STUDIES ON THE EPIDEMIOLOGY OF DIABETES IN PACIFIC POPULATIONS

HILARY OWEN MEREDITH KING, MB, BS, MSc

Department of Community Medicine,

University of Adelaide

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DR. I. PRIOR

M.D. THESIS; H.O.M. KING

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C O N T E N T S

SUMMARY

Increasing interest has been shown in the epidemiology of diabetes in the past decade. It is now clear that, because noninsulin-dependent diabetes may often remain asymptomatic for many years, epidemiological methods are vital for the accurate description of the frequency and natural history of the disease in populations.

The various island communities of the Pacific, with their ethnic and cultural diversity, their geographical integrity, and the apparent disparity in the prevalence of noninsulin-dependent diabetes between their populations, constitute an ideal natural laboratory for the study of this disease. For this reason, the Pacific region has been one of the most active areas for diabetes research in recent years.

In this thesis, six original studies are presented. They are based upon data collected from over 7000 subjects in four Pacific nations. Each addresses a key question in Pacific diabetology, some being of universal relevance. Although complimentary, each forms a discrete area of research.

Glucose tolerance in a highland population in Papua New Guinea

There has been prolonged debate as to whether Melanesians may constitute an ethnic group which is less susceptible to noninsulin-dependent diabetes than other Pacific populations, due to some genetically mediated resistance. A confounding factor in all Melanesian studies to date is that they were performed on coastal populations, which had been exposed to ancestral genetic influence from other Pacific societies known to be susceptible to diabetes.

The first study to examine a highland Melanesian population known to be free of "external" genetic admixture, using standardized methodology, is described in Chapter 1. No cases of noninsulin-dependent diabetes were found in over 300 subjects examined, and the prevalence of abnormal glucose tolerance was the lowest to be reported from the Pacific. These findings provide renewed support for the concept of genetic resistance to noninsulin-dependent diabetes in Melanesians.

Noninsulin-dependent diabetes in the Republic of Kiribati

A survey of 2938 subjects, constituting the first diabetes study in the newly independent Republic of Kiribati (formerly the Gilbert Islands) is described in Chapter 2. This Micronesian community is a neighbour of Nauru, where the highest prevalence of noninsulin-dependent diabetes yet recorded in the Pacific has been documented.

The prevalence of diabetes was found to be over twice as high in an urban, as compared with a rural, sample in Kiribati, and to be associated with high relative body weight, physical inactivity and the consumption of a non-traditional diet. Further analysis showed that obesity was not a sufficient explanation of the rural-urban difference in prevalence of noninsulin-dependent diabetes in this population.

The consequence of hyperglycaemia in Pacific populations

The study presented in Chapter 3 examines data collected in the first total population diabetes survey of adult Nauruans, which was conducted in 1982. Nauruans are known to suffer from an exceptionally high prevalence of noninsulin-dependent diabetes (one quarter of the adult population suffer from the disease).

The prevalence of diabetic retinopathy was found to be 24 per cent in diabetics. The presence of retinopathy was strongly associated with both duration of disease and plasma glucose concentration at examination. These results are in accord with those from Caucasoid and American Indian populations, and confirm that Nauruans suffer from the morbid consequences of noninsulin-dependent diabetes, rather than exhibit hyperglycaemia as an innocent biochemical trait.

The natural history of impaired glucose tolerance in Nauruans

Impaired glucose tolerance is a newly defined category of glucose tolerance, intermediate between normality and diabetes. For a sub-set of subjects examined both in the 1982 survey and in the original Nauru survey in 1975-6, data were compared at the two points in time (Chapter 4). This is the fourth study of impaired glucose tolerance to appear in the literature, and the first for a Pacific population.

Impaired glucose tolerance was found to have an unpredictable outcome, with approximately one third of subjects returning to normality, one third remaining with impaired glucose tolerance status, and one third progressing to diabetes. However, subjects with impaired glucose tolerance were at significantly higher risk of subsequent diabetes than normals, after controlling for differences in age and obesity.

Ethnic differences in susceptibility to noninsulin-dependent diabetes : a comparative study of two urbanized Micronesian communities

In Chapter 5, the prevalence of noninsulin-dependent diabetes in Nauruans is compared with that in an inactive, urbanized Micronesian sample in Kiribati. After allowing for differences in age and obesity, the risk of noninsulin-dependent diabetes was found to be threefold for Nauruans, suggesting that the high prevalence in Nauruans could not be explained by differences in age and obesity alone.

The results support genetic studies which suggest that Nauruans may have enhanced genetic susceptibility to noninsulin-dependent diabetes.

Risk factors for diabetes in Pacific populations

The association between the prevalence of diabetes and three suspected risk factors - obesity, physical inactivity and urbanization - was studied in 5519 subjects from three populations : Melanesians and migrant Asian Indians in Fiji, and Micronesians in Kiribati. The results are presented in Chapter 6.

Associations were found to be inconsistent between populations, and between the sexes within populations. In some cases obesity was strongly associated with the prevalence of noninsulin-dependent diabetes, in others the principal variable associated with diabetes appeared to be physical inactivity. More than one factor was associated with increased risk in Micronesians.

These results indicate that risk factors may be heterogeneous in their effect upon different populations,

and the findings have important implications for the planning of primary prevention programmes for diabetes.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

To the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

H. O. M. KING

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Population-based epidemiological studies often involve the examination of large numbers of subjects, and are consequently expensive - both in time and finance. Unused historical data may therefore provide a valuable source of research material. The studies which form the basis of this thesis involve the analysis of data collected from over 7000 subjects. The author was personally responsible for the collection of the original survey data from Nauru (1982) and Papua New Guinea (1983). For access to data files from surveys in Fiji (1980) and Kiribati (1981), and comparative material from Nauru (1975/6), the kind cooperation of the WHO Collaborating Centre for the Epidemiology of Diabetes Mellitus, Royal Southern Memorial Hospital, Melbourne, is acknowledged. It was the facilities of this Centre which made the research presented in this thesis possible.

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"The reason why the Pacific Islands possess such importance . . . has little to do with their total area or the aggregate size of their population, but rather derives from their geographical fragmentation, which has resulted in the growth of a unique multiplicity of small societies. Scattered over a third of the earth's surface, isolated to a varying degree by the vastly more extensive ocean surrounding them, their inhabitants have evolved over a thousand or more years of occupancy a diverse assemblage of social, economic, religious and political systems, of ideas and values, which makes the region in a sense the counterpart of the natural scientist's laboratory."

H.E. Maude (1968)

'Of Islands and Men: Studies in Pacific History'

INTRODUCTION

It is only in the last half century that the epidemiological study of chronic disease has received widespread attention, largely in the fields of cardiovascular, pulmonary and neoplastic diseases (Comstock, 1983). In the last decade, however, there has been a slow, but steady, growth in interest in the worldwide epidemiology of diabetes mellitus. Noninsulin-dependent diabetes mellitus (NIDDM), which is the predominant form of the disease, may often remain asymptomatic despite marked hyperglycaemia. Epidemiological surveys have therefore played a vital role in elucidating the true burden of noninsulin-dependent diabetes. In few parts of the world have the findings proved as alarming, though scientifically challenging, as in the Pacific.

Traditionally, the Pacific region has been divided into three geo-ethnic areas : Melanesia, Micronesia and Polynesia. Melanesia is bounded to the west by the island of New Guinea, and extends eastward to the Fiji group. Most of the islands in Melanesia are large and mountainous, and are covered by substantial areas of primary rain forest. The terrain has hindered economic and social development, and the most traditional societies in the Pacific are to be found in this area.

To the north of Melanesia lies Micronesia, a huge expanse of ocean dotted with numerous groups of small islands. Most are mere coral atolls, rising no more than a few feet above the sea. They are sparse in vegetation, the dominant forms being coconut palms, pandanus and breadfruit.

Nauru is a raised coral atoll lying within a few km of the equator in the Central Pacific. Though only 20 km in circumference, the discovery of rich deposits of phosphate on the island has lead to affluence, and dramatic modernization of lifestyle for the 4000 inhabitants. The adult population now suffers from an extremely high prevalence of noninsulin-dependent diabetes, and scientific investigation in this community has played a key role in advancing diabetes epidemiology, not only in the Pacific, but worldwide. Three original analytic studies of this exceptional population are presented in this thesis.

Bordering Melanesia and Micronesia to the north, east and south is Polynesia. The extreme land points of this geographic triangle are provided by Hawaii, Easter Island and New Zealand. This is not only the largest of the three regions of Oceania, it is also the most diverse geographically, ranging from high and fertile islands to small barren atolls.

The studies presented in Chapters 1-6 of this thesis are based upon field surveys of over 7000 subjects conducted in four Pacific nations : Papua New Guinea and Fiji in Melanesia, Nauru and Kiribati in Micronesia. Each of the six studies addresses an original question in Pacific diabetology, and the results of some are of universal relevance.

It has been suggested that Melanesia may be less susceptible to noninsulin-dependent diabetes than other Pacific populations (Zimmet, 1979), although the available evidence has been contradictory (Hingston et al., 1964,

Martin et al., 1980, Zimmet et al., 1983). A confounding factor in former Melanesian studies was that all were conducted on coastal populations.

Recent genetic and anthropological studies suggest that the ethnic divisions between Melanesia and other areas of the Pacific are not as well defined as was formerly supposed (Bellwood, 1980, Serjeantson, 1982), and the high prevalence of noninsulin-dependent diabetes reported in some Melanesian studies may result from Polynesian genetic influence. One of the few areas of Melanesia in which no "external" genetic admixture has occurred is the highlands of New Guinea, and this region therefore offers a valuable opportunity to test the hypothesis of Melanesian resistance to noninsulin-dependent diabetes. The first standardized population study of glucose tolerance conducted in the New Guinea highlands is presented in Chapter 1 of this thesis.

The Nauruan studies presented in this thesis are all based upon a population survey conducted in 1982. In Chapter 3, the morbid consequences of hyperglycaemia, in terms of microvascular disease, are assessed for the first time in a population of diabetics in the Pacific. In Chapter 4, the follow-up of a Nauruan cohort previously examined in 1975/6 has permitted the first evaluation in the Pacific of the natural history of impaired glucose tolerance, a recently introduced category of glucose tolerance intermediate between normality and diabetes (National Diabetes Data Group, 1979) upon which the World Health Organization has called for more epidemiological information (WHO, 1980).

The nearest neighbour of Nauru is the Republic of Kiribati (formerly known as the Gilbert Islands). In Chapter 5, a direct and standardized comparison between diabetes prevalence in Nauru and an urban group in Kiribati is made, after allowing for known confounding factors of environmental origin.

This study is an attempt to estimate the excess risk of noninsulin-dependent diabetes in Nauruans, which may be of genetic origin. It is hypothesized that the very high prevalence of noninsulin-dependent diabetes in Nauruans cannot be attributed to environmental factors alone, and that Nauruans constitute the upper extreme of the spectrum of susceptibility to noninsulin-dependent diabetes encountered in the Pacific. The original description of the data collected in the first diabetes survey conducted in Kiribati is presented in Chapter 2.

With the growing international recognition of the importance of primary prevention of non-communicable disease (WHO, 1982), it has become of practical importance to determine the true environmental precipitants of these diseases in susceptible persons. Population comparisons can make a valuable contribution in this field. In Chapter 6, which describes the final original study, such a comparison of factors associated with the prevalence of noninsulin-dependent diabetes is made in 5519 subjects from three ethnic groups - Melanesians and migrant Asian Indians in Fiji, and Micronesians in Kiribati, in an attempt to determine risk factors for diabetes in Pacific populations.

A review of recent developments in the epidemiology of diabetes in the Pacific is presented in Chapter 7. Particular attention is paid to the assessment of the contribution of the studies described in the preceding chapters.

A review of the epidemiology of diabetes in the ASEAN region, the ancestral home of Pacific populations, is presented in the Appendix.

Due to the size of many of the tables in this thesis, all tables and figures have been placed at the end of the manuscript. For the convenience of the reader, a supplementary set of tables and figures, separately bound, accompanies each copy. These have been collated in the exact order in which they appear in the text.

Map of the Pacific, showing the three major geo-ethnic regions, and the location of the study populations

CHAPTER 1

GLUCOSE TOLERANCE IN A HIGHLAND POPULATION IN PAPUA NEW GUINEA

SUMMARY

A diabetes survey was conducted in the highlands of Papua New Guinea in June 1983. Two villages in the Asaro Valley, Eastern Highlands Province, were selected for study. The subjects were of Melanesian ancestry, and were free of Austronesian genetic admixture. The response rate was 95 per cent and 308 subjects were examined.

As defined by current WHO criteria, there was a total absence of noninsulin-dependent diabetes in these communities. The prevalence of impaired glucose tolerance was 2 per cent. These estimates of glucose intolerance are the lowest yet to be reported from the Pacific, using currently accepted diagnostic criteria and standardized survey methods. The two-hour plasma glucose and insulin concentrations were positively correlated in both sexes.

Of the two villages studied, one had undergone a greater degree of acculturation than the other. Both the total distribution and the mean value of two-hour plasma glucose concentration were lower in the more traditional village, and these findings could not be explained by differences in age or obesity between the two communities. Mean two-hour plasma insulin concentration did not differ significantly between the two villages, and was very low in both.

The results of this study support the theory that Melanesians free of Austronesian genetic admixture are relatively, though not absolutely, resistant to the deleterious influence of acculturation upon glucose tolerance seen in other Pacific populations. However, the

notion that in this population cultural change has been insufficient, or of too recent onset for a deterioration in glucose tolerance to be manifest, cannot be excluded.

INTRODUCTION

There is conflicting evidence regarding the susceptibility of Melanesian populations to diabetes (Hingston and Price, 1964, Price and Tulloch, 1966, Martin et al., 1980, Sinnett and Whyte, 1981, Savige and Martin, 1982, Ram et al., 1982). The subject is of more than passing interest, as the great disparity in the prevalence of noninsulin-dependent diabetes in Pacific populations has been advanced as indirect evidence for a genetic basis to the disease (Zimmet, 1982).

The low prevalence of diabetes reported in most Melanesian studies led to the suggestion that Melanesians might be genetically protected from glucose intolerance (Zimmet et al., 1982). Such a theory is not without precedent (Mouratoff et al., 1967), and the hypothesis is reinforced by reports of a very low prevalence of other non-communicable diseases in traditional Melanesian societies (Page et al., 1974, Sinnett and Whyte, 1978).

Some recent studies of coastal Melanesian populations have reported a high prevalence of noninsulin-dependent diabetes, and have brought the concept of Melanesian resistance to glucose intolerance into question. However, exposure to Austronesian genetic influence is known to have occurred in these coastal societies (Serjeantson et al., 1983).

The aim of the present study was to assess glucose tolerance in a Melanesian population in the highlands of Papua New Guinea which was known to be of non-Austronesian ancestry. The data were also intended as a baseline for a

prospective investigation of the effects of acculturation in this community.

The island of New Guinea lies to the north of Australia, between latitude 3° and 11° south in the geo-ethnic region of Melanesia. The eastern half of New Guinea and neighbouring islands form the independent nation of Papua New Guinea (Figure 1.1). The New Guinea highlands, which extend from west to east down the spine of the island, form one of the world's great mountain ranges. Because of the remoteness and inaccessibility of their location, the large populations living in the highland valleys of Papua New Guinea were not exposed to western influence until the 1930's.

In the past 30 years, development and commerce have spread rapidly in the highland valleys, coffee and tea production providing an important economic incentive. Access to the Eastern Highlands Province, the centre of coffee production and the most developed of the five highland provinces, is now possible by daily jet aircraft, as well as by road from the coastal towns of Lae and Madang. The commercial and administrative centre of the Eastern Highlands Province is the town of Goroka, which lies at an altitude of 1700 m in the Asaro Valley.

SUBJECTS AND METHODS

The study sample consisted of the total adult (20 years and over) population of two villages in the Asaro Valley, not far from the town of Goroka. The villages were chosen as the inhabitants of the region were known - as a result of extensive genetic studies in the region (Serjeantson et al.,

1983)- to be of non-Austronesian Melanesian ancestry, and because preliminary dietary data had been collected in the two villages by the Papua New Guinea Institute of Medical Research. Both villages had also indicated their interest in participating in a prospective study of non-communicable disease. The survey was conducted in June 1983.

The two villages differed in their degree of acculturation. Whereas one village (Gamusi) was situated at an altitude of 2000 m, and could only be reached by a difficult and sometimes impassable road, the other village (Gimisave) lay in the valley floor at an altitude of 1700 m and was situated beside the Highlands Highway, the major route for land transport in the country. Nutritional studies had already demonstrated a more traditional diet at Gamusi than at Gimisave - though some non-traditional elements in the diet had been observed in both villages. Both villages are now involved in the cash economy, and in coffee production. Commercial enterprise is more evident in Gimisave, where it has led to limited affluence. This financial wealth was reflected in the number of wives married to Gimisave men (more than one wife being a sign of both affluence and social prestige in this society), and the consequent excess of females in that village. Coffee growing has contributed to the Gimisave economy for a number of years.

As survey work was conducted during the coffee-picking season, some of the younger adults were away from the area at the time of the study. Any bias produced by the absence of these subjects would lead to an overestimate of the

prevalence of a chronic disease which becomes more frequent with advancing age.

The subject's age was estimated by questions relating to key local historical events, and by estimation of the age of children and/or grandchildren. As age estimates were necessarily crude, age-specific data have been analysed in three broad age-groups: 20-34, 35-54 and 55 years and over.

Height, weight and triceps and subscapular skinfold thicknesses were recorded in all subjects with the exception of one elderly female who was unable to stand. Body mass index was calculated as weight (kg)/height $(m)^2$.

A census was conducted in each village immediately prior to the survey. There were a total of 329 adults present in the two villages, of whom 5 were too frail to reach the survey site. Of the remaining 324 subjects, 308 attended the survey, corresponding to a response rate of 95 per cent (Table 1.1).

Glucose tolerance was defined according to current WHO(1980) criteria, modified for field survey conditions, namely as the following venous plasma glucose values, two hours after a 75 g oral glucose load:

	plasma glucose concentration (mmol/l)
Normal	<7.8
Impaired glucose tolerance	>7.8 and <11.1
Diabetes	≥11.1

Fasting plasma glucose concentration was not examined, in the belief that the two-hour value is the more sensitive, and valuable for epidemiological surveys (Bennett et al., 1983), and in order to place no undue strain upon response and cooperation (the taking of blood is unpopular with Papua

New Guineans). All subjects were examined in the morning, after fasting overnight.

Plasma glucose was measured on site on a Yellow Springs Instrument 23AM glucose analyser, which used a glucose oxidase method of estimation (Brunsman, 1976). Plasma insulin was measured by radioimmunoassay using the method of Herbert et al. (1965). Red cells were frozen and stored, and later examined for genetic markers to confirm that the subjects were all of typical highland stock.

RESULTS

The age structure of the two populations is shown in Figure 1.2. In both sexes, the Gimisave population appears to be the older. This may have been due to more young people being away at work in Gimisave, or to a higher life expectancy in this village.

The prevalence of diabetes was zero in both populations (Table 1.2). The prevalence of impaired glucose tolerance was below 5 per cent in all sub groups, and approximately 2 per cent in the total survey population. The differences between villages were not statistically significant.

The distributions of two-hour plasma glucose values in the two villages are shown in Figures 1.3a and b. Sexes are combined in these figures as distributions were similar in males and females. Both distributions are log-normally distributed and are unimodal. Though values are low in both villages, the distribution of two-hour plasma glucose concentration lies further to the right in Gimisave, the less traditional village. The Gimisave distribution is also notable for its narrow range.

Means of selected variables in the two populations are shown in Table 1.3. Mean age was not significantly different in the two villages in either sex. There was a highly significant difference in mean two-hour plasma glucose concentration, the mean being lower in Gamusi, the more traditional village. Mean two-hour plasma insulin concentration was very low in both villages, and in both sexes, the highest mean value being 20.4 uU/ml in Gimisave females. Mean body mass index, triceps skinfold thickness, subscapular skinfold thickness and sum of skinfolds were all lower in Gamusi than Gimisave females, but this difference was not seen in males.

The relationship between two-hour plasma glucose and insulin concentrations is shown in Figure 1.4. Trends were very similar in the two sexes, which are combined in the figure. There was a positive, almost linear relationship between the two variables.

Coefficients of linear correlation between the variables of interest are shown in Table 1.4. Two-hour plasma glucose and insulin concentrations were positively correlated ($r = 0.5$ in males, $r = 0.4$ in females). Correlation between two-hour plasma glucose concentration and age was 0.3 in males, but lower in females. Neither two-hour plasma glucose nor two-hour plasma insulin concentration were strongly correlated with any other variable examined in either sex. Age was negatively correlated with body mass index in both sexes, and with the three measures of skinfold thickness in females. Correlation between body mass index and skinfold thickness

was greater in females than males. Triceps and subscapular skinfold thicknesses were highly correlated in both sexes. The correlation coefficient between sum of skinfolds and the two individual measures of skinfold thickness exceeded 0.9 in both sexes, indicating the efficiency of the product term in describing the two individual measures.

In order to further explore the relationships between two-hour plasma glucose concentration, age and the indices of obesity, mean two-hour plasma glucose concentration was calculated in each age group and in tertiles of the distribution of body mass index and sum of skinfolds. As may have been anticipated from the correlation coefficients, in males a relationship between two-hour plasma glucose concentration and age, and an inverse relationship between two-hour plasma glucose and body mass index emerged (Figure 1.5). Neither of these variables appeared to be related to two-hour plasma glucose concentration in females. There did not seem to be a strong relationship between two-hour plasma glucose and sum of skinfolds in either sex.

To determine the relationship between two-hour plasma glucose and each of these variables, after allowing for the effects of the others, analysis of variance was performed (Table 1.5). Body mass index and sum of skinfolds were grouped into quartiles. In both sexes there was a highly significant relationship between two-hour plasma glucose concentration and village of residence. Age group also had a significant effect in males, as did the village x age group interaction term. In females, no variable was significant apart from village of residence.

DISCUSSION

Early reports suggested that the prevalence of diabetes was low in Melanesian populations (Hingston and Price, 1964, Price and Tulloch, 1966). The concept that Melanesians might be genetically protected against diabetes does not refute the hypothesis proposed by Neel (1962) of a "thrifty genotype", which may have evolved in the Pacific as a result of regular periods of feast and famine. Most Melanesian communities live in large mountainous islands which are less vulnerable to the vagaries of the elements than those inhabited by Polynesians and Micronesians.

Recently, the publication of studies in Papua New Guinea (Martin et al., 1980, Savige and Martin, 1981) and in Fiji (Ram et al., 1982) cast doubt on the concept of genetic protection in Melanesians. These demonstrated a high prevalence of diabetes in some populations. However, a factor shared by these groups was their coastal location, suggesting that susceptibility to glucose intolerance may have been conferred by Austronesian genetic admixture (Austronesian admixture is known to have occurred in coastal societies in Papua New Guinea (Serjeantson et al., 1983), and some Austronesian communities in the Pacific - particularly certain Polynesian and Micronesian groups (Zimmet and Whitehouse, 1981) - have a high prevalence of glucose intolerance).

The present study has demonstrated a notable absence of glucose intolerance and hyperinsulinaemia in a Melanesian population in the highlands of Papua New Guinea, which is known to be of non-Austronesian descent. Not a single

diabetic was found amongst over 300 subjects. The estimates of the prevalence of abnormal glucose tolerance, as defined by currently accepted criteria (WHO, 1980) were the lowest yet reported from the Pacific, and the distributions of two-hour plasma glucose concentration were also very low in the two study villages.

Although a high degree of glucose tolerance is not unusual in very traditional societies, neither village included in the present study was completely unacculturated. One community (Gamusi) has been shown by previous studies (Heywood, unpublished data) to have a more traditional diet than the other. Both the mean value and the total distribution of two-hour plasma glucose concentration were higher in the less traditional village. Although means of the measured indices of obesity were significantly different in the two villages in females, this was not the case for males, in whom another explanation for the difference in mean two-hour plasma glucose concentration between villages must be sought.

Coefficients of correlation and analysis of variance failed to demonstrate a relationship between two-hour plasma glucose and three indices of obesity in either sex. However, the analysis of variance confirmed that village of residence had a highly significant association with two-hour plasma glucose concentration, which, in both sexes, was independent of differences in age and obesity. The possibility that the less traditional diet in Gimisave may have been associated with the higher distribution of

two-hour plasma glucose concentration observed in that village cannot be dismissed.

The positive association between two-hour plasma glucose and insulin concentrations is in accord with the findings of a previous study, in a rural, coastal population in Papua New Guinea (Martin et al., 1980) although values were much higher in the latter. In the coastal study a decline in two-hour plasma insulin concentration occurred at two-hour plasma glucose values above 11.1 mmol/l. It was not possible to look for this phenomenon in the present study, as no two-hour plasma glucose values exceeded 11.1 mmol/l.

Although inference is constrained by small numbers, these findings provide some support for the theory that Melanesians free of Austronesian genetic admixture are relatively, although not absolutely, resistant to the deleterious influence of acculturation on glucose tolerance seen in other Pacific populations. However, the possibility that cultural change has been insufficient, or of too recent onset in this population for a consequent deterioration in glucose tolerance to be manifest, cannot be excluded. The very low values of two-hour plasma insulin concentration observed in this study may indicate a high level of habitual physical activity in this population (in accordance with subjective observation), which may exert a protective effect on glucose tolerance (Vranic et al., 1983) despite social and dietary change.

Prospective studies, including urbanized subjects, will be required for final clarification of the hypothesis of

genetic resistance to glucose intolerance in non-Austronesian Melanesians, which has important implications for the understanding of the genetics and aetiology of noninsulin-dependent diabetes.

CHAPTER 2

NONINSULIN-DEPENDENT DIABETES IN A NEWLY INDEPENDENT PACIFIC NATION - THE REPUBLIC OF KIRIBATI

SUMMARY

A population-based survey of 2938 subjects has demonstrated a high prevalence of noninsulin-dependent diabetes in the Micronesian population of Kiribati (formerly the Gilbert Islands). This finding provides further support for evidence from Nauru, Guam, and the Marshall Islands that Micronesians are particularly susceptible to noninsulin-dependent diabetes. The age-standardized prevalence was over twice as high in an urban, as compared with a rural, sample (9.1 versus 3.0 per cent in males, 8.7 versus 3.3 per cent in females). In order to test the a priori hypotheses that obesity, reduced physical activity, and a non-traditional diet are associated with noninsulin-dependent diabetes, indices of these factors were compared in rural and urban subjects. The rural population was found to be leaner, to have a higher estimate of habitual physical activity, and to have a lower daily intake of energy derived from imported foods.

Further analysis demonstrated that obesity alone was insufficient to explain the rural-urban difference in prevalence of diabetes.

INTRODUCTION

Diabetes mellitus is not a disorder confined to western populations. In American Indians (Bennett et al., 1976), migrants from the Indian sub-continent (Marine et al., 1969), and Pacific communities (Zimmet et al., 1977), population-based studies have demonstrated a prevalence of diabetes many times higher than in European, American, or Australian Caucasoids. In the Pacific, as in American Indians, diabetes appears to be almost exclusively of the noninsulin-dependent form (Zimmet, 1982).

In the Pacific, the highest crude prevalence of non-insulin dependent diabetes recorded - 24 per cent of the total adult population - is in the small, isolated yet affluent and urbanized Micronesian island of Nauru (ibid.). There is also evidence of a high prevalence of noninsulin-dependent diabetes in Guam and the Marshall Islands (Reed et al., 1973, Kuberski and Bennett, 1980).

Lack of historical data has prevented the analysis of secular trends to date, although there is clinical and anecdotal evidence to suggest that diabetes was an uncommon disease in the Pacific until recent times (Zimmet, 1979). Annual reports of the Medical Department in Kiribati indicate little morbidity or mortality from diabetes a decade ago (Government Printing Works, Tarawa, 1973). Though noninsulin-dependent diabetes may often remain asymptomatic, the complications of the disease have been noted with increasing frequency in recent years in these islands. The disease is also recorded infrequently in early clinical records in Nauru, despite the high prevalence on this island

today (Zimmet, 1978). Furthermore, several studies based upon comparable methodology and criteria for classification have demonstrated a lower prevalence of noninsulin-dependent diabetes in traditional-living rural communities than in urbanized counterparts of similar ethnic origin.

Rural-urban comparisons in developing nations provide a valuable opportunity to test hypotheses concerning suspected environmental and behavioural determinants of noninsulin-dependent diabetes, as, in contrast to their urban counterparts, many such rural populations remain little affected by social change.

It has long been suspected that factors associated with the development of diabetes in susceptible populations include obesity, reduced physical activity, and alteration of dietary habits (West, 1978).

A population-based diabetes survey is described which for the first time documents the prevalence of noninsulin-dependent diabetes in Kiribati - a neighbour of Nauru in the Central Pacific - and associations between the prevalence of diabetes and obesity, physical inactivity and urbanization are examined.

The Micronesian population of the Gilbert Islands gained independence in July, 1979, to form the Republic of Kiribati. The most populous island, Tarawa, is about 1800 km north of Suva, Fiji (Figure 2.1). The islands are low-lying coral atolls which vary in area from 5 to 40 sq km, and few are more than 4m above sea-level. They consist of coral rock, covered with sand and a little soil, coconut palms being the dominant vegetation.

The traditional Kiribati diet consists of fish, shellfish, coconut, breadfruit, pandanus, and taro. To this, limited supplies of sugar, flour, and rice are added in the rural islands. On the urbanized Tarawa atoll, traditional foods are scarce, and heavy reliance is placed upon imported processed food.

SUBJECTS AND METHODS

The survey was conducted in April 1981. The survey population consisted of both rural and urban samples. North Tabiteuea was chosen as the rural sample. This is the largest atoll, extending for some 70 km and, after Tarawa, is the most populous island in Kiribati. The people live an essentially traditional lifestyle, and the population density is 1.2 persons per ha.

Tarawa is the administrative, commercial, and educational centre of Kiribati. The population of Tarawa is concentrated on South Tarawa, and 43 per cent of South Tarawa's population live on the tiny islet of Betio, which was selected for the urban sample. Betio is the most urbanized region of Kiribati, and has a population density of 49.6 persons per ha.

A census was conducted in both regions prior to the survey, and name, age, sex, occupation, name of household head, and years of residence were listed for all adults 20 years and over. In Betio, only those resident for five years or more were included in the survey sample, in order that any effect of urbanization on diabetes prevalence might be manifest.

Daily invitation lists were prepared from the census

registry. All subjects were asked to fast from 12 pm on the night prior to the survey, and to arrive at the survey centre between 7.30 and 9.30 am. Non-attenders were reinvited a total of three times. On arrival, they were given a survey number, and information on their age, sex, marital status, and occupation was recorded on an individual survey form.

A fasting blood sample was taken and a 75 g oral glucose load was administered. Following this, an interview was conducted by local Health Department staff. Family history of diabetes, cigarette smoking and alcohol consumption, current and past medical illnesses, current drug therapy, and obstetric history were noted. Height and weight were measured, and triceps skinfold thickness was measured using Harpenden skinfold calipers. Blood pressure (subjects in sitting position) was also recorded using the Hawksley random-zero sphygmomanometer. Two hours after the glucose load, a further blood sample was taken. A stratified random sample of 36 per cent of survey participants were interviewed at the survey site to obtain dietary data, stratification being with respect to age and sex.

Diabetes mellitus was diagnosed in accordance with a modification of current WHO(1980) criteria adapted for field survey conditions, i.e. plasma glucose concentration of 11.1 mmol/l or greater, two hours after a 75 g oral glucose load. The two-hour plasma glucose concentration has recently been recommended as the most appropriate criterion for diabetes in epidemiological studies (Bennett et al.,

1983). Impaired glucose tolerance was diagnosed on the basis of a two-hour plasma glucose concentration $\geq$ 7.8mmol/l and $<$ 11.1 mmol/l. All known diabetics were included in the diabetic category.

With respect to physical activity, each subject was graded according to a discrete score with values 1-4 corresponding to sedentary, light, moderate or heavy activity. Each subject was assigned a score by local health staff, who were instructed to take both occupational and leisure activity into account when deciding upon an individual's score.

In each region and in each sex, the response rate was in excess of 80 per cent (n = 2938: 1038 rural, 1900 urban). To assess the uniformity of response in the different age groups, the all-ages response rate was applied to the number of persons eligible in each age group to give the number of responders expected on the basis of the all-ages response. Comparing observed and expected response in each age group, a summary chi-square statistic was derived to test the uniformity of response in each sex/region sub-group. There was found to be no significant heterogeneity of response in any of the four sub-groups The total number in the dietary sub-population was 1062, and these were representative of the survey population with respect to sex and age (Table 2.1).

Figure 2.2 shows the comparative age structure of the rural and urban populations in each sex. It is apparent that in both sexes the rural population was the older. The difference was significant, and account has been taken of this age difference, by stratification or standardization, in all rural-urban comparisons.

RESULTS

The prevalence of impaired glucose tolerance and diabetes in each age group is shown in Table 2.2. With two exceptions (males aged 20-24 years and females aged 55-64 years), prevalence of both impaired glucose tolerance and diabetes was lower in the rural than the urban population in both sexes at every age group. Prevalence of both conditions rose steadily with advancing age, reaching a peak in excess of 20 per cent in both sexes in the urban population. There is some evidence of a plateau or fall in prevalence of diabetes in the oldest age group (65 years and over).

Table 2.3 shows age-standardized prevalence of abnormal glucose tolerance by region and sex. For diabetes, prevalence was 9.1 per cent and 8.7 per cent for urban males and females, compared with 3.0 per cent and 3.3 per cent respectively in the rural population. This represents a relative risk of diabetes in the urban population of 3.0 for males and 2.6 for females. These rural-urban differences were highly significant ($p < 0.001$).

Age-standardized prevalence of impaired glucose tolerance exceeded 10 per cent in both regions. The urban prevalence was greater in both sexes, resulting in a relative risk for impaired glucose tolerance in urban versus rural dwellers of 1.5 for males and 1.3 for females. The differences were significant, though less so than for diabetes ($p < 0.001$ for males, $p < 0.05$ for females).

As an indirect measure of the relationship between diabetes and obesity, physical exercise and non-traditional

diet, indices of these factors were compared in the rural (low prevalence) and urban (high prevalence) populations. The correlation coefficients between these indices were low, none exceeding 0.25 (Table 2.4).

As an indication of adiposity, body mass index ($wt(kg)/ht(m)^2$) was calculated. Table 2.5 shows mean body mass index stratified by six age groups. In both sexes, means were lower in the rural population at every age group. Analysis of variance showed these rural-urban differences to be highly significant ($p < 0.001$). A similarly significant difference between rural and urban groups was found with respect to triceps skinfold thickness (another index of obesity), the rural population being the leaner.

Data with respect to habitual physical activity are shown, similarly stratified, in Table 2.6.

In both sexes, and at every age group, the rural sample had a higher mean physical activity score than their urban counterparts, the difference being highly significant ($p < 0.01$ for males, $p < 0.001$ for females).

In the dietary sub-sample, consumption of energy derived from imported food was calculated for each individual by the 24-hour dietary recall method. Consumption of imported food was considered to be a useful index of non-traditional diet, as most of the energy derived from imported foods was obtained from highly processed foods such as rice, sugar, and flour. As there are inherent problems with 24-hour dietary recall data with respect to extreme outliers, which may unduly influence the mean, the parameter of choice was considered to be the median. Table

2.7 shows the median consumption of imported energy. In both sexes, and at each age group, the median consumption of imported energy was lower in the rural population. The differences were highly significant ($p < 0.01$ for males, $p < 0.001$ for females). In both sexes, the mean daily consumption of energy from all sources was higher in rural than urban subjects, presumably reflecting their active lifestyle. Thus, the proportion of the diet consisting of highly processed foods was markedly greater in the urban community.

Obesity has long been associated with noninsulin-dependent diabetes, and to assess whether the higher body mass, demonstrated in the urban group, could account for their higher prevalence of diabetes, age-standardized prevalence of noninsulin-dependent diabetes was calculated in rural and urban populations after stratification by tertiles of the distribution of body mass index for each sex (Figure 2.3). It is evident that, whilst increasing body mass does appear to be associated with higher prevalence, an impressive rural-urban gradient remains.

DISCUSSION

The findings of the Kiribati Diabetes Survey have confirmed earlier reports of a rural-urban gradient in prevalence of noninsulin-dependent diabetes (Prior and Davidson, 1966, Zimmet et al., 1981, Zimmet and Whitehouse, 1981). In urban Kiribati, diabetes is now 2-3 times as prevalent as in European communities. Clinical records in Kiribati suggest that the disease was not common until recently. Thus, diabetes appears to be emerging as a major

national health problem of recent onset, associated with urbanization and socio-cultural change, as in neighbouring Nauru. The plateau or fall in prevalence of diabetes apparent in the oldest age groups may be due to increased mortality in diabetics, and the exhaustion of susceptibles in the population, or may reflect a cohort effect.

The analyses have demonstrated that in Kiribati urbanization is associated with an increase in the prevalence of diabetes. Furthermore, obesity alone does not fully explain the rural-urban gradient in diabetes prevalence in either sex. It is natural to speculate as to the true nature of the risk associated with urbanization, and a component of dietary change is an attractive candidate. Grouped univariate analysis of consumption of imported energy has shown a highly significant difference between the rural and urban samples.

If Micronesians do indeed possess an increased genetic susceptibility to noninsulin-dependent diabetes, as has been suggested by a recent study - which found that increasing European genetic admixture was protective for diabetes in Nauruans (Serjeantson et al., 1983a) - the combination of both genetic and environmental influences may explain the high prevalence demonstrated in urbanized Kiribati in this study. Prevalence of diabetes has been shown to be even higher in other urbanized Micronesian communities, and the potential for further escalation of the problem of diabetes in both Kiribati and other developing regions of Micronesia

should not be underestimated. The high prevalence of impaired glucose tolerance in the rural sample, which was an unexpected finding of this study, may be an indication of deteriorating glucose tolerance even in the traditional setting.

CHAPTER 3

DIABETIC RETINOPATHY IN NAURUANS

SUMMARY

An epidemiological survey of the whole adult Micronesian population of Nauru conducted in 1982 has confirmed that Nauruans, along with Pima Indians, suffer the highest rate of abnormal glucose tolerance yet recorded. To establish the morbid effects of hyperglycaemia in this population, all responders to the diabetes survey were concurrently examined for diabetic retinopathy. In diabetic subjects, the crude prevalence of retinopathy was 24 per cent. Specific rates were determined at various levels of the following characteristics: age, two-hour post-load plasma glucose concentration, body mass index, duration of diabetes and systolic blood pressure. Prevalence was found to rise with increasing two-hour plasma glucose concentration and duration, to fall with increasing body mass index and to have a quadratic relationship with age and systolic blood pressure. The multiple logistic regression model was used to determine whether the selected characteristics were significant in increasing the risk of retinopathy. Body mass index and systolic blood pressure did not contribute significantly to this risk after controlling for age. Increasing two-hour plasma glucose significantly increased the risk of retinopathy, and duration of disease was the strongest predictor variable. This study shows that the consequences of hyperglycaemia in this Micronesian population are comparable to those already documented in European and American Indian communities.

INTRODUCTION

Few population-based epidemiological studies have assessed prevalence of retinopathy in Caucasoid or non-Caucasoid diabetics. Certain non-Caucasoid communities have been found to suffer very high prevalence rates of diabetes mellitus according to internationally defined criteria (Bennett et al., 1976, West, 1978, Zimmet, 1979). However, apart from the Pima Indians (Dorf et al., 1976) it has not been conclusively established whether these populations are suffering from diabetes mellitus itself, or have hyperglycaemia after an oral glucose tolerance load, without suffering from the specific microvascular complications of diabetes mellitus seen in Caucasoids.

In order to resolve the question as to the consequences of hyperglycaemia in these populations, diabetic retinopathy is a useful marker of the diabetic disease state. Dorf et al. (1976) in a population-based study of Pima Indians over the age of 15 years, found that the prevalence of retinopathy in diabetics was 18 per cent, and that duration of disease was the most strongly associated factor. Prevalence of retinopathy rose from 3 per cent among newly diagnosed diabetics to 47 per cent among those with a duration of 10 years or more.

Nauru is a small, isolated island in the Central Pacific, lying 60km south of the equator. The island is 20km in circumference. The indigenous population of approximately 4000 persons are of predominantly Micronesian ancestry. The discovery and subsequent exploitation of large deposits of phosphate on the island has led to

affluence, and to a high degree of urbanization since the Republic of Nauru achieved independence in 1968. The prevalence of obesity is high, few subjects engage in heavy physical activity, and large quantities of imported food and drink are consumed by the islanders. Nauruans share with the Pimas the dubious distinction of suffering the highest prevalence of diabetes mellitus in the world (ibid.). They are also a well-defined island community ideally suited for the study and elucidation of this issue with respect to Pacific populations.

Nauruans suffer almost exclusively from the adult onset (noninsulin-dependent) form of the disease. There was only one truly insulin-dependent diabetic in the sample.

In January, 1982, a total adult population diabetes survey of Nauruans was undertaken, and all subjects were concurrently examined for diabetic eye disease. The prevalence of diabetes mellitus and of diabetic retinopathy was determined, and the association of retinopathy with age, two-hour post-load plasma glucose concentration, body mass index, duration of diabetes and systolic blood pressure was examined.

SUBJECTS AND METHODS

All Nauruans aged 20 years and over who were present on the island at the time of the survey formed the target population. There were 1984 persons of a suitable age listed on the 1980 electoral roll. The presence of a person's name on the electoral roll was a necessary precursor to voting, and, as it was compiled on a house-to-house basis throughout the island, the roll was

considered an accurate estimate of the true population. The most recent census (1977) recorded 1644 Nauruan adults. The discrepancy is consistent with the recent natural population increase, and argues for the completeness of the 1980 electoral roll. Sixty-nine persons were either overseas, or too sick to attend, leaving an eligible population of 1915. Of these, 1583 attended the survey, giving a response rate of 83 per cent.

All eligible subjects were given an invitation on the day prior to the survey and advised to fast from midnight. At the survey site, fasting and two-hour plasma glucose concentrations were measured, the glucose load of 75 g being given orally. Anthropometric measurements were recorded, and blood pressure (mmHg) was measured in the sitting position using a random zero sphygmomanometer after the patient had been seated for a minimum of 10 minutes. A questionnaire concerning diabetic and hypertensive status and treatment, smoking, alcohol consumption, and family history of disease was answered. Both direct and indirect ophthalmoscopy was performed after the dilation of both pupils. The ophthalmologists were not aware of the glucose tolerance status of the subject being examined. Care was taken to distinguish intra-retinal exudates from drusen, which are sub-retinal.

Diabetes mellitus was diagnosed in accordance with a modification of current WHO (1980) criteria suited to field survey conditions, i.e. as plasma glucose concentration of 11.1 mmol/l (200 mg/100 ml) or greater, two hours after a 75 g oral glucose load. All known diabetics were classified as

diabetic, regardless of their plasma glucose concentration. Impaired glucose tolerance was diagnosed on the basis of a two-hour plasma glucose concentration intermediate between 7.8 and 11.1 mmol/l (140 and 200 mg/100 ml). The duration of disease for the known diabetics was taken to be the time since diagnosis.

Retinopathy was also defined according to accepted international criteria (Bennett, 1979). For the purpose of this analysis, retinopathy was considered as a binary variable (presence or absence), presence being one or more microaneurysm, haemorrhage or exudate in either eye, or the presence of neovascularization. Diagnostic criteria and examination techniques were similar to those described in the Pima study (Dorf et al., 1976) with the exception that, in the latter, the examining physician may not always have been a specialist ophthalmologist, as was the case in the present study.

RESULTS

The prevalence of diabetes in the Nauruan population over the age of 20 years was 24 per cent, rising to 46 per cent in those aged 35 years and over.

The crude prevalence of retinopathy in normal subjects was 1 per cent, in those with impaired glucose tolerance 3 per cent and in diabetics 24 per cent. When standardized against the age structure of the Pima Indian diabetic study population (Dorf et al., 1976), the prevalence of retinopathy in Nauruan diabetics aged 25 years and over was 22 per cent, compared with 19 per cent in the Pimas.

Microaneurysms and haemorrhages were the most common lesions. Exudates alone were found in only 2 per cent of cases. Proliferative retinopathy was present in 5 per cent of cases.

Figure 3.1 shows the prevalence of retinopathy in diabetics according to duration of disease. Prevalence rose steadily in both sexes, from less than 10 per cent in newly diagnosed cases, to more than 50 per cent in those with a duration of diabetes of 10 years or more. The trend was very similar in the two sexes.

Figure 3.2 shows a preliminary examination of the relationship between prevalence of retinopathy and various levels of five selected independent variables. Sexes are combined in this figure as trends were similar in males and females, and combination provides improved group numbers. Prevalence rose with both two-hour plasma glucose concentration and duration. The relationship with age appeared quadratic, perhaps because those with the more severe retinopathy-producing disease would be less likely to live to an advanced age. Prevalence of retinopathy fell with increasing body mass index, and it might be postulated that the more severe the disease, the leaner the subject, either due to disease or treatment. Systolic blood pressure did not seem to have a strong effect on prevalence of retinopathy.

In order to examine the independence of the selected characteristics relative to each other, a correlation matrix was constructed (Table 3.1). It is important from a statistical point of view to have low correlations amongst

the independent or predictor variables. Table 3.1 shows this to be the case for these data, the highest correlation being 0.32 between body mass index and systolic blood pressure, and between two-hour plasma glucose concentration and duration.

Mean values of the independent variables were then determined in those with and without retinopathy in each sex separately (Table 3.2). There was little difference in mean age, body mass index and systolic blood pressure between those with and without retinopathy in either sex. However, there was a highly significant difference in mean two-hour plasma glucose concentration in both sexes ($p < 0.001$) and the difference in mean duration between the two groups was the most significant of all factors examined in both sexes ($p < 0.001$). This initial univariate analysis suggests, therefore, that of the five variables selected duration of disease is the one most strongly associated with retinopathy, with two-hour plasma glucose also contributing a significant effect.

To determine the combined effect of the variables, the multiple logistic regression model was fitted for males and females separately, whose two-hour plasma glucose level was equal to or exceeded 7.8 mmol/l. The analysis was carried out using the GLIM program (Baker and Nelder, 1978). Individuals were classified into six age groups (20-24, 25-34, 35-44, 45-54, 55-64, 65 years and over), and two-hour plasma glucose, body mass index, duration and systolic blood pressure were treated as continuous variables. Allowance was made for the possibility of a

non-linear trend in the prevalence of retinopathy with age by combining individuals into age groups, and always including a constant term in the model for each age group.

The model with the four variables was compared with models which also included squared terms and interactions between the variables. These comparisons were made using the difference of the deviance between the models, and comparing them with the chi-square distribution. As these equations were not significantly better in predicting the presence or absence of retinopathy, the simpler model was selected for further analysis.

Extreme data points in this chosen model which, if included, would markedly affect the variable coefficients and fit of the model were found using the diagnostic technique of Pregibon (1981). These were excluded from the final analysis because they had the effect of swamping the general trend of the rest of the data. In all, 7 males and 9 females were excluded for this reason, leaving 155 males and 188 females.

The coefficients in the logistic regression models using all variables (the full models) are given in Table 3.3. As measures of the fit of the models, the deviance suggests that the models for both males and females are acceptable ones, while the 'entropy' of the models, as defined by Efron (1978), is 0.45 and 0.46 respectively. These values can be interpreted as the "R^2" values for the models. To determine which combination of variables gave the best prediction of retinopathy, all 24 possible models with combinations of the four variables were analysed.

For each sex, using one, two, three, and four predictor variables in addition to the six age group constants, the optimal model was found by selecting the model with the smallest deviance (Table 3.4). This procedure enables the most important set of variables to be defined at each step. In both sexes, duration was found to be the most important predictor variable after controlling for age (step two). Two-hour plasma glucose also significantly improved the models, as demonstrated by the chi-square value for differences between the optimal models at steps two and three. There was no significant improvement in the fit of the models with the addition of the two other variables, body mass index and systolic blood pressure (steps four and five), in either sex. Thus, duration and two-hour plasma glucose together predict the retinopathy status as well as all four variables, duration being the most important predictor in both sexes.

DISCUSSION

The data reported here have been analysed both by univariate methods, and also by the application of the multiple logistic regression model. Both methods of analysis show that, in both sexes, duration of diabetes is the factor most strongly associated with the presence of retinopathy, with two-hour plasma glucose also being significantly associated. After controlling for age, body mass index and systolic blood pressure had no useful predictive value when isolated from the two most important factors.

These findings are substantially in accord with data

collected on the Pima (Dorf et al., 1976) and Oklahoma Indians (West et al., 1980) and strengthen the likelihood of the truth of the apparent associations. Furthermore, the consistency of these Pacific data with similar material collected from other populations supports the notion that Pacific islanders do indeed suffer from diabetes in a form comparable to that found in Caucasoid and other more closely studied communities, rather than merely demonstrating hyperglycaemia as an innocent biochemical trait.

Although at much less risk of retinopathy than diabetics, subjects with impaired glucose tolerance nevertheless have a relative risk of retinopathy of 3 compared with normals, providing support for the inclusion of the impaired glucose tolerance category in the current WHO(1980) criteria for abnormal glucose tolerance, and confirming similar findings in American Indian and United Kingdom studies (Bennett et al., 1976, Jarrett and Keen, 1976).

Several potential sources of bias may be noted in this study, such as the exclusion of persons overseas. The exclusion of those too sick to attend could have led to a marginal underestimate of the prevalence of diabetes and diabetic retinopathy. However, as both excluded groups combined amounted to only 3.5 per cent of the population listed on the electoral roll, bias of the estimate of prevalence of a disease affecting one quarter of the total population would be minimal.

True non-attenders, who were invited to attend the survey but chose not to do so, comprised 17 per cent of the

total eligible population. The age-structure and proportion of known diabetics were found to be similar in attenders and non-attenders, indicating that the former were not an obviously biased sample of the total population.

It should also be noted that 58 per cent of the diabetics studied were aware of their disease at the time of the survey. The effect of treatment could have led to a conservative estimate of the true relationship between the two factors found to be associated with retinopathy - duration of disease and two-hour plasma glucose. However, few Nauruan diabetics were compliant with treatment at the time of examination, as judged by their fasting plasma glucose concentration.

The consistent finding in this and other studies that not only duration of diagnosed disease, but also two-hour plasma glucose level at the time of examination are significantly associated with the presence of retinopathy highlight the need for both the control of hyperglycaemia in diabetics, and also for an increased understanding of the causes of hyperglycaemia in susceptible populations with a view to the establishment of meaningful preventive measures. This clearly applies not only in Westernized societies with already well-established control programmes, but also in developing regions such as the Pacific.

CHAPTER 4

THE NATURAL HISTORY OF IMPAIRED GLUCOSE TOLERANCE IN THE MICRONESIAN POPULATION OF NAURU: A SIX-YEAR FOLLOW-UP STUDY

SUMMARY

A longitudinal study of 266 randomly selected non-diabetic Nauruans (215 normal subjects, 51 with impaired glucose tolerance) has permitted the natural history of impaired glucose tolerance to be studied in this Micronesian population. Nauruans are known to suffer from a very high prevalence of abnormal glucose tolerance.

The subjects were first examined in 1975-1976, and a follow-up examination was performed in 1982. Of the subjects with impaired glucose tolerance, 26 per cent developed diabetes during the study period (4 per cent per annum) compared with 7 per cent of normal subjects (1 per cent per annum). After controlling for the effects of both age and obesity, the risk of subsequent diabetes for subjects with impaired glucose tolerance remained significantly higher than for normals (odds ratio: 3.6, 95 per cent confidence interval 1.4-9.1). Of those with impaired glucose tolerance on initial examination, 39 per cent were normoglycaemic at follow-up.

In subjects with impaired glucose tolerance, of nine factors examined, only plasma glucose concentration at the time of the initial examination was consistent in predicting progression to diabetes, when the data were examined by both univariate and multivariate methods. Both two-hour and fasting plasma glucose values were useful predictors.

Thus, Nauruans with impaired glucose tolerance have a higher risk of subsequent diabetes than their normoglycaemic counterparts, after controlling for age and obesity. Nevertheless, the prognosis of impaired glucose tolerance is

unpredictable as a substantial proportion of such subjects return to normality. Plasma glucose concentration is the most important predictor of subsequent diabetes. These results are in accord with recent findings from longitudinal studies of impaired glucose tolerance in other populations.

INTRODUCTION

In 1982, a follow-up diabetes survey of the Micronesian population of Nauru was conducted. The initial examination had been in 1975-1976, and the average length of time between examinations was 6.2 years.

Of the 266 subjects examined in both surveys who were initially non-diabetic, 215 were normoglycaemic and 51 had impaired glucose tolerance at first examination. This report examines the prognosis of those with impaired glucose tolerance, and assesses the predictive power of selected variables in relation to the subsequent development of diabetes. The findings are compared with similar data from other populations, in an attempt to shed further light on the validity of the intermediate category of glucose tolerance, and in response to the call from the World Health Organization Expert Committee on Diabetes (1980) for further population-based evidence concerning the present diagnostic criteria for glucose intolerance.

The background to the Nauru diabetes studies is described in Chapter 3.

SUBJECTS AND METHODS

A diabetes survey of all adult Nauruan residents of a randomly selected region of Nauru (a homogeneous island with respect to lifestyle) was conducted, in two stages. The first was in May, 1975, and the second in January, 1976. In January, 1982, a diabetes survey of the whole adult Nauruan population of the island was performed. Of the 456 persons examined in 1975 who were still resident in Nauru in 1982, and who were eligible to attend the second survey (in

terms of being present on the island, and not too infirm to reach the survey site), 366 did so, giving a response rate of 80 per cent at follow-up. Of these, 266 persons were non-diabetic on initial examination, and these form the basis of the present study.

Survey methods were standardized in the two surveys. Selection procedures and survey methodology have been described in detail in the previous Chapter.

Abnormal glucose tolerance was classified in accordance with a modification of current WHO (1980) criteria suited to field survey conditions, diabetes mellitus being diagnosed on the basis of a plasma glucose concentration of 11.1 mmol/l or greater, two hours after a 75 g oral glucose load. Impaired glucose tolerance was defined by a two-hour plasma glucose concentration greater or equal to 7.8 mmol/l, but less than 11.1 mmol/l. All previously known diabetic subjects were included in the diabetic category. Subjects not fulfilling these criteria were considered to have normal glucose tolerance.

RESULTS

The age distribution of the 266 subjects with normal and impaired glucose tolerance at initial examination is shown in Table 4.1 (decade, rather than mid-decade intervals were used for consistency with earlier reports). It is evident that subjects with impaired glucose tolerance formed an older population than the normal subjects in both sexes, and the effect of age was taken into account when assessing characteristics associated with progression to diabetes.

Crude prognosis of impaired glucose tolerance

The mean time interval between examinations was 6.2 years. A comparison of the percentage of subjects in each category of glucose tolerance at follow-up within each baseline group (normal or impaired glucose tolerance) is shown in Table 4.2. Of the 51 subjects with impaired glucose tolerance, 13 (26 per cent) progressed to diabetes (males 27 per cent; females 24 per cent), compared with 14 (7 per cent) of the 215 normal subjects (males 7 per cent, females 6 per cent). The crude incidence of diabetes was 4 per cent per annum in the former (13 incident cases, 322 person years at risk). In the latter, the crude incidence of diabetes was 1 per cent per annum (14 incident cases, 1339 person years at risk). Of those initially displaying impaired glucose tolerance, 35 per cent retained this status, whereas 39 per cent were normoglycaemic at follow-up.

The risk of impaired glucose tolerance after controlling for age and obesity

In order to assess the risk attached to impaired glucose tolerance, in terms of subsequent diabetes, the multiple logistic regression model was used to predict progression to diabetes (Table 4.3). The predictor variables included in the model were : age, sex, body mass index, and presence or absence of impaired glucose tolerance at initial examination. A further dummy variable represented the date of original survey, to control for discrepancies in the period of follow-up. A squared term was included to account for a non-linear trend with age, as

it significantly improved the fit of the model. The model fitted the data adequately, as demonstrated by the log likelihood statistic, which had a value of 140 on 256 degrees of freedom. The exponents of the parameter estimates of the predictor variables represent approximate point estimates of odds ratio for the presence of each variable, controlling for the effects of all the other variables in the model (Breslow and Day, 1980). Age, age-squared, and body mass index were significant predictors of diabetes. After controlling for the effect of these factors, impaired glucose tolerance made a significant independent contribution to risk, with a parameter estimate of 1.4, corresponding to an odds ratio of 3.6 (95 per cent confidence interval 1.4-9.1). Impaired glucose tolerance was, in fact, the most significant predictor variable in the model.

Factors associated with progression to diabetes in subjects with impaired glucose tolerance

To assess which factors were associated with subsequent progression to diabetes in the subjects with impaired glucose tolerance, means of selected physiological, biochemical and environmental factors were compared in those who did, and those who did not, progress to diabetes (Table 4.4). Continuous variables (other than age) were standardized for age by analysis of covariance. There was a highly significant difference in both mean two-hour and fasting plasma glucose concentrations between the two groups ($p < 0.01$). Mean body mass index was also significantly higher in those who progressed to diabetes than those who

did not ($p < 0.01$). There was no significant difference in mean triceps skinfold thickness, or in any of the other comparisons. The trend in the proportion of subjects progressing to diabetes across quartiles of baseline plasma glucose concentration is illustrated in Figure 4.1. Over 50 per cent of subjects in the highest quartile subsequently developed diabetes.

To assess their independent contribution to the probability of progression to diabetes, the variables examined in a univariate manner in Table 4.4 were further studied by means of the multiple logistic regression model, predicting development of diabetes (Table 4.5). Because of problems relating to collinearity, fasting plasma glucose concentration and triceps skinfold thickness were dropped from the analysis. As before, a dummy variable controlled for differences in length of follow-up.

The model appeared to fit the data adequately, as shown by the log likelihood statistic of 29 on 38 degrees of freedom. However, as, for consistency with other reports (Jarrett et al., 1979, Keen et al., 1982, Sasaki et al., 1982) a number of non-significant variables were deliberately retained in the model, maximum precision was not attempted. Age and two-hour plasma glucose concentration were significant predictors of subsequent diabetes in the model. Systolic blood pressure, which was non-significant in the univariate analysis, was a significant negative predictor in the multiple logistic regression model. Conversely body mass index, which was significant in the univariate analysis, just failed to

achieve significance in the model. Interaction terms involving the variables of importance were introduced into the model, but none caused a significant improvement. The most significant variable in the final model was two-hour plasma glucose concentration. When two-hour plasma glucose concentration was replaced by the fasting value, plasma glucose concentration remained the most important predictor, though the fit of the model deteriorated slightly.

DISCUSSION

The introduction of the category of impaired glucose tolerance by the National Diabetes Data Group in 1979 and its adoption by WHO in the following year was in recognition that there were a substantial number of individuals who, though their plasma glucose concentration after a glucose challenge was insufficient to classify them as diabetic, were nevertheless at increased risk of macrovascular disease. Furthermore, studies suggested that this group, which had hitherto been classified as one of 'latent' or 'borderline' diabetes, had an unpredictable prognosis, and the use of the term 'diabetes' was therefore considered unsuitable in this context. Whereas the risk of diabetes was greater in those with impaired glucose tolerance than in normal subjects, a substantial proportion of the former subsequently appeared to revert to normality. This proportion, estimated at 30-50 per cent, was clearly too great to be explained by the phenomenon of regression to the mean, resulting from the known variability of venous plasma glucose concentration.

Three longitudinal studies of impaired glucose tolerance have recently appeared in the literature. These are the Whitehall Study (Jarrett et al., 1979) and the Bedford Survey (Keen et al., 1982), both performed in the United Kingdom, and a 7-year follow-up study in Osaka, Japan (Sasaki et al., 1982). The results described for Nauruans in this report may thus be compared with contemporary findings from Caucasoid and Japanese populations, providing an opportunity to test for consistency with the results of these studies in an ethnic group previously unstudied with respect to impaired glucose tolerance, and known to suffer a high prevalence of diabetes.

The data from Nauru confirm earlier studies, which have demonstrated that a substantial proportion of subjects with impaired glucose tolerance return to normoglycaemia, but that, nevertheless, this group are at increased risk of subsequent diabetes. This adds further weight to the notion that impaired glucose tolerance cannot be regarded simply as a pre-diabetic state.

Glucose tolerance is known to be labile, and original mis-classification may account for some of the observed changes of status at an individual level. However, the proportion of subjects with impaired glucose tolerance who subsequently change status (both for better and for worse) seems too great to be explained by this factor alone.

The study has also provided further support for the contention that the strongest predictor of future diabetes in this group is the baseline plasma glucose concentration, and that this association is independent of age and obesity.

Obesity has sometimes (O'Sullivan and Mahan, 1965, 1968, Keen et al., 1982, Sasaki et al., 1982), though not invariably (Jarrett et al., 1979, Keen et al., 1982), been related to a worsening to diabetes in subjects with impaired glucose tolerance. There appeared to be such an association in Nauruans in the initial univariate analysis, but this lost significance when examined in the multiple logistic regression model.

As previously mentioned, for the sake of consistency with other reports, all the variables of interest were included in the model presented in Table 4.5. There are, however, constraints upon the interpretation of a model developed by the unconditional use of a set number of explanatory variables, and when so many redundant variables are retained in the model. When the modelling was repeated using the forward selection procedure, body mass index had a strong effect when entered as the first variable, but lost significance upon the addition of two-hour plasma glucose concentration. Clearly, these two variables are closely related, though plasma glucose was the stronger predictor of subsequent diabetes in both the univariate and the multivariate analysis. However, the role of obesity should not be completely dismissed.

Systolic blood pressure was negatively associated with subsequent diabetes in the full logistic regression model, and also in the forward selection model when controlled for age by a linear term only. However, blood pressure lost significance upon the addition of a squared term for age in the forward selection model. It was not possible to

introduce a squared term for age into the full model, due to a limitation of the computer program, but when two non-significant variables were removed (plasma uric acid and creatinine), the squared term for age once again abolished the significance of the blood pressure variable. This suggests that the observed association between blood pressure and subsequent diabetes was due to the confounding effect of age. It is interesting to note that a similar negative association between blood pressure and subsequent diabetes has recently been reported from the Whitehall study (Jarrett et al., 1982).

In conclusion, these findings, from a Micronesian population, support reports from the United Kingdom and Japan that impaired glucose tolerance has an unpredictable prognosis, and that baseline plasma glucose concentration is the single most important predictor of subsequent diabetes of all the factors studied to date.

CHAPTER 5

ETHNIC DIFFERENCES IN SUSCEPTIBILITY TO NONINSULIN-DEPENDENT DIABETES: A COMPARATIVE STUDY OF TWO URBANIZED MICRONESIAN POPULATIONS

SUMMARY

Two urbanized Micronesian populations were recently studied by population-based diabetes surveys. These were Nauruans living on the island of Nauru, and Gilbertese resident on the islet of Betio, in the Republic of Kiribati (1982 and 1981 respectively). Nauruans are known to suffer from a very high prevalence of noninsulin-dependent diabetes. In the present study, the effects of suspected environmental risk factors for diabetes were controlled for, in an attempt to elucidate any residual difference in the prevalence of diabetes between the two groups, which might be of genetic origin. As almost all Nauruans lead a physically inactive lifestyle, only inactive subjects in either population were selected for study. The total study sample consisted of 2306 subjects.

After further controlling for the effects of age and obesity, the odds of diabetes for Nauruans, as compared with Gilbertese, was threefold. The multiple logistic regression model showed ethnicity (i.e. being Nauruan) to be the strongest of the predictor variables examined in both sexes.

In a random sub-sample of approximately one third of the total subjects (n = 694), stratified with respect to age and sex, daily intake of total energy and of three dietary components was assessed. The dietary variables were carbohydrate, fat and dietary fibre. Fat intake was found to be a weak, but significant, predictor of diabetes in females after controlling for age, though dietary fat was not predictive of diabetes after also controlling for ethnicity, or for body mass. None of the other dietary

variables had any predictive power in either sex. Ethnicity was once again the most important predictor in both sexes, and remained a significant predictor after controlling for age and body mass.

This study demonstrates that obesity is not a sufficient explanation of the high prevalence of diabetes in Nauruans, and provides further support for recent evidence of heightened genetic susceptibility to noninsulin-dependent diabetes in this Micronesian population. However, the possibility that as-yet undetermined environmental influences may also be involved cannot be discounted.

INTRODUCTION

Despite much research, evidence of a genetic component to noninsulin-dependent diabetes, in terms of HLA and other specific genetic markers, remains sparse. It is difficult to dismiss the likelihood of genetically determined susceptibilty in populations with such a high prevalence of the disease as the Nauruans (ibid.) and the Pima Indians (Bennett et al., 1970). However, such a view is not universal. It has been argued that these two populations are characterized by marked obesity, and that this factor may unmask a discrete susceptibility to diabetes (Keen et al., 1970). Dietary excess has also been incriminated (Ringrose and Zimmet, 1979).

Population-based surveys have recently been carried out in two Micronesian communities: Nauruans living on the island of Nauru and the Gilbertese inhabitants of Kiribati (formerly the Gilbert Islands), a neighbour of Nauru in the Central Pacific. The location of these islands is shown in Figure 5.1. Nauruans are an urbanized population, as a consequence of income from the rich phosphate deposits on their island. An urbanized community was also examined during the diabetes survey in Kiribati. In the present study, the prevalence of diabetes is compared between the two communities after controlling for differences in age, physical activity, obesity, daily intake of total energy, and certain dietary components. Differences in the prevalence of diabetes which remain between Nauruans and Gilbertese, after controlling for known and suspected environmental risk factors, may prove to be useful indirect evidence of relative genetic susceptiblity.

SUBJECTS AND METHODS

Kiribati has a predominantly rural community. However, the islet of Betio, in the Tarawa atoll, is an urbanized administrative and commercial centre, with a very high population density, and the inhabitants lead a non-traditional lifestyle. During the Kiribati Diabetes and Cardiovascular Disease Survey, conducted in 1981, all Gilbertese inhabitants of Betio who were over 20 years of age and who had been resident in an urbanized environment for 5 years or more were included in the survey sample. The latter restriction was imposed in order that the diabetogenic effect of urbanization and modernization of lifestyle, if operating in this community, might be manifest.

The island of Nauru is entirely urbanized, and has an affluent society as a result of the enormous and valuable deposits of phosphate on the island. In 1982, a diabetes survey of all Nauruans resident on the island was performed.

In both surveys, the response rate exceeded 80 per cent, and the respondents were representative of their populations with respect to age and sex. There were 1900 responders in Betio and 1568 in Nauru. The great majority of Nauruans lead a lifestyle characterized by marked physical inactivity. As the effect of physical activity was to be controlled for in the present study, only subjects in either community who claimed to be habitually physically inactive with respect to occupation or regular daily activity were included in the analyses. There were 941 such persons in Betio and 1396 in Nauru. Of these, 9 persons in Betio and 22 persons in Nauru were omitted from

the analyses due to missing data, leaving a total study population of 2306 subjects.

In both Betio and Nauru, approximately one third of the survey responders answered a dietary questionnaire, based upon the 24-hour recall method. The dietary sub-samples were selected randomly after stratification with respect to sex and age. There were 664 subjects in the sub-sample in Betio, and 399 in Nauru. Of these, 357 and 344 respectively were classified as physically inactive, and 7 cases were omitted due to missing data, providing a dietary sub-sample of 694 subjects.

Diabetes was diagnosed in accordance with a modification of current WHO (1980) criteria, which were adapted for field survey conditions, namely a plasma glucose concentration of 11.1 mmol/l or greater, two hours after a 75 g oral glucose load. Two-hour plasma glucose was measured on site with a Yellow Springs Instrument glucose analyser which uses a glucose oxidase method. All known diabetics were included in the diabetic category.

Body mass index (kg/m^2) was the chosen index of obesity.

Survey methods were carefully standardized in the two studies, and have been described in preceding Chapters.

RESULTS

Whereas the crude prevalence of diabetes was less than 10 per cent in the physically inactive residents of Betio, it exceeded 20 per cent in those of Nauru (Table 5.1). After standardizing for age, the relative risk of diabetes for Nauruans, as compared with Gilbertese, was 2.6 in both sexes.

As a preliminary assessment of the role of obesity in the differing diabetes prevalence between the two communities, the age-standardized prevalence of diabetes was calculated after stratifying the populations by tertiles of the combined distribution of body mass index for each sex (Figure 5.2). The lowest tertile included subjects with body mass index less than 20.8 in males, and 28.4 in females. The highest tertile included subjects whose body mass index was not less than 32.9 and 34.7 in males and females respectively. Such cut-off points indicate that these populations are relatively obese by international standards. Although the prevalence of diabetes rose with increasing body mass, particularly in the Betio sample, a marked difference remained between the two populations. In Nauruans of both sexes, prevalence was very high (approximately 20 per cent) even in the leanest third of the combined population.

Mean age did not differ between the two populations (Table 5.2), though mean body mass index was notably higher in Nauruans of both sexes.

To assess the relative power of body mass index and ethnicity (defined here as a Nauruan, as opposed to Gilbertese genotype) to predict diabetic status, the multiple logistic regression model was employed, using the GLIM program (Baker and Nelder, 1978) (Table 5.3). After controlling for the effect of age by a linear and quadratic term, body mass index made a highly significant improvement to the model in both sexes (step three). A squared term for body mass index was also introduced, but was not retained as it failed to significantly improve the model in either sex.

Finally, the predictive power of ethnicity independent of age and body mass index was tested (step four). In both sexes the model was markedly improved, suggesting that obesity, as defined by body mass index, was not sufficient to explain the difference in prevalence of diabetes between the two populations. When the data were re-analysed using the forward selection procedure, after allowing for age, ethnicity was selected before body mass index in both sexes. A term representing interaction between ethnicity and body mass failed to improve the model for either sex.

The parameter estimates for the final models are shown in Table 5.4, and are strikingly similar in males and females, indicating model stability. The standardized parameter estimates, which may be referred to tables of the normal distribution, as a test of the significance of the parameters in the regression equation (Schlesselman, 1982), indicate that ethnicity was a more powerful predictor variable than body mass index in the final model for both sexes. Although body mass index was also significant in males, this was not so for females.

For categorical variables, exponents of the parameter estimates represent approximate point estimates of relative odds of disease, given the presence of the parameter concerned (Schlesselman, 1982). In both sexes the parameter estimate for ethnicity was 1.2, which corresponds to approximate relative odds of diabetes of 3.3 for Nauruans, as compared with Gilbertese, after controlling for age and body mass index.

This analysis suggests that obesity is not a sufficient

explanation of the difference in the prevalence of diabetes between the two populations.

To determine whether dietary factors could account for the higher prevalence of diabetes in Nauruans, the association between diabetes and age, body mass index, ethnicity, daily intake of total energy (mJ), and three dietary components was examined in the dietary sub-sample. The dietary components were: carbohydrate (g), fat (g), and dietary fibre (g). Mean levels of these variables in the two populations are shown in Table 5.5. Means for age and body mass index were very similar to the respective values for the total study populations, further validating the dietary sampling technique. Mean levels of total energy, carbohydrate and fat were markedly higher, and of mean dietary fibre lower, in Nauruans than in the Gilbertese residents of Betio.

It was apparent that the correlations between total energy, carbohydrate and fat intakes were high (Table 5.6). For this reason, the forward selection logistic regression models predicting diabetes in the dietary sub-samples are presented in full (Table 5.7). At each step, the result of entering each variable is examined, in terms of the χ^2 value for the likelihood ratio test. This avoids the possibility of the importance of a given factor being overlooked due to collinearity with another variable entered at the same step. After controlling for age (step two), ethnicity was the most significant variable in both sexes (step three). Body mass index was also significant, though this factor failed to significantly improve the models after the addition of ethnicity. By contrast, ethnicity significantly improved

upon the models controlling for age and body mass index (step four), once again demonstrating that obesity could not account for the higher prevalence of diabetes in Nauruans. A term representing interaction between ethnicity and body mass index did not improve the model for either sex.

Of the dietary variables examined, only dietary fat had significant predictive power when allowance was made for age, and this finding was limited to females. None of the dietary variables improved upon the models incorporating age and ethnicity, or age and body mass index.

DISCUSSION

The results of these analyses suggest that there is an ethnic component to the excess risk of diabetes in urbanized Nauruans, as compared with urbanized Gilbertese, which is independent of differences in age, physical activity, obesity and of dietary habits with respect to intake of total energy, carbohydrate, fat and dietary fibre. There was also slight evidence of an association between prevalence of diabetes and dietary fat intake in females, although this may well have been a chance finding.

The search for specific genetic markers for noninsulin-dependent diabetes has not met with the success which has attended similar research for the insulin-dependent form of the disease, though evidence of a genetic component to the former is accumulating from other sources. Twin studies have shown that the majority of twin pairs are concordant for noninsulin-dependent diabetes, despite marked differences in body weight (Barnett et al., 1981). A recent study of Mexican Americans has demonstrated an association

between diabetes prevalence and percentage native American genetic admixture (Gardner et al., submitted for publication). A study of the American Pima Indians, a population with an extremely high incidence and prevalence of diabetes, has shown that though the population was obese, adiposity alone could not account for the observed incidence (Knowler et al., 1981).

Nauruans suffer from as high a prevalence of diabetes as any population yet reported in the literature and, furthermore, it has been shown recently that Caucasoid ancestral genetic admixture provides protection against the development of diabetes in this population (Serjeantson et al., 1983a). In the present report we have shown that none of the known or suspected risk factors examined could account for the high prevalence of diabetes in Nauruans, when compared with their Gilbertese neighbours.

It seems plausible that the unexplained component of the difference in diabetes prevalence between Nauruans and Gilbertese may be of genetic origin. Eight blood genetic markers that maintain polymorphic frequencies in Nauruans were examined in the Betio population (R.L. Kirk, personal communication). Allele frequencies at four loci, PGM1, ESD, GD and HP, were similar in both groups. However, for the red cell enzymes ACP and 6PGD, allele frequencies were markedly different in a sample of 192 from Betio compared with 240 Naurans. ACPI*A attains a gene frequency of 25.4 per cent in Nauru compared with only 2.6 per cent in Betio and, whereas PGD*C is rare in Nauru (2.9 per cent), it has a frequency of 15.4 per cent in the Betio sample. The

distributions of serum complement component BF are also disparate in the two populations, with BF*F at a frequency of 8.4 per cent in Nauru and 1.5 per cent in Betio. A rare variant of complement component C6, C6*NAURU, has an allelic frequency of 6.7 per cent in Nauruans but is completely absent in the Betio population.

The comparatively high frequency of the rare variant of C6 in Nauru highlights the powerful role of genetic forces, including mutation, random drift and possibly selection, in determining marked genetic differentiation between the two Micronesian island populations.

Mechanisms which may have served to exaggerate the apparent susceptibility of Nauruans to diabetes in this study should be considered, and include:

1. Causative environmental risk factors which have yet to be identified, and to which Nauruans are exposed to a greater degree than their neighbours.
2. Inadequate control for differences between the populations with respect to known and suspected risk factors during the analysis.

The former must remain a matter for speculation and necessarily place constraint upon the inference of a causal genetic association - though it seems unlikely that such a necessarily ubiquitous environmental factor would remain undetected. The second possibility may be addressed more directly.

Firstly, it should be remembered that the assessment of physical inactivity in these surveys was crude. Although

there is no more convenient, or sensitive, measure of habitual physical activity under field survey conditions at present, it is not inconceivable that the concept of physical inactivity differs for Nauruans and Gilbertese, resulting in systematic response bias. However, the fact that approximately 50 per cent of the Betio sample claimed to be physically active, despite urban residence, suggests that the selection procedure has controlled for physical activity to some extent.

There are also limitations to the study - on an individual basis - of dietary variables which have been examined by the 24-hour recall method, because of the possibility of large day-to-day variation (Block, 1982). Associations between dietary components and disease are notoriously weak, casting further doubt upon the adequacy of present methods of dietary assessment. However, the significance of dietary fat in the regression model for females in this study suggests that this variable has a detectable effect, despite the limitations of assessment, though its effect was negated by other, stronger predictors. Estimates of the fibre content of some traditional foods were not available in Betio, which may have reduced the observed difference between the two populations with respect to this variable. It was not possible to control for length of urban residence in this study, but all subjects had been living in an urbanized environment for a minimum of 5 years, and both Nauru and Betio have been important urban centres for some considerable time.

In summary, it has been shown, beyond reasonable doubt, that obesity is an insufficient explanation of the high prevalence of diabetes in Nauruans. The findings of this study, when assessed in the light of known differences in the frequency of certain genetic markers between the two populations examined, support recent evidence of genetic predisposition to noninsulin-dependent diabetes in Nauruans and certain other isolated non-Caucasoid populations with a high prevalence of the disease. However, the possibility that this comparative study may have been confounded by differences between the two populations with respect to environmental precipitants, not included in the analyses, cannot be excluded.

CHAPTER 6

RISK FACTORS FOR DIABETES

IN THREE PACIFIC POPULATIONS

SUMMARY

The association between the prevalence of diabetes and three suspected risk factors - obesity, physical inactivity, and urbanization - has been studied in 5519 subjects from three Pacific populations: Melanesians and migrant Asian Indians in Fiji, and Micronesians in the Republic of Kiribati.

Associations were found to be inconsistent between populations, and between the sexes within populations. In some cases, overweight was strongly associated with prevalence; in others, the principal variable associated with diabetes appeared to be physical inactivity. More than one factor was associated with increased risk in Micronesians, and some evidence of interaction between factors also emerged.

Although longitudinal studies will be required for the complete elucidation of risk factors for diabetes, these findings suggest that risk factors may be heterogeneous in their effect upon different populations, and that an assessment of risk variables operating in a given target community may be of value in the initial phase of a diabetes prevention or control programme.

INTRODUCTION

Recent epidemiological evidence suggests that the prevalence of diabetes in populations may be determined by both underlying genetic susceptibility and also the extent to which individuals in the population are exposed to various environmental risk factors. Cross-sectional diabetes surveys have been conducted in a number of populations in Oceania in recent years (Prior et al., 1966, Zimmet et al., 1977, 1979). In the Pacific region, diabetes occurs almost entirely in the noninsulin-dependent form (Zimmet, 1982). As methods have been standardized in several of these surveys, they provide a valuable opportunity for comparative study, in an attempt to elucidate risk variables for noninsulin-dependent diabetes.

One fact that has emerged clearly from Pacific studies is the wide disparity in the prevalence of diabetes between populations. Prevalence has been found to range from less than 2 per cent in rural Melanesians in Fiji and New Caledonia to 30 per cent in the affluent and urbanized Micronesian population of Nauru (rates age-standardized to the 1976 census of Western Samoa).

The attempt to isolate specific genetic determinants, or markers for diabetes in Pacific populations has met with little success to date, although it has recently been demonstrated that increasing European genetic admixture results in a decreased prevalence of diabetes in the high-prevalence population of Nauru, suggesting that a part-European genotype is protective against diabetes in Nauruans (Serjeantson et al., 1983a).

For many years interest has been focused upon behavioural and environmental risk factors which may precipitate diabetes in susceptible individuals. Obesity has long been associated with diabetes - as early as 400 BC, it was noted in India that diabetes was a disease of the well-fed (West, 1978). However, the relationship between obesity and diabetes is not inevitable. Both clinical and epidemiological records demonstrate that, on an individual basis, many grossly obese individuals never develop diabetes, and conversely that cases of diabetes may be found amongst the very lean. It has also been shown that the prevalence of diabetes is low in Eskimos, who appear to be an obese population by world standards (Mouratoff et al., 1967). Gardner et al. (1982) have recently demonstrated that obesity is not the only factor operating to produce diabetes in Mexican Americans.

Diabetes studies in the Pacific have consistently demonstrated a lower prevalence of diabetes in traditional-living rural communities, as compared with their urbanized counterparts. Whether urbanization directly increases risk, whether findings relating to urbanization represent the effect of increased obesity in the urban population, or whether both obesity and urbanization are merely markers for some other causal factor(s) has not yet been determined. A recent study in Western Samoa showed a residual rural-urban difference in the prevalence of diabetes when the populations were standardized for both age and obesity (Zimmet et al., 1981) and it was suggested that this might be due, in part, to higher levels of habitual physical activity in the rural sample. West (1978) also expressed

the opinion that the relationship between physical inactivity and diabetes was likely to be causal. A further recent study (Zimmet and King, 1982) examined the prevalence of diabetes in rural and urban communities in Pacific populations after both standardizing for age and stratifying into tertiles of body mass index (a commonly used index of overweight). Considerable heterogeneity was noted; whereas body mass bore little relationship to the prevalence of diabetes in some populations, in others it assumed more importance. In Micronesians, overweight appeared to act in concert with other factors associated with urbanization.

Further analyses have now been conducted on population-based data from three Pacific populations. In this Chapter, the relationship between diabetes and both overweight and physical inactivity is examined, and the effect of urbanization is assessed after controlling for the other two variables.

SUBJECTS AND METHODS

The ethnic groups studied in this report are: Melanesians in Fiji, migrant Asian Indians, also in Fiji, and Micronesians in the Republic of Kiribati (formerly the Gilbert Islands).

Field work was conducted in March and April 1980 in Fiji, and in April 1981 in Kiribati. Methods were carefully standardized throughout and have been described in detail in previous Chapters. In both cases, only adults aged 20 years and over were selected for study.

In Fiji, the rural sample was drawn from villages in the Sigatoka Valley, which is the only rural region where

substantial numbers of Melanesians and Indians live in close proximity. The urban samples were drawn from settlements in the capital city, Suva. Only long established settlements with stable populations were considered eligible, as the effect of urbanization was to be studied.

In Kiribati, the rural sample was the total population of the island of North Tabiteuea, the inhabitants of which maintain a traditional lifestyle. The urban sample was drawn from the inhabitants of the islet of Betio in the Tarawa atoll, which is the commercial centre of Kiribati. As the population of Betio was not as stable as that of Suva, only those resident in an urban setting for 5 years or more were included in order that any effect of urbanization on diabetes prevalence might be manifest. A house-to-house census was conducted in each area shortly before the survey, in order to enumerate the target population. Plasma glucose concentration was measured on site with the Yellow Springs Instrument Glucose Analyser, using a glucose oxidase method.

There were a total of 5576 responders. Of these, 57 had incomplete data recorded, leaving the 5519 subjects who form the basis of this study.

Diabetes mellitus was defined according to a modification of current WHO (1980) criteria, adapted for field survey conditions, namely as a plasma glucose concentration equal to, or exceeding, 11.1 mmol/l two hours after a 75 g oral glucose load. All known diabetics were classified as diabetic regardless of their plasma glucose concentration.

The chosen index of obesity in this study was body mass index, defined as weight/height^2. For the purpose of the present analyses, three levels of relative weight (low, medium and high body mass index) were defined separately for each of the six race/sex sub-samples on the basis of tertiles of their distribution of this variable. An alternative approach, in which the same critical values would be used to define levels of overweight in each population, was not employed because of the large variation between the distribution of body mass in the different ethnic groups, and in the belief that the position of an individual in relation to the distribution of his or her own racial group may be of more health-related consequence than the position relative to a cumulative distribution over a number of racial groups.

With respect to physical activity, all subjects were graded according to a discrete score with values of 1-4 corresponding to sedentary, light, moderate and heavy activity. Grading was standardized in the three ethnic groups. Each subject was assigned a score by interviewers who were local health staff. The interviewers were instructed to take both occupational and leisure activity into account when deciding upon an individual score. Unless stated otherwise, physical activity was treated as a binary variable in the present analyses, scores of 3 and 4 being classified as active and scores of 1 and 2 as inactive. The urbanization variable was also binary, and was defined according to region of residence (rural or urban).

The response rate exceeded 80 per cent in each sub-population. To test the homogeneity of response over age groups, the crude response rate was applied to the number of persons eligible in six age groups (20-24, 25-34, 35-44, 45-54, 55-64,65+) to give the number of responders expected on the basis of the crude response rate. Comparing observed and expected response in each age group, a summary chi-square statistic was derived to test the uniformity of response in each race/sex/region sub-group. There was found to be no significant heterogeneity of response in any of the 12 comparisons made, and the age distribution of the responders was therefore considered representative of that of their respective population.

RESULTS

Some baseline characteristics of the study populations are presented in Table 6.1. With the exception of Melanesian and Indian males, the rural populations were older than their urban counterparts, though mean age only differed significantly between regions in Micronesians.

In each population, mean body mass index was higher in the urban than the rural group, although the difference was not significant in the case of Melanesian males. Defining obesity according to the criteria recommended by Bennett (1979), namely as a body mass index greater or equal to 27 in males, and greater or equal to 25 in females, the proportion of the population that was overweight varied from 8 per cent in rural Indian males to 72 per cent in urban Micronesian females. Both rural and urban Indian males were notably leaner than the other groups. It has been suggested that in some populations, including

Melanesians, body mass index may represent muscularity rather than adiposity (Zimmet et al., 1983). However, the finding of a greater proportion of both male and female urban Melanesians in the overweight category, thus defined, as compared with the corresponding rural group, supports the use of body mass index as an index of obesity, as it is biologically implausible that the inactive, urban residents would be more muscular than their rural counterparts.

The characteristic which showed the most marked difference between rural and urban groups was the percentage of the population who were habitually physically inactive. The most extreme difference was observed in Melanesian males, 9 per cent of rural versus 91 per cent of urban residents being inactive. The majority of Indian females were inactive in both regions.

The prevalence of diabetes in the rural and urban sub-populations in each ethnic group is shown in Table 6.2. There was a highly significant rural-urban difference in Micronesians of both sexes, and in Melanesian females. Though the Mantel-Haenszel estimate of relative risk for urban versus rural Melanesian males was 3, this failed to reach statistical significance. By contrast with the other ethnic groups, prevalence was uniformly high in Indians in both regions, rural rates for Indians exceeding the urban rates for Melanesians and Micronesians in both sexes, demonstrating that the relative infrequency of overweight noted in Indian males was not protective for diabetes in this group.

The prevalence of diabetes in low, medium, and high tertiles of body mass index in each population is examined in Table 6.3. In all cases, crude prevalence increased with increasing body mass index. However, after age-adjustment, a significant relationship between the prevalence of diabetes and body mass index was seen in Micronesian males, and in females in all three ethnic groups, but not in Melanesian or Indian males.

Physical inactivity was associated with a significantly higher prevalence of diabetes in both Melanesian and Indian males, and in Micronesian females (Table 6.4). Though crude prevalence was also higher in inactive subjects in Micronesian males, and in Melanesian and Indian females, the difference was not significant after age-adjustment.

An important question to be addressed prior to multivariate analyses is that of correlation between the variables. Correlation between urbanization and the other variables could not be directly assessed, due to the binary nature of the urbanization factor. There was clearly a strong relationship between urbanization and physical inactivity in some groups (Table 6.1). Correlation coefficients between age, two-hour plasma glucose concentration, body mass index, and physical activity (at four ordered levels) are presented in Table 6.5. All coefficients were low, the highest being between two-hour plasma glucose concentration and age (0.20-0.36). Other coefficients to equal or exceed 0.2 were those between age and body mass index in Indian males and females, and between body mass index and two-hour plasma glucose concentration in Indian females. Though correlation with physical activity

could only be examined at four levels, a significant though weak association was seen between physical activity and some other factors in males of all three ethnic groups. Scattergrams were examined and these confirmed the absence of strong non-linear relationships between the variables.

To gain further insight into the relationship between diabetes prevalence and the risk variables of interest - obesity, physical inactivity and urbanization - the populations were stratified by the chosen levels of these factors and by six age groups. Diabetes prevalence at each combination of factor levels was then standardized for age. In this case, because of small numbers in some cells, the indirect method of standardization was used. The total survey population in Kiribati, the largest survey sample, was taken as the standard (Figures 6.1-6.3).

The impression gained from these histograms is of considerable inconsistency in the association between the prevalence of diabetes and the factors examined. In Melanesian and Indian males there is evidence of an association between the prevalence of diabetes and physical inactivity. In Melanesian males this is more marked in the urban than the rural group. There is also a suggestion of an effect of urbanization independent of overweight and physical activity in Melanesian, but not in Indian males. A trend with urbanization is also suggested by the data for Melanesian females, but is absent in Indian females. In Indian females, prevalence appears higher in the group with high body mass index.

Trends appear more consistent in the data for Micronesians of both sexes. All three factors - increasing

overweight, physical inactivity, and urbanization - appear associated with higher prevalence of diabetes.

In all six histograms, the principal departures from the general trend occurred in cells with less than 25 subjects. To further "smooth" the data and to obtain estimates of the relative importance of the study factors in predicting diabetes prevalence, the multiple logistic regression model was employed separately for each data set, using the GLIM program (Baker and Nelder, 1978). Body mass index was retained as a factor on three levels so that ordered risk ratios could be calculated for this variable, and to prevent the risk estimates being distorted by individual data points of undue influence. Initially, the data were stratified by the six age groups, with the intention of controlling for the effect of age whilst fitting the models. This procedure, however, resulted in stratification over 72 cells, and consequently sparse data. In several cases, the models did not fit the data well. The age-standardized prevalence rates shown in the accompanying figures were therefore used to obtain standardized counts of normals and diabetics at the 12 factor level combinations. When the logistic model was applied to these reduced data sets, the fits of the models which incorporated the main effects of the three factors were all improved, and each was satisfactory. Because of unresolved doubts concerning correlation between urbanization and the other predictor variables, the results of forward selection analyses are shown in full (Table 6.6), so that the effect of entering every extant variable is assessed at each step. A linear term was generated for the three levels of body mass index

in these models. The χ^2 value for the importance of the factor is the observed value of the likelihood ratio test comparing the log likelihood statistics of the models with and without the factor entered (Breslow and Day, 1980).

In Melanesian males, physical inactivity was the most important factor, although urbanization also significantly improved upon the null model at step one. Urbanization was not significant after the addition of physical inactivity (step two), as might have been anticipated from the previously noted relationship between these two factors.

In Melanesian females physical inactivity and urbanization were once again significant at step one, although in this case it was urbanization which assumed the greater importance. With urbanization entered in the model (step two), physical inactivity did not make a significant contribution. In this population alone, an interaction term (involving body mass index and physical inactivity) was found to significantly improve the model incorporating the main effects of all three variables (in logistic regression, interaction implies a relationship which is more than multiplicative).

In Indian males the only factor of importance was physical inactivity, supporting the findings of the initial analyses. In Indian females, there was a very strong relationship between the prevalence of diabetes and body mass index.

In Micronesians of both sexes, the models confirmed the visual impression gained from Figure 6.3. Body mass index, physical inactivity and urbanization were each significant

at step one. In males, urbanization was the strongest factor, and body mass index made a further significant improvement to the model at step two. Physical inactivity was not important after the addition of the urbanization factor, once again suggesting correlation between these two variables.

The strongest trends of all were observed in Micronesian females, in whom each of the three variables made a highly significant contribution to the model. The fit of the model incorporating the three main effects (log likelihood statistic = 2.9, df = 8) was such that it was not possible to test for significant interaction between the variables.

The exponents of the parameter estimates obtained from the logistic regression model represent approximate point estimates of relative risk (Breslow and Day, 1980), and their standard errors enable confidence intervals to be calculated. In Table 6.7, such estimates are presented, derived from models incorporating all the main effects, and with the tertiles of body mass index entered as separate dummy variables. As a measure of the goodness-of-fit of each model, the observed number of cases at each of the 12 factor level combinations was compared with the number fitted by the model, using the ubiquitous $\chi^2 = \Sigma(O-E)^2/E$ statistic, which has some advantages in ease of interpretation over other goodness-of-fit statistics for logistic regression, when modelling stratified counts (Breslow and Day, 1980).

Results conform closely to those of the forward selection analyses shown in Table 6.6, with the exception that no significant association was seen with urbanization in Melanesian females, and the previously noted interaction between body mass index and physical inactivity in this group also lost significance, illustrating that the significance of an estimate is dependent upon which other parameters are entered into the model.

In these models incorporating all three main effects, physical inactivity was associated with a greater than twofold increase in risk in both Melanesian and Indian males. The highest estimate of relative risk (3.7) was with high body mass index in Indian females; body mass index and urbanization were independently associated with increased risk in Micronesian males, and all three factors were once again significant for Micronesian females. An interaction term between medium body mass index and urbanization (relative risk 7.4, 95 per cent confidence interval 1.5, 37.6) significantly improved upon the model incorporating the three main effects in Micronesian males.

As a validation of the use of age-standardized counts, and grouped analyses incorporating tertiles of body mass index distribution within populations in the logistic regression models, the modelling was repeated on the full data sets, using both age and body mass index as continuous variables. The results obtained were similar to those described above, except that the estimates of risk obtained from the grouped analyses were more conservative.

In summary, logistic regression has supported the results of the univariate analyses, and the visual impression from the figures that risk variables differ between populations, and between the sexes within populations. In some cases, obesity had a strong association with risk, in others the principal risk variable appeared to be physical inactivity. More than one factor was associated with increased risk in Micronesians. In Micronesian males, there was some evidence of interaction between body mass index and urbanization. In Melanesian females, there was a suggestion of interaction between body mass index and physical inactivity.

DISCUSSION

There are several limitations to this study. Firstly, the data are cross-sectional. This not only prevents confirmation that a suspected cause preceded the effect (diabetes), but also provides the opportunity for the risk factors examined to be altered by the disease process, or by therapy. The latter is not likely to be an important bias in these Pacific communities, where many diabetics were undiagnosed prior to these studies, and where compliance with treatment is poor. However, taking biological arguments into consideration, it is likely that if diabetes influences adiposity its effect will be to reduce it. This bias will therefore tend towards an under-estimate of risk associated with this factor. By contrast, if diabetes was to reduce habitual physical activity, a spurious association between physical inactivity and diabetes could occur.

The urbanization variable used in this analysis is merely a label for a factor, or factors, involved in the process of urbanization which is associated with an increased risk of diabetes, but is unidentified to date. It is very tempting to speculate that the factor concerned is a change in dietary habit from traditional, home-grown foods to imported, processed products. This suggestion is supported indirectly by the findings reported here. A dietary survey, conducted at the same time as the medical survey, showed that, unlike the other two populations, Fijian Indians maintain similar dietary habits in both rural and urban areas. Indians were found to have a similar prevalence of diabetes in both regions. By contrast, Melanesians and Micronesians differed markedly in both food habits (Zimmet, 1983, Pargeter, in press) and prevalence of diabetes in rural and urban areas. Another explanation of the high prevalence of diabetes in both rural and urban Indians might be a heightened genetic susceptibility in this ethnic group.

Consistency is an important criterion for causal inference, but the estimates of risk presented above are notably inconsistent. The question of correlation between the variables naturally arises, and there is good evidence of correlation between urbanization and physical inactivity in some groups in this study. For this reason, the numerical value of the risk estimates obtained from the multiple logistic regression equations should be interpreted with caution. However, the finding of more than one independently significant association in Micronesians of

both sexes, the independent significance of all three factors in Micronesian females, and the finding of a significant interaction between two variables in two of the multivariate models suggest that the chosen indices were not all merely representing the same causal factor.

This cross-sectional study of risk factors should most properly be regarded as preliminary, and should serve to encourage the collection of further standardized data in these and other populations. Longitudinal studies will be required for a complete understanding of risk factors for diabetes. However, this study has demonstrated that the factors examined were independently associated with increased prevalence of diabetes in some Pacific populations. The results also suggest that risk factors may be heterogeneous in their effect upon different ethnic groups, and between the sexes within ethnic groups.

The eventual elucidation of environmental risk factors for diabetes, and the extent to which their relative power is genetically determined, has considerable implications in terms of the rationalization of prevention and control campaigns for diabetes worldwide. In the meantime, these findings may be of relevance to the planning of intervention programmes for diabetes. Rather than to embark upon a largely empirical exercise, it may be more appropriate to first identify risk factors of particular importance in individual target communities.

CHAPTER 7

A REVIEW OF RECENT DEVELOPMENTS IN THE EPIDEMIOLOGY OF DIABETES IN THE PACIFIC REGION

The geographic and ethnic diversity to be found in Oceania provides a natural opportunity for epidemiological study. In the last decade, the disparate frequency of diabetes demonstrated in early population studies in the Pacific have led to the region becoming one of the most active areas for diabetes research in the world. Standardized methodology has enabled direct and meaningful comparisons between populations, in an attempt to elucidate relative frequency and the genetic and environmental determinants of the disease.

Studies preceding those described in the present thesis have already been reviewed in detail (Zimmet, 1979, Zimmet, 1982). It is not the purpose of the present review to merely repeat the information presented in these former reviews. The central theme will rather be to place the findings described in Chapters 1-6 of this thesis in context and to examine their contribution to the pre-existing foundations of diabetes epidemiology in the Pacific.

The prevalence of diabetes in Pacific populations

The factor which has, above any other, maintained the great interest shown in diabetes epidemiology in the Pacific is the wide disparity in the prevalence of the disease demonstrated between different communities. Comparable estimates of prevalence in some Pacific communities examined prior to the present studies are shown in Table 7.1. Prevelance of diabetes can be seen to vary twentyfold between the extremes in this Table.

Early studies, though marred by a lack of standardized methodology, suggested that diabetes was rare in Melanesians (Hingston and Price, 1964, Price and Tulloch, 1966), and in traditional-living Polynesians (Prior and Davidson, 1966); but that the disease was more frequent in Polynesians and Micronesians living in urbanized environments (Prior et al., 1978, Reed et al., 1973). All studies confirmed that insulin-dependent diabetes was very rare, or absent, in Pacific communities.

The findings of this early research led to the hypotheses that Melanesians possessed a natural protection against noninsulin-dependent diabetes, but that an underlying susceptibility to the disease was unmasked by the process of urbanization in Polynesians and Micronesians.

Subsequent research casts doubt upon the genetic separation of the three Pacific geo-ethnic regions and also upon the apparent resistance of Melanesians to noninsulin-dependent diabetes. Population prevalence of diabetes in excess of 5 per cent was described in urban Melanesians in Papua New Guinea (Martin, 1980) and Fiji (Zimmet, 1982). However, Austronesian admixture was known to have occurred in the coastal societies examined in these surveys (Serjeantson, 1983).

In Chapter 1 it has been shown that in a highland population in Papua New Guinea, which was free of Austronesian genetic admixture, no cases of diabetes were encountered in over 300 subjects, although a comparison of two villages exposed to different degrees of acculturation showed the distribution of plasma glucose values to be

significantly lower in the more traditional group. This study provides renewed support for the concept of genetic resistance to noninsulin-dependent diabetes in non-Austronesian Melanesians, although it cannot be excluded that environmental precipitants of the disease were present to an insufficient degree in these populations to lead to overt disease. Further study, of less traditional communities in the Papua New Guinea highlands, will be required to settle this important question.

An unresolved dilemma regarding the susceptibility of Micronesians to noninsulin-dependent diabetes was whether the prevalence reported in Nauruans - in excess of one quarter of the adult population (Zimmet et al., 1977) - was an unique finding, or whether the prevalence of the disease had been seriously underestimated in other Micronesian communities. The analyses presented in Chapter 2 demonstrated a substantial association between urbanization and the prevalence of diabetes in the population of Kiribati, a neighbour of Nauru, but also showed a prevalence of less than 10 per cent in the urban sample, indicating that the high prevalence seen in Nauru may indeed be uniquely determined. This issue is raised in greater depth later ('The genetics of noninsulin-dependent diabetes in the Pacific').

The consequences of hyperglycaemia in Pacific populations

The current diagnostic criteria for diabetes are based, to a large extent, upon the observation that the microvascular complications of the disease are rare in

subjects whose plasma glucose concentration is below the standard cut-off points (WHO, 1980) and upon the bimodal distribution of plasma glucose concentration demonstrated in some populations with a high prevalence of diabetes such as the Pima Indians (Rushforth et al., 1971) and Nauruans (Zimmet and Whitehouse, 1978). The very high prevalence of diabetes, thus defined, reported in Nauruans (Zimmet, 1977) led naturally to the question of whether the diagnostic criteria were appropriate for Pacific populations, or whether hyperglycaemia might exist as an innocent biochemical phenomenon in such communities.

To date, the only studies of microvascular disease in Pacific diabetics have been inconclusive. Wise et al. (1976) found little evidence of diabetic retinopathy in Australian Aborigines, although a more recent study - of only 71 subjects - by McCann et al. (1981) showed a prevalence of retinopathy of 44 per cent in diabetics of this ethnic group. Four of nine diabetic Maoris examined by Mann and Potter (1969) were found to have retinopathy. Cassidy (1967) reported a prevalence of retinopathy of 24 per cent in Melanesian diabetics in Fiji. The few morbidity and mortality studies of Pacific diabetics which have appeared in the literature indicate an excess in these parameters, as compared with non-diabetics, in the Chamorros of Guam (Kuberski and Bennett, 1980), the Tolais of New Britain (Savige and Martin, 1982) and the Nauruans (Taylor and Thoma, 1983).

The research presented in Chapter 3 represents the first detailed, large-sample, population-based study of

diabetic retinopathy in a Pacific population. It was shown that the prevalence of retinopathy in Nauruan diabetics was 24 per cent, a figure comparable with those observed in other populations. Duration of disease and post-challenge plasma glucose concentration were the factors most strongly associated with retinopathy. This study supports the notion that hyperglycaemia is a true manifestation of diabetes in the Pacific, rather than being of little pathological consequence in these populations. The findings provide material support for the need for diabetes-related health programmes in high-risk groups in the region.

Impaired glucose tolerance in Pacific populations

The concept of impaired glucose tolerance, a category of glucose tolerance intermediate between normality and diabetes, is of recent introduction (National Diabetes Data Group, 1979, WHO, 1980) and there has been a call by the World Health Organization Expert Committee for Diabetes for population-based information on the natural history of impaired glucose tolerance (WHO, 1980). By comparing data collected during the 1982 Nauru Diabetes Survey with historical data collected in 1975/6 during the first Nauru survey, the glucose tolerance of normals and subjects with impaired glucose tolerance was compared 6 years after initial examination. Three such longitudinal studies of impaired glucose tolerance have appeared in the scientific literature to date; two from the United Kingdom (Jarrett et al., 1979, Keen et al., 1982) and one from Japan (Sasaki

et al.,1982). The research reported in Chapter 4 is the first such study in a Pacific population, and was designed to be directly comparable with the other three.

As in the other three studies, impaired glucose tolerance ran an unpredictable course in Nauruans. At follow-up, approximately one third of such subjects retained this status, one third had reverted to normal glucose tolerance, and one third had progressed to diabetes. Subjects with impaired glucose tolerance were shown to have a threefold excess risk of subsequent diabetes, compared with subjects with normal glucose tolerance, after controlling for the effects of differences in age and obesity between the two groups.

The results of this study suggest that the natural history of impaired glucose tolerance is similar in Micronesians to that in previously studied populations.

The genetics of noninsulin-dependent diabetes mellitus in the Pacific

In a recent review of the Genetic Epidemiology of Diabetes Mellitus, Kirk et al. (1983) concluded:

> ".. we have to admit that so far we have not been able to identify any specific genetic factor, or constellation of factors which markedly increase the chance that Pacific Island individuals will develop diabetes of the noninsulin-dependent type. There are some tantalizing bits of evidence indicating that some genetic predisposition is

involved, particularly the chromosome 6 markers HLA, BF and GLO in Polynesians. As well the Vitamin-D binding protein system may be involved in Polynesians.

The evidence that the introduction of foreign HLA haplotypes significantly reduces the risk of becoming diabetic in Nauru is so far the best evidence for genetic susceptibility for noninsulin-dependent diabetes. This conclusion needs to be tested by further studies of the effects of foreign admixture in other populations and by careful epidemiologic studies to rule out the effects of subtle environmental effects which could confound these admixture effects."

The study described in Chapter 5 was designed to augment these recent genetic findings, using a comparative, epidemiological approach. The prevalence of diabetes in Nauru was compared with that in physically inactive subjects in the urbanized population of the island of Betio in Kiribati, another Micronesian community. The increased risk of noninsulin-dependent diabetes in Nauruans was assessed after controlling for differences in known environmental associations between the two populations. It was found that none of the environmental factors examined - either individually or collectively - could explain the high prevalence of diabetes in Nauruans, providing further support for the concept of a heightened genetic susceptibility in this group. Although it cannot be

Page 108. For "an allelic frequency of 67% (Line 10) read "an allelic frequency of 6.7%".

excluded than an as-yet unidentified environmental factor may have caused the observed differences, the theory that a genetic determinant of noninsulin-dependent diabetes may have reached a high frequency in the isolated population of Nauru is supported by studies of the relative frequency of non-HLA genetic markers in Nauru and Betio (Kirk, personal communication). In addition to several differences with respect to red cell enzyme frequency between the two populations, a rare variant of complement component C6, C6* NAURU, has an allelic frequency of 67 per cent in Nauruans (Ranford et al. 1982) but is completely absent in the Betio population. The comparatively high frequency of the rare variant of C6 in Nauru highlights the powerful role of genetic forces, including mutation, random drift and possibly selection, in determining marked genetic differentiation between the two Micronesian island populations.

The environmental precipitants of noninsulin-dependent diabetes in Pacific populations

Of great practical interest and importance are the behavioral and environmental precipitants of a chronic disease, such as diabetes, in susceptible individuals. A knowledge of such precipitants enables the rational formulation of Public Health programmes to limit the disease by Primary Prevention, currently recognised as the most effective method of reducing the burden of disease at a population level (WHO, 1982).

Obesity has long been associated with diabetes, and has been widely regarded as having a causal relationship with the disease (West, 1978). However, Zimmet et al. (1981) have shown that diabetes is more common in non-obese urban dwellers in Western Samoa than in rural subjects of similar body mass, suggesting that obesity alone was not a sufficient explanation of the observed rural/urban difference in the prevalence of noninsulin-dependent diabetes. Taylor and Zimmet (1983) provided evidence of a relationship between noninsulin-dependent diabetes and physical inactivity in an analysis of data from Fiji.

Because of the potential practical importance of the relationships between diabetes and obesity, physical inactivity and urbanization, the data from Fiji and Kiribati were combined, to enable a direct comparison of these suspected risk factors in three ethnic groups in the Pacific (Chapter 6). Owing to the complexity of such a multivariate study, and the unknown inter-relationships between the variables of interest, these analyses were the most comprehensive undertaken in the six studies presented in this thesis.

It was shown that factors associated with noninsulin-dependent diabetes differed between the populations, and between the sexes within populations. In some cases obesity was strongly associated with diabetes; in others the principal association was with physical inactivity. In Micronesians, more than one factor was associated with increased risk of diabetes, and the relationship between the risk variables was multiplicative.

Although further, longitudinal studies are still required in these Pacific populations, the study suggests that risk factors may be heterogeneous in their effect upon different populations. This finding, if substantiated, may have important implications for diabetes control programmes throughout the world.

APPENDIX

A REVIEW OF THE EPIDEMIOLOGY

OF DIABETES MELLITUS

IN THE ASEAN REGION

SUMMARY

A review of the available literature indicates that the prevalence of diabetes mellitus is of the order of 2-5 per cent in ASEAN populations. There is evidence that there are ethnic differences in population prevalence.

The complications of hyperglycaemia have been demonstrated in all studies of diabetics in the ASEAN region, and it has been estimated that over 50 per cent of diabetics suffer from one of more of the recognized complications of the disease.

The available evidence suggests that typical insulin-dependent diabetes is rare throughout the region, though further studies are needed to confirm this. There is inadequate information upon the prevalence of tropical malnutrition diabetes in the region.

Based upon population estimates, and the costs of diabetes in other communities, it appears that the cost of diabetes to the ASEAN nations may be approximately US$700 million per annum. This figure excludes invisible loss in terms of job productivity, and the quality of life of the individuals concerned.

High priority should clearly be given to the development of integrated prevention and control programmes for diabetes in the region.

The purpose of this report, originally prepared for the Planning Meeting of the ASEAN-Australian Collaborative Project on Diabetes (Genting Highlands, Malaysia, May, 1983) is to review the available evidence, from published sources, concerning the epidemiology of diabetes mellitus in the ASEAN region (Figure A.1). This region is thought to be the ancestral homeland of present Pacific populations. Collation of these data permits cautious estimates of rates of disease and complications, and of the burden of diabetes to the nations concerned. The report highlights the inadequate data base presently available regarding diabetes in these large populations, and emphasizes the need for standardized research methods, such as those used in the studies described for Pacific populations in the preceding Chapters.

The prevalence of diabetes mellitus in the ASEAN region

In order to assess the population prevalence of diabetes, it is necessary to examine population-based statistics. This is because many cases of noninsulin-dependent diabetes, the predominant form of the disease, remain asymptomatic for some time after the onset of disease, so that hospital or clinic records seriously underestimate true prevalence. Hospital patients are also not always representative of their respective populations.

A summary of some published accounts of the prevalence of diabetes in the ASEAN region is presented in Table A.1. It is immediately apparent that direct comparisons are constrained by the lack of uniformity of diagnostic criteria, and by the study of populations of varying ages.

The age structure of the individual populations may also be expected to exert an influence on crude prevalence of diabetes. This, however, is not a problem confined to the ASEAN region, and it is only very recently that standardized methods have been applied in diabetes research.

The lowest estimate of prevalence is 1.0 per cent in Singapore Chinese (Cheah et al., 1974). This is the only ethnic group in which some heterogeneity of rates may be noted. The highest estimate of prevalence for Chinese was 4.7 per cent in a Malaysian study (West and Kalbfleisch, 1966) though it should be noted that only 127 subjects were studied, as compared with 627 and 12812 subjects respectively in two later studies in Singapore, which reported prevalence in the range of 1-2 per cent (Cheah et al. 1974, 1978). A prevalence of 1 per cent was reported in over 100,000 Chinese subjects in Shanghai, supporting the lower estimate (Shanghai Diabetes Research Cooperative Group, 1980).

The estimates for Indonesians and for Malays are very similar: 1.5 - 2.3 per cent in Indonesians (Djokomoeljanto et al., 1976, 1982) and 1.4 - 2.4 per cent in Malays (Cheah et al., 1974, 1978).

Three studies all demonstrated higher rates for Indians in Malaysia and Singapore, estimates of prevalence varying from 4.2 per cent to 6.1 per cent (West and Kalbfleisch, 1966, Cheah et al. 1974, 1978). These findings are in accord with reports from other parts of the world of a high prevalence of diabetes in Indians living outside their native country (Zimmet, 1983). By contrast, the prevalence of diabetes in Indians living in India has been estimated at 1.8 per cent (Indian Council of Medical Research, 1977).

The prevalence of diabetes in Thailand has been estimated at approximately 3.5 per cent (Bunnag et al., 1982). The highest rates in the ASEAN region are described from the Philippines, two studies estimating prevalence of at least 8 per cent (Fernando, 1965, Germar and Villanueva, 1966). It is now thought that these high rates may be a consequence of study methodology. A more recent study has shown the prevalence of diabetes in an urban Filipino community to be 4.2 per cent (Cabral et al., 1982).

Thus, these studies suggest that the prevalence of diabetes may vary in the different ethnic groups in the ASEAN region. Prevalence is almost certainly at least 2 per cent in all populations, and in some may approach 10 per cent.

Morbidity from diabetes in the ASEAN region

Some published reports of the frequency of complications in diabetics in the ASEAN region are listed in Table A.2. The estimates vary somewhat, though general trends emerge.

It appears that 10-20 per cent of diabetics suffer from diabetic retinopathy. This is in accord with studies of the prevalence of retinopathy in Pacific diabetic populations (ibid.). Approximately 10-30 per cent of diabetics appear to suffer from nephropathy. There is no general agreement about the prevalence of coronary heart disease (CHD), and estimates derived from cross-sectional prevalence studies might be expected to considerably underestimate the true consequence of diabetes with respect to CHD, as in many

cases the duration of disease is short. Cardiovascular disease was the most common cause of death in a study of Thai diabetics (Bunnag et al. 1982a). Most Asian studies estimate a prevalence of hypertension of approximately 20 per cent in diabetics. The prevalence of peripheral vascular disease and of gangrene appears to be between 2 per cent and 8 per cent. A recent study in Singapore (Tan et al., 1982) suggests that diabetic complications are the most common indication for amputation of the lower limb at the Singapore General Hospital. Estimated rates of neuropathy vary widely, but three estimates of the prevalence of tuberculosis (TB) are all in the region of 20 per cent.

These studies provide a testament to the high rates of morbidity suffered by diabetics in the ASEAN region. In an Indonesian study (Sujono and Sukaton, 1971) only 46 per cent of diabetics had no complications. Though it must be noted that most of these studies are based upon hospital records, the population survey by Cheah et al. (1978) found rates comparable to the other studies with respect to retinopathy and hypertension.

Insulin-dependent diabetes in the ASEAN region

In populations worldwide, the minority of diabetics suffer from the insulin-dependent form of the disease. However, in general, they have an earlier age of onset and the sequelae of their disease are more severe. Estimates of population prevalence vary from 0.07 per 1000 Japanese children aged 15 years and under, to 3.5 per 1000 in the United Kingdom (Zimmet, 1983).

There appears to be no consensus as to the prevalence of insulin-dependent diabetes in the ASEAN region. Whereas no cases were found amongst 3238 Filipino school children, 1.4 per cent of 2573 cases at two diabetic clinics were insulin-dependent (Fernando, 1976). The same author (1979) found that 2 per cent of clinic patients were insulin-dependent at a Manila hospital.

Childhood diabetes appears to be very rare in Indonesia. Sujono and Sukaton (1971) reported 3 cases in 15 years at the General Hospital, Jakarta. Djokomoeljanto (1976) reported 2 cases in 12 years at a Semarang hospital.

Insulin-dependent diabetes also appears to be rare in Singapore, though less so for Indians than for Chinese and Malays (Boon, 1981).

Most of the studies cited above were hospital-based, or only examined young children. Of interest is a study by Rao et al. (1966), demonstrating a prevalence of 0.3 per cent in a population survey of subjects less than 20 years old in Hyderabad, which would suggest that Indians suffer from a relatively high prevalence of insulin-dependent, as well as noninsulin-dependent diabetes.

It is clear that our knowledge of the epidemiology of insulin-dependent diabetes in the ASEAN region is far from complete.

Tropical malnutrition diabetes in the ASEAN region

Little appears to have been published from the ASEAN region on tropical malnutrition diabetes, or J-type diabetes, first described in Jamaica (Hugh-Jones, 1955).

However, it has been reported from Malaysia (Hugh-Jones, 1955), from Indonesia and Brunei (Tulloch and McIntosh, 1961), from Pakistan (Ibrahim, 1962) and from India (Ahuja et al., 1965). Hazra (1982) has recently reported that 20 per cent of 800 patients registered at a diabetic clinic in Agra were young, ketosis resistant, but insulin-dependent. They were usually thin, and had a high prevalence of complications. A high frequency of certain viral antibodies was also reported.

The conditions thought to precipitate this disease are widespread in the ASEAN region, and many of the lean, insulin-dependent diabetics with early onset of disease treated in ASEAN countries may, in fact, be suffering from this form of diabetes, rather than the typical insulin-dependent form. The subject warrants further study.

Genetic and environmental risk factors for diabetes in ASEAN populations

There is now a considerable body of evidence to support the theory of genetically-mediated predisposition to diabetes in certain individuals, and the notion that the trait(s) responsible may be more common in some populations than others. Genetic susceptibility to insulin-dependent diabetes has been demonstrated in many populations (Zimmet, 1983).

Ninety-four Chinese insulin-dependent diabetics were studied by Yeo (1982), whose histocompatibility studies confirmed that Chinese patients showed similar associations with locus B antigens to those reported in Caucasoid and

Japanese subjects. There was also evidence of increased rates of complications in patients who were positive for HLA B17, and this group may well have a poorer prognosis than their B17-negative counterparts. Another study in Singapore (Lee et al., submitted for publication) showed an association with HLA BW22, B17 and AW33 in Chinese insulin-dependent diabetics.

There is increasing evidence of genetic predisposition to noninsulin-dependent diabetes, and Indians are one of the ethnic groups in which this has been demonstrated (Zimmet, 1983). Nauruans, who have recently been shown to have genetic affinities to Filipinos (Serjeantson et al., 1983) have one of the highest prevalence rates of noninsulin-dependent diabetes in the world (Zimmet, 1977).

Of environmental risk factors for diabetes, obesity has long been incriminated. In Indians, the association has been noted since antiquity (West, 1978). Other reports confirming the association in Asian populations include those of West and Kalbfleisch (1966), Djokomoeljanto et al. (1976), Fernando (1976), Cheah et al. (1978), and Waspadji (1982).

There is increasing evidence, however, that obesity is not the only environmental precipitant of diabetes. Both habitual physical inactivity, and various components of diet are almost certainly associated with diabetes, and the process of urbanization is strongly associated with the prevalence of diabetes in many developing communities. This latter association has been shown to be independent of obesity (ibid.).

It is clearly of the utmost importance to undertake further study of both genetic and environmental precipitants of diabetes in the ASEAN region, in order to provide a rationale for future prevention and control programmes.

The burden of diabetes to ASEAN countries

By applying the estimates of prevalence to the estimated populations of the ASEAN countries, very approximate estimates of the number of diabetics in each country may be obtained. The results are shown in Table A.3, from which it may be judged that there are roughly 7 million diabetics in the ASEAN region. Furthermore, this appalling figure is likely to be an underestimate, as standardized field surveys have probably not yet investigated all areas of higher-than-average prevalence, and many asymptomatic cases undoubtedly remain undetected.

Applying the same population denominators to the population-based morbidity data of Cheah et al. (1978), it appears that almost 1 million diabetics in the region probably suffer from retinopathy and nephropathy, and 2 million from hypertension (Table A.4).

A recent study in Kuwait estimated the annual cost of hospitalization at US$100 for every diabetic. This is considerably lower than the Australian total-cost estimate of A$1300 per diabetic. If the Kuwait figure was applicable to the ASEAN region, the cost of diabetes, in terms of hospital services, would amount to US$700 million per annum. This enormous figure excludes invisible loss in terms of job productivity and, most importantly, the quality of life of the individuals concerned.

There is strong evidence to suggest that the frequency of diabetes may be increasing worldwide. With the burden already heavy in Asian countries, there is clearly a pressing need to develop comprehensive, scientific programmes for diabetes research, prevention and control in the region.

Specific areas requiring further investigation include:

- The study of typical insulin-dependent and tropical malnutrition diabetes.
- The elucidation of risk factors for noninsulin-dependent diabetes.
- The evaluation of the protective role of traditional diet.
- The evaluation of the efficacy of traditional, herbal cures for diabetes.
- The identification of sub-groups with high genetic predisposition to diabetes, and of the genetic traits responsible.
- The assessment of the efficiency of primary health care measures in the primary and secondary prevention of diabetes.
- The assessment of the value of community education programmes.
- The assessment of community compliance with specific risk-modification measures.

With their large and varied populations, the ASEAN countries have a unique opportunity to benefit from collaborative projects on diabetes and other non-communicable diseases.

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TABLE 1.1: Response rates. Asaro Valley diabetes survey, Papua New Guinea, 1983

Village	Available population	Responders	Response rate (%)
Gamusi	192	188	98
Gimisave	132	120	91
Total	324	308	95

TABLE 1.2: The prevalence of impaired glucose tolerance and diabetes. Asaro Valley diabetes survey, Papua New Guinea, 1983

	No. studied	Prevalence (%) Impaired glucose tolerance	Diabetes
Gamusi			
Males	97	4.1	0.0
Females	91	1.1	0.0
Sexes combined	188	2.7	0.0
Gimisave			
Males	47	2.1	0.0
Females	73	1.4	0.0
Sexes combined	120	1.7	0.0

TABLE 1.3: Mean (SEM) for selected variables. Asaro Valley diabetes survey, Papua New Guinea, 1983

	GAMUSI		GIMISAVE	
	M	F	M	F
n	97	91†	47	73
Age (years)	39.9(1.5)	39.4(1.5)	42.9(2.1)	38.8(1.4)
2 h plasma glucose (mmol/l)	3.8(0.2)***	3.8(0.1)***	4.7(0.2)	4.7(0.1)
2 h plasma insulin (μU/ml)	17.6(1.7)	18.3(1.6)	15.0(1.2)	20.4(1.5)
Body mass index (kg/m^2)	22.0(0.2)	21.3(0.3)**	22.2(0.3)	22.3(0.3)
Triceps skinfold thickness (mm)	6.6(0.2)	10.5(0.4)**	7.2(0.3)	12.2(0.5)
Subscapular skinfold thickness (mm)	9.9(0.2)	12.3(0.5)*	10.6(0.4)	14.1(0.6)
Sum of skinfolds (mm)	16.5(0.4)	22.8(0.9)**	17.8(0.6)	26.3(1.0)

* $p < 0.05$)
** $p < 0.01$) for comparison between Gamusi and Gimisave (Student's t-test)
*** $p < 0.001$)

† Anthropometric measurements unavailable for one subject

TABLE 1.4: Coefficients of linear correlation between selected variables. Asaro Valley diabetes survey, Papua New Guinea, 1983

	2 h plasma glucose	Age	2 h plasma insulin	Body mass index	Triceps SFT	Subscapular SFT
MALES						
Age	0.3					
2 h plasma insulin	0.5	0.1				
Body mass index	-0.2	-0.4	0.0			
Triceps SFT	0.1	-0.1	0.2	0.4		
Subscapular SFT	0.0	-0.1	0.0	0.4	0.7	
Sum of skinfolds	0.1	-0.1	0.1	0.4	0.9	0.9
FEMALES						
Age	0.1					
2 h plasma insulin	0.4	-0.1				
Body mass index	0.1	-0.6	0.1			
Triceps SFT	0.1	-0.4	0.1	0.6		
Subscapular SFT	0.1	-0.5	0.1	0.7	0.8	
Sum of skinfolds	0.1	-0.5	0.2	0.7	0.9	1.0

SFT Skinfold thickness

TABLE 1.5: Analysis of variance of two-hour plasma glucose concentration by village of residence, age group and quartiles of body mass index and sum of skinfolds. Asaro Valley diabetes survey , Papua New Guinea, 1983

	Sum of squares	d.f	F	P
MALES (n = 144)				
Main effects:				
Village of residence	15.0	1	7.1	<0.01
Age group	14.5	2	3.4	<0.05
Quartile of body mass index (kg/m^2)	13.9	3	2.2	N.S.
Quartile of sum of skinfolds (mm)	12.0	3	1.9	N.S.
Village x age group interaction	16.8	2	4.0	<0.05
FEMALES (n = 163)†				
Main effects:				
Village of residence	30.2	1	22.9	<0.001
Age group	1.4	2	0.5	N.S.
Quartile of body mass index (kg/m^2)	2.9	3	0.7	N.S.
Quartile of sum of skinfold (mm)	3.4	3	0.9	N.S.

† Anthropometric measurements unavailable for one subject

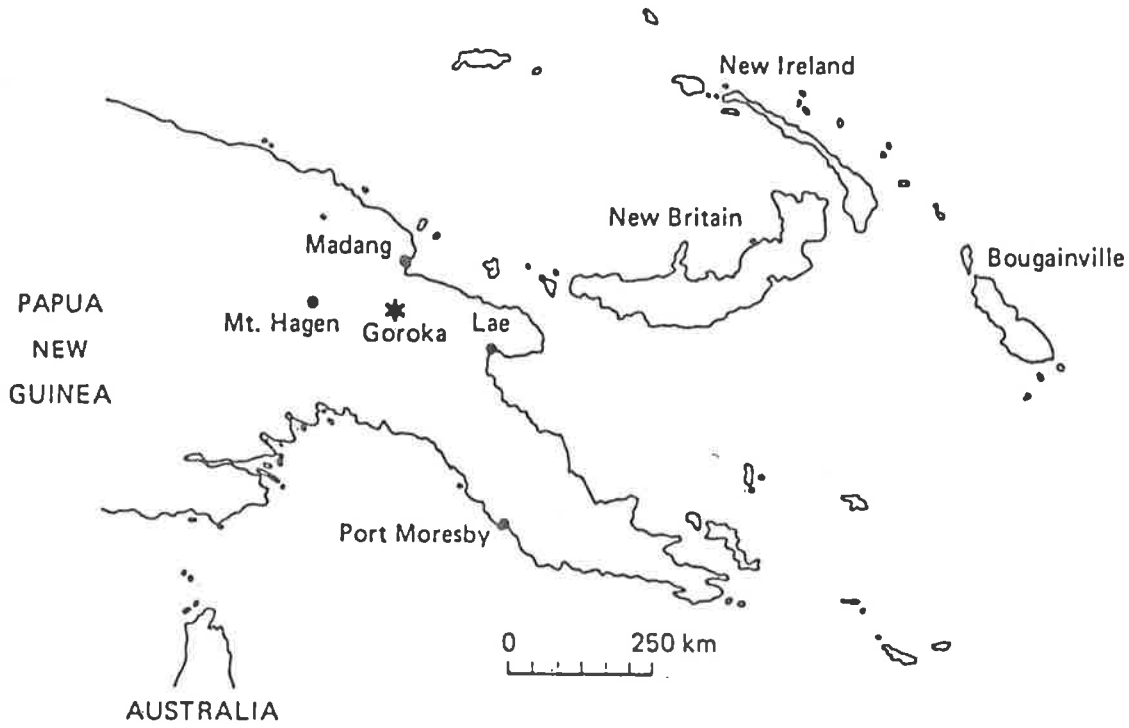

FIGURE 1.1: Map of Papua New Guinea

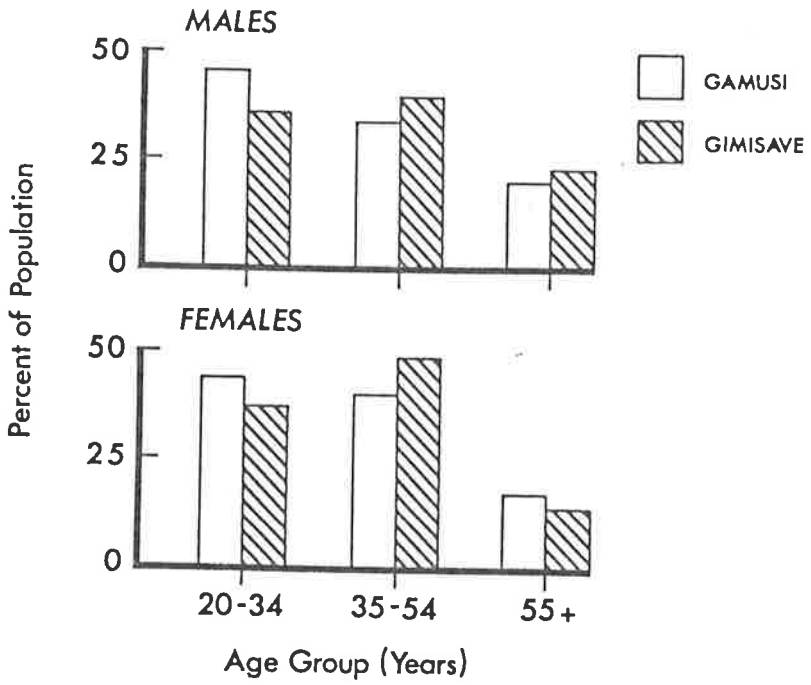

FIGURE 1.2: The age structure of the two village populations. Asaro Valley diabetes survey, Papua New Guinea, 1983

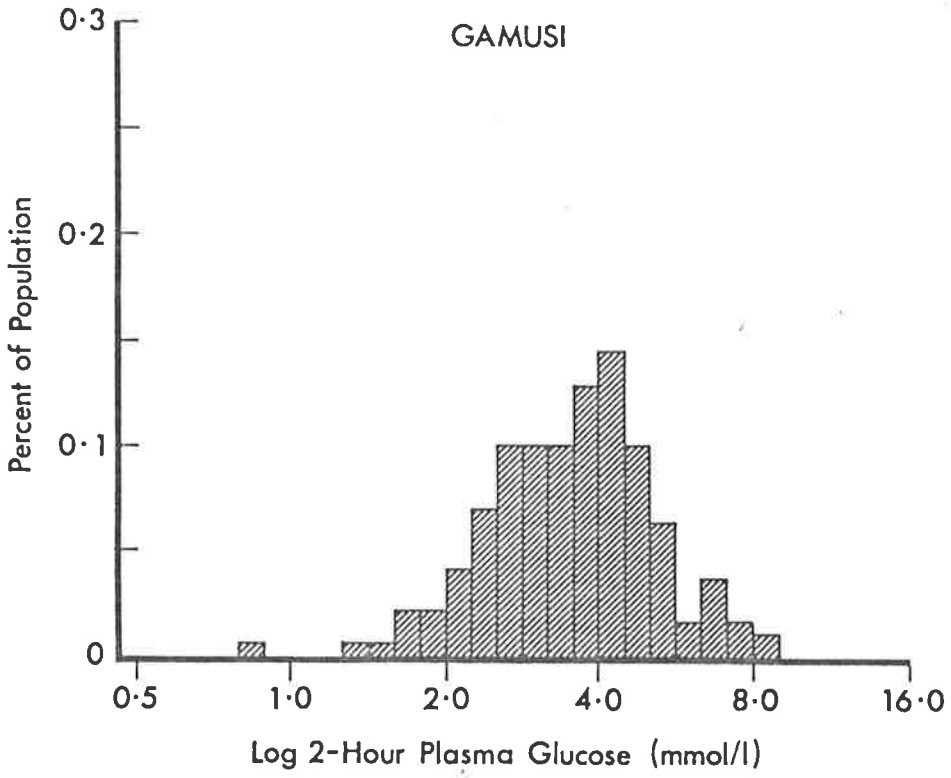

FIGURE 1.3a: Distribution of Log two-hour plasma glucose concentration (mmol/l) in Gamusi. Sexes combined (n = 188). Asaro Valley diabetes survey, 1983

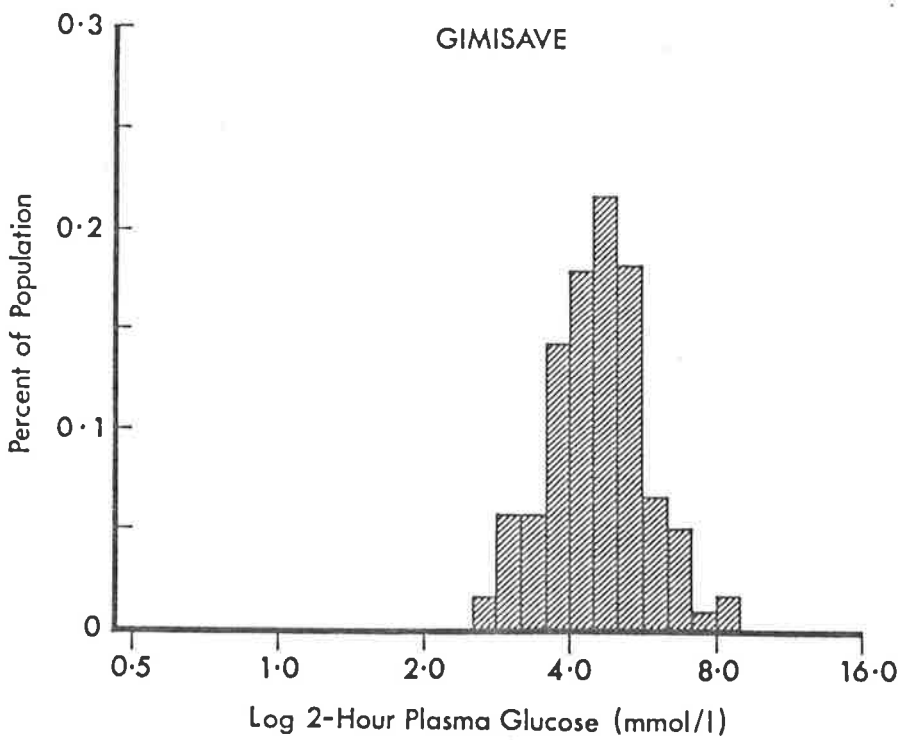

FIGURE 1.3b: Distribution of Log two-hour plasma glucose concentration (mmol/l) in Gimisave. Sexes combined (n = 120). Asaro Valley diabetes survey, 1983

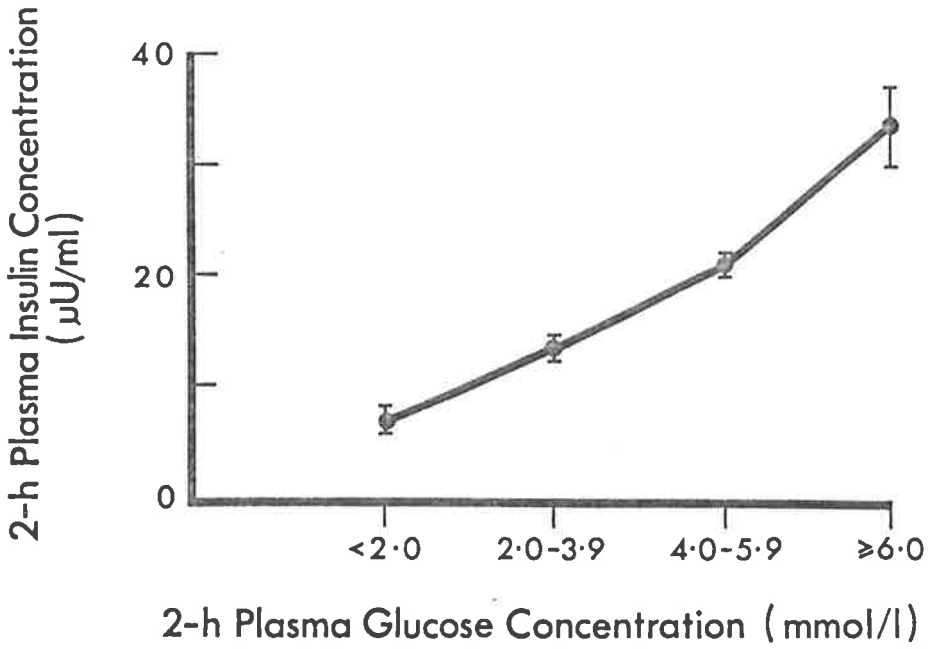

FIGURE 1.4: The relationship between two-hour plasma glucose concentration (mmol/l) and two-hour plasma insulin concentration (μU/ml) in the whole study population (n = 308). Results expressed as mean ± SEM. Asaro Valley diabetes survey, 1983

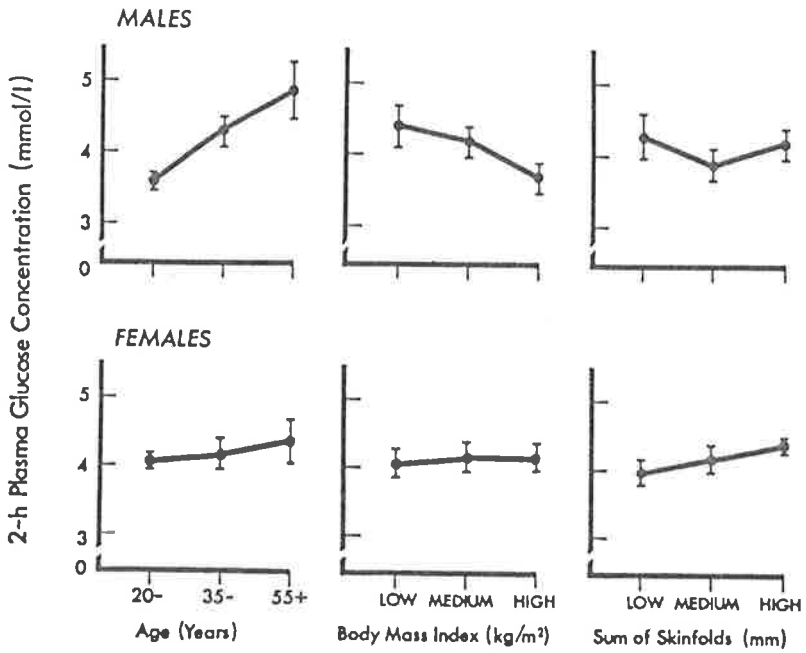

FIGURE 1.5: Two-hour plasma glucose concentration (mmol/l) in age groups and in tertiles of the distribution of body mass index and sum of skinfolds. Results expressed as mean ± SEM. Asaro Valley diabetes survey, 1983

TABLE 2.1: Age and sex distribution of Kiribati survey population and dietary sub-sample Kiribati diabetes survey, 1981

	MALES				FEMALES			
	20-34	35-54	55+	All ages	20-34	35-54	55+	All ages
Rural survey population	176	191	107	474	238	212	114	564
Dietary sub-sample	65	77	40	182	82	89	45	216
Proportion in dietary sub-sample(%)	36.9	40.3	37.4	38.4	34.5	42.0	39.5	38.3
Urban survey population	491	368	60	919	549	349	83	981
Dietary sub-sample	159	128	26	313	198	127	26	351
Proportion in dietary sub-sample (%)	32.4	34.8	43.3	34.1	36.1	36.4	31.3	35.8

TABLE 2.2: Prevalence(%) of impaired glucose tolerance and diabetes mellitus in Kiribati by region, age group, and sex*. Kiribati diabetes survey, 1981

Sex	Age group (years)	IMPAIRED GLUCOSE TOLERANCE				DIABETES MELLITUS			
		Rural		Urban		Rural		Urban	
		No.	%	No.	%	No.	%	No.	%
Males	20-24	79	3.8	168	4.8	79	1.3	168	0.6
	25-34	97	4.1	314	11.1	97	1.0	314	3.5
	35-44	96	14.6	223	17.5	96	3.1	223	8.5
	45-54	93	15.1	143	23.8	93	5.4	143	19.6
	55-64	49	18.4	41	36.6	49	6.1	41	26.8
	65+	57	26.3	18	27.8	57	7.0	18	16.7
	All ages	471	12.5	907	15.0	471	3.6	907	8.1
Females	20-24	114	6.1	217	10.6	114	0.9	217	1.4
	25-34	122	12.3	329	16.1	122	2.5	329	3.6
	35-44	114	14.9	207	16.9	114	3.5	207	8.2
	45-54	98	20.4	139	25.9	98	5.1	139	15.8
	55-64	57	15.8	49	12.2	57	8.8	49	22.4
	65+	55	21.8	32	34.4	55	3.6	32	21.9
	All ages	560	14.3	973	16.9	560	3.6	973	7.4

* Two-hour plasma glucose unknown in 7 rural and 20 urban subjects

TABLE 2.3: Age-standardized prevalence (%)* of impaired glucose tolerance and diabetes mellitus in Kiribati by region. Kiribati diabetes survey, 1981

Sex	Status	Prevalence (%) Rural	Urban	R.R.†	χ^{2}**	P
MALES						
	Impaired glucose tolerance	10.6	16.1	1.5	13.0	<0.001
	Diabetes mellitus	3.0	9.1	3.0	24.4	<0.001
	Impaired glucose tolerance and diabetes mellitus	13.6	25.2	1.9	28.3	<0.001
FEMALES						
	Impaired glucose tolerance	13.7	17.9	1.3	6.2	<0.05
	Diabetes mellitus	3.3	8.7	2.6	18.6	<0.001
	Impaired glucose tolerance and diabetes mellitus	17.0	26.6	1.6	16.8	<0.001

* By the direct method using the combined rural and urban study populations as the standard

† Relative risk

** Using the Mantel extension of the Mantel-Haenszel procedure on one degree of freedom

TABLE 2.4: Simple correlation coefficients between body mass index, physical activity score and consumption of imported energy (kJ)* in rural and urban males and females. Kiribati diabetes survey, 1981

	Rural males		Rural females	
	Body mass index	Physical activity	Body mass index	Physical activity
Physical activity	-0.02	-	0.13	-
Imported energy consumption	0.24	-0.14	0.11	-0.21
	Urban males		Urban females	
	Body mass index	Physical activity	Body mass index	Physical activity
Physical activity	0.06	-	0.06	-
Imported energy consumption	0.05	0.04	0.19	-0.08

* Dietary sub-sample only

TABLE 2.5: Mean body mass index by age group, region and sex. Kiribati diabetes survey, 1981

		AGE GROUP (YEARS)					
		20-24	25-34	35-44	45-54	55-64	65+
Males	Rural	24.5	25.5	16.6	25.5	24.0	23.0
	Urban	26.1	27.7	28.7	27.8	28.1	25.4
	Analysis of variance			SS	DF	F	P
	Region			18.0	1	49.3	<0.001
	Age group			14.4	5	7.9	<0.05
		AGE GROUP (YEARS)					
		20-24	25-34	35-44	45-54	55-64	65+
Females	Rural	24.7	25.5	25.5	24.4	22.7	20.4
	Urban	27.0	29.2	28.6	28.5	27.5	25.1
	Analysis of variance			SS	DF	F	P
	Region			42.9	1	92.4	<0.001
	Age group			28.3	5	12.2	<0.01

TABLE 2.6: Mean physical activity score by age group, region, and sex. Kiribati diabetes survey, 1981

		AGE GROUP (YEARS)					
		20-24	25-34	35-44	45-54	55-64	65+
Males	Rural	3.3	3.1	3.1	3.1	2.9	2.3
	Urban	2.7	2.5	2.5	2.3	2.1	2.1
	Analysis of variance			SS	DF	F	P
	Region			1.08	1	45.0	<0.01
	Age group			0.79	5	6.6	<0.05
		AGE GROUP (YEARS)					
		20-24	25-34	35-44	45-54	55-64	65+
Females	Rural	2.8	3.0	3.1	2.9	2.6	2.3
	Urban	2.3	2.4	2.6	2.4	2.3	2.0
	Analysis of variance			SS	DF	F	P
	Region			0.61	1	81.0	<0.001
	Age group			0.58	5	15.6	<0.01

TABLE 2.7: Median consumption of imported energy (kJ) per caput/day by age group, region, and sex*. Kiribati diabetes survey, 1981

		AGE GROUP (YEARS)					
		20-24	25-34	35-44	45-54	55-64	65+
Males	Rural	3151	2548	1775	3312	3049	2562
	Urban	5915	5505	4549	4530	4195	4223

Analysis of variance	SS	DF	F	P
Region	13062533.3	1	37.2	<0.01
Age group	2409216.6	5	1.4	NS

		AGE GROUP (YEARS)					
		20-24	25-34	35-44	45-54	55-64	65+
Females	Rural	2465	1900	1019	1554	770	1786
	Urban	4044	4238	3548	3877	3277	2649

Analysis of variance	SS	DF	F	P
Region	12279610.1	1	55.3	<0.001
Age group	2480560.4	5	2.2	NS

* Dietary sub-sample only

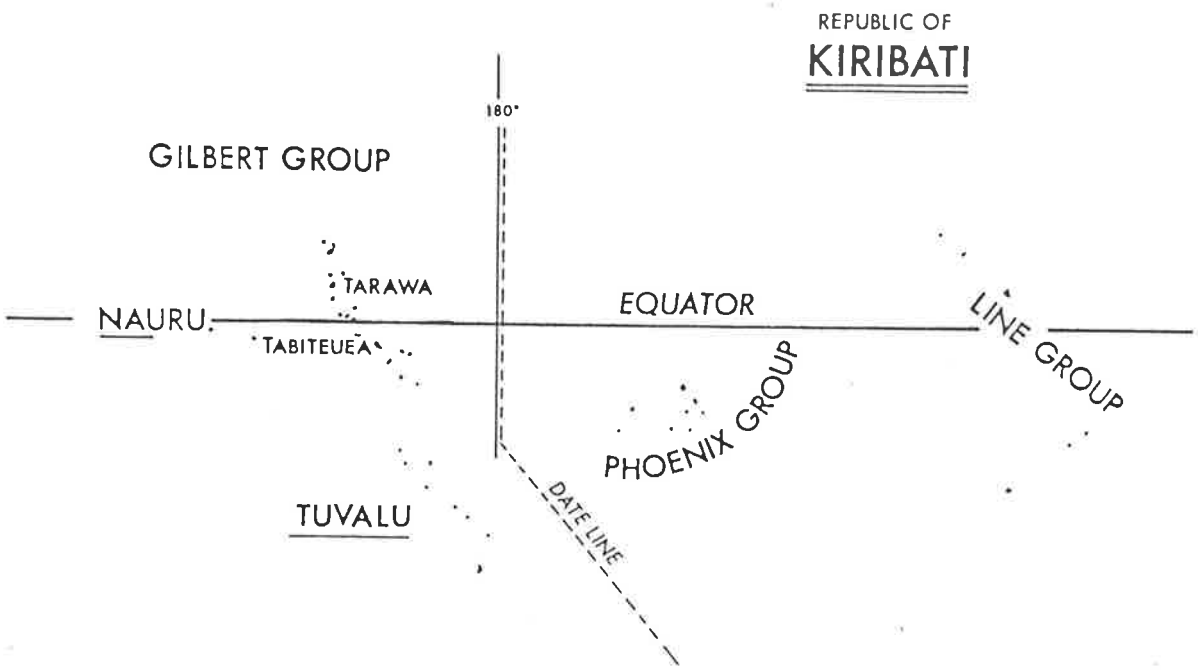

FIGURE 2.1: The Republic of Kiribati and adjacent neighbours

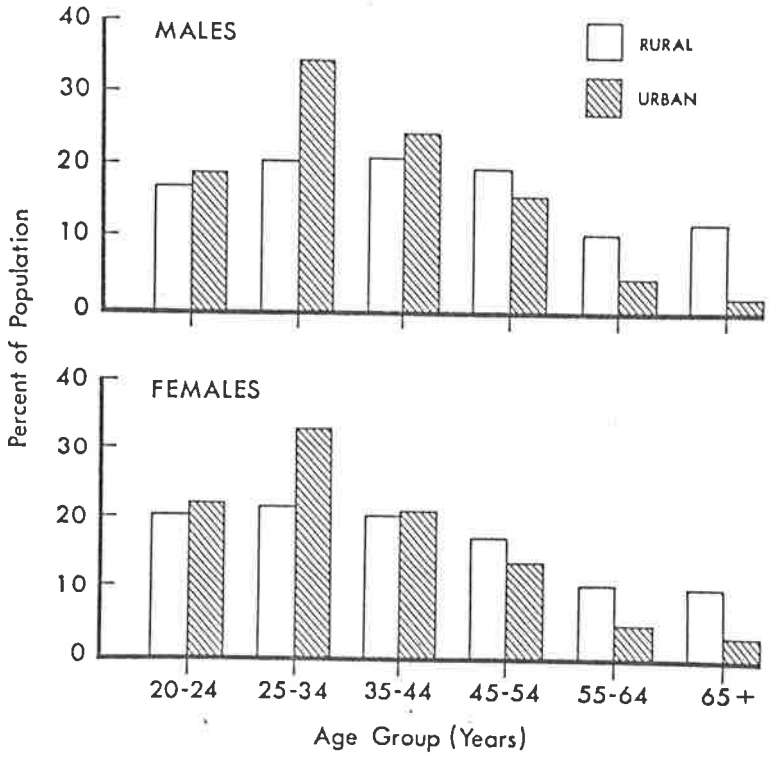

FIGURE 2.2: Age structure of rural and urban population by sex. Kiribati diabetes survey, 1981

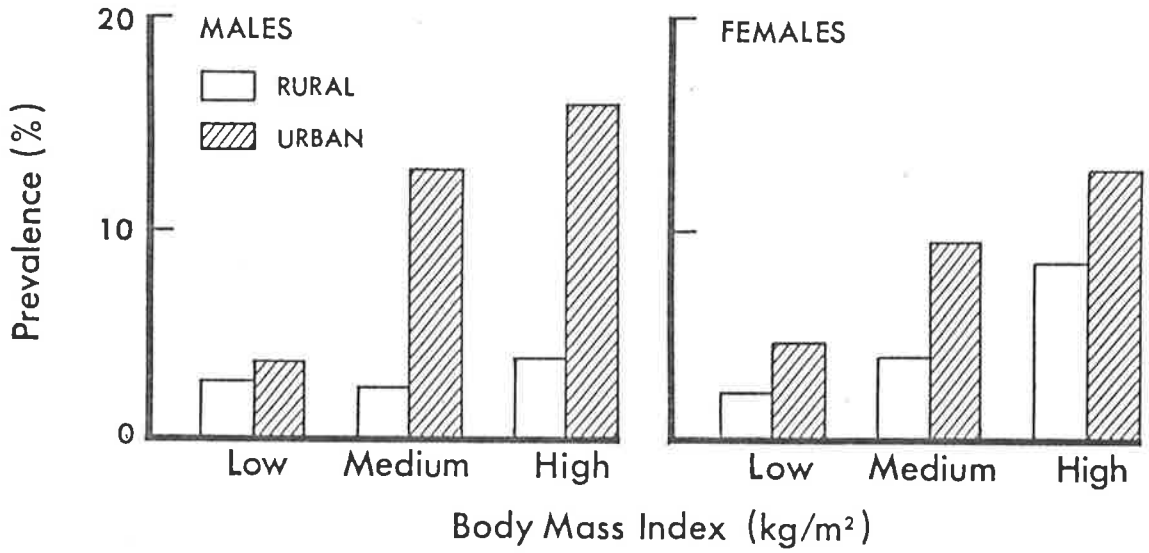

FIGURE 2.3: Age-standardized prevalence (%) of diabetes in rural and urban samples stratified by tertiles of body mass index. Kiribati diabetes survey, 1981

TABLE 3.1: Correlation coefficients between selected characteristics, sexes combined. Nauruan diabetics, 1982

	Age	Two-hour plasma glucose	Body mass index	Duration
Two-hour plasma glucose (mmol/l)	0.01	-	-	-
Body mass index (kg/m^2)	-0.26	-0.20	-	-
Duration (years)	0.16	0.32	-0.17	-
Systolic blood pressure (mmHg)	0.09	-0.11	0.32	-0.08

TABLE 3.2: Mean ± SEM of selected characteristics according to sex and retinopathy status. Nauruan diabetics, 1982

	MALES		FEMALES	
Retinopathy	Present	Absent	Present	Absent
Age (years)	48.5±1.5	47.4±1.2	48.8±1.4	44.6±1.0*
Two-hour plasma glucose (mmol/l)	19.9±0.7	17.0±0.4***	21.2±1.0	17.4±0.4***
Body mass index (kg/m²)	32.8±0.7	33.7±0.6	33.9±1.0	36.7±0.6*
Duration of diabetes (years)	6.9±0.7	2.7±0.3***	8.5±1.0	2.6±0.3***
Systolic blood pressure (mmHg)	136.3±3.4	133.3±2.4	136.2±4.3	134.1±2.0

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Student's t-test

TABLE 3.3: Coefficients and other characteristics of the full logistic regression models predicting retinopathy status. Each model includes the six age group constants. Nauruan diabetics, 1982

	Males (n=155)	Females (n=188)
Duration (years)	0.45(0.09)†	0.33(0.08)
Two-hour plasma glucose (mmol/l)	0.21(0.07)	0.08(0.04)
Systolic blood pressure (mmHg)	0.02(0.01)	0.01(0.01)
Body mass index (kg/m^2)	0.02(0.05)	0.06(0.04)

Measures of the fit of the full models

	Males (n=155)	Females (n=188)
Deviance	93.9	101.4
Degrees of freedom	145	178
Entropy	0.45	0.46

† Number in parentheses indicates standard error

TABLE 3.4: Comparison of optimal logistic regression models with one, two, three and four variables included. The six age group constants were included in each model. Nauruan diabetics, 1982

Step	Variables in the model	Degrees of freedom	Deviance	χ^2† (d.f.= 1)
MALES (n = 55)				
1	Age	149	155.3	47.9***
2	Age, duration	148	107.4	10.8**
3	Age, duration, two-hour plasma glucose	147	96.6	2.5
4	Age, duration, two-hour plasma glucose, systolic blood pressure	146	94.1	0.2
5	Age, duration two-hour plasma glucose, systolic blood pressure, body mass index	145	93.9	
FEMALES (n = 188)				
1	Age	182	154.1	45.8***
2	Age, duration	181	108.3	4.2*
3	Age, duration, two-hour plasma glucose,	180	104.1	1.4
4	Age, duration, two-hour plasma glucose, body mass index	179	102.7	1.3
5	Age, duration, two-hour plasma glucose, body mass index, systolic blood pressure,	178	101.4	

† The χ^2 value is the observed value for a likelihood ratio test. Each model is compared with the preceding model to test for the significance of the inclusion of the additional predictor variable

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

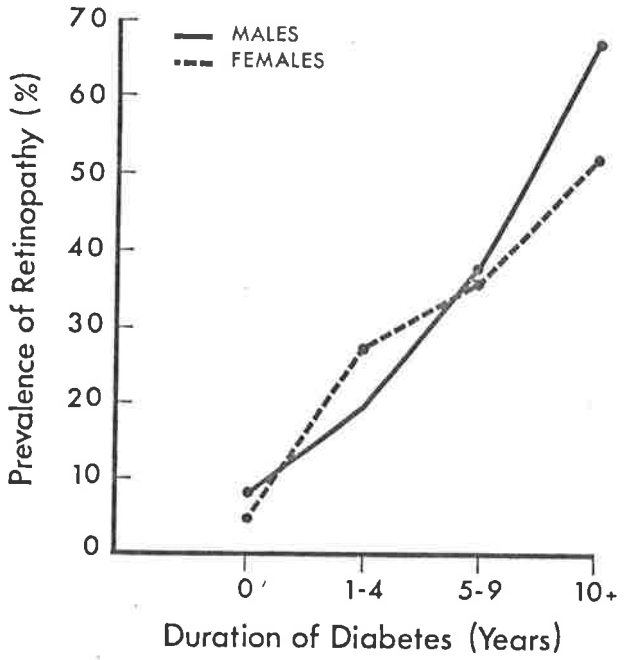

FIGURE 3.1: The relationship between duration of diabetes and prevalence of retinopathy. Nauruan diabetics, 1982

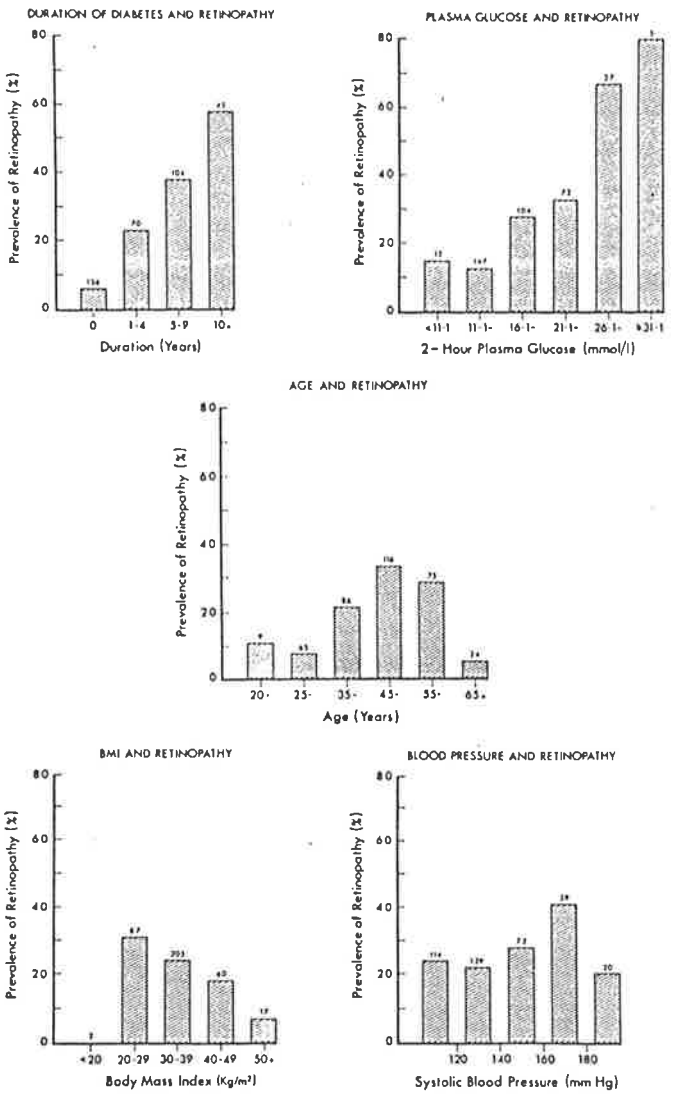

FIGURE 3.2. The relationship between five selected characteristics and the prevalence of retinopathy. Nauruan diabetics, 1982 (sexes combined)

TABLE 4.1: Distribution of the 266 non-diabetic subjects by age and diabetic status at initial examination. Nauru follow-up study, 1965/6-1982

	Normal		Impaired glucose tolerance	
	No.	% of total	No.	% of total
MALES				
0-19	26	27.1	2	9.1
20-29	38	39.6	7	31.8
30-39	14	14.6	3	13.6
40-49	15	15.6	6	27.3
50-59	3	3.1	2	9.1
60+	0	0.0	2	9.1
All ages	96	100.0	22	100.0
FEMALES				
0-19	42	35.3	2	6.9
20-29	43	36.1	8	27.6
30-39	16	13.5	6	20.7
40-49	11	9.2	10	34.5
50-59	6	5.0	3	10.3
60+	1	0.8	0	0.0
All ages	119	100.0	29	100.0

TABLE 4.2: Comparison of diabetic status of Nauruan non-diabetics in 1975-1976 and follow-up status in 1982

Diabetic status in 1975-1976	Diabetic status in 1982			
	Normal	Impaired glucose tolerance	Diabetic	Total
MALES				
Normal	72	17	7	96
Impaired glucose tolerance	7	9	6	22
FEMALES				
Normal	95	17	7	119
Impaired glucose tolerance	13	9	7	29
SEXES COMBINED				
Normal	167	34	14	215
Impaired glucose tolerance	20	18	13	51

TABLE 4.3: Parameter estimates, standard errors, and standardized parameter estimates for selected baseline variables, derived from the multiple logistic regression model† predicting progression to diabetes (n = 264).†† Nauru follow-up study, 1975/6-1982

Variable	Parameter estimate	Standard error	Standardized parameter estimate§
Age (years)	0.32	0.14	2.3*
Age squared	$-4x10^{-3}$	$-2x10^{-3}$	-2.1*
Sex (female)	-0.51	0.46	-1.1
Date of first examination	-0.10	0.45	0.2
Body mass index (kg/m^2)	0.09	0.03	2.5*
Impaired glucose tolerance	1.40	0.47	3.0**

† Log likelihood statistic : 140.3 on 257 degrees of freedom (see results)

†† Two cases deleted due to missing data

* $p < 0.05$

** $p < 0.01$

§ The standardized parameter estimate may be referred to tables of the normal distribution as a test of significance of the parameter in the regression equation

TABLE 4.4: Mean† values of selected baseline variables in subjects not progressing, compared with those progressing to diabetes.†† Nauru follow-up study, 1975/6-1982

Variable	Not progressing to diabetes (n = 37)	Progressing to diabetes (n = 13)
Age (years)	35.9	40.7
2-h plasma glucose (mmol/l)	8.6	9.5**
Fasting plasma glucose (mmol/l)	5.6	6.4**
Body mass index (kg/m²)	30.7	35.3**
Triceps skinfold index (mm)	25.8	31.5
Plasma cholesterol (mmol/l)	5.3	5.3
Plasma triglycerides (mmol/l)	1.3	1.6
Plasma uric acid (mmol/l)	0.4	0.4
Systolic blood pressure (mmHg)	136	131
Urinary creatinine (mmol/l)	0.1	0.1
% cigarette smokers	50.0	46.2
% positive family history of diabetes	51.7	50.0

† Continuous variables standardized for age by analysis of covariance

†† Subjects with impaired glucose tolerance only (n = 50) one case deleted due to missing data

** $p < 0.01$ (F test)

TABLE 4.5: Parameter estimates, standard errors, and standardized parameter estimates for selected variables derived from the multiple logistic regression model† predicting progression to diabetes.†† Nauru follow-up study, 1975/6-1982

Variable	Parameter estimate	Standard errror	Standardized parameter estimate§
Age (years)	0.15	0.07	2.2*
Sex (female)	-1.33	1.58	-0.8
Date of first examination	0.46	1.43	0.3
2-h Plasma glucose (mmol/l)	2.52	1.06	2.4*
Body mass index(kg/m²)	0.22	0.11	1.9
Plasma cholesterol(mmol/l)	-1.31	1.19	-1.1
Plasma triglycerides(mmol/l)	2.68	1.64	1.6
Plasma uric acid(mmol/l)	11.26	11.05	1.0
Urinary creatinine(mmol/l)	-36.23	36.59	-1.0
Systolic blood pressure(mmHg)	-0.11	0.06	-2.0*
Cigarette smoking	-3.00	1.62	-1.9

* $p < 0.05$

† Log likelihood statistic : 29.4 on 38 degrees of freedom (see results)

†† Subjects with impaired glucose tolerance only (n = 50, one case deleted due to missing data)

§ The standardized parameter estimate may be referred to tables of the normal distribution as a test of significance of the parameter in the regression equation

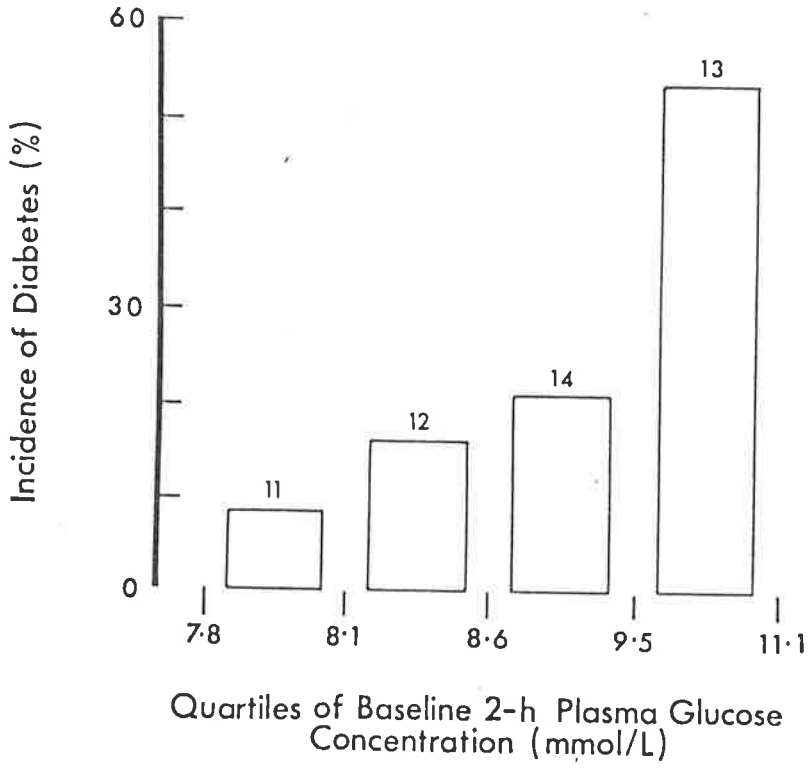

FIGURE 4.1: The incidence of subsequent diabetes during the study period in the four quartiles of baseline two-hour plasma glucose concentration in subjects with impaired glucose tolerance. Nauru follow-up study, 1976/6-1982

TABLE 5.1: The prevalence of diabetes in the full Betio and Nauru samples (n = 2306). Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

	No. examined	Crude prevalence (%)	Age-standardized† prevalence (%)	Relative risk for Nauruans
MALES				
Betio	435	9.9	10.7	2.6***
Nauru	561	25.7	28.9	
FEMALES				
Betio	497	9.3	11.3	2.6***
Nauru	813	23.9	28.3	

† To the census population of Western Samoa, 1976 by the direct method

*** $p < 0.001$ [using the Mantel extension of the Mantel-Haenszel procedure (Mantel, 1963)]

TABLE 5.2: Mean(±S.E.M.) age and body mass index in the full Betio and Nauru samples (n = 2306). Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

	MALES		FEMALES	
	Betio (n = 435)	Nauru (n = 561)	Betio (n = 497)	Nauru (n = 813)
Age (years)	37.8(0.6)	37.5(0.6)	35.8(0.6)	35.5(0.5)
Body mass index (kg/m^2)	27.9(0.2)	33.1(0.3)	28.1(0.2)	34.8(0.3)

TABLE 5.3: Results of the multiple logistic regression models predicting diabetic status in the full Betio and Nauru samples. Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

Step	Variables in the model	d.f.	Log-likelihood statistic	χ^2†(d.f.)	
MALES (n = 996)					
1	Null model	995	962	191***	(2)
2	Age, age²	993	771	35***	(1)
3	Age, age², body mass index	992	736	31***	(1)
4	Age, age², body mass index, ethnicity	991	705		
FEMALES (n = 1310)					
1	Null model	1039	1248	200***	(2)
2	Age, age²	1037	1048	20***	(1)
3	Age, age², body mass index	1036	1028	36***	(1)
4	Age, age², body mass index, ethnicity	1035	992		

† The χ^2 value is the observed value for the likelihood ratio test

Each model is compared with the preceding model to test for the significance of the inclusion of the additional predictor variable

*** $p < 0.001$

TABLE 5.4: Parameter estimates, standard errors and standardized parameter estimates† from the final multiple logistic regression models predicting diabetic status in the full Betio and Nauru samples. Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

Parameter (n = 996)	Males (n = 996)			Females (n = 1310)		
	Parameter estimate	Standard error	Standardized parameter estimate	Parameter estimate	Standard error	Standardized parameter estimate
Age (years)	0.35	0.05	7.5^{***}	0.26	0.04	6.7^{***}
Age squared	$-3x10^{-3}$	$4x10^{-4}$	-5.9^{***}	$-2x10^{-3}$	$4x10^{-4}$	4.9^{***}
Ethnicity (Nauruan)	1.19	0.22	5.4^{***}	1.18	0.20	5.8^{***}
Body mass index (kg/m^2)	0.06	0.02	3.2^{**}	0.02	0.01	1.4

** $p < 0.01$
*** $p < 0.001$
† The standardized parameter estimate may be referred to tables of the normal distribution as a test of significance of the parameter in the regression equation

TABLE 5.5: Mean (±SEM) age, body mass index and daily intake of selected dietary variables in Betio and Nauru dietary sub-samples (n = 694). Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

	MALES		FEMALES	
	Betio (n = 154)	Nauru (n = 176)	Betio (n = 188)	Nauru (n = 176)
Age (years)	39.7(1.1)	37.6 (1.0)	35.3(1.0)	36.8 (1.1)
Body mass index (kg/m²)	27.5(0.4)	33.1 (0.5)	28.2(0.4)	35.5 (0.6)
Daily nutrient intakes:				
Total energy (mJ)	7.6(0.2)	13.5 (0.5)	6.5(0.2)	10.6 (0.4)
Carbohydrate (g)	249.4(7.7)	349.2(11.2)	214.7(5.7)	305.9(12.0)
Fat (g)	49.7(2.4)	105.3 (6.6)	50.0(2.4)	90.5 (4.9)
Dietary fibre (g)	9.5(0.6)	8.3 (0.5)	8.6(0.5)	7.4 (0.4)

TABLE 5.6: Correlation coefficients between continuous variables in Betio and Nauru dietary sub-samples (n = 694). Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

		Age	Body mass index	Total energy	Carbohydrate	Fat
MALES (n = 330)	Body mass index	0.00				
	Total energy	-0.17	0.35			
	Carbohydrate	-0.22	0.25	0.74		
	Fat	-0.12	0.27	0.73	0.34	
	Dietary fibre	-0.03	0.02	0.23	0.32	0.22
FEMALES (n = 364)	Body mass index	0.03				
	Total energy	-0.14	0.39			
	Carbohydrate	-0.17	0.34	0.88		
	Fat	-0.08	0.29	0.84	0.59	
	Dietary fibre	-0.04	-0.01	0.32	0.31	0.32

TABLE 5.7: Results of the forward selection procedure using the multiple logistic regression model to predict diabetic status in the Betio and Nauru dietary sub-samples. At each step, the χ^2 value associated with the introduction of each variable is shown.† For each sex, age is controlled for at Step 2. Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

Step	Variables in the model	d.f.	Log-likelihood	χ^2 value associated with the addition of each variable to the model					
				Ethnicity	BMI	ENER	CHO	FAT	DFIB
Males (n = 330)									
1	Null model	329	324.6						
2	Age, age²	327	259.7	28.8***	8.1**	2.8	3.5	0.4	0.4
3	Age, age², ethnicity	326	230.9	-	0.6	1.0	0.0	1.5	0.0
4	Age, age², BMI	326	251.6	21.3***	-	0.8	1.7	0.0	0.5
Females (n = 364)									
1	Null model	363	353.5						
2	Age, age²	361	290.9	15.8***	12.4***	2.9	0.4	5.4*	0.0
3	Age, age², ethnicity	360	275.1	-	2.7	0.0	0.7	1.0	0.0
4	Age, age², BMI	360	278.5	6.1*	-	0.0	0.5	1.6	0.0

BMI Body mass index (kg/m²). ENER total energy consumption (mJ). CHO total carbohydrate (g). FAT total fat (g). DFIB Dietary fibre (g).

† The χ^2 value is the observed value for the likelihood ratio test comparing models with and without the variable included, whilst retaining the variables shown to be entered at the particular step

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

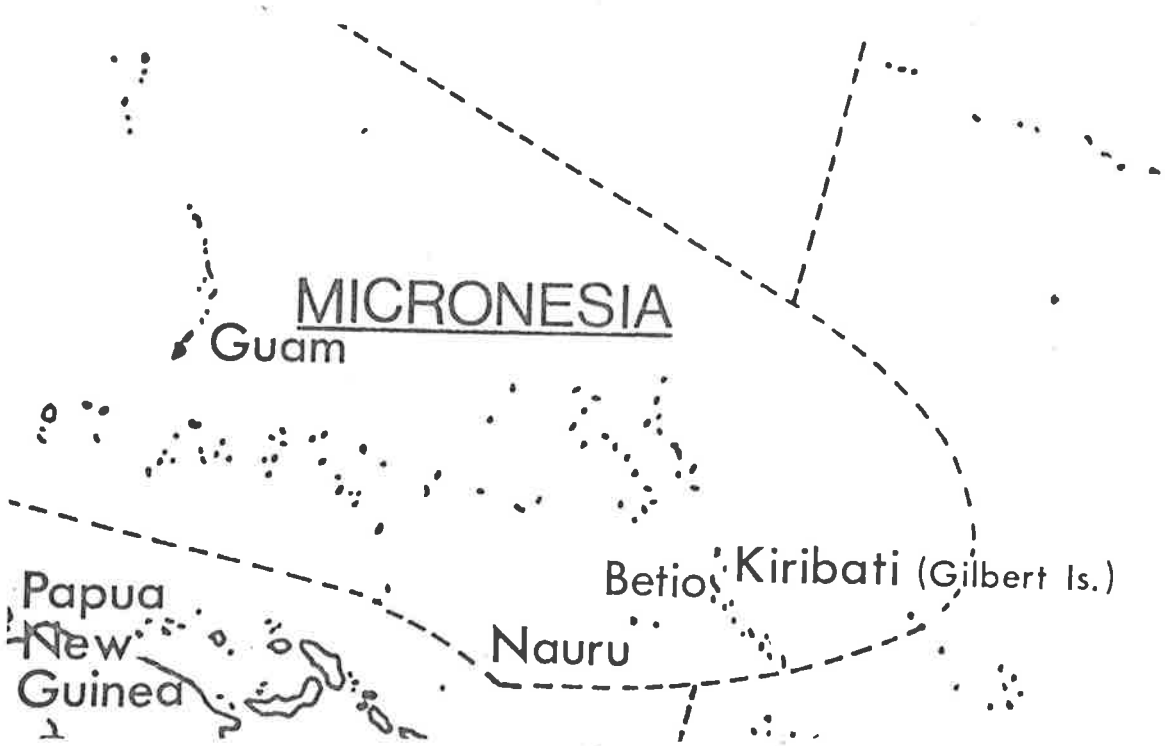

FIGURE 5.1: Map of Micronesia showing the positions of Betio, in the Republic of Kiribati, and of Nauru

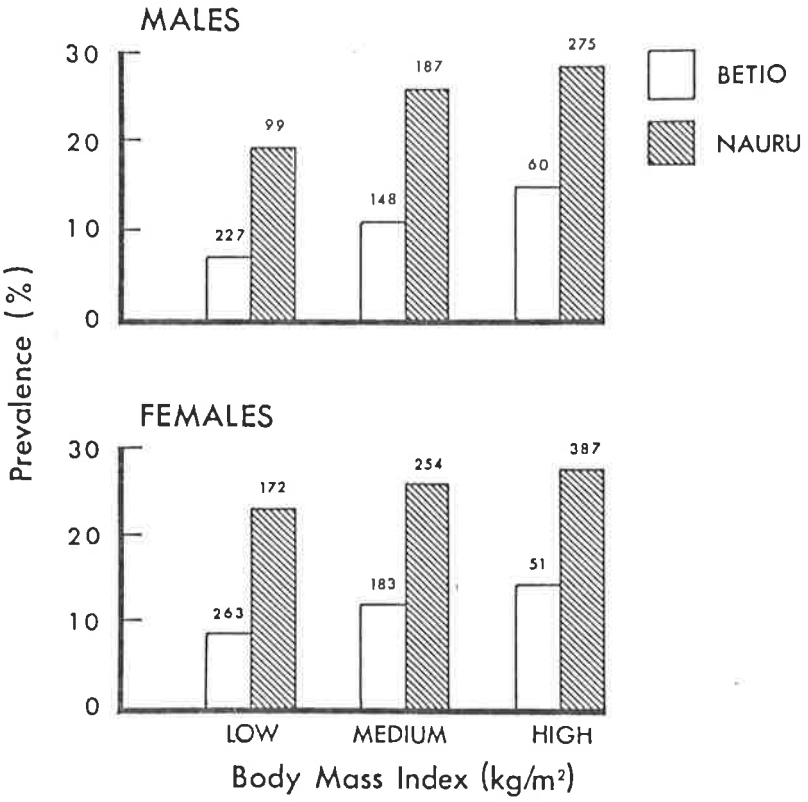

FIGURE 5.2: Age-standardized* prevalence of diabetes (%) in inactive urbanized subjects in Betio and Nauru, stratified by tertiles of the combined distribution of body mass index for each sex. Kiribati diabetes survey, 1981; Nauru diabetes survey, 1982

* to the survey population in Kiribati by the indirect method

TABLE 6.1: Baseline characteristics of the study populations. Melanesians and Indians, Fiji, 1980; Micronesians, Kiribati, 1981

	Melanesians		Indians		Micronesians	
	Rural	Urban	Rural	Urban	Rural	Urban
MALES						
No. examined	239	396	212	381	469	906
Mean age (years)	40.0(0.9)†	40.0(0.7)	37.8(0.9)	38.9(0.7)	42.1(0.7)	35.7(0.4)**
Mean body mass index (kg/m²)	25.6(0.2)	26.1(0.2)	21.6(0.3)	23.0(0.2)**	25.1(0.2)	27.7(0.1)**
Per cent of population overweight§	25	36**	8	13	25	55**
Per cent of population physically inactive	9	91**	17	73**	25	48**
FEMALES						
No. examined	236	460	239	454	556	971
Mean age (years)	40.5(1.0)	39.0(1.8)	38.4(0.9)	37.4(0.6)	40.6(0.7)	35.2(0.4)**
Mean body mass index (kg/m²)	26.4(0.3)	28.2(0.3)**	23.3(0.3)	24.1(0.3)*	24.4(0.2)	28.3(0.2)**
Per cent of population overweight§	56	68**	34	40	40	72**
Per cent of population physically inactive	47	94**	76	97**	19	51**

* $p < 0.05$; ** $p < 0.01$ for rural-urban difference within populations
† numbers in parentheses indicate standard error
§ body mass index ≥27 for males or ≥25 for females

TABLE 6.2: The prevalence of diabetes in rural and urban Melanesians and Indians in Fiji, 1980 and Micronesians in Kiribati, 1981

	Number examined	Crude prevalence (%)	Relative risk†	χ^2MH	p
MALES					
Melanesians					
Rural	239	1.7	3.0	3.04	N.S.
Urban	396	4.8			
Indians					
Rural	212	12.7	1.2	0.19	N.S
Urban	381	14.2			
Micronesians					
Rural	469	3.6	3.5	19.28	<0.001
Urban	906	8.1			
FEMALES					
Melanesians					
Rural	236	1.7	6.6	12.34	<0.001
Urban	460	8.0			
Indians					
Rural	239	13.0	1.0	0.00	N.S
Urban	454	12.6			
Micronesians					
Rural	556	3.6	2.8	15.87	<0.001
Urban	971	7.3			

† Calculated by the Mantel extension of the Mantel-Haenszel procedure (Mantel, 1963) after stratifying the populations by six age groups

TABLE 6.3: The prevalence of diabetes in tertiles of the distribution of body mass index. Melanesians and Indians, Fiji, 1980; Micronesians, Kiribati, 1981

	Number examined	Crude prevalence (%)	Relative risk†	χ^2MH	p
MALES					
Melanesians					
Low body mass index	210	3.3			
			1.2	0.00	N.S
Medium body mass index	208	3.4			
			0.9	0.01	N.S
High body mass index	217	4.1			
Indians					
Low body mass index	197	9.1			
			1.1	0.01	N.S
Medium body mass index	196	11.7			
			1.6	1.38	N.S
High body mass index	200	20.0			
Micronesians					
Low body mass index	448	3.3			
			2.5	6.48	<0.01
Medium body mass index	462	6.5			
			3.6	15.10	<0.001
High body mass index	465	9.7			
FEMALES					
Melanesians					
Low body mass index	230	1.7			
			3.8	4.72	<0.05
Medium body mass index	232	6.9			
			5.6	7.48	<0.01
High body mass index	234	9.0			
Indians					
Low body mass index	222	5.4			
			1.4	0.39	N.S.
Medium body mass index	240	9.2			
			3.0	8.74	<0.01
High body mass index	231	23.4			
Micronesians					
Low body mass index	503	3.8			
			1.9	3.35	N.S.
Medium body mass index	509	5.1			
			3.8	18.2	<0.001
High body mass index	515	8.9			

† Calculated by the Mantel extension of the Mantel-Haenszel procedure (Mantel, 1963) after stratifying the populations by six age groups. Prevalence in medium and high tertiles is compared with prevalence in the low tertile (1 df)

TABLE 6.4: The prevalence of diabetes in active and inactive Melanesians and Indians in Fiji, 1980 and Micronesians in Kiribati, 1981

	Number examined	Crude prevalence (%)	Relative risk†	χ^2MH	p
MALES					
Melanesians					
Active	421	1.9	2.7	3.98	<0.05
Inactive	214	7.0			
Indians					
Active	280	9.3	2.0	5.37	<0.05
Inactive	313	17.6			
Micronesians					
Active	823	5.0	1.4	1.78	N.S.
Inactive	552	8.9			
FEMALES					
Melanesians					
Active	161	3.1	2.4	2.84	N.S.
Inactive	535	6.7			
Indians					
Active	72	11.1	0.9	0.00	N.S.
Inactive	621	12.9			
Micronesians					
Active	924	4.0	2.4	13.79	<0.001
Inactive	603	9.0			

† Calculated by the Mantel extension of the Mantel-Haenszel procedure (Mantel, 1963) after stratifying the populations by six age groups

TABLE 6.5: Correlation coefficients between selected variables. Melanesians and Indians, Fiji, 1980; Micronesians, Kiribati, 1981

	Melanesians			Indians			Micronesians		
	Age	2h PG	BMI	Age	2h PG	BMI	Age	2h PG	BMI
MALES									
2h PG	0.27*	-	-	0.35*	-	-	0.25*	-	-
BMI	0.17*	0.13*	-	0.20*	0.14*	-	-0.06*	0.15*	-
Physical activity	-0.14*	-0.12*	0.00	-0.12*	-0.04	-0.12*	-0.12*	-0.13*	-0.14*
FEMALES									
2h PG	0.34*	-	-	0.36*	-	-	0.20*	-	-
BMI	0.11*	0.14*	-	0.27*	0.28*	-	-0.16*	0.13*	-
Physical activity	0.03	-0.04	-0.04	-0.03	0.03	0.04	-0.01	-0.07	-0.06

* $p < 0.001$
BMI Body mass index; 2h PG Two-hour plasma glucose

TABLE 6.6: Results of the forward selection logistic regression analyses. At each step, the χ^2 value associated with the addition of each variable is shown†. Melanesians and Indians, Fiji, 1980; Micronesians, Kiribati, 1981

Step	Variables in the model	Log likelihood statistic	df	χ^2 value associated with the addition of each factor to the model (1 df) BMI	PA	URB	Interaction
MELANESIAN MALES							
1	Null model	14.6	11	0.0	8.4**	4.1*	-
2	PA	6.2	10	0.0	-	0.8	-
3	PA, URB	5.4	9	0.1	-	-	-
MELANESIAN FEMALES							
1	Null model	21.3	11	3.2	4.2*	8.5**	-
2	URB	12.8	10	1.7	0.5	-	-
3	URB, BMI	11.1	9	-	0.5	-	-
4	URB, BMI, PA	10.6	8	-	-	-	4.2* (BMIxPA)
INDIAN MALES							
1	Null model	16.9	11	3.5	6.8**	0.2	-
2	PA	10.2	10	2.4	-	1.4	-
3	PA, BMI	7.8	9	-	-	2.0	-
INDIAN FEMALES							
1	Null model	25.3	11	18.9***	0.0	0.4	-
2	BMI	6.4	10	-	0.0	0.8	-
3	BMI, URB	5.6	9	-	0.2	-	-
MICRONESIAN MALES							
1	Null model	41.8	11	15.3***	4.2*	19.6***	-
2	URB	22.2	10	8.0**	1.3	-	-
3	URB, BMI	14.2	9	-	1.2	-	-
MICRONESIAN FEMALES							
1	Null model	40.0	11	18.7***	16.2***	18.5***	-
2	BMI	21.3	10	-	8.0**	9.4**	-
3	BMI, URB	11.9	9	-	8.9**	-	-

BMI body mass index (kg/m^2); PA physical activity; URB urbanization
*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
The χ^2 value is the observed value for the likelihood ratio test comparing models with and without the variable included, whilst retaining the variables shown to be entered at the particular step

TABLE 6.7: Estimates of relative risk of diabetes associated with selected factors derived from multiple logistic regression equations (standardized for age). Melanesians and Indians, Fiji, 1980; Micronesians, Kiribati, 1981

Risk factor	Melanesian Males	Melanesian Females	Indian Males	Indian Females	Micronesian Males	Micronesian Females
Medium tertile of body mass index§	0.8	1.6	1.3	1.6	2.5 (1.3,4.7)†	1.5
High tertile of body mass index§	0.9	1.8	1.7	3.7 (1.9,7.2)	2.6 (1.4,5.0)	2.5 (1.4,4.5)
Physical inactivity	2.9 (1.1,7.7)	1.5	2.3 (1.3,4.2)	1.2	1.3	1.9 (1.2,3.0)
Urbanization	1.7	2.6	0.6	0.8	2.6 (1.4,4.8)	1.8 (1.0,3.2)
χ^2 (7 df)	6.8	9.5	3.7	3.3	9.0	2.9

† Numbers in parentheses indicate 95% confidence interval of risk ratios significantly greater than 1.0

§ The comparison being with the lowest tertile of body mass index

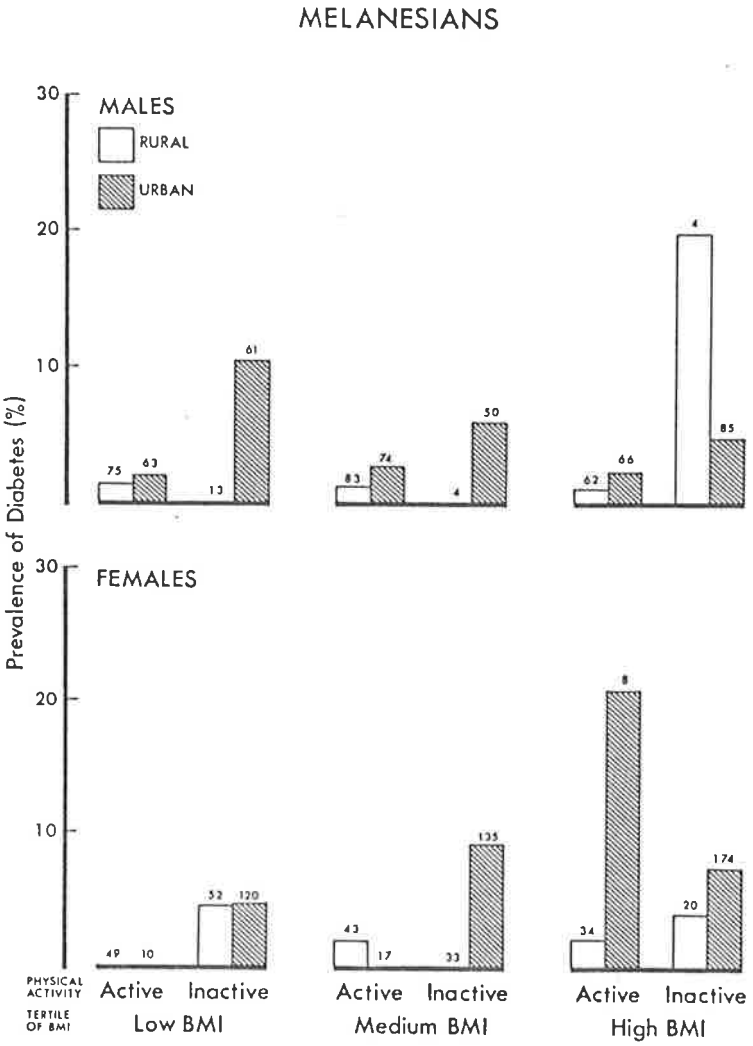

FIGURE 6.1: Prevalence of diabetes (%) stratified by tertiles of body mass index distribution, level of physical activity and urbanization. Melanesians, Fiji, 1980

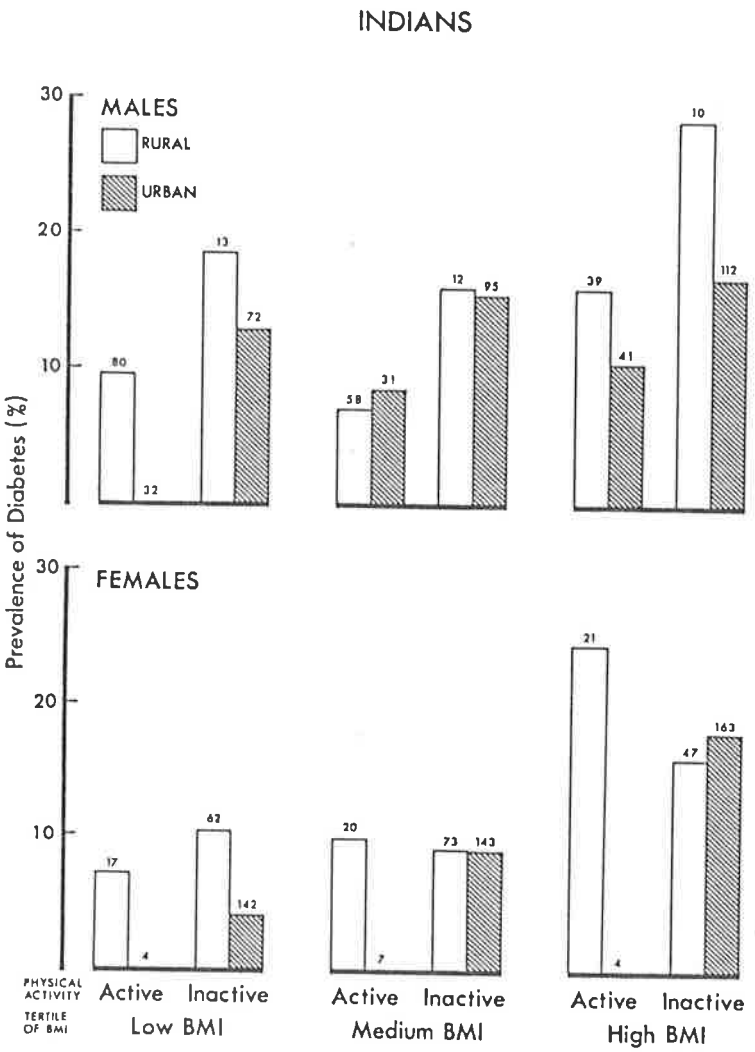

FIGURE 6.2: Prevalence of diabetes (%) stratified by tertiles of body mass index distribution, level of physical activity and urbanization. Indians, Fiji, 1980

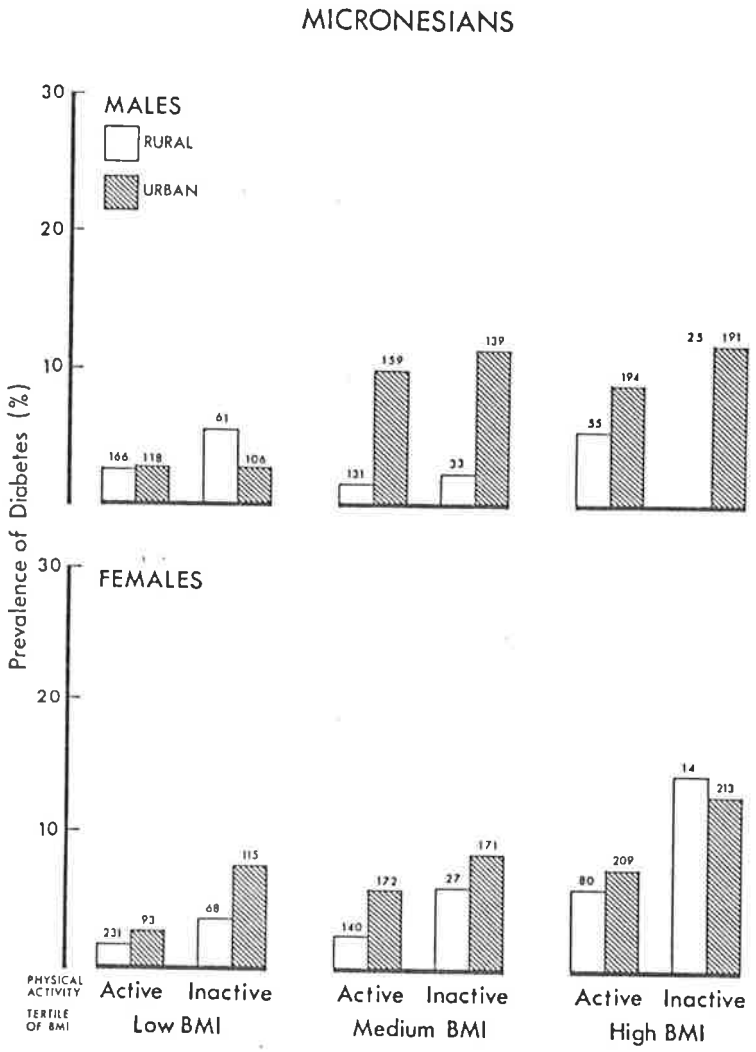

FIGURE 6.3: Prevalence of diabetes (%) stratified by tertiles of body mass index distribution, level of physical activity and urbanization. Micronesians, Kiribati, 1981

TABLE 7.1: Age-standardized* prevalence (subjects 20 years and over) of Type 2 diabetes in Pacific populations surveyed by Royal Southern Memorial Hospital Epidemiology Unit, Melbourne, (1975-1980)

Country	Ethnic group	Prevalence † (%)
Nauru	Micronesian	30.3
Tuvalu	Polynesian	3.9
Western Samoa	Polynesian (rural)	2.7
	(urban)	7.0
New Caledonia (mainland)	Melanesian (rural)	1.5
New Caledonia (Loyalty Islands)	Melanesian	2.0
	Polynesian - Melanesian (mixed)	5.8
Fiji	Melanesian (rural)	1.8
	(urban)	6.9
	Indian (rural)	13.3
	(urban)	14.8
Wallis Islands	Polynesian	2.9

* Standardized to the 1976 census of Western Samoa
† WHO Criteria (1980) for diabetes mellitus

(Taken from Zimmet, 1982)

TABLE A.1: Some published population-based studies of the prevalence of diabetes in ASEAN countries

Investigator	Date of published source	Country	Region	Ethnic group	Number studied	Age	Prevalence (%)	Diagnostic criteria
West & Kalbfleisch	1966	Malaysia	Urban & rural	Malay	281	Mostly >35	1.8	>150(1g/kg)
"	"	"	"	Chinese	127	"	4.7	"
"	"	"	"	Indian	144	"	4.2	"
Fernando	1965	Philippines	Urban	Filipino	3638	'adult'	8.0	?
Germau & Villanueva	1966	"	Rural	"	?	?	9.7	?(100g)
Cheah et al.	1974	Singapore	Urban	Malay	288	30-66	1.4	>140(50g)
"	"	"	"	Chinese	627	"	1.0	"
"	"	"	"	Indian	220	"	6.4	"
"	1978	"	"	Malay	2268	15+	2.4	"
"	"	"	"	Chinese	12812	"	1.6	"
"	"	"	"	Indian	1169	"	6.1	"
Djokomoeljanto et al.	1976	Indonesia	"	Mostly Indonesian	1571	14+	1.5	"
"	1982	"	Semi-urban	"	2822	25+	2.3	?(75g)
Waspadji et al.	1982	"	Urban	"	2749	15+	1.6	WHO criteria (1980)

Prevalence estimates(%): Chinese 1.0-4.7; Malay 1.4-2.4; Indonesian 1.5-2.3; Indian 4.2-6.4; Filipino 8.0-9.7

TABLE A.2: Some published reports of complications of diabetes in ASEAN countries

Investigator	Date of published source	Country	Ethnic group	No. studied	Prevalence (%) in diabetics							
					RETINOPATHY	NEPHROPATHY	CHD	HYPERTENSION	PVD	GANGRENE	NEUROPATHY	TB
Sujono, Sukaton†	1971	Indonesia	Mostly Indonesian	407	8	19	8	22	6	6	56	17
Fernando†	1976	Philippines	Filipino	Review of several studies	8-40	5-31	5-57	15	2	-	15-49	24
Sukono et al.†	1976	Indonesia	Indonesian	1734	16	-	6	22		1	41	16
Jones et al.†	1978	Malaysia	Mixed	132	-	-	20	-	-	8	-	-
Cheah et al.*	1978	Singapore	Mixed	133	9	10	6	27	-	-	3	-

† Study of hospital patients; * population-based data

TABLE A.3: Approximate population size and estimated number of diabetics by country. ASEAN Region

Country	Population	Estimated prevalence of diabetes (%)	Estimated number of diabetics
Indonesia	147,000,000	2	2,940,000
Malaysia	15,000,000	3	450,000
Philippines	45,000,000	4.5	2,025,000
Singapore	2,500,000	2	50,000
Thailand	47,000,000	3.5	1,645,000
Total	256,500,000	2.8	7,110,000

TABLE A.4: Estimated number of subjects with complications of diabetes*. ASEAN region

Country	Retinopathy	Nephropathy	CHD	Hypertension
Indonesia	264,600	294,000	176,400	793,800
Malaysia	40,500	45,000	27,000	121,500
Philippines	182,250	202,500	121,500	546,750
Singapore	4,500	5,000	3,000	13,500
Thailand	148,050	164,500	98,700	444,150
Total	639,900	711,000	426,600	1,919,700

* According to population-based data (Cheah et al. 1978)

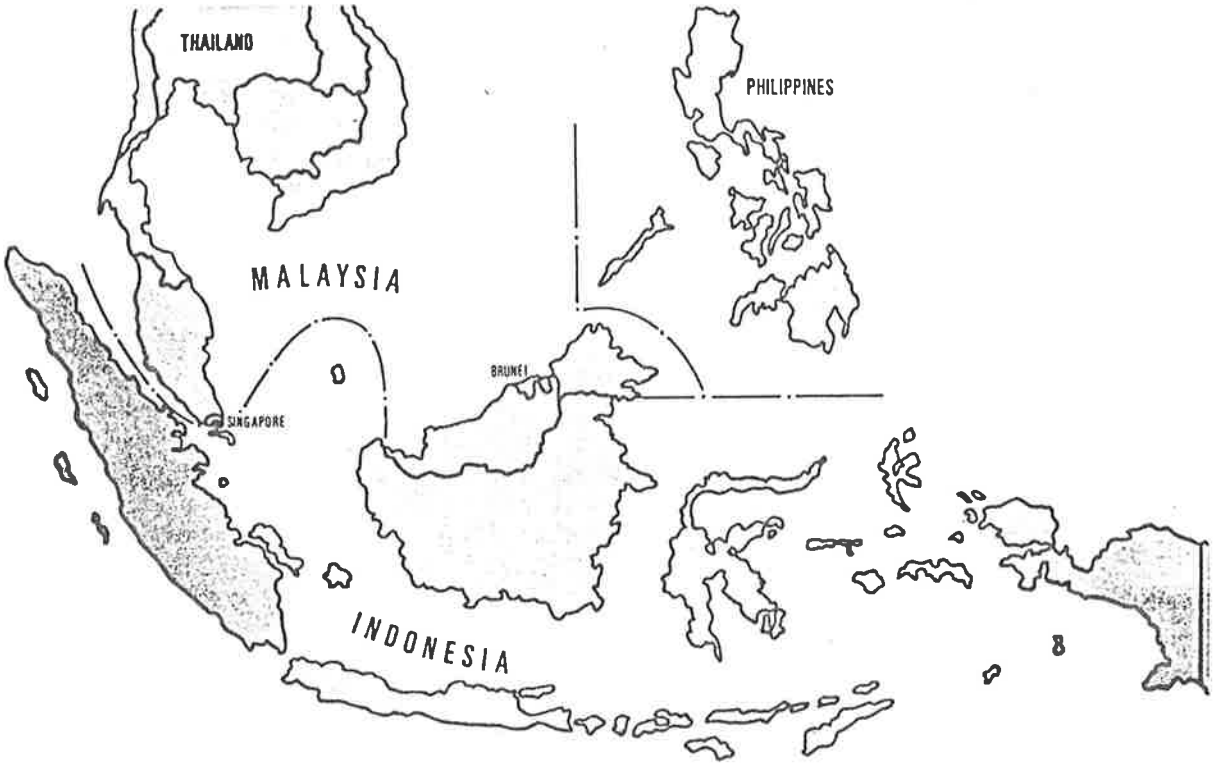

FIGURE A.1: Map of the ASEAN region

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