25)	12 (34)
Diabetes	0 (0)	0 (0)	6 (75)	6 (17)
Total (Test 1)	15 (43)	12 (34)	8 (23)	35 (100)

Number (%)

Table : 6.3

Plasma glucose and serum insulin concentrations and total area under the curve (AUC) in the subjects who had a repeat OGTT.

	Test	Glucose Tolerance Category (Test 1)			All
		Normal	IGT	Diabetes	
Glucose (mmol/l)					
Fasting	1	5.3 ± 0.1	5.7 ± 0.1	9.5 ± 1.5	6.4 ± 0.4
	2	5.2 ± 0.1	5.8 ± 0.1	9.1 ± 1.7	6.3 ± 0.5
1 h	1	9.2 ± 0.7	11.9 ± 0.5	17.7 ± 2.1	12.1 ± 0.8 ^a
	2	8.6 ± 0.7	11.4 ± 0.5	16.5 ± 1.9	11.4 ± 0.7
2 h	1	5.4 ± 0.3	9.1 ± 0.2	18.8 ± 2.2	9.7 ± 1.0
	2	5.6 ± 0.3	8.7 ± 0.4	18.5 ± 2.9	9.6 ± 1.1
Glucose AUC (mmol/l/h)	1	18.1 ± 0.8	23.7 ± 0.7	39.8 ± 5.0	25.0 ± 2.0 ^a
	2	17.5 ± 0.9	23.0 ± 0.8	37.9 ± 5.6	24.0 ± 2.0
Insulin (mU/l)					
Fasting	1	18.1 ± 2.5 ^c	18.0 ± 1.8	18.4 ± 2.5 ^b	18.1 ± 1.3 ^c
	2	10.0 ± 1.3	13.1 ± 2.0	11.7 ± 2.9	11.4 ± 1.1
1 h	1	113.8 ± 11.7	116.2 ± 7.1	59.2 ± 13.8	102.1 ± 7.4
	2	122.4 ± 22.8	109.0 ± 13.0	58.2 ± 13.0	103.1 ± 11.7
2 h	1	85.2 ± 10.7	120.4 ± 8.9	70.6 ± 14.2	93.9 ± 7.0
	2	80.2 ± 15.2	116.4 ± 12.9	64.2 ± 15.2	89.0 ± 9.1
Insulin AUC (mU/l/h)	1	190 ± 20	214 ± 12	127 ± 24	184 ± 12 ^a
	2	186 ± 32	200 ± 21	113 ± 20	174 ± 17

Mean ± SEM

a, p < 0.05 ;

b, p < 0.01 ;

c, p < 0.001 compared to repeat test.

Table : 6.4**Insulin : glucose ratios (IGR) in the subjects who had a repeat OGTT.**

	Test	Glucose Tolerance Category (Test 1)			All
		Normal	IGT	Diabetes	
Fasting	1	3.3 ± 0.4 ^c	3.1 ± 0.3 ^a	2.2 ± 0.4 ^a	3.0 ± 0.2 ^c
	2	1.9 ± 0.3	2.2 ± 0.3	1.7 ± 0.6	2.0 ± 0.2
1 h	1	12.3 ± 0.9	9.9 ± 0.8	4.1 ± 1.0	9.6 ± 0.8
	2	13.6 ± 1.9	9.9 ± 1.3	4.2 ± 1.2	10.2 ± 1.2
2 h	1	16.2 ± 2.1	13.5 ± 1.3	4.5 ± 1.1	12.6 ± 1.3
	2	13.5 ± 1.8	13.9 ± 1.8	4.8 ± 1.3	11.7 ± 1.2

Mean ± SEM

a, p < 0.05 ;

c, p < 0.001 compared to repeat test.

RESULTS

CHAPTER SEVEN

DIETARY EVALUATION

CHAPTER CONTENTS :

- Summary.
 - 7.1 Introduction.
 - 7.2 Subjects and methods.
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 - 7.4 Discussion.
-

" Diabetes is the disease of the rich and one that is brought about by the gluttonous overindulgence in oil, flour and sugars. "

(Ekoé 1988 - p. 99)

SUMMARY

The dietary habits of the Saudi Arabian population have been influenced by the influx of foreign workers into the country, increased availability of a wide range of imported goods and increased spending power. This study, done by questionnaire interview, describes the types of dietary pattern becoming commonplace in the Kingdom, particularly the western urban province and examined how the dietary habits or food could be influencing glucose tolerance.

7.1 INTRODUCTION

The prevalence of NIDDM and IGT in population living in Saudi Arabia and residing in Jeddah [Chapter 5] is very high suggesting an environmental component in the aetiology of this disease, perhaps interacting with a basic genetic predisposition to diabetes. An important environmental variable is diet. However, the role of diet in the aetiology of NIDDM is as yet uncertain.

Since the beginning of this century many arguments have been raised to support the idea that either a high sugar intake (*Yudkin, 1969*), or a high fat intake (*Himsworth, 1935*) is responsible for an increased risk of diabetes. Dietary factors that may be involved in the epidemiology of diabetes have been addressed before (*West, 1978; WHO, 1985*), but the role of qualitative aspects of the diet remains unclear and the evidence implicating specific macronutrients was inconclusive. Further research has addressed calorie excess as it relates to obesity, which has been thought to play an important role in the epidemiology of diabetes (*Baird, 1972*). Other studies suggest, however, that it is not only the overconsumption of calories leading to obesity that puts a person at risk for diabetes but also the anatomic location of the deposited excess fat (*Vague et al, 1988*).

Investigations of an aetiological role for carbohydrates, specifically a high refined-sugar intake, has had few supporters (*Keen et al, 1974*). However, a high-fat "Western" diet appears to be more frequently linked to diabetes and its vascular complications (*Himsworth, 1935*). Dietary protein has received less attention than has fat as a dietary risk factor (*Nuttall, 1984*). In addition, a 'protective' effect of high dietary fibre intake was suggested (*Trowell, 1975*).

Since the discovery of oil in Saudi Arabia in 1938, many changes have occurred in the lifestyle of the population. From being an isolated, nomadic

Bedouin population, rapid urban development has occurred bringing the trappings of the twentieth century (*Sebai, 1981*). Along with the increased wealth of the country has come the inevitable changes in lifestyle for the majority of the population. The sedentary lifestyle unknown to the people before has become the norm as people move to the cities and the diseases of affluence are appearing. The dietary habits previously determined by the limited availability of food have changed; in particular, due to the influx of expatriate workers from the west and third world countries. Traditional eating habits still prevail but intermingle with a range of good and bad eating habits from the west associated with an upsurge in the incidence of non-communicable diseases [NCD] such as diabetes and obesity (*Sebai, 1981*). Since NIDDM is common in Saudi Arabia, a role for environmental factors in the aetiology of this disease is suggested and thus dietary intake was assessed. Therefore, the proposed objectives of this aspect of the cross-sectional study, as described in this chapter were two-fold; 1) to describe the diet and food intake habits of a sample of urban men living in Jeddah as a whole; and 2) to investigate possible cross-sectional differences between glucose tolerance groups and the frequent intake of different food items representing dietary carbohydrates, fibre and fat.

7.2 *SUBJECTS and METHODS*

Habitual dietary intake was assessed using the food frequency questionnaire [FFQ] method only. The study of present eating habits was carried out by questionnaire interview between each subject alone and a single observer. The aim of the interviews was to try to ascertain the quality of the diet by asking about the types of foods taken and the frequency with which they were eaten. This was not a quantitative study although it is hoped to do this in the future.

Ninety five [95] individuals were interviewed, all were males with ages ranging from 20-64 yrs. Although the individuals interviewed came from different nationalities, all had lived in Jeddah for a while. Details of subjects recruited, anthropometric measurements and sampling protocol for plasma

glucose were described earlier [Chapter four]. Dietary assessment was performed and the results compared in those with NIDDM [n=15], those with IGT [n=25], and the NGT group [n=55].

Dietary methodology :

Background. Nutritional assessment procedures were initially described in 1932 by the Health Organization of the League of Nations (*Gibson, 1990*). These can be defined as: the interpretation of information obtained from dietary, biochemical, anthropometric and clinical studies. The information is used to determine the health status of individuals or population groups as influenced by their intake and utilization of nutrients. Nutritional assessment systems (NAS) can take one of three forms: surveys, surveillance, or screening (*WHO, 1976*). The next few paragraphs outlined briefly methods used in nutritional assessment.

The nutritional status of a selected population group may be assessed by means of a cross-sectional survey. This nutritional survey may establish baseline nutritional data and/or ascertain the overall nutritional status of the population. NAS utilize a variety of methods which are based on a series of dietary, laboratory, anthropometric, and clinical measurements, used either alone or, more effectively, in combination. Food consumption assessment methods produce qualitative or quantitative information from food consumption surveys. Survey data, collected at the national, household, or individual levels, can be expressed in terms of nutrients and/or foods. This study used methods suitable for measuring food consumption at the individual level.

Methods. The available methods used for measuring food consumption of individuals can be classified into two major groups. The first group, known as quantitative daily consumption methods, consist of recalls [24 hour or reflected 24 hour] or records [estimated food or weighed food], designed to measure the quantity of the individual foods consumed over a one-day period. The second group of methods includes dietary history and food frequency questionnaires [FFQ], both of which obtain retrospective information on the patterns of food use

during a longer, less precisely defined time period. Such methods are most frequently used to assess usual intake of foods or specific classes of foods. With modification, they can provide data on usual nutrient intakes.

There is no ideal method for assessing food or nutrient intakes, the choice depending primarily on the objectives of the study. Additional factors which should be considered when choosing a method for assessing the food consumption of individuals are the characteristics of the subjects within the study population, the respondent burden of the method, and the available resources. Generally, the more accurate methods are associated with higher costs, greater respondent burden, and lower response rates. In population groups it is possible to estimate the average use of specified foods by means of a FFQ. Such data can be used for international comparisons of the relationship of patterns of food use to health and susceptibility to chronic disease.

None of the current methods are devoid of systematic errors, or prevent alterations in the food habits of the subjects. Since the desired information required for my study was group or individual patterns of food use, and the proportion of the population with a particular pattern and/or average use of a particular food or food group, the food frequency questionnaire was used as the preferred approach (*Gibson, 1990*).

FFQ. A FFQ is designed to obtain qualitative, descriptive information about usual food consumption patterns. It does not generally provide quantitative data on food or nutrient intakes. The questionnaire consists of two components: (a) a list of foods, and (b) a set of frequency-of-use response categories. The list of foods may focus on specific groups of foods, particular foods, or foods consumed periodically in association with special events/seasons, when it is designated a focused questionnaire (*Anderson, 1986*). Alternatively, the food list may be extensive to enable estimates of total food intake, and hence dietary diversity, to be made.

The aim of the FFQ is to assess the frequency with which certain food

items or food groups are consumed during a specific time period (e.g. daily, weekly, monthly, yearly). The record is obtained by interview, or self-administered questionnaire. The questionnaire can be semiquantitative when subjects are asked to quantify usual portion sizes of food items, with or without the use of food models. Specific combinations of foods included in a focused questionnaire can be used as predictors for intakes of certain nutrients or non-nutrients, provided that the dietary components are concentrated in a relatively small number of foods or specific food groups. Examples include the frequency of consumption of whole grain cereals, legumes, nuts, fruits, and vegetables as predictors of dietary fiber intake. The method can also be used to assess the intake of artificial sweeteners, certain contaminants present in specific foods, alcohol, and condiments (*Hunts, 1984; Anderson, 1986*).

The FFQ should relate to simple, defined food categories: open-ended questions should be avoided, as pre-formatted lists of food categories act as a memory prompt. The data for the FFQ may be obtained by a standardized interview or self-administered questionnaire, the former way is applied in this study and took 15-30 minutes to complete. The results generally represent usual intakes over an extended period of time and are easy to collect and process. The FFQ imposes less burden on respondents than most of the other dietary assessment methods. It is often used by epidemiologists studying associations between dietary habits (both usual and past) and disease (*Hankin et al, 1970*), although its use for estimating food intakes in the remote past has not been clearly established (*van Stavern et al, 1986*). FFQ can also be used in combination with more quantitative methods, providing additional or confirmatory data.

The data from a food frequency questionnaire are often used to rank subjects into broad categories of low frequency and high frequency intakes of certain foods, as in my study. In epidemiological studies, such rankings are often compared with the prevalence and/or mortality statistics for a specific disease within the population studied. Food scores can be calculated from food frequency

data, based on the frequency of consumption of certain food groups (*Guthrie and Scheer, 1981*). The scores can then be examined in relation to psychosocial influences (e.g. level of education, income) as well as vital statistics. Comparisons of the dietary patterns of different ethnic groups can also be made using a food scoring system.

Studies on the precision of FFQ are limited but in one 90 % of the responses differed by less than one point from the original measurement, suggesting that the FFQ precision for classifying the frequency of food used was good (*Gibson, 1990*).

Despite the increasing use of FFQ in epidemiological studies the dietary methods in general and FFQ in particular are the most difficult to validate because the 'truth' is never known with absolute certainty, and there is no guarantee that the records represent the usual food intake (*Block, 1982*). Thus, subjects may eat atypically during a dietary period, even though every effort is made to discourage this. When FFQ was tested for validity (*Mullen et al, 1984*), they indicated that a large proportion of individuals could accurately estimate their food intake using the FFQ. The method is rapid with a low respondent burden and high response rate but accuracy is a little lower than for other methods.

In this study, the collection of dietary data followed a format adapted from the *Laparasky (1987)* diet-history method using the FFQ method only (Appendix 4). Each participant was asked his usual frequency of consumption of the listed food items for the 1-2 month period before participation in the study. The list consisted of 86 questions including food items that are rich sources of the nutrients of interest and locally available. This study was intentionally comprehensive to establish baseline data for future studies. Much of the difficulty in finding strong diet-disease correlations arises from the inherent problems of using dietary data collection methods in a free-living population (*Morgen et al, 1978; Gordon et al, 1984*).

Background information was gathered before the FFQ was administered to

understand as fully as possible features of the subject's lifestyle that were relevant to his eating habits. Information pertaining to his medical history, occupation, socioeconomic status, education level, marital status, and physical activity was noted. Usual meal and snacking frequencies, specific diet modifications prescribed by a physician, or self-imposed, and frequency of home dining were also solicited. The background information was used to elicit specific details in the FFQ and to gain rapport with the subject to enhance reliability of reporting. The variables assessed for this purpose were grouped into protein, fat, carbohydrates, and beverages.

In this study, coding the responses to the food items frequencies were aggregated and presented as percentages. Seven times a week or 1-6 times per week were considered together as more frequent response and shown here only because the number for each coding category is small. Similar aggregation were performed when comparisons were made by glucose tolerance category.

Statistic. To test overall differences between the three or two diagnostic groups, nonparametric chi-square tests were used. All statistics were computed by use of SPSS software [SPSS, Inc, Chicago]. All *P* values are based on two-sided tests of statistical significance and $P < 0.05$ accepted as indicating significance.

7.3 RESULTS

Overall dietary habits and specific food intake for the whole population are described first, followed by habits and selected dietary items in relation to glucose tolerance groups. Subject characteristics were described earlier for the whole population and by glucose tolerance groups [Chapter 5].

General dietary informations were presented in Table 7.1. The subject's meal habits showed that the majority [88%] usually eat three main meals namely; breakfast, lunch and dinner, with 12% eating two and none eating one meal. The main meal was lunch in the majority [94%] and dinner in only 6% . Few [11%] omitted breakfast, but if it was taken [73%] it was usually between 7:30 am and 10:30 a.m. with minority in the early [13%] or late [3%] morning. The same

applies for lunch where the majority [78%] eat their lunch between 14:00 - 16:00 and the minority in either early [13%] or late [9%] afternoon. Taking snacks between main meals was found in 53% and, in those taking snacks this was usually between lunch and dinner [74%], while the rest [26%] ate the snacks either before breakfast, between breakfast and lunch and after dinner or before sleeping. All lunches and dinners and the majority of breakfasts [73%] and snacks [53%] were taken at home. This is supported by the fact that 86% of them eat at their homes.

In the same table [7.1], the practices of dietary modification are shown in the form of adding salt in 48%, decreasing the amount of fat in only 10% or decreasing of sugar in only 8%. Furthermore, all subjects were asked to identify the brand name of seven food items including some dairy products and some fat-containing food. These questions addressed the ability of the subjects to recall some common products used daily. The table [7.1] shows that the trade name of oil or fat items was known by 98% of the subjects, unlike milky-containing foods [17%] and butter [27%]. Beliefs about diet and health would be of interest but this was not examined in this study.

Food items representing different foods categories, which were taken at least once per week, are shown in table [7.2]. Rice was the most popular carbohydrate being taken by 96% and bread [89%] was the second. Pasta [47%], potatoes [42%] and cornflakes [31%] were the least along with the honey [43%] and jam [33%]. The traditional wholewheat products of kabsah, ghorsan and jareesh were not asked about specifically, however, dates a traditional fruit, are still fairly popular [65%]. Simple sugar was taken in tea by 92% while 28% took sweetened coffee. Soft drinks were popular [86%].

Confectionery consumption is shown as well [Table 7.2]. Biscuits [35%] and nuts [35%] were the most commonly used while ice-cream [17%] and sweets [15%] were the least. All of these foods were most commonly consumed during weekend picnics and family gatherings.

The frequency of fruit and vegetable consumption is shown in Table 7.2. Large proportion of this population admitted eating at least once per week of oranges [98%] and salad vegetables [98%]. These results may be a bit ambiguous as in some Arabic dialects the same word is used for fruit and vegetables. Dates [65%] are still the most popular fruit and tinned fruit [7%] was not widely consumed.

Foods containing protein are shown in Table 7.2. The most popular forms of animal protein were chicken [94%] and lamb [93%]. This was followed in popularity by fish [62%], beef [23%] and tuna [23%]. A high consumption of eggs was found in only 12% and offal was taken fairly frequently [36%]. Vegetable protein [Beans, 78%] in the form of pulses were popular.

Food items representing fat and oil intake are shown in Table 7.2. The majority of those questioned used vegetable oil [79%] for cooking, although some used butter and ghee. The consumption of other high fat foods, such as "kabseh", a traditional dish of rice, spices and usually meat or chicken cooked in oil, was not asked. Olives [60%] and cream [30%] were the other popular foods, being taken usually at breakfast with bread.

Dairy product food items are shown in Table 7.2. Cheese [93%], laban [70%] and milk [68%] are popular foods that have been taken traditionally in the diet and their consumption is still quite high although cows milk has taken over in popularity from camel and goats milk [not shown].

Finally, beverages and drinking habits consumption are shown in Table 7.2. Soft drinks as a whole [86%] or fizzy drinks [79%] were popular and tea [98%] consumed more often than coffee [70%].

General eating habits and selected food items based on glucose tolerance groups are shown in table [7.2]. Taking snacks between meals was found more in those subjects with NIDDM [80%] compared with IGT [64%] and NGT [73%]. Also those with NIDDM [25%] practised changing diet more frequent than those either with IGT [19%] or with NGT [9%]. However, none of these showed

statistical significance.

Moreover, certain commonly used food items were selected and presented to discover whether any differences existed between the groups [Table 7.3]. Rice and bread were eaten more frequently by NIDDM subjects compared to both IGT and NGT. However, honey and jam were less commonly eaten by NIDDM subjects. Interestingly, eating more than 7 eggs per week was found most commonly in subjects with NIDDM, intermediate in those with IGT and lowest in those with NGT. Dates, other fruits and soft drinks were less commonly taken by those with NIDDM. However, none of these showed significance when compared.

7.4 DISCUSSION

Foods assessed in this study can be conveniently classified in ten categories: Cereals; Starchy roots; Sugars and syrups; Pulses, nuts and seeds; Vegetables; Fruits; Meat, fish and eggs; Milk and milk products; Oils and fats; and Beverages. These can also be grouped under the essential nutrients of carbohydrates, fats, proteins, minerals and vitamins.

It is known that restrictions on the food supply of a community affect diabetes and this is well illustrated in U.K between 1940-1947 during which mortality from diabetes was reduced by nearly 50% (*Himsworth, 1949*). Mortality rates do not necessarily reflect prevalence rates but there is no doubt that rationing was beneficial to individuals susceptible to diabetes. On the other hand, prosperity or westernization of a country might influence the prevalence of diabetes. Saudi Arabia has passed through a prosperous phase during the last two decades which, of course, has influenced food supply and intake, but no data are available to show differences of diabetes prevalence before and after this increase in food supply.

A single report, which analysed the import and export data at the national level, showed that the trends in the diet shifted away from the traditional foods and show a dramatic increase in the consumption of sugars, fats and oils during

the period 1970-1980. It also showed a remarkable increase in the consumption of cereals, fruits, potatoes, meat, eggs, milk, sugar, and fat and oil with a declining consumption of fish and vegetables (*Musaiger, 1987*).

This study explains partly the drastic change in food consumption patterns in Saudi Arabia. The traditional diet which consisted of dates, milk, rice, bread and fish has changed to a more diversified diet. Red meat and poultry are consumed more frequently than marine food, and mutton and lamb are preferred to beef. Rice is still the most staple cereal and it is eaten almost daily with other food and camel meat still used. Wheat is mainly consumed as bread or pasta. Milk and dairy products have become essential items in meals, particularly laban. Chips, chocolates and sweets are the main foods consumed in between meals as snacks. Tea is the most popular drink and is consumed sweetened, with or without milk. Alcoholic drinks are forbidden by law in Saudi Arabia.

A few studies were concerned with nutrient intake in Saudi Arabia, and in one was on pre-school children (*Sawaya et al, 1985*). The impression from the literature revealed that the Saudi diet is typically high in fat (*Sawaya et al, 1985*), high in carbohydrates, particularly complex (*Sawaya et al, 1984*), and moderate in protein content (*Sawaya et al, 1986*). In addition, the chemical and nutritional quality of six Saudi Arabian dishes based on cereals and legumes was investigated (*Al-Jebrin et al, 1985a,b*), and 14 Saudi Arabian dishes based on meat, fish or eggs were investigated for their nutrient composition as well (*Sawaya et al, 1986*). However, these dishes could provide an appropriate amount of protein and energy to meet the Recommended Dietary Allowances (RDA) if consumed in adequate quantities.

Half of our male subjects added salts to food, which might explain previous studies which showed that sodium content was high [> 160 mg/100g] in most dishes, particularly four dishes, and relatively low [< 36 mg/100g] in two dishes (*Al-Jebrin et al, 1985*). Added to the salt content is the high use of spices, especially cumin, coriander leaves and cloves which contain a high amount of

sodium. Whether these salty dishes have a relation to the high rate of hypertension that is common in Saudi Arabia [Chapter, 5] would be of interest to investigate.

Rice is second to wheat in global importance as a staple food for man. In Saudi Arabia rice is the main food followed by bread. However, this study supports a previous impression that rice is never eaten alone but always consumed with meat, fish or poultry. This naturally improves the nutritional value of the rice (*Musaiger, 1987*). The rice consumed in Saudi Arabia is polished. The practice of washing and straining leads to the removal of some water soluble nutrients. Another important factor is cooking the dish at a very high temperature for a long time, which may enhance or reduce its nutritional value, since overheating of dishes may render some of amino acids in the protein unavailable and inactivate vitamins.

Bread, as shown in this study, is consumed less by the inhabitants of the Saudi Arabia when compared to rice. Nevertheless, it is the main food item for breakfast and supper. Five main types of bread consumed in Saudi Arabia have been analysed [white and brown Arabic breads, European, Yemeni and Somali breads] (*Sawaya et al, 1984*). They confirm that the whole wheat flour contains three times as much dietary fibre as white flour. This gives it a mild laxative effect.

Increasing prosperity always leads to a more varied diet and a decreasing consumption of cereals. In this study, almost 30 % ate breakfast cereal [cornflakes] which is an example of westernization of eating habits.

Honey and jam which contain about 60 % sugar contributed moderately to the caloric intake in this group.

Care should be taken with regard to snacks which were composed mainly of confectionery. This comprised up to 70% of carbohydrate and nuts which mostly have a high content of fat and protein.

Red meats and beans taken in the morning are the two main source of protein. The protein quality of foods consumed in the Saudi Arabia was also

investigated previously (*Al-Jebrin et al, 1985a*). Amino acid profiles were found to be good in Saudi meat-based dishes and in breads when compared with FAO/WHO [1973] reference protein (*Sawaya et al, 1984, 1986*).

Attempts have been made to analyse content of two high cholesterol of dishes; mutabak ma'lahm (meat paste) and shakshuka (egg omelet). Obviously the use of eggs in these two dishes has contributed to the high level of cholesterol in each of them. It was found that most of the Saudi dishes had a high fat content and a low ratio of polyunsaturated/saturated fatty acids. This may contribute to the prevalence of atherosclerosis in the country (*Sawaya et al, 1985a*).

Vegetable oils are relatively newcomers to the diet in Saudi Arabia and contribute greatly to the total fat and calorie content of the diet. The practice of pouring melted fat or butter on top of the rice to enhance the flavour before eating, might increase the amount of fat in the rice.

Milk and dairy products have traditionally been a major contributor to the protein and calorie content of the diet. The consumption of these foods is still high although other sources of animal protein are consumed regularly as they are now freely available.

Humans are not very fond of plain water and prefer flavoured fluids such as tea, coffee, cocoa, fruit juice, or even synthetic 'colas' and 'lemonades'. They are also a source of energy and a few provide small amounts of micronutrients. The hot climate in Saudi Arabia encourages people to drink various types of soft drinks, carbonated beverages being the most common. This study showed that 80% regularly consumed soft drinks. However, most soft drinks are sweetened. If sugar is used, this may contribute to obesity and the drink is unsuitable for diabetics.

Adding milk and sugar adds significantly to the dietary energy of some people. In Saudi Arabia tea was once a rare and expensive commodity in the diet [the traditional cardomon coffee being previously more popular and taken without sugar]. Tea is taken sweetened and in large quantities throughout the day,

contributing greatly to the calorie content of the diet. Coffee is a popular drink and in moderate amounts a mild cerebral stimulant and diuretic. Alcohol was not a problem in our community.

However, it is worthwhile mentioning that these dishes are eaten alongside other foods such as laban, dates, and fresh vegetables which supplement the nutritional value of the dishes, particularly in some minerals and vitamins, as well as fibre [which was found to be deficient in the dishes].

Although the reason(s) for dietary modification are not shown here, 10% of this population practised dietary modification by several means. This indicates that only a small proportion showed some alterations in dietary habits for one reason or another.

Several factors are known to have an influence on food consumption patterns in Saudi Arabia. Increase in income may be one of the most significant factors responsible for the change in food consumption patterns. Among other factors are educational level, food prices, beliefs and attitudes, mass media and household size. Added to this is the availability of fast foods such as beefburgers and fried chicken which are widely consumed especially by the young generation. Canned and other processed foods are widely available on the market and have become an important component of the diet. However, these factors were not examined specifically in this study.

Another aspect in this study is the relation of diet to glucose tolerance status. A number of diseases, many of which are common and well-known, are considered for one or both of two reasons; 1) the nature of the previous diet may play some part in aetiology which is multiple and complex, and 2) modification of the usual diet or the provision of a special diet reduces the metabolic burden on discorded organs, or relieves symptoms and other manifestations of disease. Among these disorders is diabetes. Dietary factors may increase the risk of an individual developing diabetes. Thus, diabetes, hypertension and cardiovascular disease can be linked to diet, at least in relation to obesity (*Barrett-Connor, 1985*).

Since subjects with elevated blood glucose levels are at higher risk for subsequent development of NIDDM (*Jarrett et al, 1979; Chapter 2*) another way of exploring the relation between diet and the onset of diabetes is to study its relationship to glucose tolerance. In several epidemiological studies no clear relationship could be demonstrated between dietary factors and the onset of diabetes (*Baird, 1972; Medalie et al, 1975; Lundgren et al, 1989; Feskens et al, 1989*). However, recent studies have suggested that energy balance and the use of carbohydrate-rich foods are related to the development of glucose intolerance in an elderly population (*Feskens et al, 1991*). The intake of saturated fat and dietary cholesterol may be detrimental to glucose tolerance, in contrast to the intake of pectin and mono and disaccharides (*Feskens et al, 1990*).

The hypothesis that a low fibre diet contributes to the aetiology of diabetes has also been proposed, but it is difficult to see how a deficiency of fibre could cause the disorder (*Trowell, 1975*). The hypothesis was based on African countries where the fibre content of the diet is high and prevalence of diabetes low. In prosperous communities this relationship tends to be reversed. This is often considered with the proposed that a large consumption of sugar may predispose to diabetes although West (*1978*) lists 21 papers supporting this claim, but also 22 papers which do not.

However the biggest diet related problem that is prevalent in Saudi Arabia is obesity [Chapter 5]. Data kept over a 6 month period on diabetic admissions to Riyadh Armed Forces Hospital (*Gibbon, 1988*) showed that out of 161 diabetic males, 52% were more than 10% over IBW and 13 % were more than 30% over IBW. The results for women were even more significant, 86% of the diabetic females were more than 10% above IBW and 48% were more than 30% above IBW. In the past obesity was a status symbol and it is only relatively recently that the population has started to become aware of the effect on health.

To obtain data on the incidence of diet related disease, Kingdom-wide, is difficult and it is only possible to extrapolate from the trends seen in this

population. This study showed no relationship between most commonly used food items and glucose intolerance in this small group of middle-aged urban men [Table 7.11], and favours that dietary factors play no role in the aetiology of diabetes. In Saudi Arabia this is the product of the adoption of dietary habits influenced by increased wealth, traditional social habits and very heavy advertising by western food manufacturers. In the older section of the population there is very little knowledge of the functioning of the body. To grasp the concept that food can be harmful proves difficult. It is also difficult to dispel the fatalistic belief that you cannot control your own health.

However, the population is becoming more aware of the effect bad dietary habits are having on their health and are showing an interest in helping themselves. The media used to provide this information must be chosen wisely bearing in mind the high rate of illiteracy and social and religious influences on the diet.

Further research in this direction would be of interest particularly a quantitative-type of study in a large population, but taking into consideration several factors; 1) the absence of food composition tables for use in Saudi Arabia which should be established, since currently used tables [USA, RDA; FAO/WHO] are lacking in many foods and dishes commonly consumed in this country. Once these tables are available, these should provide useful information, especially on ingredients, preparation and composition of composite dishes and of ready-made foods available on the market. Thus, the development of regional RDAs is required, taking into account body weight, dietary pattern and bioavailability of nutrients in local foods, 2) the measurement of actual food intake for each member in the family is difficult to obtain, since Saudi families often eat together from the same plate. The food is served on a big tray (especially at lunch) and all the family members surround it, eating the food using their fingers sometimes. Thus establishing an appropriate technique for collecting dietary intake, taking into consideration the socio-cultural aspects of the

community, is highly supported, 3) the lack of qualified and trained staff to collect dietary information, 4) the difficulty in obtaining actual quantities of ingredients used in the local composite dishes.

In the meanwhile some practical comments are worthy of mention. Physician and general practitioners alike should be aware of the dietary habits of diabetic individuals before instituting a dietary plan and advise, and the present study should provide some help in this direction. Also the practice of circulating "translated dietary sheets" from a western designed diet regimen should be stopped. Failure to observe these suggestions will greatly reduce compliance and produce a lack of adherence of the diabetic individual to follow the prescribed diet.

Table 7.1 :
General dietary information :

Title	%
Meals habits :	
-Three meals or more a day	88
-Lunch as a main meal	94
-Taking snacks between meals	53
The snack between lunch and dinner	74
-Eating at home in general	86
-Brakfast mainly at 7:30 - 10:30	73
Don't take breakfast	11
-Lunch time mainly at 14:00 -16:00	78
-Dinner time mainly at 21:00 - 23:00	71
Dietary modification :	
Subjects [%] state that they :	
-Added salt either when not enough or always before eating	48
-Changed their diet,	10
-Decreased the amount of :	
Fat	10
Sugar	8
Salt	4
Bread	3
Identification ability (%) of brand name(s) or contents for some commonly used food items	
<u>Food item</u>	<u>Known (%)</u>
-Oil or fat	98
-Cheese	92
-Milk	78
-Yoghurt	75
-Cream	33
-Butter	27
-Milky-made foods	17

Table 7.2 :

Frequency of eating selected foods as a percentage of those interviewed. These responses indicate foods that were taken at least once/week.

	<u>percentage</u>
<u>Carbohydrates</u>	
Rice	96
White bread	89
Beans	78
*Tamees [commonly used white flour bread]	66
Brown bread	55
Lentils	52
Pasta	47
Potatoes	42
Honey	43
Jam	33
Flour-made food	34
Cornflakes	31
Soft drinks [all]	86
Tea, sweetened with sugar	92
Coffee, sweetened with sugar	28
Dates	65
<u>Confectionary</u>	
Biscuits	35
Nuts (all types)	35
Cakes	27
Jellies	24
Chocolates	20
Ice Cream	17
Sweets	15
<u>Vegetables and fruit</u>	
Salad	98
Cooked Vegetables eg. Akra	92
Carrots	66
Spices eg. pepper	52
Oranges	98
Apples	83
Bananas	75
Dates	65
Tinned fruit	7

Proteins**percentages**

Chicken	94
Lamb	93
Fish	62
Organs [liver, kidney, heart]	36
Beef	23
Tuna	23
Meat pies pastries	13
Camel	3
Tinned meat	3
Beans	78
Eggs more than 7 / week.	12

Fats and oils

Oil or fat used at home of plant origin	79
Olives	60
Cream	30
Butter, ghee or margarine	24
Eggs more than 7 / week.	12

Milk and milk products

Cheese, any kind	93
Cheese, > 250 grams per week	19
Laban [Yoghurt]	70
Milk [amount]	68
-One glass milk or more per day	78
-None	22
-Liquid milk	54
-Dried milk	24
Adding milk or cream with tea or coffee	41
Milky-made food	19
Milk pudding	11

Beverages and drinking habits

Water \geq 3 litre per day	8
-Increasing water drinking mainly due to kidney problem	22
Sweetened tea with sugar	92
Sweetened coffee with sugar	28
Soft drinks [all]	86
-Natural juices	15
-Fizzy drinks like pepsi and similar	79

Table 7.3
Eating habits by glucose tolerance groups [%].

	NGT	IGT	NIDDM
n (%)	55 (58)	25 (26)	15 (16)
General habits :			
Main meal as lunch	91	100	93
Taking snacks between meals	73	64	80
Changed diet	9	19	25
Adding salt	48	50	44
Specific, each food items taken at least once/week :			
Rice	93	100	100
White bread	88	88	94
Brown bread	57	46	62
Beans	74	88	75
Potatoes (a)	67	87	62
Honey	43	50	31
Jam	29	42	31
More than 7 eggs per week	10	12	19
Milk	69	77	50
-Milk one glass or more	79	81	69
-Yoghurt	67	77	69
Eating cheese	93	96	88
Cheese amount > 250 g/week	21	8	31
Lamb	93	96	88
Chicken	98	88	88
Salad	96	100	100
Dates	66	73	50
Apples	84	85	75
Bananas	76	77	69
Oranges	83	96	94
Soft drinks	91	81	75

RESULTS

CHAPTER EIGHT

PHYSICAL ACTIVITY ASSESSMENT

CHAPTER CONTENT :

	Summary
8.1	Introduction
8.2	Subjects and methods
8.3	Results
8.4	Discussion

"When the population is often obese and sedentary, exercise would be expected to have beneficial effects both in promoting weight reduction and in improving glucose regulation".

Zinman and Vranic, 1985

SUMMARY

In the Jeddah CVD pilot study, 95 of 125 men [76%] aged 20-65 years completed a questionnaire concerning six aspects of physical activity and had a venous plasma glucose measurement on a sample taken at 0 h and 2 h after a 75 g glucose load. An activity score was calculated by grouping subjects into three broad categories: inactive, moderately active, and active. The responses revealed an 'inactive community' and there was no significant differences in the activity score between the three glucose tolerance groups.

8.1 INTRODUCTION

There are considerable differences in the prevalence of NIDDM both between and within populations. A putative factor to explain some differences and/or changes in the frequency of NIDDM is physical activity. Physical inactivity has been implicated as a risk factor for development of NIDDM (*West et al, 1978*). Studies examining the acute and chronic effects of physical activity on carbohydrate metabolism and glucose tolerance provide evidence for the biological plausibility for such a relationship. Yet, despite both of these facts, epidemiological data on the role of physical activity in the aetiology of NIDDM or in the worsening of glucose tolerance are still scarce. Results from a few recent cross-sectional studies suggest that physical inactivity may be an independent risk factor for NIDDM (*Taylor et al, 1984; Cederholm et al, 1985; Lindgärde et al, 1981*), whereas two large earlier studies had not found a significant relationship between glucose tolerance and habitual physical activity (*Jarrett et al, 1986; Montoye et al, 1977*).

The relationship between habitual physical activity and glucose or NIDDM has been explored in few populations and with inconsistent results (*Montoye et al, 1977; Taylor et al, 1984; Cederholm, 1985*). Most recently the Whitehall Study provided the opportunity for a further exploration of the relationship, with the potential advantage of large numbers and observations (*Jarrett et al, 1986*). Similar observation was also described for Mauritius where physical inactivity was correlated with the prevalence of NIDDM and IGT (*Dowse et al, 1991*). Thus, this study aimed at describing the physical activity status in an urban male population of Saudi Arabia and exploring differences between the three glucose tolerance groups.

8.2 METHODS

Background. Methods of acquiring information on physical activity may involve (a): questioning or self-recording, (b): some form of measurement of movement, (c): heart rate recording, or (d): measuring energy expenditure (*Durnin, 1990*). Several useful general reviews of these methods have been published (*Montoye et al, 1984; Washburn et al, 1986*). The most common technique of assessment is to measure physical activity by questionnaire or by a diary record. Some questionnaires require a skilled interviewer and can take up to 1½ hour, whereas others can be self-administered and completed in 10-15 min (*Durnin, 1990*). In addition, although other possible measurements are on the horizon, questionnaires and interviews, still appear to be the most convenient methods for assessing exercise habits in epidemiological studies at present (*Montoye, 1990*). Testing the validity of the different types of questionnaire is difficult and there is still great uncertainty in this field (*Durnin, 1990*). Moreover, none of the newly developed questionnaires and interviews have been validated, mainly because of a lack of an acceptable criterion (*Montoye, 1990*). The goal of measuring physical activity as an essential indicator in the survey is not to measure physical activity as a whole, but to measure those parts which can be influenced by individual attitudes (*Leparsky et al, 1987*).

This study. In this study, therefore, the questionnaire for physical activity which recommended by the Countrywide Integrated Noncommunicable Diseases Intervention Programme [CINDI] (*Leparsky et al, 1987*) was extended and applied [Appendix 5]. This contains twenty two questions in six parts which cover various forms of possible physical activity including : work [Q1-4], household [Q5-7], leisure-time [Q8-12], sports [Q13-16], recreational walking [Q17-19] and general[Q20-22]. Subsequently an activity score was calculated by grouping the subjects into three broad categories: inactive, moderately active, and active [values 1-3]. The activity score covered four types of activity, i.e home activity, leisure time activity, sport activity and recreational walking. 'Active' had three or

more [yes] responses, 'moderately active' had intermediate combination of responses and 'inactive' had three or more [no] responses. These categories, in other studies, have shown some relationship with subsequent rates of mortality (*Marmot, 1984*). The latter group including those men who participated in vigorous sporting activities such as swimming and football. The technique used was direct questioning by the investigator and this section required up to 15 minutes for each subject which was only completed in 76 % [n=95] of the total subjects screened [n=125]. Data on other survey measurements was also available for this cohort [n=95] including age, BMI, WHR, blood pressure and fasting and 2-h plasma glucose and insulin [Chapter 4].

Statistical approach: Descriptive analysis was shown in percentages for the whole group. Crosstabulation and χ^2 was used. Mann-Whitney was used to compare activity score between groups and to compare variables between active groups.

8.3 RESULTS

The responses to the physical activity questionnaire, for the whole population, are shown diagrammatically [Fig 8.1-8.6] where each diagram represent responses to a single question. Then, the responses to some physical activity questions and the activity score by glucose tolerance groups are shown [Table 8.1]. Finally, subject characteristics by activity score groups are presented [Table 8.2].

Work related activity [Fig 8.1] responses revealed that only 4 % walked to and from work and the great majority [95 %] use their own cars or public transport as a means to travel to work. Daily time spent of less than 30 min walking to and from work was found in 83 %. All of those interviewed were working and their types of work were mainly sedentary [62%], since walking while at work of less than 2 hours was found in [61 %].

Household activity questions [Fig 8.2] revealed that one third [33%] of subjects participated in household work. Half [46%] spent less than 2 hr per week

doing so and one fifth [21 %] had perspiration and required rest following that work.

Participation in leisure-time activity [Fig 8.3] was even lower [14%]. Leisure time was rarely spent in walking [8%], maintaining activity [6%] and none performed regular training. Of those who were performing activity, the majority [64%] took exercise up to 2 times per week. Moreover, duration of an activity episode of less than 30 minutes was found in 64%, and the frequency of perspired activity of less than once per week was found in 36%.

Participation in sport [Fig 8.4] was also poor [17%]. Swimming [56%] and football [19%] were the most common types of sport enjoyed in this population. However, the majority [76%] spent less than 2 hours per week in sports, and 12% stated that the present sport times was more than previous times.

Participation [56%] in recreational walking [Fig 8.5] was found in rather more of the population. However, nearly half [45%] walked less than 2 hours per week.

Finally, the general perception on activity [Fig 8.20-8.22] showed that a third of subjects [35 %] were satisfied with their current physical condition, although 70% never seriously increased their leisure-time physical activity and 61% showed no change during the preceding six months in their leisure-time physical activity.

In general, coding these various aspects of physical activity into three categories showed that 77% of this population of urban men were inactive, 10% moderately active and only 13% were active.

Comparisons of some of these aspects of physical activity by glucose tolerance group are shown in [Table 8.1]. The inactivity values tended to be higher in NIDDM, intermediate in IGT and lower for NGT. This was also clearly found in the activity score where the inactivity score was highest in NIDDM [93%], intermediate in IGT [80%] and lowest in those with NGT [70%]. However, no significant differences were found between these glucose tolerance

groups, perhaps because of small numbers.

Characteristics of the subjects by activity score groups are shown in Table [8.2]. Inactivity was 3-fold more prevalent than activity, although both groups had comparable age ranges. Those found to be inactive tended to have higher values for most of the examined variables. Thus, the inactive group had higher BMI and WHR, their lipids values were higher, their fasting glucose and insulin were greater and they were more resistant to insulin. None of these when compared showed statistical significance, however.

8.4 DISCUSSION

Diabetes mellitus, like hypertension and other chronic disorders, is included in the list of so-called lifestyle diseases. Although diabetes is strongly genetically determined, heredity cannot totally explain the high rates found. Among the environmental factors that might be implicated in the outburst of diabetes in a certain population, physical activity superimposed on overnutrition plays a fundamental role.

At present, epidemiological data on the role of physical activity in the aetiology of NIDDM or in the worsening of glucose tolerance are still scarce. Studies are not available in the literature which described physical activity in relation to diabetes mellitus in Saudi Arabia or in the surrounding Gulf countries which share a more or less similar environment. Moreover, these prevalence studies (*Fatani et al, 1985; Bacchus et al, 1982; Chapter 3*) which suggested that inactivity might play a role, did not assess it. This was the rationale behind my intention to assess physical activity in our urban population and to investigate the relationship of this activity to glucose tolerance group.

In this inactivity has been demonstrated in many physical activity facets and one can rightly label this community as an 'inactive community'. The number, although reasonable for a pilot investigation, needs to be larger, perhaps in the range of thousands, to show significant differences in terms of glucose tolerance or activity score groups. This study did, however, show that a greater

number of subjects with NIDDM and IGT did not participate actively in various lifestyle activities. Moreover, inactivity being lower in NGT [70%], intermediate in IGT [80%] and higher in NIDDM [93%] provides support that physical inactivity, at least in this subpopulation, tended to be commoner in subjects with glucose intolerance.

One direct study relevant to life style is that of Taylor et al (1984), who studied males of two ethnic groups - Indian and Melanesian - living in Fiji. Diabetes prevalence was calculated from known plus newly diagnosed, the latter comprising men with 2-h plasma glucose levels of 11.1 mmol/l or more. Physical activity was classified as sedentary, light, moderate or heavy, based principally upon occupation. Comparing sedentary/light with moderate/heavy activity groups, age adjusted 2 h blood glucose levels were higher in the sedentary/light groups in both populations, but the difference was statistically significant only in Melanesians [0.4 mmol/l; $p = 0.03$]. For reasons which are not apparent, the difference in prevalence of diabetes [higher in the less active groups] was more evident in the Indians.

Approximately 20 years ago, Björntorp and his colleagues suggested that physical training is associated with lower plasma insulin concentrations and improved insulin sensitivity (Björntorp et al, 1972). They found that physically active middle-aged men who regularly participated in sports had much lower plasma insulin concentrations both while fasting and after the administration of glucose than did inactive men matched for age and weight who had similar blood glucose concentrations. Our study was similar in that we showed relatively, although not significantly, higher values for fasting insulin and insulin resistance in the inactive group.

The hypothesis that exercise might provide some protection against the development of NIDDM rests upon observed reductions in glycaemia and insulinaemia following acute exercise or exercise programmes and the substantially increased incidence of NIDDM in populations where life-style,

including occupational exercise has changed drastically during the 20th century. Reviewing the experimental studies in NIDDM, Zinman and Vranic (*Zinman et al, 1985*) state "When the population is often obese and sedentary, exercise would be expected to have beneficial effects both in promoting weight reduction and in improving glucose regulation. Documentation of improving insulin sensitivity and glucose tolerance has been shown. However, the effects have not been of large magnitude and are often of short duration".

The Whitehall study despite the large numbers of observations (Jarrett et al, 1986) could find no association between estimated leisure time activity or a surrogate measure of energy expenditure and glucose tolerance as indicated by the blood glucose level 2-h after an OGTT. Further, although in many fewer subjects, there were no significant differences in estimated leisure time activity in men with established or newly diagnosed diabetes compared with non-diabetic subjects.

A similar investigation to the Whitehall Study, although with several methodological differences, was performed in the Tecumseh Health Study (*Montoye et al, 1977*) in which 1300 men aged 16-64 were classified into three groups on the basis of their habitual leisure and occupational physical activity [in the Whitehall Study occupational activity was not considered as most subjects had sedentary occupations]. There was no significant correlation between glucose tolerance and physical activity.

Cederholm and Wibell (*Cederholm et al, 1985*) studied glucose tolerance and reported leisure time activity in 371 men and 435 women, aged 47-54 years, derived from the register of the County Council of Uppsala. The subjects were divided into two groups: low [682] and high [125] activity. After adjustment for co-variables the mean 2 h blood glucose level was 0.52 mmol/l higher in the less active group ($p < 0.001$), but when the sexes were compared separately the difference was only significant in men.

The Whitehall Study and the other studies reviewed above provide little or no support for the hypothesis that physical activity provides some protection

against the risk of developing NIDDM. Even when statistically significant, differences in glucose tolerance between activity groups are trivial in degree. Moreover, although a role for physical conditioning in the prevention of NIDDM has been suspected on the basis of population and cross-sectional studies, no effect of exercise independent of other factors has been identified (*Horton, 1991*). It is possible, however, that as these studies were cross-sectional in design that they may lack power in detecting a putative beneficial effect. Thus, prospective studies would have a greater chance of detecting an effect, if it exists, but the logistic problems in mounting a study of adequate size and duration would provide a considerable deterrent.

A recent long-term study presented convincing evidence that there was an inverse relation between energy expenditure in leisure-time physical activity and the development of NIDDM during the subsequent 15 years (*Helmrich et al, 1991*). This prospective study proved that the protective effect of physical activity was independent of other risk factors and was particularly strong among men who participated in vigorous sports, although participation in less vigorous activities was also protective. Moreover, in a selected high-risk subgroup, habitual physical activity had the greatest protective effect, decreasing the incidence of diabetes by 24 % from the highest activity group to the lowest. These findings strongly support the position that persons who are at substantial risk for NIDDM should be encouraged to maintain a high level of physical activity in their daily lives.

At this point, this advice is of utmost importance to the urban male population in Saudi Arabia, since the prevalence of both IGT and NIDDM were found very high. Thus, improving the present style of physical activity might help in this direction and an a large-scale intervention study would be of interest.

Regular physical exercise has long been considered an important part of the treatment of NIDDM and is frequently prescribed, along with diet, oral hypoglycaemic agents, or insulin. In addition to lowering blood glucose levels in the short term, exercise may improve long-term glucose control, as indicated by

glycated haemoglobin. Insulin sensitivity is also increased. Other benefits of exercise extend to several cardiovascular risk factors, such as improvement in mild-to-moderate hypertension, improved lipid profiles, and more effective weight reduction (*Horton, 1988*).

Clearly, regular physical activity is an important component of a healthy lifestyle for all of us, but it may be particularly important for those at increased risk for chronic diseases such as NIDDM, hypertension, and hyperlipidaemia.

In conclusion, physical activity responses revealed a great inactive sector in this urban community. Encouraging activity by any means should be one of many advisory practices among not only the high-risk or diabetic population in particular, but also among the general population as a whole.

Table 8.1
Physical activity responses and score [%] by glucose tolerance group [n=95]

	NGT	IGT	NIDDM
n (%)	55 (58)	25 (26)	15 (16)
Don't walk :			
To and from work	69	84	87
While at working days	18	24	26
Subjects <u>not</u> participating in activity :			
Household	62	68	87
Leisure-time	84	88	93
Sport	78	84	100
Recreational walking	40	44	60
Perception of current physical condition :			
Bad or very bad	11	24	27
Never increased leisure time activity	62	88	74
Perceived no change in preceding 6 months activity	54	76	60
The activity score :			
Inactive	70	80	93
Moderately active	15	4	7
Active	15	16	0

Statistical comparisons showed no significance.

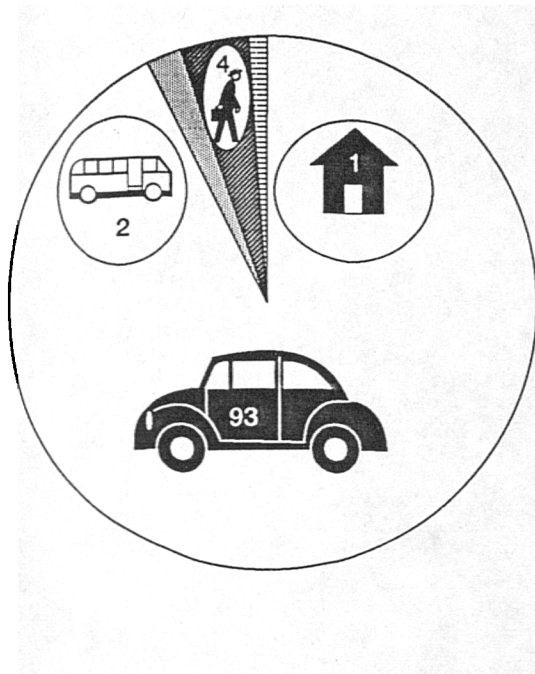
Table 8.2
Subjects [n=95] characteristics by activity score.

		Inactive	Active
n		73	22
(%)		(77)	(23)
Age	years	38 ± 1	36 ± 1
(range)		(20-55)	(22-50)
BMI	h/m ²	28.6 ± 0.5	27.4 ± 0.8
WHR		1.01 ± 0.01	1.00 ± 0.01
Systolic blood pressure	mmHg	121 ± 2	121 ± 3
Diastolic blood pressure	mmHg	75 ± 1	74 ± 2
Cholesterol	mmol/l	4.7 ± 0.1	4.5 ± 0.2
Triglyceride	mmol/l	1.5 ± 0.1	1.2 ± 0.1
Fasting glucose	mmol/l	6.1 ± 0.2	5.4 ± 0.1
2-h glucose	mmol/l	8.7 ± 0.6	6.7 ± 0.5
Glucose AUC	mmol l ⁻¹ h	17.1 ± 0.8	14.5 ± 0.6
Fasting insulin	mU/l	17.8 ± 1.5	15.5 ± 2.3
Insulin AUC	mU l ⁻¹ h	147 ± 7	149 ± 15
proinsulin pmol.l/ Insulin pmol.l	molar ratio	0.13 ± 0.1	0.12 ± 0.02
HOMA model assessment of :			
β-cell function		169 ± 18	179 ± 32
Insulin resistance		4.9 ± 0.4	3.7 ± 0.5

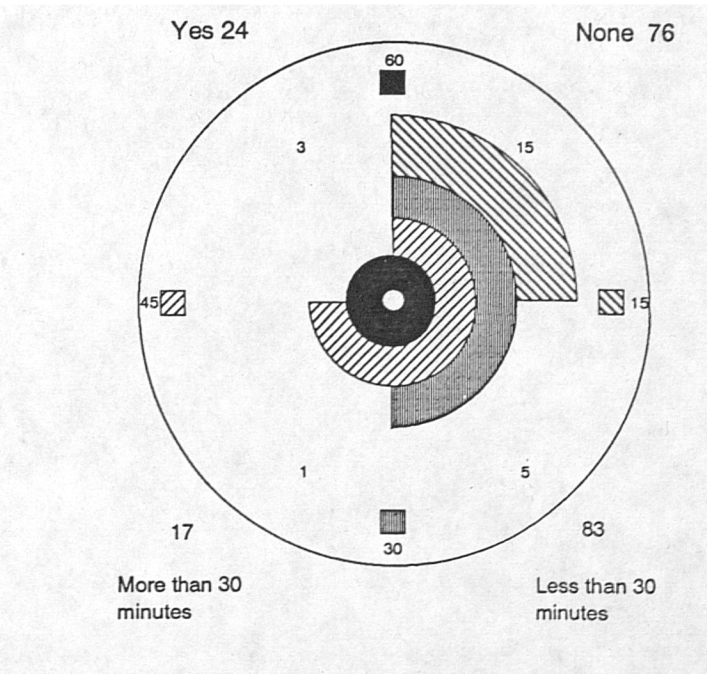
Mean ± SEM. Statistical comparisons showed no significance.

Fig 8.1 WORK RELATED ACTIVITY (%)

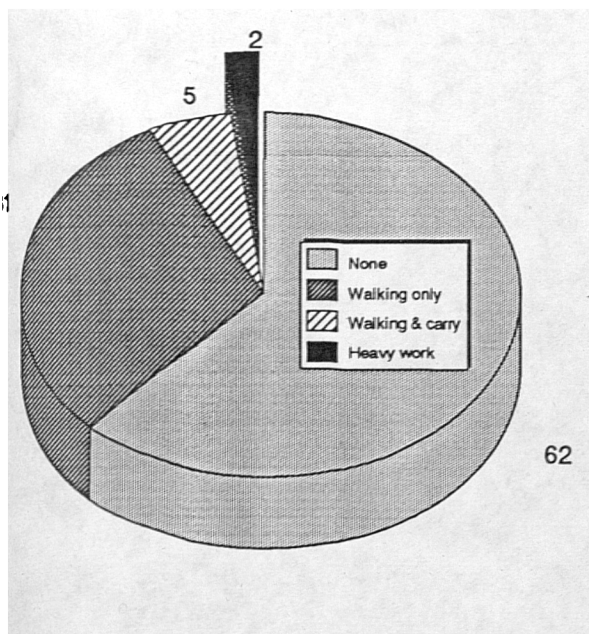
A Means of travel to work



B Daily time spent walking to & from work (minutes)



C Work types identified by physical activity



D Walking hours while at work

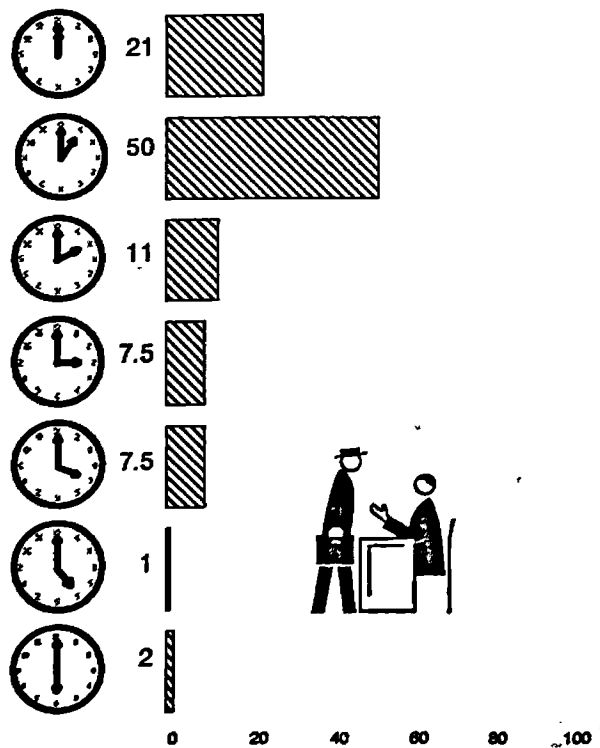
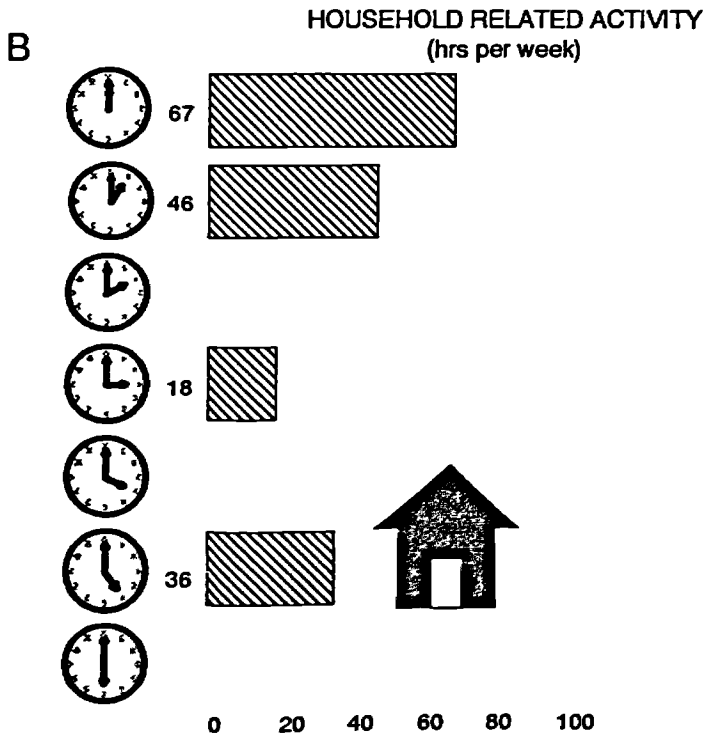
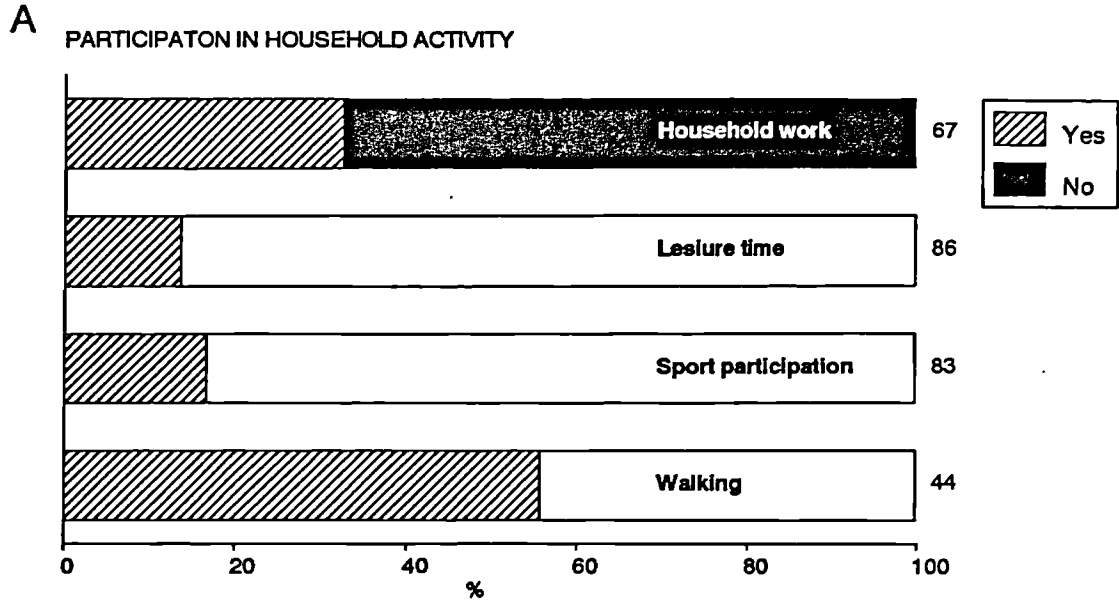


Fig 8.2 HOUSEHOLD ACTIVITY (%)



C DOES THE HOUSEHOLD WORK REQUIRE REST AFTERWARDS ?

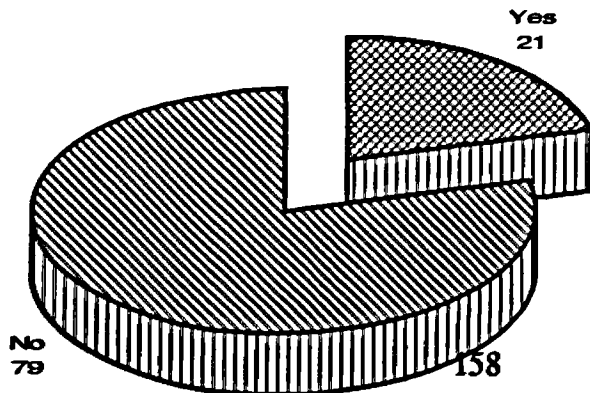
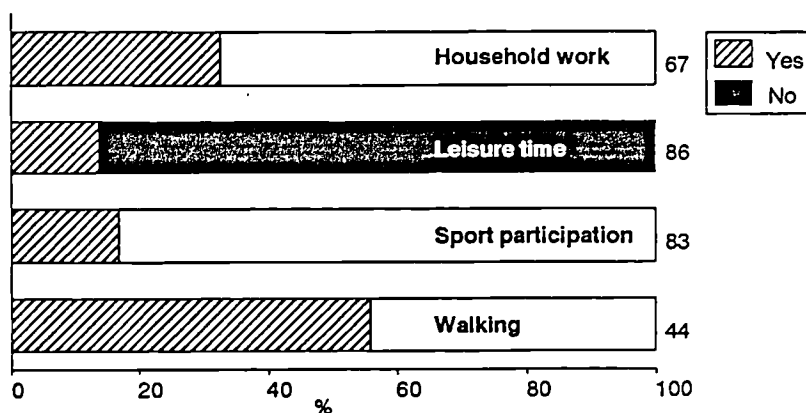


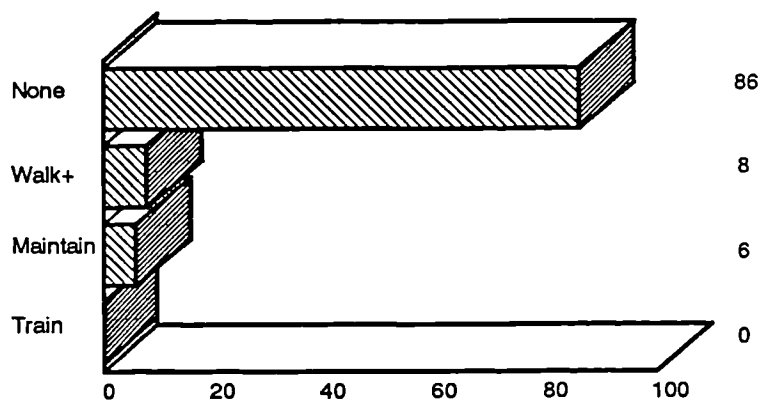
Fig 8.3 LEISURE TIME ACTIVITY (%)

A PARTICIPATION IN LEISURE ACTIVITY



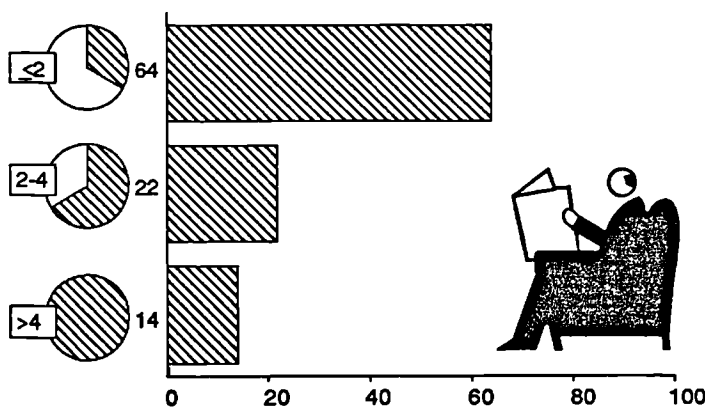
B

TYPE OF LEISURE-TIME ACTIVITY



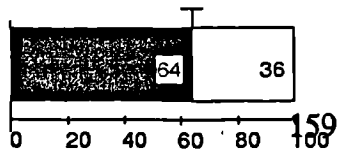
C

FREQUENCY OF LEISURE-TIME PHYSICAL ACTIVITY (Times per week)



D

DURATION OF AN ACTIVITY EPISODE < 30 Min >



E

PERSPIRED ACTIVITY FREQUENCY < Once / week >

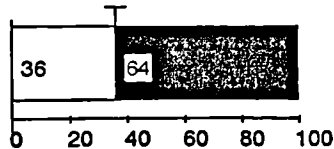


Fig 8.4 SPORTING ACTIVITY (%)

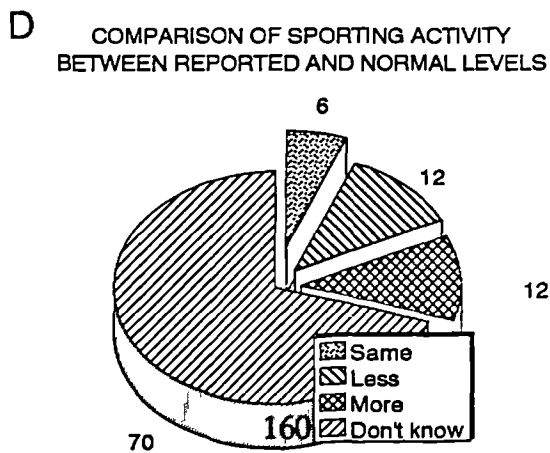
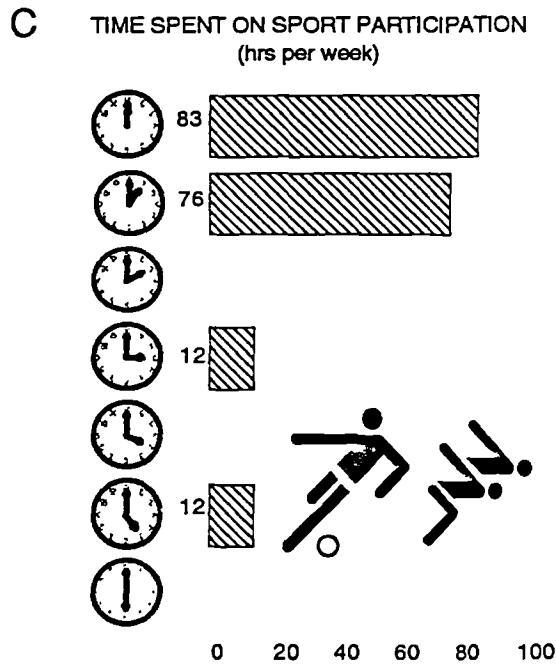
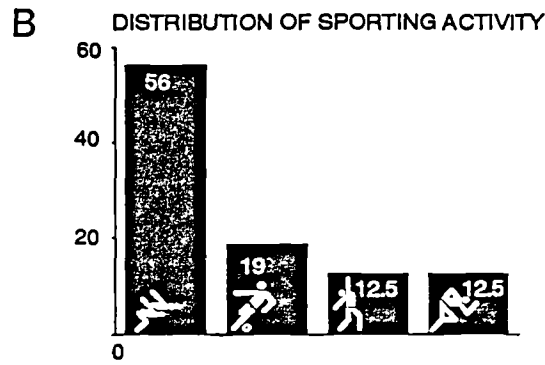
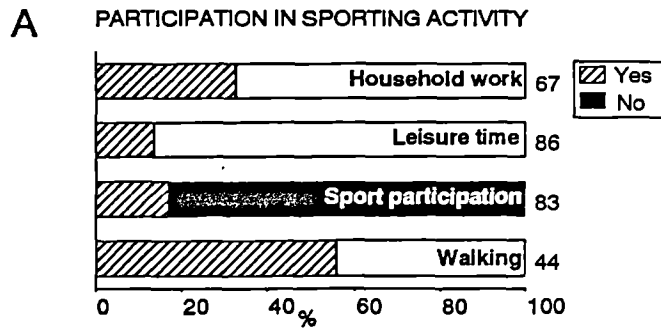


Fig 8.5 RECREATIONAL WALKING (%)

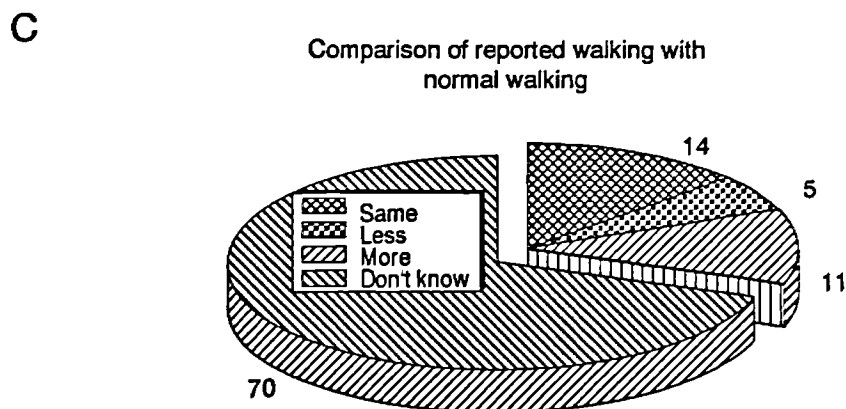
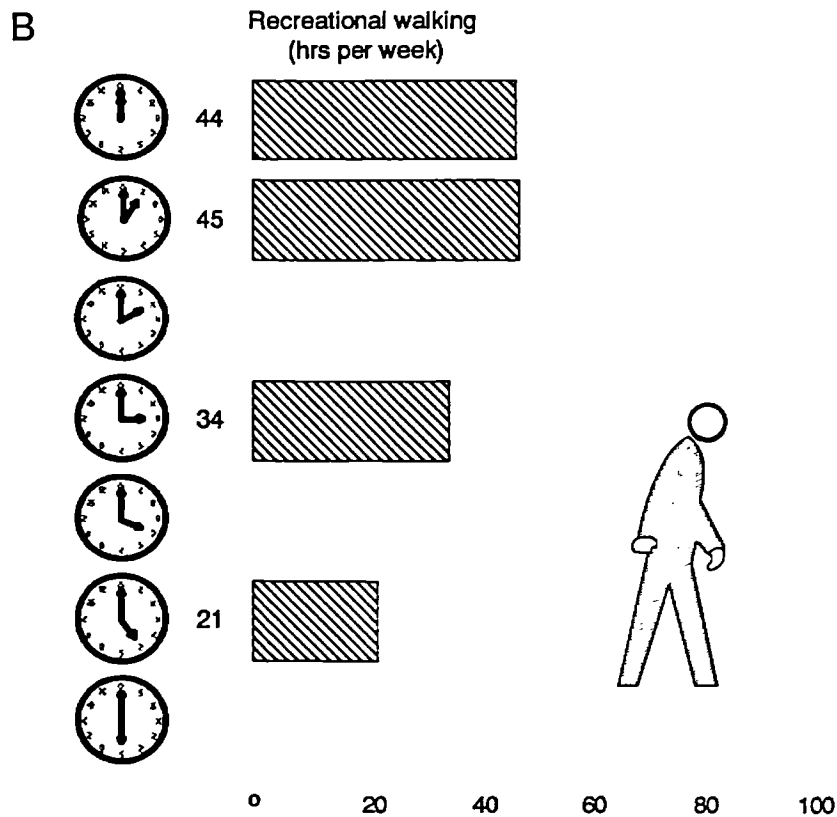
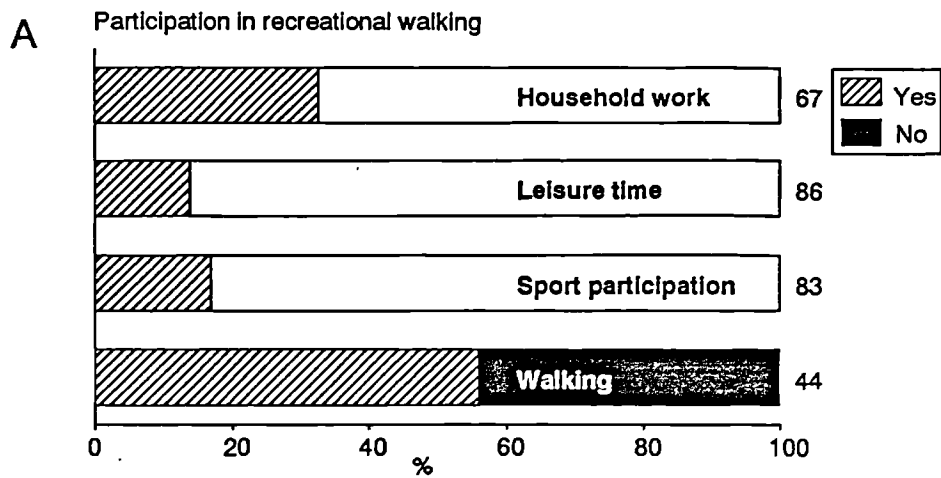
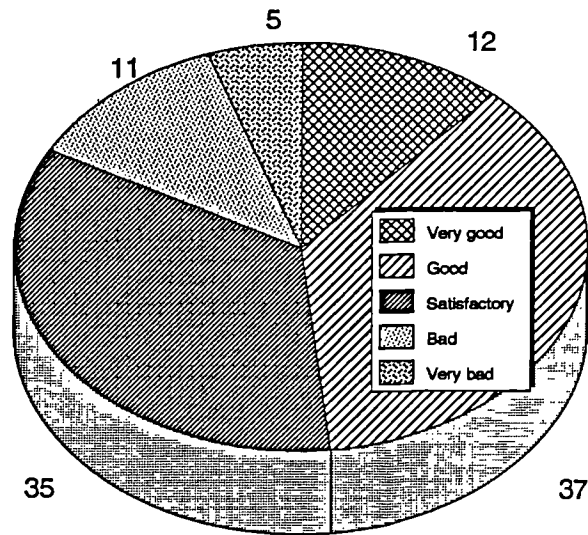
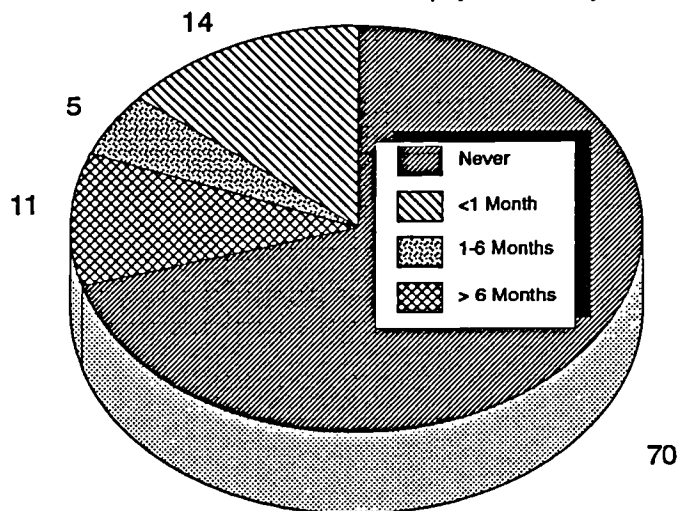


Fig 8.6 GENERAL PERCEPTION ON ACTIVITY

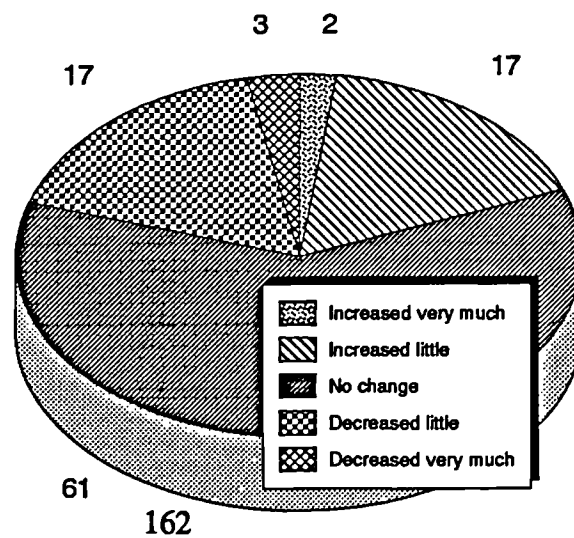
A Perception of current physical condition



B Increases in leisure time physical activity



C Perception of change in physical activity over the last 6 months



RESULTS

CHAPTER NINE

Nationals vs non-Nationals

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Ethnicity is one kind of patent difference, and although it is difficult to define it accurately, it does convey the idea of peculiar characteristics assigned to some group of persons who can be easily recognizable and can be differentiated from others. G. Alleyne in (*Cruickshank ea al, 1989*)

SUMMARY

The aim of this chapter is to examine similarities or differences that might existed between Saudi and non-Saudi citizens. The available variables were carefully examined in this respect and are presented here.

9.1 INTRODUCTION

The estimated total population living in Saudi Arabia was about 12 million in 1985 (*James et al, 1990*). Throughout the centuries, a large proportion of the population has consisted of Muslims of different national origin, who came for Hajj and later settled in the Arabian peninsular. In addition, there have been a few non-Muslims who came for trade, business, work or diplomacy. Since commercial drilling for oil commenced in Saudi Arabia in 1938, the influx of expatriate workers from the West and Third World Countries increased dramatically. The foreign population in the whole Kingdom was estimated to be 28.4 % in 1985 (*James et al, 1990*). This reached 53 % in Jeddah (*Al-Harbi, 1988*), perhaps because it is the main west sea-port and the gateway to the Holy Cities, Makkah and Madinah. This background justifies the main theme of this chapter which aimed to examine the effects of nationality on different metabolic, dietary and physical activity variables.

9.2 SUBJECTS and METHODS

The study subjects [n=125; 95 for the dietary and physical activity studies], the questionnaire, the survey physical procedures and blood measurements, laboratory assaying methods, definitions and cut-off points were all described in previous chapters. Here for the purpose of nationality differences, Saudi nationality was defined as those who were holding Saudi Identity Cards, which almost always indicated that the father [one generation] and or his offspring were born in Saudi Arabia. All other nationalities, due to the small number for each, were grouped collectively under non-nationals.

The data were then, analysed with the SPSSPC+ using nationality as a dichotomous explanatory variable against all the available response variables

separately. Comparison between the two nationality groups were performed using the Mann-Whitney U test or X^2 test. A p value < 0.05 was taken to be significant.

9.3 RESULTS

The results are shown in Tables [9.1-9.8]. Nationalities are shown in Table [9.1]; Saudi were found to be the majority (61%). The non-Saudi constituted 11 nationalities, the majority of them were from Arabic-speaking countries [Egypt, 41%] and few from non-Arabic-speaking countries such as Afghanistan and Somalia. The non-nationals originated from four different ethnic groups, namely, Mediterranean [85 %], African [11 %], and equal percentages from the Indian subcontinent [2%] and South East Asia [2%].

Socioeconomic and environmental features are shown in Table [9.2]. Saudi Arabia as a place of origin was found in 96% of nationals but, not surprisingly, in only 14 % of non-nationals. There were, also not surprisingly, differences between nationals and non-nationals with respect to residency duration, educational level and income. Thus, 65 % of nationals had lived 15 years or more in Saudi Arabia versus 20 % of non-nationals; higher education was less in nationals [35%] versus non-nationals [47%], but higher income [>4500 SR/month] were mote frequent among nationals [77 % vs 12 %]. However, income class was the only factor which showed a significant difference [p < 0.05].

Nationals [65%] smoked more frequently than non-nationals [55%], although they had low rates for smoking cigarettes only [40 % vs 53 %], but high rates of smoking both cigarettes and shisha [10 % vs 6 %]. These and CVD symptoms were not significant between nationals and non-nationals.

The prevalence rates of glucose intolerance and risk factors by nationality are shown in Table [9.3]. The rates of diabetes mellitus were not different in nationals [13.1 %] vs non-nationals [14.3%] in contrast to IGT where rates approached 30% in the nationals compared with 22.4% in non-nationals. There were, however, no significant differences in the rates of abnormal glucose tolerance, due to small numbers. The rates of obesity and increased WHR were

not significantly higher in nationals compared to non-nationals. Hypertension and hyperuricaemia rates were slightly lower in nationals. Nationals also had significantly higher rates of hypercholesterolaemia but no significant differences in hypertriglyceridaemia compared to non-nationals.

General and anthropometric measurements are shown in Table [9.4]. Both groups exhibit comparable age and BMI and there was no significant differences in WHR, systolic or diastolic blood pressure.

Glucose and insulin values during the OGTT, fructosamine and AUC values are shown in Table [9.5]. β -cell function and relative insulin resistance calculated from the HOMA model are also shown. There were no significant differences in these variables between the two nationality groups. However, fasting and 2-h plasma glucose values tended to be higher in non-nationals, although not significantly. Both nationalities had comparable fasting insulin levels but 2-h insulin values were significantly higher in nationals [$p < 0.05$].

The metabolic-endocrine group of risk factors are shown in Table [9.6]. There were no significant differences between the two nationalities for cholesterol, triglyceride, uric acid, fasting insulin, proinsulin, proinsulin/insulin molar ratio or SHBG values.

Selected dietary habits and physical activity score are shown in Table [9.7]. Taking snacks between meals tended to be greater in nationals [61 %] versus non-nationals [45 %, ns] and in particular those snacks that were taken between lunch and dinner [84 % vs 59 %]. No food items showed significant differences between nationals vs non-nationals except for brown bread [78 % vs 31 %] and dates [84 % vs 45 %] [Both, $p < 0.05$]. The nationals, however, had significantly greater inactivity scores compared to non-nationals [86 % vs 32 %, $p < 0.05$]. Apart from these observations no significant differences existed in the many variables assessed between nationals and non-nationals.

9.4 DISCUSSION

The concept of 'ethnic origin' is not simple. There are fundamental

questions of definition of 'ethnicity' to be addressed and any investigation of ethnic groups requires a method to identify their members. For example, does the term include solely immigrants, or also those in the 'new' country to parents [or grandparents] born overseas ?. If the latter, is membership of a particular ethnic group restricted to those with both parents born in the same country; how are those of mixed parentage to be assigned ?. To a great degree the choices to be made rest upon the requirements and orientation of the researcher (*Cruickshank, 1989*). In this study, the nationwide difference was the only feasible approach due to the small size of the group.

The association between ethnic/racial group and disease and the differences in the frequencies of various diseases among a wide range of ethnic and racial group is well-known and was discussed comprehensively recently (*Polednak, 1989*).

Both diversity and similarity across populations need to be recognised, whether one is dealing with sociocultural characteristics, biological characteristics, or risk of disease. Cross-sectional studies of human behaviour, including those related to dietary habits, and reactions to the stresses of acculturation and migration, are important from an epidemiologic perspective. The variability in disease patterns within groups and the opportunity to study the processes of migration, acculturation, and urbanization has also been amply demonstrated in diverse groups as South American Indians, Melanesian, and Polynesians (*Polednak, 1989*).

This chapter attempted to explore this concept of ethnic differences within Saudi Arabia, since at least third of its inhabitants are foreigners. Ethnic groups may differ in sociocultural factors and this was clearly observed in this group with respect to income where a high socioeconomic class was much more frequent among nationals, if income was considered as social class indicator. But these patterns in sociocultural aspects may change rapidly with time as shown in various migrants groups (*Cruickshank, 1989*).

The previous studies on the prevalence of diabetes mellitus in Saudi Arabia examined rural/urban differences and were from the central and western regions [Chapter 3]. However, unfortunately, none of these studies, although their sample size was large, differentiated between nationals and non-nationals.

The prevalence rate of diabetes in this study was almost the same between nationals and non-nationals, but that for IGT was higher among nationals. However none of the risk factors showed any significance differences except cholesterol where hypercholesterolaemia [≥ 5.7 mmol/l, $p=0.04$] was found three times more among nationals. However values at cut-off points of ≥ 5.2 and 6.5 mmol/l were insignificant. A recent report (*Inam et al, 1991*) with larger sample [$n=8291$] on importance of cholesterol screening in Saudi Arabia found that 38% had serum total cholesterol concentrations > 5.2 mmol/l but this report did not examine ethnic differences.

The prevalence of NIDDM varies greatly both among members of the same ethnic group living in different environments, and among members of different ethnic groups living in the same environment (*King et al, 1988*). These patterns provide evidence that NIDDM is the result of an interaction between environmental and genetic determinants. Expatriate Indian communities in many part of the world have much higher prevalence of diabetes than in most regions within India itself (*Ahuja et al, 1979*). However, Indians living in an affluent suburb of New Delhi also had high rates which were similar to those living in Southall in West London (*Verma et al, 1986*). Also, differences have been found in the prevalence of diabetes among Japanese migrants living in the island of Hawaii [12.3%] and those within Japan itself living in Hiroshima [6.9%] (*Kawate et al, 1979*).

"The Bedouin diet was limited to milk products, dried fruit and grains from settled villagers when available. Meat was only eaten when an animal was slaughtered for special ceremonies. Their diet was, on occasions, supplemented by raiding from settled villagers (*Encyclopaedia Britannica*)". This quoted

statement may not be true for Saudi Arabia today. Moreover, the dishes consumed in Saudi Arabia are considerably different in their ingredients to those consumed in other Middle East or Western countries, since the Middle Eastern diet which depends on cereals and legumes as a source of protein may not apply to the Saudi diet where the diet is composed of many animal protein foods such as eggs, meat, fish and poultry (*Musaiger, 1987*).

The traditional diet of Saudi Arabia has regional variations influenced by climate [which varies from the hot arid desert of the central region to the humid coastal plains and the cooler mountain regions of the south], availability of fertile land, the sea and the annual influx of Pilgrims to Makkah. The Hejaz or Makkah region has been influenced by Pilgrims and foods of Indian and Indonesian origin have been incorporated into the diet. The southern region which includes the Asir mountains and the coastal plain traditionally grew millet, sorghum and wheat as their staples. The central region had wheat as their staple but production was limited because of the low and unreliable rainfall.

Social and religious aspects of food are quite peculiar. As is the case in many traditional societies, food has a great social meaning and it is the tradition in Saudi Arabia to share food with ones neighbour. Food is offered to all who enter the home and to refuse is to cause great offence. Food also has religious connotations particularly during specific times such as Ramadan. Honey is believed to have health giving properties and therefore has a special place in the diet as do dates (*Quran*).

The high percentage of immigrants with various nationalities has led to a wide range of foods available on the market. This is mainly because of the different food habits of those immigrants. There were more than 1,900 different kinds of processed foods available on the market which are imported from 38 countries (*Musaiger, 1987*). Thus, immigrants have influenced food consumption by introducing many food habits to the region. For example, the Arab group, mainly Palestinians, Lebanese, Egyptians and Jordanians, have had an impact on

food habits. They introduced many popular dishes such as falafel, himmos, lebeneh, fowl moudams, tabbouli, shawarma, bakalawah and knafeh. Indians and Pakistanis have influenced the food habits. Indian dishes, such as keema, dhal, biriyani, mutton curry and chapati, are widely consumed in these countries. The wide usage of spices in cooking and the availability of various kinds of spices on the market is the most striking example of the influence of the Indian subcontinent. In Saudi Arabia, the influence of Yemenis was also observed as several Yemeni foods are consumed such as Yemeni bread, mutabak leham and mutabak mamuz (*Sawaya et al, 1986*).

Dates are a good source of non-haem iron and some other minerals in addition to simple sugars. The habit of eating them was, not surprisingly, found to be higher among nationals since this was part of their customs. However, a similar explanation would be unlikely for the higher rates of eating brown bread among nationals. Although, the differences in dietary habits were confined to these two food items [and perhaps snacking habits] it would be enough to shed some light into the importance of ethnic differences in planning dietary advise.

The ethnicity of the group of Nisei men did not seem to affect greatly the nutrient character of their diet (*Tsunehara et al, 1990*). Population or ethnic differences in CVD risk factors are apparently related largely to differences in intake of specific dietary constituents such as total fats or specific types of fat, fibre, and sodium. This study did not show marked ethnic differences in CVD risk factors although certain, unrelated, dietary constituents were changed.

The differences in activity score can be clearly explained on the basis of social class differences between nationals and non-nationals. Thus, high inactivity rate among nationals might be related to the high income rate which facilitates more lazy albeit luxurious life-style.

Therefore, this study showed certain biological and behavioural differences on an ethnical basis in a population sharing one environment. It illustrated differences in insulin responses, in the rate of hypercholesterolaemia, in

certain socioeconomic and dietary aspects, and in the level of activity. However, the lack of difference in diabetes and CVD risk factors between nationals and non-nationals suggests environmental factors are dominant over the genetic background in these populations or there is some common genetic material.

Thus describing and explaining of associations between ethnic group and disease has several applications (*Polednak, 1989*). In clinical practice recognition of diversity in disease risk by ethnic group among patients can be helpful in diagnosis and in planning of both prevention and treatment strategies. Also, the applications of knowledge of ethnic differences in disease for clinicians relates to decisions about possible diagnostic tests and avoidance of unnecessary tests. In contrast to misdiagnosis based on lack of awareness of ethnic group as a risk factor, clinical oversight may occur with regard to diseases not expected to be found in an ethnic group. Finally, primary care physicians may need to learn to apply techniques such as goal setting or community group involvement in the treatment of diabetes, dietary aspects or overweight.

In general, part of effective preventive medicine involves recognition of modifiable factors involved in disease causation or progression. This recognition may be aided by the results of studies that consider ethnic group, which may provide clues to more specific and modifiable risk factors and better prediction of outcome. The explanation of population differences in rates of disease, which sometimes follow ethnic lines of demarcation, will require attention to multiple potential differences including sociocultural and biological factors.

The diversity of nationalities that formed this population in Jeddah is an index to the actual mixture of ethnic groups that constituted the whole community. A future work should consider this diversity and a comparative study, perhaps, between the endogenous and the exogenous population as a whole or between the two different exogenous ethnic groups, or between a single ethnic group and its counterpart in the place of origin, would be of future interest.

9.1 :
Population nationalities.

	n [%]
All	125 (100)
Saudi	76 (61)
non-Saudi	49 (39)
Components of non-Saudi nationalities :	
1. Egypt	20 (41%)
2. Sudan	9 (18%)
3. South Yemen	4 (9%)
4. North Yemen	3 (6%)
5. Tunisia	3 (6%)
6. Palestinian	3 (6%)
7. Jordan	2 (4%)
8. Lebanon	2 (4%)
9. Pakistan	1 (2%)
10. Afghanistan	1 (2%)
11. Somalia	1 (2%)
Total	49 [100]

Table 9.2 :
General historical characteristics by nationality [n=95].

	Nationals	non-Nationals
n	48	47
(%)	(51)	(49)
Place of origin:		
Saudi Arabia	96	14
Elsewhere (Mediterranean Indian, South East Asian, Africa)	4	86
Residence duration in Saudi Arabia:		
up to 15 yrs	35	80
> 15 yrs	65	20
Education level:		
Up to secondary school	65	53
University or above	35	47
¹Income (SR):		
Up to 4500	23	88
> 4500	77	12
<hr/>		
Smoking	65	55
<hr/>		
Symptoms of CVD:		
-Pain or discomfort in chest	6	8
-Severe pain across the front of chest lasting for half an hour or more	4	0
-Pain in either leg on walking	27	20
-Weakness or loss of strength in an arm or leg lasting for 24 hrs	0	0

1, P < 0.05.

Table 9.3 :
Prevalence (%) of glucose intolerance and CVD risk factors by nationality in 125 subjects.

		Nationals %	non-Nationals %
n		76	49
[%]		(61)	(39)
NGT		57	64
IGT		30	22
NIDDM		13	14
Overweight	BMI ≥ 27 km/m²	51	57
Obesity	BMI ≥ 30 kg/m²	32	31
WHR	> 1.00	51	49
Hypertension	WHO, 1978	4	6
Hypercholesterolaemia	≥ 6.5 mmol/l	11	2
¹ Hypercholesterolaemia	≥ 5.7 mmol/l	24	8
Hypercholesterolaemia	≥ 5.2 mmol/l	32	24
Hypertriglyceridaemia	≥ 2.2 mmol/l	11	20
Hypertriglyceridaemia	≥ 1.7 mmol/l	25	31
Hyperuricaemia	≥ 4.2 mmol/l	39	41

1, P < 0.05.

Table 9.4 :
Clinical characteristics by nationality. Mean \pm SEM or range [n=125].

	Nationals	non-Nationals
n (%)	76 (61)	49 (39)
Age (yrs)	38 \pm 8 (20-60)	38 \pm 7 (27-64)
Weight (kg)	78 \pm 15	82 \pm 13
Height (m)	1.69 \pm 0.1	1.70 \pm 0.1
BMI (kg/m²)	28 \pm 5.0	28 \pm 4
Waist (cm)	96.5 \pm 11.6	98.5 \pm 10.5
Hip (cm)	95.8 \pm 10.9	97.9 \pm 10.3
WHR	1.01 \pm 0.03	1.01 \pm 0.03
Systolic BP (mmHg)	119 \pm 15	120 \pm 15
Diastolic BP (mmHg)	74 \pm 11	76 \pm 10

Statistical comprison showed none significance.

Table 9.5 :
Glucose and insulin during OGTT (75g) , fructosamine and the calculated area under the response curve (AUC) for glucose and insulin expressed in mean \pm SEM .

	Nationals	non-Nationals
Glucose (mmol/l) :		
Fasting	5.6 \pm 0.1	6.2 \pm 0.3
1-h	10.3 \pm 0.4	10.7 \pm 0.6
2-h	8.0 \pm 0.4	8.3 \pm 0.8
AUC (mmol l ⁻¹ h)	15.9 \pm 0.6	16.8 \pm 1.1
Fructosamine (mmol/l)		
	2.5 \pm 0.04	2.5 \pm 0.05
Insulin (mU/l):		
Fasting	15.7 \pm 1.4	15.8 \pm 1.5
1-h	118.8 \pm 6.0	103.9 \pm 7.2
¹ 2-h	108.2 \pm 8.2	86.7 \pm 7.8
² AUC (mU l ⁻¹ h)	162 \pm 9	138 \pm 10
Pathogenesis :		
β -cell function	166 \pm 18	155 \pm 19
Insulin resistance	4.0 \pm 0.4	4.3 \pm 0.4

1,2; P < 0.05

Table 9.6 :
Metabolic-endocrine group of risk factors by nationality. Mean \pm SEM and range [n=125].

	Nationals	non-Nationals
Cholesterol (mmol/l)	4.9 \pm 0.1 (2.9-7.3)	4.7 \pm 0.1 (3.3-6.9)
Triglyceride (mmol/l)	1.4 \pm 0.1 (0.5-5.4)	1.5 \pm 0.1 (0.4-3.1)
Uric acid (mmol/l)	3.8 \pm 0.1 (0.7-6.3)	3.9 \pm 0.1 (0.9-5.6)
Fasting insulin (pmol/l)	94.4 \pm 8.6 (12-490)	94.8 \pm 9.1 (15-360)
Proinsulin (pmol/l)	13.2 \pm 1.2 (1.6-51.7)	12.0 \pm 1.3 (1.9-38.5)
Proinsulin/ insulin molar ratio	0.16 \pm 0.01 (0.02-0.45)	0.14 \pm 0.01 (0.05-0.48)
SHBG (nmol/l)	33.8 \pm 2.5 (10.2-162.5)	36.9 \pm 3.0 (12.7-109)

Statistical comparison showed none significance.

Table 9.7
Eating habits and activity score [%] by nationality [n=95].

	Nationals	non-Nationals
n (%)	48 (51)	47 (49)
General habits :		
Main meal as lunch	98	90
Taking snacks between meals	61	45
-Time of snacks between lunch and dinner	84	59
Specific, each food items taken at least once/week :		
More than 7 eggs per week	12	13
Milk	66	69
Lamb	96	90
Chicken	94	94
Honey	47	39
Jam	39	26
Beans	78	77
White bread	84	94
¹ Brown bread	78	31
Rice	100	92
Potatoes	55	71
Salad	98	98
² Dates	84	45
Apples	78	88
Bananas	74	75
Oranges	88	88
Soft drinks	78	79
Activity score (%):		
Inactive	86	68
³ Active	14	32
Moderately active	6	15
Active	8	17

1, 2, 3 ; P < 0.05

RESULTS

CHAPTER TEN

SUBSTRATES and HORMONAL ESTIMATION

CHAPTER CONTENT :

- Summary.
 - 10.1 Introduction.
 - 10.2 Subjects and methods.
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SUMMARY

The aim of this chapter is to investigate the differences and/or the similarities between subjects diagnosed as IGT and NIDDM compared with normals. The emphasis is on some hormonal and metabolic aspects following an oral stimulus.

10.1 INTRODUCTION

A full account of the subjects with IGT was given in Chapter 2 and only a brief introduction is given here. The redefinition and classification of diabetes mellitus by the World Health Organization (*WHO, 1985*) and the National Diabetes Data Group of USA (*NDDG, 1979*) introduced the category of Impaired Glucose Tolerance (IGT). Justification for a group interposed between normal and frankly diabetic patients was provided by epidemiological data showing that only a small proportion show worsening to diabetes each year and that they only rarely develop specific diabetic complications (*Jarrett et al, 1979; Fuller et al, 1980*). Nevertheless, identification of these patients was recommended since they have an increased risk of developing atherosclerosis, but not the microvascular complications of diabetes (*Fuller et al, 1980*).

IGT is common in obesity and is associated with abnormalities of intermediary metabolites both fasting and during the OGTT which suggested decreased insulin sensitivity not only with regard to glucose, but also in non-esterified fatty acid (NEFA) and ketone body metabolism (*Robertson et al, 1990*). Furthermore, IGT in obesity may be associated with reduced insulin clearance and additional insensitivity to insulin action in hepatic and peripheral glucose metabolism and fatty acid re-esterification, but that appears not to be the case for lipolysis or ketogenesis (*Robertson et al, 1991*). Those patients with IGT were mainly recruited from hospital clinics and they were grossly obese (BMI > 45). It is unclear whether the abnormality of blood glucose in subjects with IGT is accompanied by other metabolic abnormalities which characterized this group and might lead in some of them to overt diabetes. Thus, the study described in this chapter sought any hormonal and intermediary metabolites abnormalities during

fasting and also in the response to an OGTT in non-obese healthy male subjects with IGT recruited in the community. Results are compared with those found in subjects with NGT and NIDDM.

10.2 SUBJECTS and METHODS

Subjects :The recruitment procedure for the whole population was described earlier [Chapter 4]. Those who were found to have either IGT or NIDDM using WHO screening criteria (*WHO, 1985*) were given a further confirmatory OGTT without informing them about their results, in order to establish the diagnosis. Those who agreed and came for the second OGTT were informed about their results. They were then asked to agree to a further extended OGTT to look at their metabolic responses in more detail. An age and weight-matched cohort was selected from those with normal glucose tolerance [NGT] on screening and acted as normal controls. Thus, the whole group [n=43] involved in this study consisted of subjects with IGT [n=17], with NIDDM [n=9] and with NGT [n=17]. All subjects gave informed, written consent to the protocol before enrolment for the last OGTT. No subjects were taking any medications including thiazide diuretics, corticosteroids, and they had no evidence of other disease as was shown by the questionnaire in the screening phase. The study took place in the 'investigation room' established by the investigator at the Diabetic and Hypertension Centre [DHC] of Jeddah, Saudi Arabia.

Protocol: Subjects were asked to eat their normal diet which usually contained a minimum of 300 g carbohydrate. None of the subjects drank alcohol. No special instruction was given to avoid vigorous physical activity in the 48 hour prior to study since the preceding questionnaire revealed that the cohort was inactive. Special instruction was given to the subjects the day before the study day to abstain from eating or drinking from 11:00 pm and to come early next morning by 8:30 am to ensure an overnight fast of 10 - 12 h. Those who failed to follow the instructions were given another appointment [2 subjects]. Throughout the study subjects remained semi-recumbent and were not smoke. Entertainment was

provided via educational pamphlets or video-cassettes during the waiting time to avoid boredom. An 18-gauge Brannula cannula was inserted into an antecubital vein at least 30 minutes before sampling. After two fasting blood samples [at -15 and 00 minutes] had been taken each subject drank 75 g anhydrous dextrose in 300 ml water over 5 min. Additional blood samples were taken at 30, 60, 90, and 120 minutes from the start of the glucose drink for insulin, C-peptide, proinsulin, glucagon, glucose, lactate, pyruvate, alanine, 3-hydroxybutyrate, glycerol and NEFA. A further two samples were taken for insulin, C-peptide and proinsulin at 10, and 20 minutes. At each sample time at least 10 ml blood was withdrawn after discarding the initial 0.5 ml: 1 ml was mixed with refrigerated 5 ml perchloric acid solution and centrifuged immediately to remove the protein precipitate; 2 ml was placed in lithium heparin tubes for measurement of plasma NEFA, and 2.25 ml in traysolol (0.25 ml) tubes for glucagon. The remainder of the blood was placed in plain tubes for measurement of serum insulin, C-peptide and pro-insulin. The perchloric acid extract and separated plasma or serum were stored at - 40 °C until assay. The detailed analytical methods were described above [Chapter 4].

Statistical analysis. The results have been analysed by calculating the areas under the responses curves [AUC] of the different variables were calculated using the trapezoidal rule and were compared for the three groups of subjects (*Leyland et al, 1991; Mathews et al, 1990*). As most of the variables studied were not normally distributed, non-parametric statistical methods have been used. Comparisons between two groups were performed using the Mann-Whitney U-test. Comparisons between the three glucose tolerance groups were performed with Kruskal-Wallis one-way analysis of variance by ranks. A p-value (two-tailed) less than 0.05 was considered statistically significant. All results are expressed as mean \pm SD and SEM in text and as mean \pm SEM in the figures.

10.3 RESULTS

Details of subjects and basic parameters are shown in Table 10.1. Age in those with IGT and NIDDM was almost identical and non-significantly higher

than those with NGT. Subjects with IGT had slightly (but non-significantly) higher BMI [29 ± 2] compared to the BMI found in NGT and NIDDM subjects. Fructosamine values, not surprisingly, were significantly higher in the NIDDM group compared with those with NGT [$p < 0.004$] or IGT [$p < 0.002$]. Area under the response curve [AUC] following OGTT by glucose tolerance groups are shown also [Table 10.2].

Hormone concentrations: The mean [\pm SEM] concentrations are shown for serum insulin [Fig 10.1], C-peptide [Fig 10.2], proinsulin [Fig 10.3] and glucagon [Fig 10.4]. Areas under the curve for insulin [mU/l/h] were higher in NGT [193 ± 23], intermediate in IGT [168 ± 22] and lowest in those NIDDM [86 ± 14] but a significant difference [$p < 0.04$] was only shown between IGT vs NIDDM. Although the basal plasma insulin values tended to be lower for NGT [9.6 ± 1.5] vs IGT [13 ± 2] and NIDDM [13 ± 3], the incremental values were reversed and were significantly higher in NGT [111 ± 13] vs IGT [96 ± 13 , $P = 0.03$] and vs NIDDM [48 ± 8 , $P = 0.02$]. The absolute insulin concentrations were intermediate throughout in subjects with IGT between the highest values found in NGT and lowest values found in NIDDM. The peak insulin concentration occurred at 60 - 90 minutes for both IGT and NGT whereas it was at 90 - 120 minutes in NIDDM.

C-peptide AUCs were similar in subjects with NGT and IGT [3.5 ± 0.03] but both were higher than in NIDDM [2.7 ± 0.02]. However, no significant difference was found between the three groups except at 20 min [IGT vs NIDDM, $P = 0.04$] and at 60 minutes [NGT vs NIDDM, $P = 0.03$]. The AUC for proinsulin was lowest in NGT [36 ± 4], intermediate in IGT [41 ± 4] and highest in NIDDM [54 ± 14], although these differences did not reach significance. Similar patterns were found for glucagon values with no significant difference between the three groups NGT [81 ± 6], IGT [81 ± 5] and NIDDM [107 ± 13].

Substrate concentrations :

The mean concentrations are illustrated for glucose in Fig 10.5, lactate [Fig 10.6], pyruvate [Fig 10.7], alanine [Fig 10.8], 3-hydroxybutyrate [Fig 10.9],

NEFA [Fig 10.10], and glycerol [Fig 10.11]. Blood lactate concentrations were intermediate for IGT between NGT which were the lowest and NIDDM which were the highest. This was clearly seen in the basal state and at the late time points. Pyruvate concentration differences broadly followed those of lactate except that the IGT group were the highest, and those with NIDDM were intermediate. 3-hydroxybutyrate values were highest in those with IGT while the values for NGT and NIDDM were almost identical. There were no significant differences between the three groups for intermediary metabolite concentrations of lactate, pyruvate, 3-hydroxybutyrate and alanine. However, significant differences were found for glycerol and NEFA. NEFA concentrations were significantly higher, compared with NGT, in subjects with IGT [$p=0.01$] and NIDDM [$p=0.006$] which was also the case for glycerol [NGT vs IGT, $p=0.02$; NGT vs NIDDM, $p=0.04$] [Fig 10.10, Fig 10.11].

10.4 DISCUSSION

The insulin response to oral glucose, which was significantly lower in the subjects with IGT, contrasts with the findings of previous studies of 'chemical diabetes' (*Reaven et al, 1968; Savage et al, 1975*) and the earlier finding of defects of insulin-stimulated glucose uptake in chemical diabetes (*Reaven et al, 1977; Kolterman et al, 1981*). This could be due to heterogeneity among subjects with IGT which is well known, or selection bias could conceivably have produced a normal glucose tolerance cohort with high basal insulin values.

The data cannot determine whether, in non-obese subjects with IGT, it is resistance to insulin-stimulated glucose uptake into muscle or failure of suppression of hepatic gluconeogenesis which is the more important component of the hyperglycaemia following oral glucose.

It is of interest to note that in these subjects the early (60 min) insulin response is similar in those groups despite subjects with IGT having a significantly higher blood glucose concentration. An additional component of the hyperglycaemia might be a degree of impairment or delay in insulin secretion in

response to oral glucose (*Prager et al, 1987*). A reduced insulin response was a striking finding in the studies of first-degree relatives of Type 2 diabetic patients (*Barnett et al, 1981; O'Rahilly et al, 1986*). Population and clinical studies indicate that glucose-stimulated hyperinsulinaemia is associated with deterioration from normal to IGT whereas a reduced insulin response is a marker of subsequent progression to diabetes (*Sicree et al, 1987; Kadowaki et al, 1984*). In this study, subjects with IGT and NIDDM, abnormalities were present in lipid metabolism when IGT was compared with NGT and these were similar in NIDDM. Despite similar basal insulin concentrations, subjects with IGT had significantly raised NEFA which were accompanied by higher glycerol concentrations. Plasma NEFA concentrations were also significantly higher in IGT throughout the OGTT [$p < 0.05$]. The findings for NEFA and glycerol indicate resistance to the action of insulin in adipocytes.

The results of the comparison of IGT with NGT and NIDDM in non-obese subjects suggest that IGT is associated with reduced insulin concentrations, a high insulin: proinsulin ratio, insulin resistance and reduced insulin secretion, in addition to increased peripheral fatty acid mobilization. Previous studies of insulin insensitivity in subjects with IGT where insulin receptor binding has been measured have reached conflicting conclusions, with insensitivity attributed solely to decreased binding (*Kolterman et al, 1981*) or purely to post-binding defects (*Nagulesparan et al, 1980*).

Both NIDDM (*Banerji et al, 1989*) and lesser degrees of glucose intolerance (*Reaven et al, 1979*) were heterogeneous in terms of insulin insensitivity of glucose metabolism, and it would not be unreasonable to suppose that this heterogeneity will extend to other aspects of insulin action. Consequently, generalizations from this cohort of subjects with IGT to other groups is not possible.

In summary, significant differences in NEFA and glycerol concentration both fasting and in response to OGTT were observed between non-obese subjects

with NGT and IGT and also NGT and NIDDM but not between IGT and NIDDM. Thus, non-obese subjects with IGT have abnormalities of fat metabolism as well as of carbohydrate metabolism. These findings suggest resistance to the action of insulin occurs in a number of different tissues, already in the "prediabetic" state.

Table 10.1
Subjects characteristics by glucose tolerance group. Mean \pm SEM .

	NGT	IGT	NIDDM
n	17	17	9
Age (yrs)	39 \pm 2	43 \pm 3	44 \pm 3
Weight (kg)	78 \pm 3	83 \pm 3	79 \pm 5
Height (m)	1.7 \pm 0.02	1.7 \pm 0.01	1.7 \pm 0.03
BMI	27 \pm 1	29 \pm 1	27 \pm 1
^{1,2} Fructosamine (mmol l ⁻¹)	2.5 \pm 0.1	2.3 \pm 0.1	3.1 \pm 0.2

1, NIDDM vs NGT p = 0.004
2, NIDDM vs IGT p = 0.002

Table 10.2
Area under the curve [AUC] following OGTT by glucose tolerance groups. Mean \pm SEM.

	NGT	IGT	NIDDM
Hormones :			
*Insul AUC (mU l ⁻¹ h)	193 \pm 23	168 \pm 22	86 \pm 14
C-pep AUC (nmol l ⁻¹ h)	3.5 \pm 0.3	3.5 \pm 0.3	2.7 \pm 0.2
ProInsulin AUC (pmol l ⁻¹ h)	36.4 \pm 4.5	40.8 \pm 4.1	54.4 \pm 13.5
Glucagon (pmol l ⁻¹ h)	80.7 \pm 5.6	81.3 \pm 4.9	106.6 \pm 13.0
Substrates			
Glu AUC (mmol l ⁻¹ h)	13.5 \pm 0.5	16.4 \pm 0.7	21.5 \pm 1.5
Lac AUC (μ mol l ⁻¹ h)	2004 \pm 168	2063 \pm 151	2125 \pm 138
Pyr AUC (μ mol l ⁻¹ h)	121 \pm 9	138 \pm 17	129 \pm 15
Ala AUC (μ mol l ⁻¹ h)	548 \pm 32	605 \pm 30	639 \pm 39
3-HB AUC (μ mol l ⁻¹ h)	34 \pm 9	59 \pm 23	35 \pm 11
*NEFA AUC (mmol l ⁻¹ h)	0.41 \pm 0.05	0.58 \pm 0.05	0.63 \pm 0.05
*Gly AUC (μ mol l ⁻¹ h)	51 \pm 4	72 \pm 6	59 \pm 3

* Means presence of significance, see text.

Fig. 10.1: Serum insulin values; basal and post-glucose.

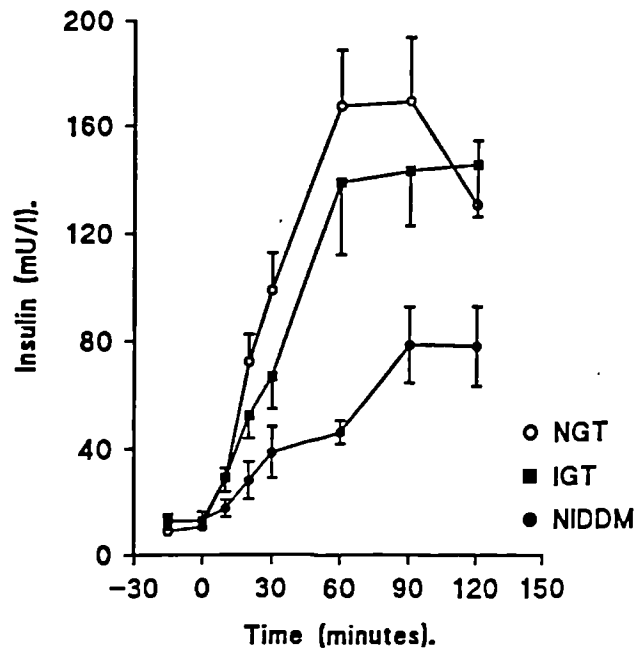


Fig. 10.2: Serum C-peptide values; basal and post-glucose.

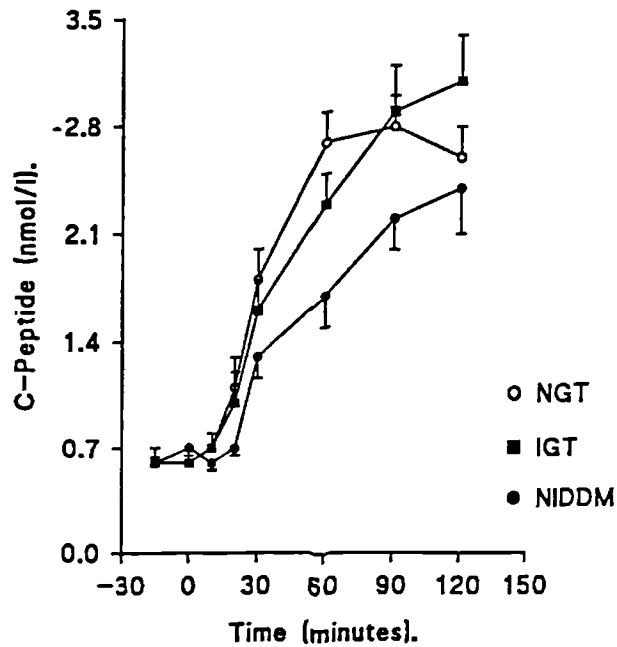


Fig. 10.3: Serum proinsulin values; basal and post-glucose.

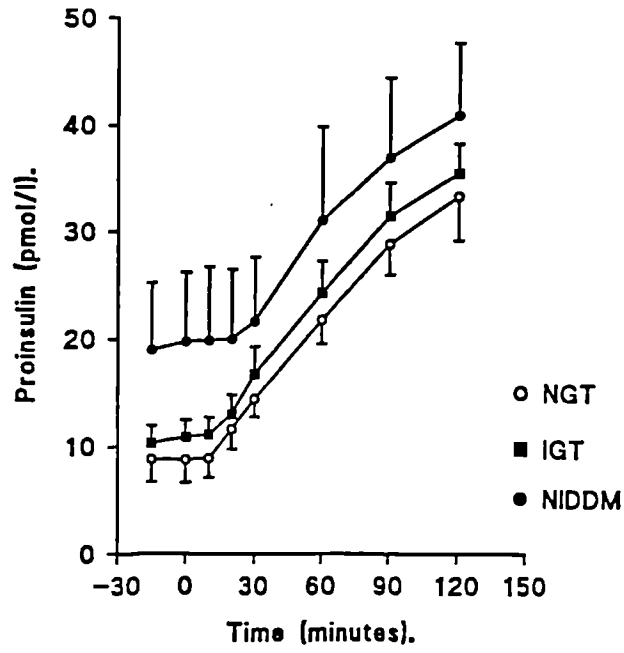


Fig. 10.4: Plasma glucagon values; basal and post-glucose.

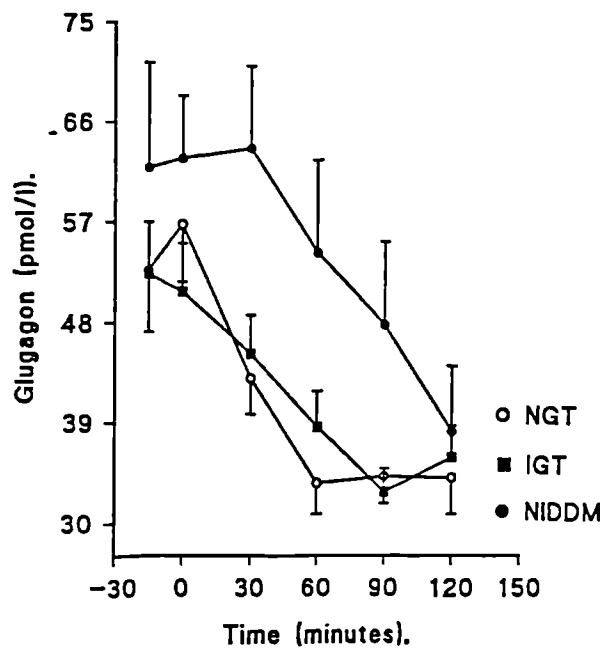


Fig. 10.5: Blood glucose values; basal and post-glucose.

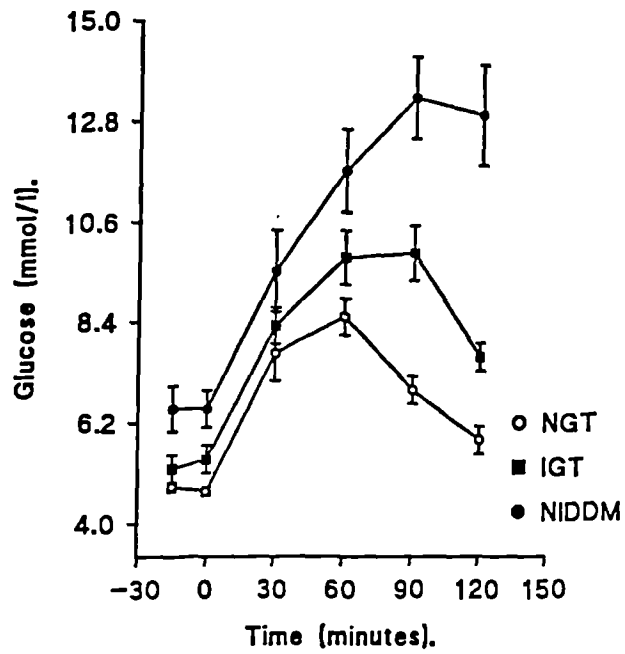


Fig. 10.6: Blood lactate values; basal and post-glucose.

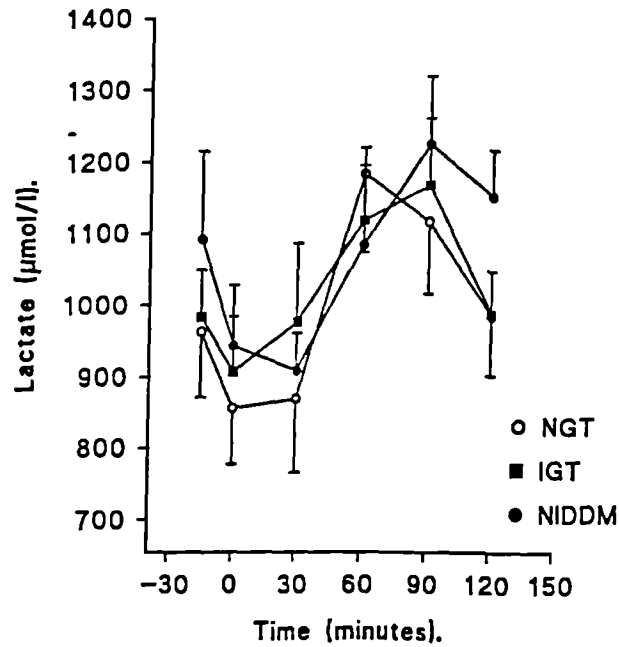


Fig. 10.7: Blood pyruvate values; basal and post-glucose.

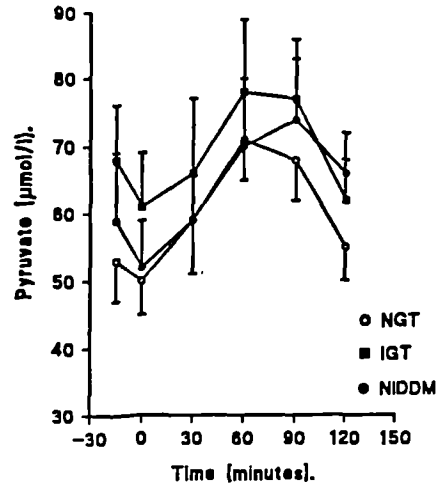


Fig. 10.8: Blood alanine values; basal and post-glucose.

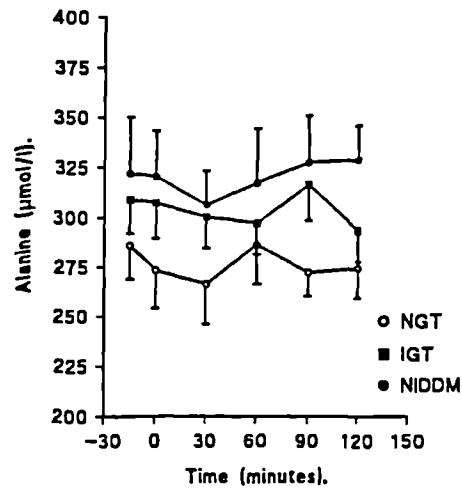


Fig. 10.9: Blood 3-hydroxybutyrate values; basal and post-glucose.

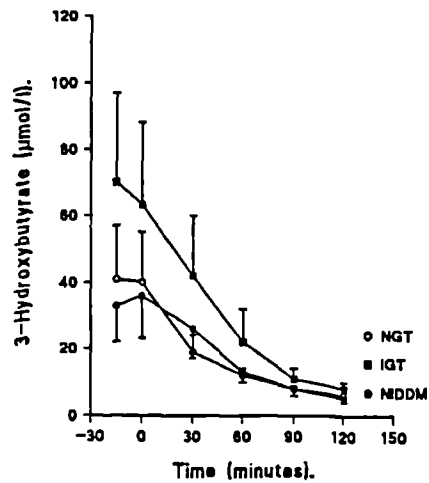


Fig. 10.10: Plasma NEFA values; basal and post-glucose.

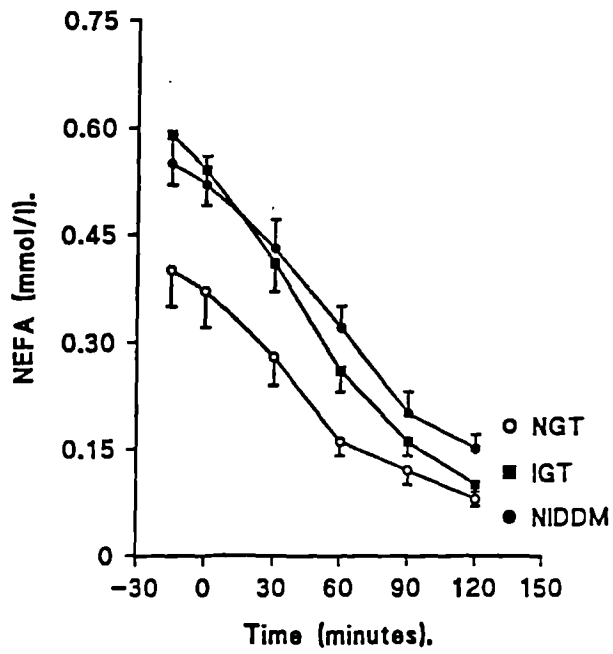
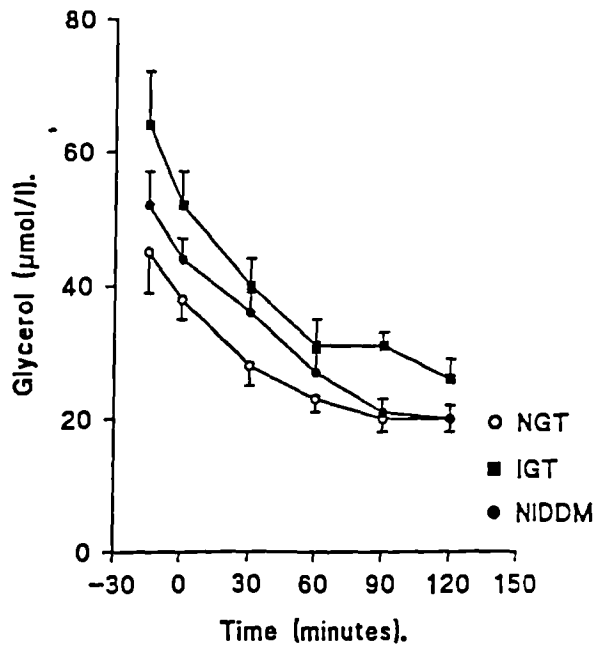


Fig. 10.11: Blood glycerol values; basal and post-glucose.



GENERAL SUMMARIES

CHAPTER ELEVEN

CONCLUSIONS and FUTURE

CHAPTER CONTENT :

- 11.1 Conclusions.**
 - 11.2 Potential for future studies.**
-

11.1 CONCLUSIONS

The application of epidemiology to the study of NIDDM is providing new insights into many aspects of this major public-health problem, including its natural history, prevalence, incidence, morbidity, and mortality in diverse populations around the globe. These studies, on epidemiology, are providing direction for research into the possible molecular defect or defects and biochemical mechanism or mechanisms underlying NIDDM and important information on the extrinsic [social, cultural, environmental] risk determinants. This study is just one example. It highlights the high prevalence of glucose intolerance and CVD risk factors such as hypertension, dyslipidaemia and hyperinsulinaemia and demonstrated the importance of regional adipose tissue distribution, particularly upper-body obesity and physical inactivity in enhancing the risk of NIDDM. These findings have important implications for the primary prevention of NIDDM.

There is an increasing prevalence of diabetes mellitus in Saudi Arabia, as shown here, and perhaps in other Gulf countries (*Asfour et al, 1990*), and makes a high demand on the existing health services. Several measures should be taken into consideration for the control of diabetes in the Saudi Arabian community. These include proper health education for the public and training medical and paramedical health workers about diabetes. In many hospitals and health centres in the region the management of diabetes is insufficient, mainly because of shortage of physicians or general practitioners interested in diabetes. Moreover, there is a lack of a team work approach to care including diabetic nurses, dietitians, chiropodist and ophthalmologists.

This study, also shows the importance of social habits such as smoking. Cigarette smoking is a major risk factor which is increasing dramatically in Saudi

Arabia and may partly be responsible for the increased risk of heart disease, since there was an increase of 47% in imports in one year 1982-1983. Alcohol consumption, although forbidden has also shown a gradual increase which may be because of the increased frequency of those travelling outside the country to drink alcohol.

This study identified several other problems including hypertension, and hyperlipidaemia. Many people were, perhaps, unaware of their condition, and there was limited public concern regarding hypertension. A large proportion of cases did not receive regular treatment and there was a lack of routine measurements of blood pressure or lipids by the physician in patients attending the polyclinics.

Another emerging risk factor presented here is obesity which is becoming one of the most important public health problems in Saudi Arabia. Although it is more prevalent among middle-aged adults, childhood obesity has also been reported (*Musaiger, 1987*). Unfortunately, there has until now been no well-designed study to determine the prevalence of obesity in this community. Most of the studies are based on weight and height measurements, which are a less accurate index, as overweight may be due to an increase in muscle mass or body fluid or body fat.

There are several factors contributing to the incidence of obesity in Saudi Arabia. With the greater availability of housemaids, cars, televisions and other sophisticated household appliances, the physical activity of the people has significantly diminished. Among women the problem is more serious, as watching television and eating snacks are the main activities during their leisure time, especially when the majority of women are unemployed. Their life is more sedentary even though they do not consume high amounts of food. Also, perhaps, most of the inhabitants of Saudi Arabia seek easy work and rely on services. In many cases they rely on sources of revenue other than those derived from employment and hard work. Recently there has been an interest in physical

fitness programmes, but only few people joined such activities.

The attitude towards obesity is another important factor. The traditional clothing style of Saudi Arabian people also plays a vital role. The long, comfortable and wide clothes worn by men and women have made them not feel the gradual gain in weight. This is because these dresses have more space to absorb weight gain. Once these people change over to western style clothing, they then realize how much fat they have gained. Many other factors are responsible for the occurrence of obesity in the Saudi Arabia such as multipregnancies, shifting from breast to bottle-feeding and environmental factors. A well-designed study to determine the factors associated with obesity in Saudi Arabia is strongly supported.

Among all these factors, diet is of key importance in the aetiology of CHD. The transition to a more westernized diet is likely to result in a high intake of animal fat and hence saturated fatty acids and dietary cholesterol. The intake of foods rich in cholesterol such as eggs, red meats and chicken, has increased as highlighted in this study. The cultural background of the various nationalities and their food habits are among the factors which influence the control of diabetes in Saudi Arabia and should be carefully assessed and implemented. Physicians should be well instructed in the dietary management of diabetes. Information regarding loss of weight, physical exercises and sound food habits should be a major component in any health education programme for the public.

Excessive intake of food is also responsible for obesity in the region. There is good evidence that the energy intake of the people has increased. The availability and promotion of high carbohydrate snacks such as chocolates, sweets and biscuits as well as the high-energy content of traditional dishes also contributes to obesity. However, whether people with glucose intolerance tended to have different dietary habits compared to normals needs further clarification, since this study does not prove it.

In Saudi Arabia the following major barriers of diabetes activities in the field of nutrition could be encountered. Nutrition is given little or no priority in health education to the diabetic subjects. The role of sound nutrition in improving the health status of these subjects is underestimated by the physicians.

This is, perhaps, due to shortage of local qualified personnel specializing in nutrition or other related fields such as dietetics and food sciences. More studies are needed to investigate the composition of diets in the region and the role of these diets in the aetiology of diseases.

Thus, affluence, change in food habits, the prevalence of hypertension, overweight and diabetes, as well as stress of modern life seem to be largely prevalent in this urban male community and it may be responsible for the increasing morbidity and mortality in Saudi Arabia.

Diabetes and CVD risk factors have also affected foreign workers in Saudi Arabia. Those living in the area, especially those from the north-east Africa and the Indo-Pakistani subcontinent probably need special consideration. It may be that the foreign workers in the Saudi Arabia are highly stressed due to a combination of low pay, overwork, job insecurity, undernutrition, and the significant factor of being parted from their families for long periods of time.

As shown in different populations, those identified as IGT or NIDDM in this community, were characterised by hyperfunction of the β -cell in IGT, hypofunction of the β -cell in NIDDM and associated with immature secretion of proinsulin. The insulin resistance which was profound in NIDDM and intermediate in IGT was characterised by high glycerol and NEFA which were suggestive of insulin insensitivity at the level of adipose tissue.

The category of IGT proved to be a valuable epidemiological index when taken in association with the frequency of diabetes mellitus within populations. It will probably find increasing use as an indicator to lesser degrees of glucose intolerance in larger studies of the effects of preventive measures for diabetes applied in population studies as descriptors.

Health activities in terms of education and evaluation should be encouraged. There are already some health activities going on in the health centres to patients with diabetes or others with NCD, but still few when compared to the size of the problem. Most if not all the work in health education to the public is carried out by the Ministries of health, and mainly by the health education departments. Posters, booklets and leaflets are widely used as a tool for diabetic education in Saudi Arabia. However, we do not know whether this method of education is a suitable one in this community which is characterized by a high percentage of illiteracy and less educated people. The televised health education programme which is called 'Salametic' (Your Safety), is a very useful means if used properly and consists of 52 series of 25 min each for television, and a message of 2-3 min daily on the radio. Giving health information does not guarantee that the dietary habits of the people will change. Unfortunately, there is no evaluation about the effectiveness of the printed materials on the knowledge, attitudes and practices of the people in Saudi Arabia.

Preventive measures against diabetes and risk factors should started as soon as possible. Obesity and atherosclerosis are difficult to treat in adulthood, and this puts a drain on the health services by providing facilities to treat large numbers of patients. Physicians often check for diabetes but rarely pay attention to the associated risk factors. Therefore, more emphasis should be placed on improvement of the awareness and skills of the physicians towards detecting these diseases.

Thus, in short:

- 1). This study shows a high prevalence rates of NIDDM and IGT in an urban male community. These rates are much higher compared to previous studies.
- 2). The prevalences of CVD risk factors [smoking, obesity, hypertension, hypercholesterolaemia and hypertriglyceridaemia] are common.

- 3). A single OGTT is not enough to confirm the diagnosis of diabetes mellitus and IGT in asymptomatic individuals.
- 4). The IGT group stands as an independent category and they are more likely to have a higher prevalence of combination of CHD risk factors as compared to those with NGT.
- 5). Physical inactivity and westernised dietary habits are emerging lifestyle problems. A series of talks should be given to the community regarding their dietary habits and sedentary life-style.
- 6). Ethnic difference is of interest.
- 7). Subjects with IGT are characterised by hyperfunction of the β -cell, immature secretion of proinsulin and adipose tissue insulin insensitivity.

WHICH WAY FORWARD ?. As shown in chapter 3, data on diabetes mellitus are still scarce in Saudi Arabia. The general impression from the limited literature available, no doubt, is that it is an emerging problem in Saudi Arabia, particularly in urban societies. An increasing prevalence of the disorder may be related to the changes in social life and dietary pattern as a result of the rapid economic growth. People are eating foods rich in carbohydrates and fat and leading sedentary lives. Because of the scarcity of data, the epidemiology of the disease is not yet fully understood. Many questions concerning the magnitude of the problem, its distribution, contributing factors, pathogenesis and criteria for diagnosis still need to be answered. Since, most of the studies carried out, so far, have been hospital-based dealing with small unrepresentative samples, there is an urgent need for collective efforts, perhaps via the Saudi Diabetes and Endocrine Association, from researchers in universities and health service organizations to conduct more comprehensive and coordinated research work.

For proper control, programmes of health education, early diagnosis and early treatment should be implemented. Health education should emphasize the importance of physical activity, balanced diets, the avoidance of being overweight, excessive worries and intermarriage within diabetic families.

Modifying lifestyle is probably the biggest challenge.

In short, NIDDM and IGT are very common. Cardiovascular risk factors should not be ignored during any epidemiological studies. Some features and risk factors were peculiar to this community. IGT tolerance category stands as its own as independent category. Prevention should be the target and the aims for this high diabetic prevalence and further studies are required in that direction and in other directions of the wide diabetes field research. Since, prevention of diabetes is the simplest, most rational and generally most economical approach to treatment, primary prevention is perhaps becoming a reality (*Alberti, 1986*). The time, perhaps, is right to start action in populations in which the prevalence of diabetes is known to have clearly increased recently (*Tuomilehto et al, 1987*).

In Saudi Arabia, there is a wealth of research material available but disappointingly there is not more activity in this area. One of hindering factors which appeared in this study is the people attitude towards research. As perhaps, with other developing country the research which faces and involved the public is scarce and minimally practised which makes the public less exposed to the research activity. A well explained and continuous description of any protocol will be a temporary remedy and makes people appreciate your research work. The next are some potential thoughts for future work.

11.2 POTENTIAL for FUTURE STUDIES

The continuing health of the diabetic, whether in Saudi Arabia or elsewhere, depends on both effective health care and related research. Globally, the past 20 years have seen a major expansion in research related to diabetes. Techniques currently in use for diabetes research run the entire spectrum from genetic engineering to psychological testing. The methods in diabetic research are broadly classified in the areas of basic, clinical and behavioural/educational methods. There is no natural division between different aspects of research but coordination between them is needed to protect the health of those with diabetes.

Many different types of research are potentially required in Saudi Arabia;

population studies, basic research and clinical research, but all need to be coordinated to optimize their effect upon the health of diabetics in this region. The focus of research must include the spectrum from epidemiological studies to basic investigation. However there are still areas where promising research developments, health care provision and health sciences are desirable.

Interestingly would be research into preventive aspects investigating the effects of weight reduction, antidiabetic drugs, dietary manipulation or an increase in physical activity upon progression from IGT to NIDDM. A carefully planned large cooperative epidemiological study will assist in the elucidation of the true causes of diabetes in Saudi Arabia, and thus may provide a rational basis for the prevention and control of the disease in this geographic location. Such a study will help to quantify the true contributions of the three major aetiologic components namely genetics, lifestyle and environment.

1). Diabetes mellitus and CVD survey :

The Saudi Arabian population is approximately 11,542,000 (*James et al, 1990*). This constitutes 40.3% [1-12 ys], 8.2% [13-17 years], 20.1% [18-29%], 25.2% [30-59 years] and 4.2% [\geq 60 years]. There are an equal number of males and females at different age distribution except at the age of 18-59 years where the numbers of males are greater by one third than the females. Inhabitants of Jeddah number approximately 1,000,000. Therefore, a proper urban area prevalence study in Jeddah would be a logical extension from this study. There are 40 primary health care centre or more so far in the region of Jeddah city. Selecting 100 subjects 50 for each sex from each primary health care centre would be much more representative and give proper risk rates for both diabetes and CVD risk factors. Those registered in each centre would be selected and the investigation would move around each centre after prior registration. Known diabetic and hypertensive patients will be included. This should give an urban population of 4,000 subjects.

2). Diabetes and Hypertension Centre at Jeddah [Jeddah DHC] :

The recently established diabetes and hypertension centre [Summer, 1989] needs to be evaluated. Those registered in this centre reached a number of 5,000 by December 1990. The investigator has gained access to these data and has requested to start exploring and evaluating the results. Preliminary analysis showed that males outnumbered females [58% vs 42%]. The majority of them were middle-aged and the age distribution revealed that 11% were below 35, 79% were 35-64 years and 10% \geq 65 years. The BMI distribution showed that 27% had BMI < 25, 35% had BMI of 25-30, 38% of BMI > 30 and 16% had BMI > 35. This is, so far the largest national centre in term of population and further in-depth analysis of the available recorded data might reveal an insight into the pattern of diabetes in this region.

3). Prevalence of hyperglycemia during Haj period :

The ritual gathering of over 1 500 000 Moslem pilgrims while performing Haj in the Holy places and Jeddah for a period of 2 - 8 weeks creates a unique situation with particular medical problems. There are many factors that might contribute to the health problems of these pilgrims including austere living conditions in tents with deficient water supply, poor sanitation and poor nutrition. Old age and pre-existing medical illness like diabetes mellitus or hypertension are also important. Many workers have studied the medical problems that could afflict these pilgrims and those in their service. Emphasis has been on heat-induced syndromes (Khogali et al, 1983), and the recently reported different forms of the 'Diabetic Haj Foot' was interesting (Tawfik et al, 1991).

As an extension to the concept of changing diabetes prevalence between different nationalities and ethnic groups, it would be of interest to examine this question in a time where different nationalities are congregated in one place. Moreover the burden of diabetes problem, although, temporary, could be investigated. Two stages of this investigation are suggested. The first period would be in Haj 1412 (July, 1992) during which a 'Diabetes Health Card' should

be filled in by all pilgrims arriving within 1 month prior to the Haj time at one place of entry (Jeddah Airport). The Diabetes Health Card should have information including age, sex, country of origin, known diabetics, duration of diabetes and type of therapy, diet, OH drugs or insulin, do you carry your diabetic medicine with you or not, etc. This card will be introduced in three languages namely Arabic, English and French. The second stage would be during the Haj 1413 (May-June, 1993) during which time the prevalence of hyperglycaemia would be investigated by capillary blood estimation using a test strip and Boehringer Mannheim Instrument for example.

4). Insulin-dependent diabetes mellitus registry :

Searching the literature of diabetes mellitus in Saudi Arabia reveals no information about IDDM, although NIDDM in the common form in this area. It would be important to conduct an appropriate enquiry and to start registering IDDM.

APPENDICES

SURVEY QUESTIONNAIRE

Appendix 1 : GENERAL Questionnaire :

-Name: _____ -Questionnaire Date: __/__/__ .

-Address/District: _____ -Tel : _____ .

-Primary Health Care Centre (PHCC) No: _____ Health File No: _____ .

1-Code No . : __/__/__ .

2-What is your age in years? . : ____:

3-Are your: 1 = Male. 2 = Female.

4-What is your nationality? .

1 = Saudi.

2 = Non-Saudi., please specify: _____ .

5-What is your ethnic background? .

1 = Arabian.

2 = Mediterranean.

3 = Indian.

4 = South East Asian.

5 = Negro.

6 = Others.

6-How long have you been in Saudi Arabia ? .

1 = Up to 5 years.

2 = Up to 10 years.

3 = Up to 15 years.

4 = Up to 20 years.

5 = More than 20 years.

7-What is your level of education? .

1 = Illiterate,

2 = Writing and Reading,

3 = Primary,

4 = Elementary and Secondary.

5 = University or Above.

8-Are you employed in ? .

1 = Government.

2 = Private firm.

3 = Self.

4 = Retired.

5 = Unemployed.

9-What is exactly your occupation or occupation title ? .

: _____.

10-What is approximately your monthly income (SR)? .

- 1 = 1500 or less,
- 2 = 3000 or less,
- 3 = 4500 or less,
- 4 = 6000 or less,
- 5 = 7500 or less,
- 6 = More .
- 7 = I don't know.

12-Are you ? .

- 1 = Married with one wife.
- 2 = Married with two wives.
- 3 = Single.
- 4 = Divorced.

13-Is your wife first degree relative to you? .

- 1 = Yes.
- 2 = No.

-How many children do you have ? .

14-I have: 1 2 3 4 5 6 7 8 9 10 boy(s) alive

15-I have: 1 2 3 4 5 6 7 8 9 10 boy(s) dead

-I don't have boys (99)

16-I have: 1 2 3 4 5 6 7 8 9 10 girl(s) alive

17-I have: 1 2 3 4 5 6 7 8 9 10 girl(s) dead

-I don't have girls (99)

18 Do you suffer from diminished sexual desire (impotence) ? .

- 1 = Yes.
- 2 = No.

-Have you ever been told by a doctor that you have one of the following? .

19-Diabetes.

- 1 = Yes.
- 2 = No or don't know.

20- High lipids in your blood.

- 1 = Yes.
- 2 = No or don't know.

21- High Blood Pressure.

- 1 = Yes.
- 2 = No or don't know.

22- Heart diseases.

- 1 = Yes.
- 2 = No or don't know.

23- Stroke.

- 1 = Yes.
- 2 = No or don't know.

24- Are you currently taking any medicine for any reason? .

- 1 = Yes.
- 2 = No or don't know.

25- What is/are the actual name/s of drug/s that you are still using recently ?

- Name of drug: _____.
- Name of drug: _____.
- Name of drug: _____.

26-Is your father alive ? .

- 1 = Yes.
- 2 = No or don't know.

27-Is your mother alive ?

- 1 = Yes.
- 2 = No or don't know.

-How many brothers and sisters do you have ?

- 28-I have: 1 2 3 4 5 6 7 8 9 10 brother(s) alive
- 29-I have: 1 2 3 4 5 6 7 8 9 10 brother(s) dead
- I don't have brothers (99)

- 30-I have: 1 2 3 4 5 6 7 8 9 10 sister(s) alive
- 31-I have: 1 2 3 4 5 6 7 8 9 10 sister(s) dead
- I don't have sisters (99)

-Is your father suffering from any of the following diseases? .

32-Diabetes.

- 1 = Yes.
- 2 = No or don't know.

33- High Blood Pressure.

- 1 = Yes.
- 2 = No or don't know.

34- Heart diseases.

- 1 = Yes.
- 2 = No or don't know.

35- Stroke.

1 = Yes.

2 = No or don't know.

-Is your mother suffering from any of the following diseases? .

36-Diabetes.

1 = Yes.

2 = No or don't know.

37- High Blood Pressure.

1 = Yes.

2 = No or don't know.

38- Heart diseases.

1 = Yes.

2 = No or don't know.

39- Stroke.

1 = Yes.

2 = No or don't know.

-Are your brothers or sisters suffering from any of the following diseases? .

40-Diabetes.

1 = Yes.

2 = No or don't know.

41- High Blood Pressure.

1 = Yes.

2 = No or don't know.

42- Heart diseases.

1 = Yes.

2 = No or don't know.

43- Stroke.

1 = Yes.

2 = No or don't know.

44-Are any of your children suffering from diabetes? .

1 = Yes.

2 = No or don't know.

-At present do you have?

45-Increased urine volume (Polyuria).

1 = Yes

2 = No or don't know.

46-Thirst and increased drinking (Polydipsia).

1 = Yes

2 = No or don't know

47-Hunger and ingestion of large quantities of food (Hyperphagia):

1 = Yes

2 = No or don't know

48-Weakness and fatigue.

1 = Yes

2 = No or don't know

49-Inability to concentrate.

1 = Yes

2 = No or don't know

50-Do you think that, over the past three month, your weight is ?

1 = Same.

2 = Changed by decreasing.

3 = Changed by increasing.

4 = Changes by decreasing and Increasing (ups and downs).

Appendix 2

1- Have you ever had pain or discomfort in your chest ?

OR

Have you ever had any pressure or heaviness in your chest ?.

1 = Yes.

2 = No or don't know.

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

1 = Yes.

2 = No or don't know.

3- Do you get pain in either leg on walking ?.

1 = Yes.

2 = No or don't know.

4- Have you ever had weakness or loss of strength in an arm or leg lasting for 24 hours ?.

1 = Yes.

2 = No or don't know.

Appendix 3

SOCIAL HABITS

CIGARETTES :

1- Do you smoke CIGARETTES now or did you ever smoked CIGARETTES before ?

1= Yes, I smoke CIGARETTES NOW.

2= Yes, I used to smoke CIGARETTES but stopped now.

9= No or don't know.

2- Do you consider your smoking habits of CIGARETTES ?

1= Regular.

2= Occasional (usually less than one CIGARETTE/day).

9= No , don't smoke.

3- On the average, about how many cigarettes do you now smoke or used to smoke a day ?

1= Number :|___|___|.

99= No , don't smoke.

4- For how long have you been smoking CIGARETTES till present or previously ?

1= Years :|___|___|.

(Proper one considered for less than a year or part of the year).

99= No , don't smoke.

SHISHA :

5- Do you smoke SHISHA now or did you ever smoked SHISHA before ?

1= Yes, I smoke SHISHA NOW.

2= Yes, I used to smoke SHISHA but stopped now.

9= No or don't know.

6- Do you consider your smoking habits of SHISHA ?

1= Regular.

2= Occasional (usually less than one SHISHA/week).

9= No , don't smoke.

7- On the average, about how many SHISHA do you now smoke or used to smoke a week ?

1= Number :|___|___|.

99= No , don't smoke.

8- For How long have you been smoking SHISHA till present or previously ?

1= Years :|___|___|.

(Proper one considered for less than a year or part of the year).

99= No , don't smoke.

PIPE :

9- Do you smoke PIPE now or did you ever smoked PIPE before?

- 1= Yes, I smoke PIPE NOW.
 - 2= Yes, I used to smoke PIPE but stopped now.
 - 9= No or don't know.
-

CIGARS :

10- Do you smoke CIGARS now or did you ever smoked CIGARS before ?

- 1= Yes, I smoke CIGARS NOW.
 - 2= Yes, I used to smoke CIGARS but stopped now.
 - 9= No or don't know.
-

ALCOHOL DRINKING :

11- Do you drink ALCOHOL now or have you ever drunk ALCOHOL before ?

- 1= Yes, I drink ALCOHOL NOW.
 - 2= Yes, I had past experience of drinking ALCOHOL but not now.
 - 9= No or don't know.
-

QAT EATING (Herbs from Yemen) :

12- Do you eat QAT now or have you ever ate QAT before ?

- 1= Yes, I eat QAT NOW.
 - 2= Yes, I had past experience of eating QAT but not now.
 - 9= No or don't know.
-

1= Means proper SMOKER, or DRINKER, or EATER.
2= Means EX-SMOKER, or EX-DRINKER, or EX-EATER.
9 or 99 are negative responses.

Appendix 4

DIETARY QUESTIONNAIRE

DIRECTIONS

The following questions are about your dietary habits and about foods that you usually eats. It contains two sections. The first set of questions is about your general dietary habits and the second set of questions will enquire about some food items.

For both sets :

Please ring the **ONE** most appropriate answer.

For the second set :

For each foods or drinks encircle only **ONE** answer which is the most applicable to you according to the following ?

1 2 3 4 5 6 7 M R

-If you eat a food every day or seven times a week irrespective of any day, then ring the :

7

-If you eat a food once or several times a week up to six times, then ring the appropriate number accordingly :

1 2 3 4 5 or 6

-If you eat a food less than Once a week and once or more than once a month; for example every 10 days, or fortnightly, or every three weeks, then ring :

M

-If you eat a food less than once a month, for example every two or three months, or every six months, or yearly, or rarely, or even never, then ring :

R

SECTION ONE

GENERAL QUESTIONS :

1- How many meals do you eat per day ?

2- What is usually your main meal ?

*When do you usually eat your main meals, please indicate the time in hours ?.

3- Breakfast, at: |__| 4- Lunch , at: |__| 5- Dinner , at: |__|

6- Do you usually eat anything between your main meals and how often, regardless times of snack a day ?.

7- When do you usually eat your extra-meal , or snacks ?

*- Where do you usually eat your main or other meals ?.

8- Breakfast, 9- Lunch , 10- Dinner , 11- Snacks (extrameals).

12- How frequent do you eat outside home ?

13- Do you suffer from any long-term illness (s) ,and if YES what is it ?

14- Are you on any special diet as indicated by the following answers ?

15- Have you changed your diet for health reasons during the past 1-2 months ?

*- If Yes, in what way ?

16 -Is the amount of fat increased or decreased.

17 -Is the type of fat changed.

18 -Is the use of vegetables increased or decreased.

19 -Is the amount of sugar increased or decreased.

20 -Is the amount of salt increased or decreased.

21 -Is the amount of bread consumption increased or decreased.

22 -Others.

SECTION TWO

SPECIFIC QUESTIONS :Types of food and Frequency.

- 23- How many whole eggs (boiled fried or cooked) do you usually eat in one week ?
- 24- How many days a week do you drink milk ?
- 25- How much milk do you drink per day either alone , with cereals like cornflakes or in tea or coffee ?
- 26- What type of milk do you use most ?
- 26a- Can you specify the brand name of the most type of milk you use ?
- 27- How many days a week do you drink yoghurt ?
- 27a- Can you specify the brand name of the most type of yoghurt you use ?
- 28- How many days a week do you use cream ?
- 28a- Can you specify the brand name of the most type of cream you use ?
- 29- How many days a week do you eat some milky-made food items such as Labna,Mesh or Haloub ?
- 29a- Can you specify the type this milky-made food that you frequently eat ?
- 30- What is the most type of cheese you eat ?
- 30a- Name the cheese you eat most often ?
- 31- How much cheese would you say you ate per week ?
- 32- How many days a week do you eat butter or margarine ?
- 32a- Can you specify the brand name of the butter or margarine you mostly use ?
- *- How many days of the week do you eat the following foods ?
- 33 -Honey.
- 34 -Jam.
- 35 -Olives.
- 36 -Beans including chickpeas.
- 37 -Cornflakes or similar items
- 38 -White e.g Shami, Samoli bread.
- 39 -Brown e.g Hab bread.
- 40 -Tamees bread.
- 40a -Other kind of bread.
- 41 -Rice.
- 42 -Spaghetti and other pasta.
- *-How many days a week do you eat the following kinds of meat ?
- 43 - Lamb or Cheep.

- 44 - Beef.
 - 45 - Camel.
 - 46 - Chicken or other poultry.
 - 47 - Liver or kidney or heart.
 - 48 -Meat pies or pasties.
 - 49 -Tinned meat (all types).
 - 50 -Fish.
 - 51 -Tuna, sardines or similar tinned marine items.
-

- 52- Green vegetable or salad like tomato, cucumber and lettuce.
 - 53- Carrots or other root vegetables.
 - 54- Potatoes: a)-Boiled, backed or meshed.
 - 55- Potatoes: b)-Chips or fried (cooked at home).
 - 56- Potatoes: c)-Chips or fried (from shop).
 - 57- Onions (cooked, raw or pickled).
 - 58- Beans including lentils.
 - 59- Vegetables which needs cooking.
 - 60- Spices like pepper.
-

- 61- Tinned fruit:
 - 62- Dates.
 - 63- Apples.
 - 64- Oranges.
 - 65- Bananas.
-

- 66- Flour-made food.
- 67 -Cakes and similar:
- 68 -Jellies and similar :
- 69 -Milk pudding (e.g. tapioca) :
- 70 -Biscuits (all types) :
- 71 -Chocolates :
- 72 -Sweets :
- 73 -Nuts (all types) :
- 74 -Ice-cream (all types) :
- 75- What type of oil or fat do you usually use in your home for cooking frying or baking ?
 - 1- Plant origin.
 - 2- Animal origin.

3- Both type.

4- I don't know or the food which is cooked, fried or baked is not made at my home.

75a- Can you specify the brand name of the butter or margarine you mostly use ?

76- Do you add salt to your meals at the table ?

77- How much water do you usually drink per day over the last three months ?

78- Have you been asked to increase drinking water ?

79- What was the reason ?

80- Do you drink tea ?

1-Sweetened tea with sugar.

2-Sweetened tea with agents.

3-Unsweetened tea.

4-Both sweetened and unsweetened tea.

5-I don't drink tea at all.

81- How many glass of tea do you usually have a day ?

82- Do you drink coffee ?

1-Sweetened coffee with sugar.

2-Sweetened coffee with agents.

3-Unsweetened coffee.

4-Both sweetened and unsweetened coffee.

5-I don't drink coffee at all.

83- How many cup of coffee do you usually have a day ?

84- Do you use milk or cream in your coffee or tea ?

1-No milk or cream added.

2-Milk only.

3-Cream only.

4-Both milk and cream.

85-How many days of the week do you drink soft drinks ?

86-What is the type of the soft drinks you mostly used ?

1-Natural juices.

2-Fizzy drinks like Pepsi and similar.

3-I don't drink.

4-Both.

END OF DIETARY QUESTIONS

PHYSICAL ACTIVITY QUESTIONNAIRE

WORK-RELATED :

1- How do you usually go to your work ? |__|

- 1= Using my car, public transport such as buses or taxis.
- 2= Using a bicycle or motorcycle.
- 3= Walking.
- 4= None of the above means, e.g my workplace is at home.

2- How many minutes a day do you spend walking, on going to and coming from work ? |__|

- 1= Less than 30 minutes a day.
- 2= More than 30 minutes a day.
- 9= I don't walk or get physical activity on the way to work.

3- Which of the following describes how much physical activity is involved in your job ? |__|

Occupations are divided into four groups. If you do not work, mention group 1.

- 1= I do not walk much during my work. My work is mainly sitting work.
Examples :Office work at a desk.
- 2= I walk in quite a lot in my work but I do not have to lift or carry heavy things.
Examples :Office work where one has to move , shop assistant.
- 3= I walk and carry a lot in my work or often to climb staircases or go uphill.
Examples :Carpenter, Work in engine-shop or car-repair shop.
- 4= My work is heavy physical work, where I have to carry or lift heavy things.
Examples :Heavy construction and industrial work.

4- While at work, how many hours per work day do you spend walking with or without lifting or carrying heavy objects ? |__|

- 1= Up to 2 hour.
 - 2= 2 - 4 hour.
 - 3= More than 4 hour.
 - 4= I don't walk at work.
-

HOUSEHOLD WORK :

5- Do you spend time doing household work ? |__|

1= Yes.

2= No, I don't know.

6- How many hours per week,approximately, do you spend doing household work such as scrubbing floors, vacuuming, cooking, washing dishes or clothes , making beds or shopping ? |__|

1= Up to 2 hour.

2= 2 - 4 hour.

3= More than 4 hour.

9= I don't do household work.

7- When you do these household chores,do you usually work so hard that you need to take a rest to catch your breath ?. |__|

1= Yes.

2= No, I don't know.

9= I don't do household work.

AT LEISURE-TIME :

8- Do you do physical activity during your leisure-time ? |__|

1= Yes.

2= No, I don't know.

**9- Which of the following best describes the way you spend your leisure time ?
If it varies with the seasons, mention one group that best represents the average of the year.** |__|

1= In my leisure-time I read, watch television and do things which do not need physical activity.

2=In my leisure-time I walk, ride a bicycle or run at least for four hours a week.

In this is included walking; but not including going to and coming from work.

3= In my leisure-time I have physical activities to maintain my condition such as ball-games swimming or similar works.

4= I train in my leisure-time regularly for competitions several days a week, running, ball-games or other physically heavy sports.

10- How many times a week do you do such leisure-time physical activities you mentioned in the above question ? |__|

1= Up to 2 times per week.

2= 2 - 4 times per week.

3= More than 4 times per week.

9= I don't do physical activity at my leisure-time.

11- How long do your physical activity episodes last ?

- 1 = Less than 30 minutes per time.
- 2 = More than 30 minutes per time.
- 9 = I don't do physical activity at my leisure-time.

12- How often do you do physical activities lasting at least 20-30 minutes which make you short of breath and perspire ?

- 1 = Less than once a week.
- 2 = Once or more than once a week.
- 9 = I don't do physical activity at my leisure-time.

SPORTS :

13- Do you participate in sports ?

- 1 = Yes.
- 2 = No, I don't know.

14- What sort of sport activities do you usually do ?

Specify, please:

- 1 = Football.
- 2 = Swimming.
- 3 = Sweedy.
- 4 = Jogging.
- 5 = Others.
- 9 = I don't participate in sports.

15- Normally, about how many hours per week , do you spend participating in sports and physical activity excluding walking ?

- 1 = Up to 2 hour per weak.
- 2 = 2 - 4 hour per weak.
- 3 = More than 4 hour per weak.
- 9 = I don't participate in sports.

16- Is the level of activity that you have just described normal for you or are you usually more or less active ?

- 1 = My activity is usually the same.
- 2 = I am usually less active than that amount.
- 3 = I am usually more active than that amount.
- 4 = I don't know.
- 9 = I don't participate in sports.

RECREATIONAL WALKING :

17- Do you go walking ?.

- 1 = Yes.
- 2 = No, I don't know.

18- Normally, about how many hours per week do you usually spend walking outside of your home or place of employment, which reflect back over the past six months ?

- 1= Up to 2 hour per week.
- 2= 2 - 4 hour per week.
- 3= More than 4 hour per week.
- 9= I don't walk.

19- Is the walking that you reported above normal for you or do you usually walk more, same or less than that amount ?

- 1= I usually walk the same amount .
- 2= I usually walk less than that amount .
- 3= I usually walk more than that amount .
- 4= I don't know.
- 9= I don't walk.

GENERAL :

20- How do you consider your present physical condition ?.

- 1= Very good.
- 2= Good.
- 3= Satisfactory.
- 4= Bad.
- 5= Very bad.

21- Have you ever seriously increased your leisure-time physical activity and if so, when last ?.

- 1= Yes, during the last month.
- 2= Yes, one month to six months.
- 3= Yes, more than six months.
- 4= Never.

22- Has your leisure-time physical activity, changed during last six months ?.

- 1= Increased very much.
 - 2= Increased a little.
 - 3= No change.
 - 4= Decreased a little.
 - 5= Decreased very much.
-

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