*This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization*

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# PREVENTION OF DIABETES MELLITUS

Report of a
WHO Study Group

**World Health Organization**

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# WHO Study Group on Prevention of Diabetes Mellitus

Geneva, 16–20 November 1992

## Members*

Professor H. Akerblom, University of Helsinki Children's Hospital, Helsinki, Finland

Professor K. G. M. M. Alberti, Department of Medicine, University of Newcastle upon Tyne, England

Professor J.-P. Assal, Diabetes Treatment and Teaching Unit, Cantonal University Hospital, Geneva, Switzerland

Professor S. Baba, Hyogo Institute for Research in Adult Diseases, Akashi, Japan

Dr P. H. Bennett, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AR, USA

Professor I. Dedov, National Research Centre for Endocrinology, Russian Academy of Medical Sciences, Moscow, Russian Federation

Professor H. Keen, Unit for Metabolic Medicine, Division of Medicine, Guy's Hospital, London, England

Dr R. Klein, Department of Ophthalmology, University of Wisconsin, Madison, WI, USA

Professor J. Nerup, Steno Diabetes Centre, Gentofte, Denmark (*Co-Chairman*)

Dr Pan Xiao-Ren, Department of Endocrinology, China–Japan Friendship Hospital, Beijing, China

Dr F. E. Puchulu, University of Buenos Aires, Buenos Aires, Argentina (*Co-Rapporteur*)

Professor J. Skyler, School of Medicine, University of Miami, Miami, FL, USA

Dr G. Steiner, University of Toronto, Toronto, Ontario, Canada (*Co-Rapporteur*)

Dr A. Swai, Muhimbili Medical Centre, Dar es Salaam, United Republic of Tanzania

Professor P. Zimmet, International Diabetes Institute, Caulfield, Australia (*Co-Chairman*)

## Secretariat

Professor J. S. Bajaj, All India Institute of Medical Sciences, New Delhi, India (*Temporary Adviser*)

Dr K. Borch-Johnsen, Steno Memorial and Hvidore Hospital, Gentofte, Denmark (*Temporary Adviser*)

Professor E. Chazov, Director, Cardiology Research Centre, Moscow, Russian Federation (*Temporary Adviser*)

Dr N. G. Khaltaev, Acting Chief, Diabetes and other Noncommunicable Diseases, WHO, Geneva, Switzerland (*Secretary*)

Dr H. King, Medical Officer, Diabetes and other Noncommunicable Diseases, WHO, Geneva, Switzerland

Dr J. Tuomilehto, Department of Epidemiology, National Public Health Institute, Helsinki, Finland (*Temporary Adviser*)

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* Unable to attend: Dr H. Mahtab, Diabetic Association of Bangladesh, Dhaka, Bangladesh.

## Abbreviations

The following abbreviations are used in this report:

| | |
|---|---|
| GDM | gestational diabetes mellitus |
| GIGT | gestational impaired glucose tolerance |
| HDL | high-density lipoprotein |
| HLA | human leukocyte antigen |
| IDDM | insulin-dependent diabetes mellitus |
| IGT | impaired glucose tolerance |
| LDL | low-density lipoprotein |
| NIDDM | non-insulin-dependent diabetes mellitus |
| OGTT | oral glucose tolerance test |

# 1. Introduction

A WHO Study Group on Prevention of Diabetes Mellitus met in Geneva from 16 to 20 November 1992 to review current possibilities for the prevention of diabetes and its consequences, to consider the development of national prevention and control programmes and to identify areas where further research is needed. The meeting was opened by Dr N. G. Khaltaev on behalf of the Director-General of the World Health Organization.

## 1.1 Background[1]

Diabetes mellitus has long been a concern of the World Health Organization (WHO), and official relations were established between WHO and the International Diabetes Federation as early as 1957. The WHO Expert Committee on Diabetes Mellitus in 1979 and the WHO Study Group on Diabetes Mellitus in 1985 produced important technical reports (*2*, *3*) which have become international standard reference documents on public health aspects of diabetes.

In 1989, a landmark resolution on the prevention and control of diabetes was adopted by the World Health Assembly (*4*). This resolution (see Box) was the culmination of many years of effort and concern by diabetes specialists, governments and lay organizations all over the world to draw attention to the wide impact of the disease. It provided, for the first time, an official mandate for joint action by governments, health care providers and the representatives of people with diabetes.

The first international diabetes research project directly sponsored by WHO was the Multinational Study of Vascular Disease in Diabetics (*5*). The project commenced in the 1970s, and continues to provide valuable information on diabetes complications.

International research on diabetes has been further strengthened by an expanding network of childhood diabetes registries (*6*, *7*). The WHO Multinational Project for Childhood Diabetes (WHO DIAMOND) was launched officially in January 1990 (*8*).

At the country level, WHO has provided technical support for epidemiological studies of diabetes in many of the WHO regions. Such surveys fill important gaps in knowledge of diabetes and its risk factors in adult populations, as does the participation of a number of WHO Collaborating Centres for Diabetes in the WHO integrated programme for community health in noncommunicable diseases (INTERHEALTH) (*9*).

In Europe, a meeting of representatives of government, the health care sector and diabetic people, organized jointly by the WHO Regional Office for Europe and the European Office of the International Diabetes Federation in October 1989, led to the St Vincent Declaration on Diabetes

[1] This section of the report is based substantially on reference *1*.

**Forty-second World Health Assembly, May 1989**
**Resolution WHA42.36**
**Prevention and control of diabetes mellitus***

The forty-second World Health Assembly,

Recognizing that diabetes mellitus is a chronic, debilitating and costly disease attended by severe complications including blindness and heart and kidney disease;

Noting that diabetes already represents a significant burden on the public health services of Member States, and that the problem is growing, especially in developing countries;

Aware of the support of the International Diabetes Federation and the WHO collaborating centres on diabetes;

1. *Invites Member States:*

   — to assess the national importance of diabetes;
   — to implement population-based measures, appropriate to the local situation, to prevent and control diabetes;
   — to share with other Member States opportunities for training and further education in the clinical and public health aspects of diabetes;
   — to establish a model for the integrated approach to the prevention and control of diabetes at community level;

2. *Requests the Director-General to strengthen WHO activities to prevent and control diabetes, in order:*

   — to provide support for the activities of Member States with respect to the prevention and community control of diabetes and its complications;
   — to foster relations with the International Diabetes Federation and other similar bodies with a view to expanding the scope of joint activities for the prevention and control of diabetes;
   — to mobilize the collective resources of the WHO collaborating centres on diabetes.

* Reference *4*.

Research and Care in Europe. This provided the first official initiative to develop plans and policies for the improvement of diabetes care at the regional level. Following a further meeting in March 1992 in Budapest, guidelines for the implementation of the Declaration were issued (*10*). It was proposed that national plans in all European countries should be formulated in accordance with the Declaration.

An important element of the guidelines is the emphasis on the rights and roles of patients – what the patient may expect from the health care team and what the health care team can expect from the patient. The guidelines have been approved and promoted by all European diabetes organizations. The approach involves the use of a care card, on which data for

the patient are recorded at every visit. The card is carried by the patient and can be used as a "passport" when treatment away from home is necessary.

The development of national diabetes programmes is seen as the key to implementation of resolution WHA42.36. To assist governments, as well as local authorities, WHO has prepared a document entitled *Guidelines for the development of a national programme for diabetes mellitus* (*11*), which was issued in 1991.

While for individual patients an interdisciplinary approach to prevention and treatment, i.e. teamwork among health care providers, may be sufficient, meeting the needs of the population as a whole may require an intersectoral approach, involving a wider group of professional and non-professional participants.

A prerequisite for the development of diabetes prevention and control programmes is an epidemiological assessment of the current situation to determine the frequency of the major forms of diabetes, their morbidity and mortality, and associated costs. These aspects will be addressed later in this report.

There is every reason to suppose that diabetes will remain a threat to public health in the year 2000 and beyond. Demographic and epidemiological evidence suggests that, in the absence of effective intervention, diabetes will continue to increase in frequency worldwide. Thus, prevention of diabetes and its consequences is not only a major challenge for the future, but essential if health for all is to be an attainable target.

## 1.2 The nature of the problem

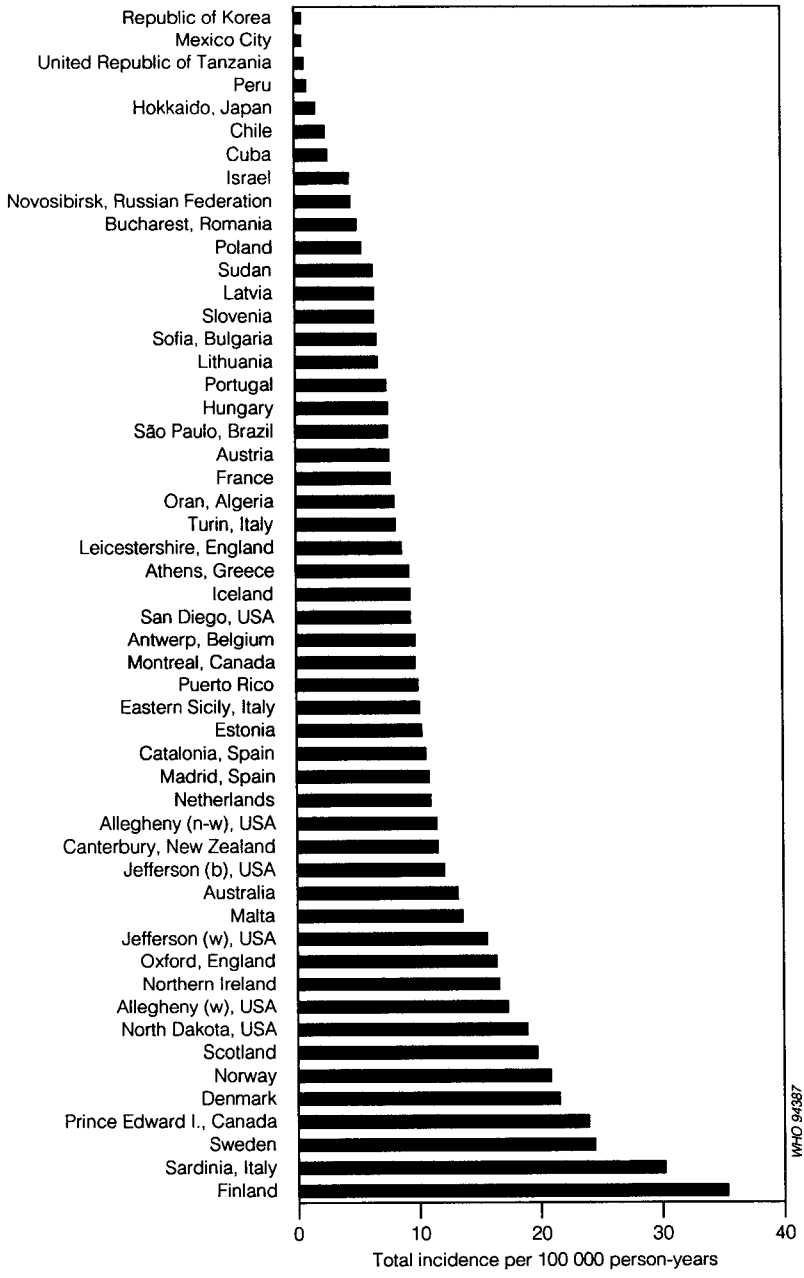
Diabetes mellitus can be found in almost all populations throughout the world, but the incidence and prevalence of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) and the relative distribution of these two major types of diabetes show major differences between countries and between different ethnic groups within individual countries (*12-14*).

Population-based studies of the incidence of IDDM in children using comparable methods of assessment are summarized in Fig. 1. There is a 20- to 60-fold difference between the countries with the highest incidence rates and those with the lowest. Recent studies have not only identified new high-risk areas for IDDM, but have also suggested an increasing incidence of IDDM, particularly in Europe but also elsewhere (*16, 17*). The incidence is highest in populations of Caucasian origin. In many populations, the incidence of IDDM has increased markedly during recent decades and an epidemic-like, temporal fluctuation in incidence has been reported from several countries (*17*). By 1992, the estimated number of IDDM patients throughout the world was 6 million.

The prevalence of NIDDM, estimated from population-based studies using the 1985 WHO Study Group's standard classification of and criteria

Figure 1

**Incidence of IDDM in children aged under 15 years[a]**




[a] Data for boys and girls have been pooled. For Allegheny and Jefferson, USA: b = black; n-w = non-white; and w = white population. Reproduced, with permission, from reference *15*.

for NIDDM (see section 2), is shown in Fig. 2. There are major differences in the age-adjusted prevalence of NIDDM between the populations shown. It is obvious that the lifestyle changes that have occurred in newly industrialized and developing countries have been followed by dramatic increases in the incidence and prevalence of NIDDM (*19*). Furthermore, many populations not of Caucasian origin are apparently more susceptible to developing NIDDM, given modernization or westernization of their lifestyle, and prevalence has reached very high levels in a number of these communities.

It is likely, therefore, that the number of individuals with NIDDM in the world will increase substantially and may exceed 100 million by the year 2000. The major part of this increase will probably occur in the developing countries.

### 1.2.1 *Consequences for the individual*

Development of diabetes mellitus is associated with increased mortality and a high risk of developing vascular, renal, retinal and neuropathic complications leading to premature disability and death (*2, 3, 10*).

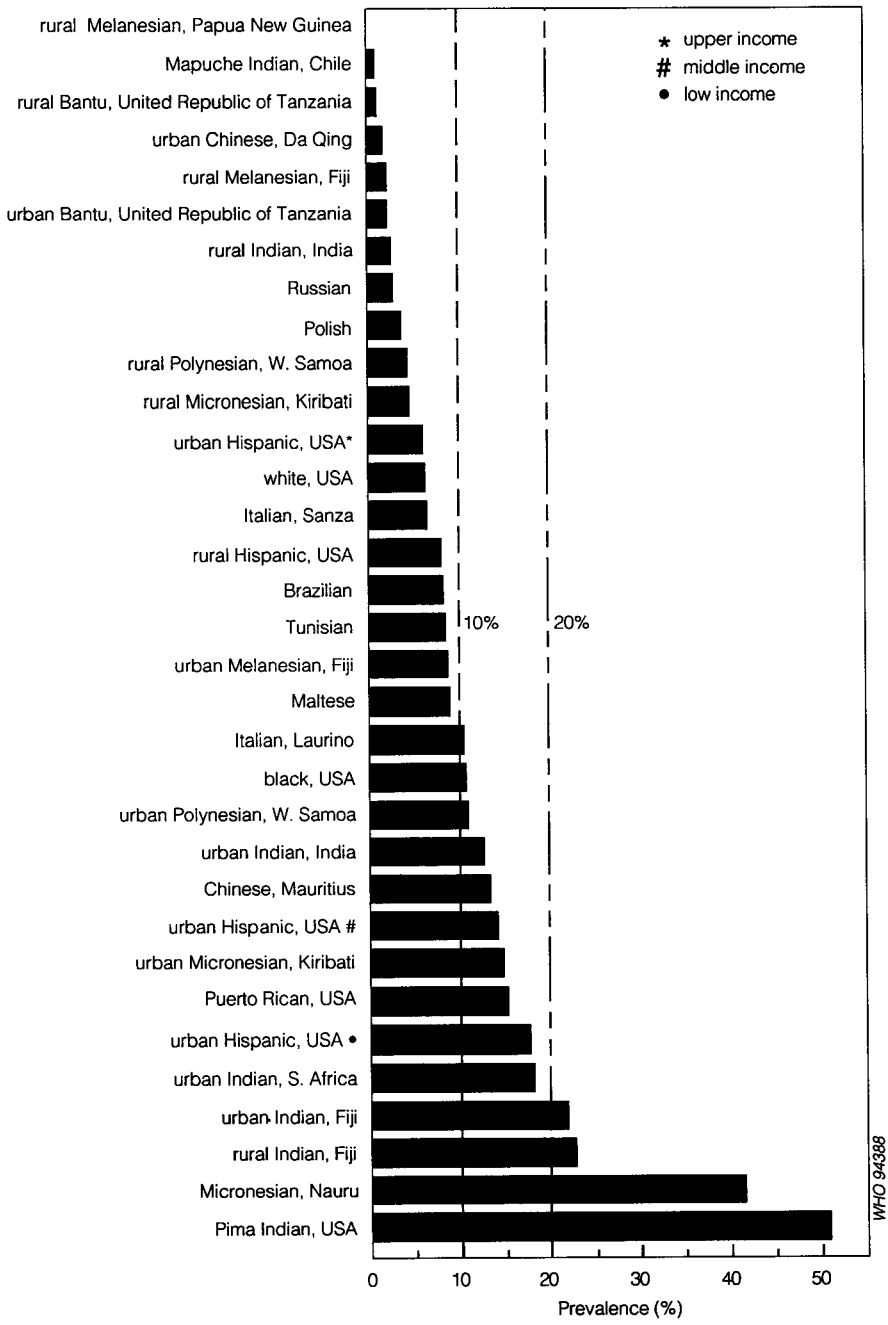
In some developing countries, mortality from acute complications appears to be unacceptably high, owing to a lack of the basic requirements for treatment (e.g. insulin) (*2, 3*). Similarly, inadequate facilities for secondary and tertiary prevention in both NIDDM and IDDM patients will result in the development of early complications, which will progress to early functional impairment and disability in a moderate proportion of patients. In developed countries, life expectancy has increased at a much faster rate in IDDM patients than in the non-diabetic population. Mortality in young-onset IDDM patients, however, varies considerably between countries (*20*), which suggests that premature mortality among the young with diabetes is largely preventable. The majority of children with IDDM in developing countries die within 5 years of diagnosis, whereas in industrialized countries, the median life expectancy of an IDDM patient today is approximately 70–80% of that in the general population (*20*).

The incidence of renal and retinal complications has been reduced by 25–50% in the past three decades (*21*), and this, in combination with early detection and effective treatment of complications, has substantially reduced the risk of disability in IDDM patients. In NIDDM patients, early detection and prompt treatment of renal and retinal microvascular complications and prevention and treatment of foot problems have also improved prognosis by reducing the risk of disability.

Although diabetes implies a relatively poor prognosis for the individual developing the disease, there is a distinct prospect of significant improvement in prognosis with the implementation of effective existing preventive strategies and the development of new strategies at the primary, secondary and tertiary levels.

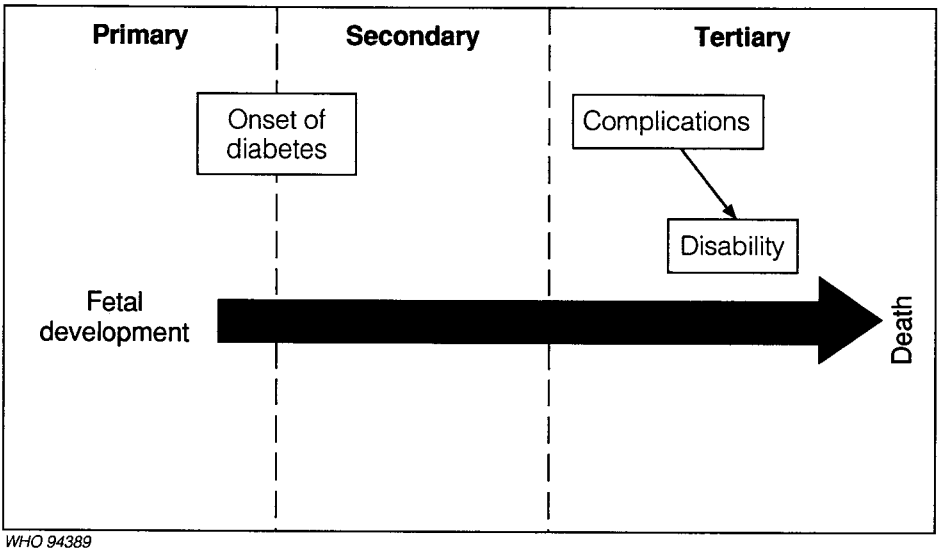
Figure 2

**Prevalence of NIDDM in the age range 30–64 years in selected populations (age-standardized, sexes conbined)** [a]




[a] Reproduced from reference *18*.

Figure 3
**The windows of opportunity in the prevention of diabetes mellitus and its consequences**

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### 1.2.2 *Impact on society*

Prevention and screening programmes for diabetes may be seen as a heavy economic burden on society, which may be an obstacle to their implementation. However, the costs of the treatment of diabetes mellitus and its consequences are so high that prevention would be beneficial in economic terms quite apart from the benefits to the health of individuals and society. In the United States of America, where the prevalence of diabetes mellitus is approximately 7% in adults, it has been estimated that the combined direct and indirect costs of diabetes in 1987 were US$ 20.4 billion (*22*). Tertiary prevention (i.e. prevention of the consequences of diabetes) by screening and early intervention is particularly likely to be cost-effective in the light of the enormous costs of caring for patients with complications (*23*). These issues are discussed further in section 7.1.

## 1.3 Types of prevention

Opportunities for prevention exist at three different levels, as defined below and shown in Fig. 3.

*Primary prevention* covers activities aimed at preventing diabetes from occurring in susceptible individuals or populations through modification of environmental and behavioural risk factors/determinants, or specific intervention for susceptible individuals. In practice this includes any activity undertaken prior to development of clinically evident diabetes

mellitus, i.e. the fulfilling of the diagnostic criteria recommended by the 1985 WHO Study Group (see section 2.3), with the specific aim of preventing such development. There are two types of primary prevention:

- Activities targeted at reducing the frequency or level of the causal risk factors for development of diabetes in whole populations or groups of individuals, particularly those at high risk (the population approach).
- Activities targeted at preventing specific individuals who are already manifesting early markers of the disease process from developing the full clinical expression of diabetes (the high risk approach). These could include intervention strategies (pharmacological or non-pharmacological) in individuals with abnormal glucose tolerance or other metabolic abnormalities or immunological or other markers of beta-cell destruction.

These approaches are discussed further in section 1.4.

*Secondary prevention* covers activities such as screening, which aim at early detection of diabetes and prompt and effective management of the condition with the purpose of reversing the condition and/or halting its progression. In practice this includes any strategy aimed at the detection of as yet undiagnosed cases of diabetes. Again activities can be targeted at populations or high-risk groups or at high-risk individuals.

*Tertiary prevention* is any measure undertaken to prevent complications and disability due to diabetes, i.e. to prevent or delay the negative health consequences of diabetes among individuals who have already developed the disease. In practice this means early detection, effective management, education and metabolic control, as well as the correction or reduction of major risk factors for specific disorders among people with diabetes. Tertiary prevention has three successive stages:

- prevention of development of complications;
- prevention of progression of a complication to clinically manifest organ or tissue disease;
- prevention of disability due to organ or tissue failure.

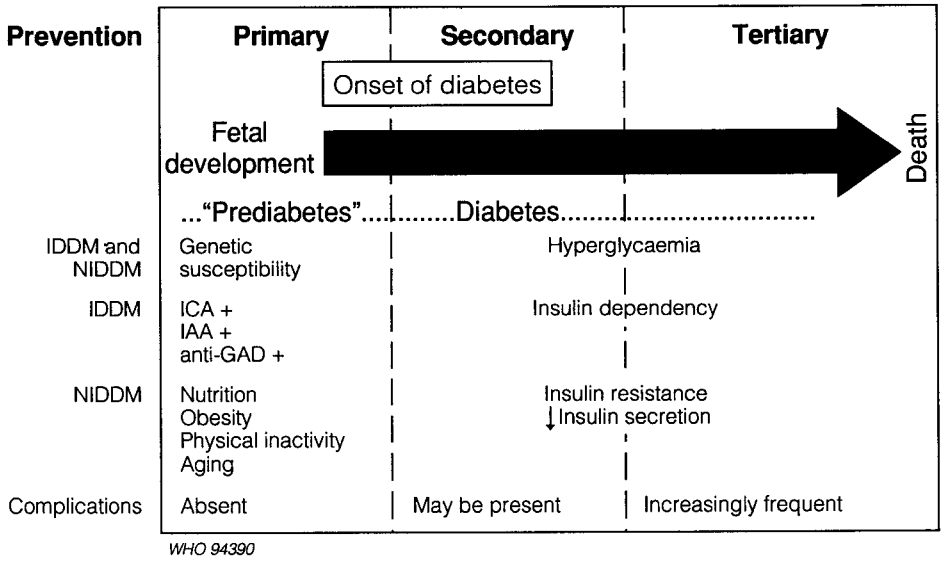
Information on how to undertake each of these levels of prevention is provided in sections 3-6. The natural history of the two major forms of diabetes and the complications of the disease and their relevance to prevention are shown in Fig. 4.

## 1.4 Prevention strategies and principles

As for other noncommunicable diseases, there are two major strategies for the primary prevention of diabetes (*24*):

- *The population approach.* Activities are aimed at modifying the levels of causal risk factors in populations or groups of individuals as a whole, without regard to the specific level of risk of the individual. Previously

Figure 4
**The natural history of diabetes mellitus**[a]




[a] ICA, islet-cell cytoplasmic antibodies; IAA, insulin autoantibodies; anti-GAD, antibodies to glutamate decarboxylase.

this has included various environmental control methods; more recent approaches involve attempts to alter some of the behavioural patterns in society.

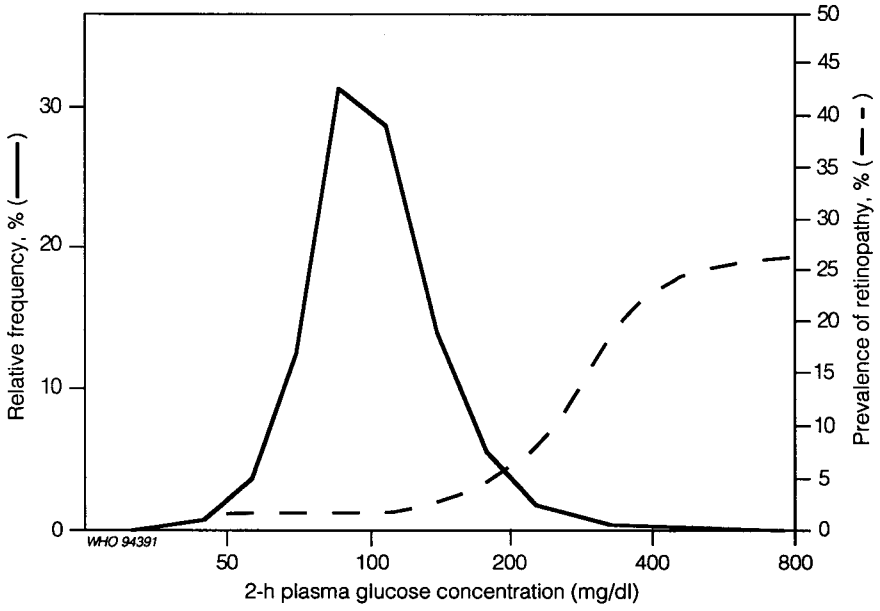
An important prerequisite for this approach is that the risk of morbid events is unacceptably high or that it rises with the level of the underlying risk factor over a large part of the curve of risk factor distribution. Such a relationship has been demonstrated between the risk factors hypertension and elevated blood cholesterol and the risk of developing coronary heart disease (*25*). However, for elevated blood glucose, the risk of developing diabetes appears to rise only towards the upper end of the distribution of this risk factor, i.e. the rate of complications is very low below the "cut-off" point that is considered to be diagnostic of diabetes mellitus (Fig. 5). In this situation the population approach may not be cost-effective, and alternative strategies should be sought.

- *The high-risk approach.* Intervention is targeted selectively at individuals who are identified as being at elevated risk of the disease and hence receive special attention, education and advice.

Population and high-risk strategies are generally complementary (*28*). Moreover, there are strong ethical grounds for both approaches: it is

Figure 5

**Relationship of diabetic retinopathy to plasma glucose concentration**[a]




[a] For plasma glucose concentration, the relative frequency is based upon the number of people in each decile of the plasma glucose distribution in the general population of the USA (venous plasma glucose 2 hours after a 75-g glucose challenge); the prevalence of retinopathy is shown for Pima Indians. Data from references *26* & *27*.

unreasonable to ignore those in a society who are especially prone to adverse health outcomes and it is also incumbent upon public health authorities to give the community reasoned advice about maximizing health for all.

While the population approach may be appropriate in societies with particularly high genetic susceptibility for the disease (in which case the two strategies are effectively the same), the high-risk strategy may have advantages in communities of low to moderate genetic risk in which the majority of the population will not develop the disease, and also in those communities where diabetes is the most common non-communicable disease. The high-risk strategy must also be entertained when there is still uncertainty as to whether the relationship between risk factors and disease is truly causal. Yet another consideration is the profile of risk within the community. If risk factors are spread broadly throughout the community, the population approach is the more logical. However, if risk factors tend to cluster in certain individuals, families or subsets of the community, the high-risk strategy may be the more cost-effective. The relative importance of the two strategies can be determined only on the basis of an understanding of the distribution of both diabetes and its determinants in the target population.

# 2. Definition, classification and diagnostic criteria

Diabetes mellitus represents a heterogeneous group of disorders. Some can be characterized in terms of specific etiology and/or pathogenesis, but in many cases these processes are not yet fully understood (*29*).

This report adheres to the definition, classification and diagnostic criteria proposed by the 1985 WHO Study Group on Diabetes Mellitus (*3*).

## 2.1 Definition

Diabetes mellitus is characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism that are associated with absolute or relative deficiencies in insulin action and/or insulin secretion. Therefore, although diabetes is an endocrine disease in origin, its major manifestations are those of a metabolic disease. The characteristic symptoms are excessive thirst, polyuria, pruritus, and otherwise unexplained weight loss. Diabetes may also become manifest through the presence of one or more of its many related complications. Diabetes mellitus, particularly NIDDM, may be asymptomatic, in which case the diagnosis is often made as a result of an abnormal routine blood or urine glucose test.

The potential for subsequent development of diabetes mellitus may be recognized before abnormalities of glucose tolerance become apparent (Fig. 4, page 9). For example, immunological disturbances, such as the presence of islet-cell and other autoantibodies, may antedate the appearance of IDDM by months or even years (*30–33*). New knowledge of the genetic aspects of diabetes may offer possibilities for identifying susceptible individuals more accurately at any time in life (*34–36*).

## 2.2 Classification

Although the etiology and pathogenesis of the common types of diabetes are now better understood, the extent to which heterogeneity occurs among these types remains uncertain. The widely accepted classification of diabetes mellitus (Table 1), recommended by the 1985 WHO Study Group, was based primarily on clinical descriptive criteria, and its retention is recommended for the present. It seems likely that, as a result of increasing knowledge of the causes of diabetes, further refinement or revision of the classification will soon be possible.

The classification includes a number of clinical classes and two increased-risk categories (designated statistical risk classes). The latter permit the classification of individuals who have previously had an abnormality of glucose tolerance and who have now reverted to normal ("previous abnormality of glucose tolerance") as well as those who can be designated as having increased likelihood of developing an abnormality of glucose tolerance in the future ("potential abnormality of glucose tolerance").

Table 1
**Classification of diabetes mellitus and allied categories of glucose intolerance (*3*)**

A. *Clinical classes*

Diabetes mellitus
Insulin-dependent diabetes mellitus

Non-insulin-dependent diabetes mellitus

(a) Non-obese
(b) Obese

Malnutrition-related diabetes mellitus

Other types of diabetes associated with certain conditions and syndromes:
(1) pancreatic disease; (2) disease of hormonal etiology; (3) drug-induced or chemical-induced conditions; (4) abnormalities of insulin or its receptors; (5) certain genetic syndromes; (6) miscellaneous.

Impaired glucose tolerance

(a) Non-obese
(b) Obese
(c) Associated with certain conditions and syndromes

Gestational diabetes mellitus

B. *Statistical risk classes* (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)

Previous abnormality of glucose tolerance

Potential abnormality of glucose tolerance

The classification of the three major clinical forms, IDDM, NIDDM, and malnutrition-related diabetes mellitus, is based on fundamental differences in etiology, natural history and clinical picture and on the vital clinical and therapeutic distinction as to whether or not the person requires insulin to prevent death.

The category of impaired glucose tolerance (IGT) includes those whose glucose tolerance test is beyond the boundaries of normality as defined by the 1985 WHO Study Group (*3*). As a group, such people have a higher likelihood of progression, and many ultimately develop and meet the criteria for diabetes mellitus.

Gestational diabetes mellitus (GDM) is defined as diabetes first recognized during pregnancy. The degree and severity of hyperglycaemia in this form of diabetes vary considerably. Following parturition some women with glucose intolerance first recognized in pregnancy (gestational IGT, GIGT) will revert to normal glucose tolerance, whereas others may continue with IGT or diabetes, which can then be classified more specifically as IDDM or NIDDM.

### 2.2.1 *Insulin-dependent diabetes mellitus*

IDDM is characterized by absolute insulin deficiency, abrupt onset of severe symptoms, proneness to ketosis and dependence on exogenous insulin to sustain life. The age at clinical onset or diagnosis is usually below 30 years, although the disorder may occur at any age. It is the commonest form of diabetes among children and young adults in populations of European origin (see Fig. 1, page 4).

The diagnosis of IDDM is usually made on the basis of symptoms and an elevated blood glucose concentration. An oral glucose tolerance test (OGTT) is seldom, if ever, required (*2, 3, 29*).

*Diagnosis and terminology*

IDDM includes diabetes that was formerly known as juvenile-onset diabetes, ketosis-prone diabetes, and more recently Type 1 diabetes (*3, 29*). The term "Type 1", however, has also been used to signify a particular disease process (see section 3). Therefore, the use of this term as synonymous with IDDM is no longer recommended.

Most patients with IDDM present with one or more of the classical symptoms mentioned in section 2.1. Glucose concentrations are unequivocally elevated in fasting blood ($\geq$120 mg/dl or $\geq$ 6.7 mmol/l) or plasma ($\geq$140 mg/dl or $\geq$7.8 mmol/l), and glucose and ketones are usually present in the urine. Patients with IDDM can present with diabetic ketoacidosis, a serious and potentially fatal condition.

*Insulin treatment versus insulin dependence*

After initial treatment with insulin, some patients experience a temporary fall in insulin requirements, known as the "honeymoon period". During this interval, which sometimes extends to several months, exogenous insulin may not be necessary to prevent ketosis, but insulin dependency inevitably returns. People with diabetes, especially those with a clinical onset of diabetes before the age of 30 years, often receive insulin treatment on the basis of an elevated blood glucose concentration or symptoms related to hyperglycaemia, without documented evidence of proneness to ketosis. Patients with NIDDM are often treated with insulin to control hyperglycaemia, but do not spontaneously develop ketoacidosis if insulin is withdrawn. It may, therefore, be difficult in retrospect to determine which form of diabetes such patients have. An indication of the extent of the insulin deficiency can be obtained by measuring the serum C-peptide concentration (*37*), either in the fasting state or after a stimulus, e.g. food or glucagon.

*Etiology*

IDDM is primarily the result of pancreatic beta-cell destruction. The possible mechanisms for this are discussed in detail in section 3.2.

### 2.2.2 *Non-insulin-dependent diabetes mellitus*

NIDDM constitutes about 85% of all cases of diabetes in developed countries (*38*), and the majority of cases in some developing countries, especially those with a high prevalence of diabetes (*39*).

NIDDM tends to be familial, and exceptionally high prevalence rates (up to 35% of all adults) have been documented in populations who have changed from a traditional to a modern lifestyle, e.g. certain groups of Indigenous Americans, Pacific islanders, Australian Aborigines and migrant Asian Indians (*13, 19, 40*) (see Fig. 2, page 6). The diagnosis is usually made after the age of 40 years in those of European origin. However, NIDDM is seen at a younger age in high-prevalence populations such as those mentioned above.

Diabetic ketoacidosis does not develop spontaneously in such patients, but occasionally coma may result from extreme hyperglycaemia and hyperosmolarity. However, it is possible for acidosis and ketosis to occur in patients with NIDDM in the presence of severe infections, other major debilitating illnesses or starvation.

*Diagnosis and terminology*

NIDDM is often asymptomatic for many years, and patients may present as a result of complications of diabetes or incidentally with an abnormal blood or urine glucose test. The most simple initial confirmatory test is a fasting blood glucose determination. If the fasting blood glucose concentration is elevated to the levels accepted as diagnostic of diabetes (see Table 2, page 17), the diagnosis is established. If the fasting blood glucose concentration is below the diagnostic level, an OGTT is needed to confirm or exclude the diagnosis of NIDDM or to classify the patient as having IGT.

NIDDM can present at any age, although it does so most commonly in adults. NIDDM is often – but not necessarily – associated with obesity, which may exacerbate insulin resistance and precipitate hyperglycaemia (*19, 40, 41*). In some developing countries a majority of those with diabetes may not be obese if simply assessed by weight for height.

*Etiology*

The genetic component for the risk of NIDDM is very strong (*19, 40, 42*). However, the identification of genes related to the susceptibility to NIDDM has been slow.

Many patients with NIDDM and IGT exhibit insulin resistance and hyperinsulinaemia in association with dyslipoproteinaemia, central obesity, hyperuricaemia and hypertension (*19*). This cluster of cardiovascular risk factors has been described by a number of names, such as "syndrome X" (*43*), the chronic metabolic syndrome and the insulin resistance syndrome (*19*). The prevalence and pattern of this cluster vary among different ethnic groups, and the extent to which this constellation represents a single disease process is still uncertain (*44*).

Certain forms of NIDDM in adolescence and in young adults show a dominant type of inheritance. The term maturity-onset diabetes of the young has been widely used to describe this form of NIDDM (*29*), but the condition is also heterogeneous, and use of the term should be restricted to families where there is a strong autosomal dominant inheritance pattern (*45*). Recently, mutations of the adenosine deaminase gene (*36*) and glucokinase gene (chromosome 7p) (*35*) have been demonstrated in some, but not all, families who have this form of diabetes.

Pancreatic beta-cell destruction of the type that is well recognized as a major cause of IDDM can also result in NIDDM if loss of the beta-cell mass is incomplete (*46*).

### 2.2.3 *Malnutrition-related diabetes mellitus*

In developing countries in the tropics, young people with diabetes may present with a constellation of clinical features including onset usually below 30 years of age, a body mass index of $<20$, moderate to severe hyperglycaemia, non-proneness to ketosis in the absence of precipitating situations such as infections, the requirement for a large dose of insulin for metabolic control, and, frequently, a history of malnutrition in infancy and early childhood (*47, 48*).

The term "malnutrition-related diabetes mellitus" has been assigned to this syndrome (*3*). Although the main descriptive symptomatology is similar, there may be considerable variations in different geographical regions. The syndrome has been further subclassified into fibrocalculous pancreatic diabetes and protein-deficient pancreatic diabetes. While the former is characterized by stone formation in the main pancreatic duct and its branches, together with extensive fibrosis affecting both exocrine and endocrine pancreas, the protein-deficient subtype is distinguished by: (a) absence of radiographic or other evidence of intraductal pancreatic calcification or dilation of the ducts; (b) absence of a history of recurrent bouts of abdominal pain; and (c) absence of demonstrable malabsorption of nutrients caused by exocrine insufficiency.

### 2.2.4 *Impaired glucose tolerance*

IGT may represent a stage in the natural history of diabetes, because those with IGT are at higher risk of developing diabetes than the general population (*3, 29, 49*). When retested 5–10 years after the diagnosis of IGT, about one-third have developed diabetes. However, a similar proportion return apparently spontaneously to normal glucose tolerance and the rest remain in the IGT class (*46*).

IGT may have a wide variety of causes, including certain medications and many of the specific genetic syndromes and other conditions that are also associated with NIDDM (*29, 46*). IGT is more frequent in obese than non-obese people, and is often, but not always, associated with hyperinsulinaemia and insulin resistance (*19*). Whenever possible this relationship

should be defined, as appropriate management may prevent progression to diabetes. In many subjects, however, IGT represents a transient stage during the development of NIDDM (*49*). IGT cannot be defined on the basis of fasting glucose concentrations and an OGTT is needed (*3*).

Several longitudinal epidemiological studies have provided the scientific basis for defining the condition IGT (*46*). Individuals with IGT are not diabetic, and clinically significant microangiopathic renal and retinal complications characteristic of diabetes are very rare. Studies of groups of individuals with IGT have, however, shown an increased prevalence of atherosclerotic disease (*3, 46*) and association with other known cardiovascular disease risk factors including hypertension, dyslipidaemia and central obesity (*43, 44*). Thus IGT, particularly in otherwise healthy and ambulatory individuals, may have important prognostic implications.

### 2.2.5 *Gestational diabetes mellitus*

GDM is restricted to pregnant women in whom the onset or recognition of glucose intolerance first occurs during pregnancy (*3*). Women with previously recognized diabetes who become pregnant do not belong to this category. GDM occurs in about 3% of pregnancies in industrialized nations, and clinical recognition is important because offspring are at increased risk of macrosomia, although rates of perinatal mortality and congenital malformations appear to be no greater than in pregnancies in women with normal glucose tolerance (*50*). In the majority of cases, glucose tolerance returns to normal postpartum, but the life-time risk for IGT and NIDDM is substantially increased (*46*).

GDM is most often of the non-insulin-dependent type, but may be insulin-dependent. IGT may also be first detected during pregnancy. The diagnosis of GDM or gestational IGT (GIGT) should alert the attending physician or obstetrician to the high-risk nature of the pregnancy, and to the need postpartum to reassess and classify more definitively the type and severity of glucose intolerance and to anticipate subsequent development of clinical diabetes. The term GIGT has been introduced in this report to clarify and reinforce the recommendation of the 1985 WHO Study Group that IGT during pregnancy should be treated in the same way as GDM (*3*).

### 2.2.6 *High-risk classes*

These categories allow classification of people: (a) who have previously exhibited IGT or diabetes, but who now have normal glucose tolerance ("previously abnormal glucose tolerance"); and (b) who can be recognized as having an increased likelihood of developing diabetes, but who currently have normal glucose tolerance ("potentially abnormal glucose tolerance"). For example, women who manifest diabetes or IGT in pregnancy, and in whom glucose tolerance is normal after delivery, fall into the former category. The type of previous abnormality should be specified, because of the likelihood that remission may occur. The

category "potentially abnormal glucose tolerance" defines people who, although they have not yet developed disease, are at high risk of diabetes or IGT. Such individuals include those who have a high titre of islet-cell cytoplasmic antibodies, insulin autoantibodies or antibodies to glutamate decarboxylase (*30*) and those who are siblings of IDDM patients identical in respect of specific histocompatibility antigens (human leukocyte antigen, HLA), siblings of NIDDM patients or monozygotic twins of diabetic individuals. The associated features should be specified to enhance diagnostic specificity in the future. Although previously not widely used, these classes are useful for research purposes and for the identification of "high-risk" subjects for primary prevention programmes.

## 2.3 Diagnostic criteria

Diagnostic criteria are shown in Table 2. The diagnosis of diabetes carries consequences that are considerable and lifelong. If the patient has classical symptoms or drowsiness or coma, and marked glycosuria and/or ketonuria, the diagnosis can be readily established by demonstrating fasting hyperglycaemia. If the fasting blood glucose concentration is in the diagnostic range shown in Table 2, an OGTT is not required. In such instances, however, a confirmatory test should be performed as incomplete fasting may give rise to a spurious diagnosis. Clinical diagnosis should never be based on the presence of glycosuria alone. If the patient is asymptomatic or has only minimal symptoms and the fasting blood or

Table 2
**Diagnostic values for the oral glucose tolerance test**

| | Glucose concentration, mmol/litre (mg/dl) | | | |
|---|---|---|---|---|
| | Whole blood | | Plasma | |
| | Venous | Capillary | Venous | Capillary |
| Diabetes mellitus | | | | |
| Fasting value | ≥ 6.7 (≥ 120) | ≥ 6.7 (≥ 120) | ≥ 7.8 (≥ 140) | ≥ 7.8 (≥ 140) |
| 2 hours after glucose load[a] | ≥ 10.0 (≥ 180) | ≥ 11.1 (≥ 200) | ≥ 11.1 (≥ 200) | ≥ 12.2 (≥ 220) |
| Impaired glucose tolerance | | | | |
| Fasting value | < 6.7 (< 120) | < 6.7 (< 120) | < 7.8 (< 140) | < 7.8 (< 140) |
| 2 hours after glucose load[a] | 6.7–10.0 (120–180) | 7.8–11.1 (140–200) | 7.8–11.1 (140–200) | 8.9–12.2 (160–220) |

[a] For epidemiological or population screening purposes, the 2-hour value determined by a specific enzymic assay after an oral glucose load (75 g in 250–300 ml of water for adults and 1.75 g/kg of body weight, up to a maximum of 75 g, for children) may be used alone or with the fasting value. The fasting value alone is considered less reliable since true fasting cannot be assured and spurious diagnosis of diabetes may more readily occur.

plasma glucose concentrations are not unequivocally in the diagnostic range shown in Table 2, an OGTT should be performed. Details of the performance of the OGTT are given in Annex 1.

The results of the OGTT should be interpreted according to Table 2. It is important to note that the diagnostic levels differ to some extent according to whether capillary or venous blood is collected and whether glucose is assayed in plasma or whole blood. For research purposes, glucose tolerance can be considered normal if the 2-hour post-load glucose levels lie below those used to define the lower boundary of IGT. People who fall into the classes of previously and potentially abnormal glucose tolerance also have glucose tolerance that meets this definition, but should be separately identified if possible. Normal glucose tolerance cannot be established solely on the basis of a fasting blood glucose determination. Normal fasting glucose levels are typically < 5.5 mmol/litre (100 mg/dl) for venous or capillary plasma and < 5.0 mmol/litre (90 mg/dl) in whole blood, but people with fasting levels below these limits may have IGT.

The much higher fasting glucose levels that are given as diagnostic criteria for diabetes are highly specific for the diagnosis of diabetes (*51*). People with fasting glucose levels above those characteristically present in normal individuals but below those diagnostic of diabetes have a high chance of having diabetes or IGT. Such levels are a primary indication for performing an OGTT to confirm or exclude the diagnosis of diabetes or IGT.

The diagnosis of GDM and GIGT should be based on the same 75-g OGTT and criteria as those used in non-pregnant subjects (*3*). However, IGT in pregnancy (i.e. GIGT) should be managed in a similar manner to GDM (*3*). The use of the 75-g test in pregnancy has gained wide acceptance in many parts of the world, but not in the United States of America, where continuation of the previous screening and diagnostic methods was again endorsed in 1991 (*52*). This issue is addressed in section 4.5.4.

# 3. Primary prevention of insulin-dependent diabetes mellitus

## 3.1 Overview

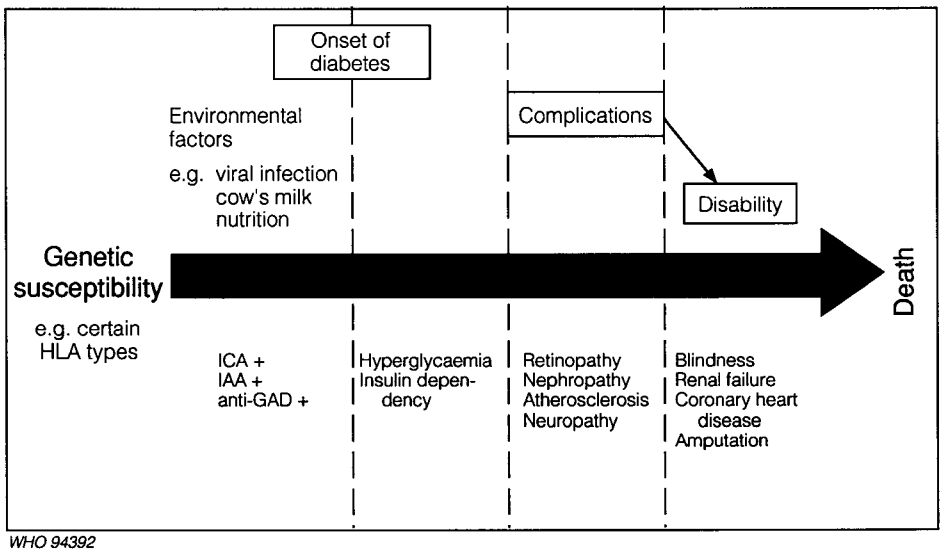
The majority of cases of IDDM develop as a result of the Type I pathogenetic process (*53*). Section 3 deals only with this form of IDDM, which is therefore referred to as Type I diabetes mellitus. Further research is needed to define the pathophysiology of other forms of IDDM before a rationale for their prevention can be developed. Moreover, it should be appreciated that not all individuals with the Type I pathogenetic process develop IDDM. Indeed, many such individuals present in adulthood with mild hyperglycaemia which, at least initially, may not require insulin therapy, and may be treated as NIDDM (*54*).

Type I diabetes mellitus arises in genetically susceptible individuals from pancreatic beta-cell destruction associated with certain immunological features. It is an insidious process which may occur over many years. During the "prediabetic" stage of disease evolution, such individuals can often, but not always, be recognized by the presence of immunological markers and by a decline in pancreatic beta-cell function (*30*) (Fig. 6). This condition is discussed further in section 3.3.

Primary prevention of Type I diabetes can be initiated at the prediabetic stage. However, by the time it is possible to identify individuals at this stage, the Type I pathogenetic process has already started. "True" primary intervention prior to onset of the Type I process may be possible, i.e. before the development of any markers of prediabetes or, on a population basis, where no data on markers are available, for example by altering nutrition in the neonatal period and early infancy. However, the Type I pathogenetic process may be initiated *in utero*, as is the case in individuals with congenital rubella.

There is now a reasonable rationale for conducting carefully designed primary (and true primary) prevention studies designed to arrest (or prevent) the Type I diabetes process. There is currently no basis for a broad clinical application of such approaches. However, the widespread recruitment of prediabetic individuals into controlled trials is warranted, particularly in high-risk groups, e.g. first-degree relatives of probands with Type I diabetes.

Figure 6
**The natural history of insulin-dependent diabetes mellitus**[a]

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[a] HLA, human leukocyte antigen; ICA, islet-cell cytoplasmic antibodies; IAA, insulin autoantibodies; anti-GAD, antibodies to glutamate decarboxylase.

As these clinical trials are initiated in the prediabetic stage, there is a need to proceed with caution. Individuals with prediabetes are asymptomatic. Therefore, only preventive modalities that are safe should be evaluated. Intervention trials should be carefully designed and follow accepted guidelines and ethical principles.

These trials, and the efforts needed to screen individuals for entry, are costly; many thousands of relatives must be screened to identify the few who will meet all of the inclusion criteria for a given clinical trial. Yet, if successful, intervention during prediabetes could spare these individuals from a lifelong disease associated with morbid complications and its human and socioeconomic costs. The Study Group therefore considered the conduct of such studies justifiable, and recommended that they should be supported by major national and international agencies.

## 3.2 Pathogenesis

The pathogenesis of Type I diabetes involves a genetic predisposition to the disease, and putative environmental triggers that may activate mechanisms leading to a progressive loss of pancreatic islet beta cells.

### 3.2.1 *Genetic factors*

Evidence for genetic predisposition comes from studies in twins that demonstrate a higher concordance rate for Type I diabetes in monozygotic twins (25-30%) than in dizygotic twins (5-10%) (*55*). In addition, the empirical risk of Type I diabetes is increased in first-degree relatives of probands with the disease. In the United States of America, among whites, the overall risk is 0.2-0.4%. However, in siblings of probands with Type I diabetes, the risk is about 5%, while offspring of diabetic parents have a 2-3% risk if the mother has the disease, and a 5-6% risk if the father has the disease (*55*). Type I diabetes is commonest in populations of Caucasian origin (*12*).

The major genetic predisposition is conferred by genes located on the short arm of chromosome 6, either within or in close proximity to the major histocompatibility complex, i.e. the HLA region (*56*). Investigations are under way to determine whether there are any additional diabetogenic genes on other chromosomes.

The genes in the HLA region that confer risk of Type I diabetes regulate the immune response. These genes, also known as class II alleles of the major histocompatibility complex, include the HLA-DR, -DQ, and -DP loci (*57*). However, no single HLA allele or combination is specific for susceptibility to Type I diabetes. It should also be stressed that only a proportion of genetically susceptible individuals will actually develop Type I diabetes. The readily measured DR3 and DR4 alleles of the HLA-DR locus occur more frequently in those of European origin with Type I diabetes, and there is a disproportionate increase in heterozygote DR3/DR4 (30-40% of subjects with Type I diabetes, compared to only

3% of the general population). About 95% of individuals of European origin with Type I diabetes are DR3, DR4 or DR3/DR4. Predisposition is also related to HLA-DQ alleles, and these associations are consistent across all ethnic groups. Thus, the specific predisposition to Type I diabetes in those of European origin is associated with HLA-DR3, DQw2 (also known as DQB1*0201) and with HLA-DR4, DQw8 (also known as DQB1*0302). Type I diabetes is strongly associated with particular HLA-DQ-encoded heterodimers. The strongest association for Type I diabetes in those of European origin is with DQA1*0501-DQB1*0302. On the other hand, some alleles of the major histocompatibility complex confer protection against the development of Type I diabetes. These include HLA-DR2 and HLA-DQB1*0602. Protective alleles appear to have dominance over susceptibility alleles.

### 3.2.2 *Environmental factors*

There are major ethnic and geographical differences in the prevalence and incidence of IDDM (see Fig.1, page 4). The highest reported rates are in the Nordic countries, with the highest incidence in Finland (35 cases/year per 100 000 of the population in the age group 0–14 years), and the lowest incidence is seen in Asia (0.5–1.3 cases/year per 100 000) (*12*); low rates are generally also reported in Africa and Latin America. The 20- to 60-fold difference is possibly due to variation in both environmental and genetic determinants (*6, 17*). There is also evidence that environmental factors may initiate the pathogenetic sequence in certain genetically predisposed animal models. Evidence for their role in Type I diabetes in human beings is currently less secure. It has been argued that the substantial discordance in identical twins is strong evidence that environmental factors must play a role in Type I diabetes in humans. However, this view has been challenged by invoking the potential for genetic diversity between such "identical" twins.

Another potential environmental influence is the nutrition given during the neonatal period and early infancy. Consumption of cow's milk proteins, particularly early in life, may increase susceptibility to Type I diabetes (*58, 59*). In addition, several chemical toxins have been shown to have the potential for initiating injury to pancreatic beta cells.

Exposure to a variety of viruses may influence the development of Type I diabetes. Fully 20% of children with congenital rubella develop Type I diabetes. Here, the exposure is remote in time from the clinical onset, occurring *in utero*. In addition, a number of human viruses can infect and damage islet beta cells *in vitro*. The potential role of viruses in disease pathogenesis is still unclear and requires further study.

### 3.2.3 *Immunological factors*

Although pancreatic beta-cell destruction has immunological associations, the immunological mechanisms concerned have not yet been clearly defined. The cells and pathways involved in the initial or primary

attack are not yet known. Further, in the subsequent response, there may be several different pathogenetic sequences that lead to beta-cell destruction. Some appear to be antigen-specific, involving T-cell-mediated beta-cell destruction. Others may be non-specific inflammatory responses, e.g. macrophage production of cytokines that induce the release of free oxygen and nitric oxide radicals, to which beta cells may be particularly vulnerable (*60*).

A number of potentially relevant initiating autoantigens have been identified through studies of islet-cell cytoplasmic antibodies, insulin autoantibodies and antibodies to glutamate decarboxylase. Such antigens are often but not always present early in the course of the disease, prior to clinical diagnosis (*31-33, 61*). T-cell reactivity to glutamate decarboxylase has also been found (*62*). A further possibility is a pancreatic beta-cell surface protein p69, to which antibodies can be found at diagnosis of Type I diabetes. Interestingly, these antibodies were initially found to be directed against a sequence of 17 amino acids in bovine serum albumin, which has led to the proposal that exposure to cow's milk proteins may be an environmental trigger initiating the immune attack on beta cells (*63*).

Identification of the antigen(s) responsible for initiation of the immune attack would permit the design of potentially specific therapies, in particular vaccination using the antigens themselves, relevant epitopes of these antigens or competitive peptide analogues that could serve to counter the immune attack. Yet, most of the antibodies detected so far (especially islet-cell cytoplasmic antibodies) seem only to be circulatory markers reflecting beta-cell damage and/or ongoing immune activity.

## 3.3 Prediabetes

First-degree relatives of individuals with IDDM are at increased risk of developing the disease. It is now clear that, in such individuals, islet immunopathology may begin several years prior to the clinical onset of disease. In prospective studies amongst first-degree relatives of individuals with Type I diabetes, antibodies (islet-cell cytoplasmic antibodies, insulin autoantibodies and antibodies to glutamate decarboxylase) have been demonstrated up to 10 years before the clinical onset of diabetes as recognized by the appearance of hyperglycaemia (*61, 64*). Concomitantly, a decrease may be found in early first-phase insulin release during an intravenous glucose tolerance test (*65*).

Identification of prediabetes and screening for it involve identification of genetic, immunological and metabolic markers in asymptomatic individuals. In populations of Caucasian origin, the prevalence of IDDM is about 0.2-0.5% in general, but about 3-6% among first-degree relatives of individuals with the disease. Therefore, as a substitute for population-based screening for genetic markers, it is possible to focus on first-degree relatives as a high-risk group. Yet, even in this enriched population with a 10-fold increased risk, the vast majority (95-97%) will

not develop the disease. Furthermore, 85-90% of individuals developing IDDM do not have a first-degree relative with the disease, and would be missed by any effort directed at such relatives. Nevertheless, screening of high-risk individuals (e.g. first-degree relatives of IDDM patients) should be encouraged, providing that individuals with positive results are referred to centres participating in cooperative intervention studies or other scientific investigations. All patients screened and not entered into a study should be counselled as to their risk of diabetes, and follow-up should be offered.

To identify individuals in any of the stages of prediabetes, massive screening efforts are required. Even then, it must be appreciated that not all individuals so identified will actually progress to clinical disease. Moreover, screening efforts among the general population are not indicated, because of the massive expense and the relatively poor positive predictive value of current approaches (42% versus 88% in first-degree relatives) (*30*). Once genetic markers are defined sufficiently to permit their use in narrowing the scope of screening of the general population, the situation is likely to change.

## 3.4 Prevention strategies

### 3.4.1 *Current approaches*

The following strategies are currently under consideration for studies on the primary prevention of Type I diabetes:

- "true" primary prevention, e.g. deprivation of cow's milk proteins in the neonatal period and early infancy;
- administration of free radical scavengers, e.g. nicotinamide;
- allowing beta-cell rest, e.g. through administration of early insulin therapy;
- encouraging the development of antigen tolerance, e.g. through administration of early insulin therapy or oral antigens;
- immunosuppression or immunomodulation.

Currently, studies are confined to high-risk individuals (e.g. first-degree relatives) (*66*). Depending on the intervention used, it may also be desirable to include as an entry criterion the presence of immunological and/or metabolic markers defining the prediabetic stage. Eventually, there may be studies involving routine screening of the general population (perhaps at birth) for diabetogenic genes, and the inclusion of such individuals in intervention trials. Again, these individuals may be further categorized on the basis of immunological and/or metabolic markers.

### 3.4.2 *Potential obstacles*

Ethical considerations are paramount in the design and implementation of studies on the prevention of IDDM. This is particularly important because asymptomatic individuals are being studied and because, by their very

nature, such trials must include studies of young children unable to provide their own informed consent. Moreover, it must be appreciated that participation in screening studies may arouse anxiety or induce stress in both the subjects and their families. Further, subjects and their families need to understand the nature of such studies, including the requirement for placebo controls.

In intervention trials, it is desirable that an external monitoring group review unmasked data on a regular basis, with the authority to interrupt any trial should either early benefit or unacceptable risk be demonstrated.

#### 3.4.3 *Evaluation*

Since prevention of IDDM is still confined to research studies, it is important that such studies be carefully designed. All such studies must include an appropriate control group (preferably randomly allocated), and a sufficient number of subjects to allow meaningful statistical analysis. There should be careful definition and standardization of methods, procedures, assays, entry criteria and the end-point, which may be prevention of hyperglycaemia (either diabetes or IGT) or preservation of beta-cell function, depending on the study design.

### 3.5 Conclusions

In the future it should become possible to prevent a considerable proportion of potential cases of IDDM. However it will be some years before the results of ongoing intervention trials become available, and newly emerging prevention strategies have still to be tested in large-scale, long-term and well planned clinical trials. General preventive measures should not be implemented without objective evidence of their effectiveness. Success is dependent on continued scientific advances, collaborative efforts among investigators, and the cooperation of individuals around the world who are willing to participate in the necessary clinical trials.

## 4. Primary prevention of non-insulin-dependent diabetes mellitus and related disorders

### 4.1 Overview

People qualifying for a diagnosis of diabetes mellitus (see Table 2, page 17) who are judged clinically not to be in urgent need of insulin to preserve life are classified as non-insulin-dependent. This "classification by exclusion", discussed in more detail in section 2, although satisfactory in operational terms, requires further comment in the light of possible preventive strategies. NIDDM covers a wide spectrum of degrees of glucose intolerance, ranging from the totally asymptomatic to the severely symptomatic. Metabolic status may deteriorate with time or improve with treatment. The subdivision of NIDDM into obese and non-obese forms is

recognized and is included in the 1985 WHO Study Group's classification (*3*) (see Table 1, page 12). Malnutrition-related diabetes mellitus is discussed in section 4.4.

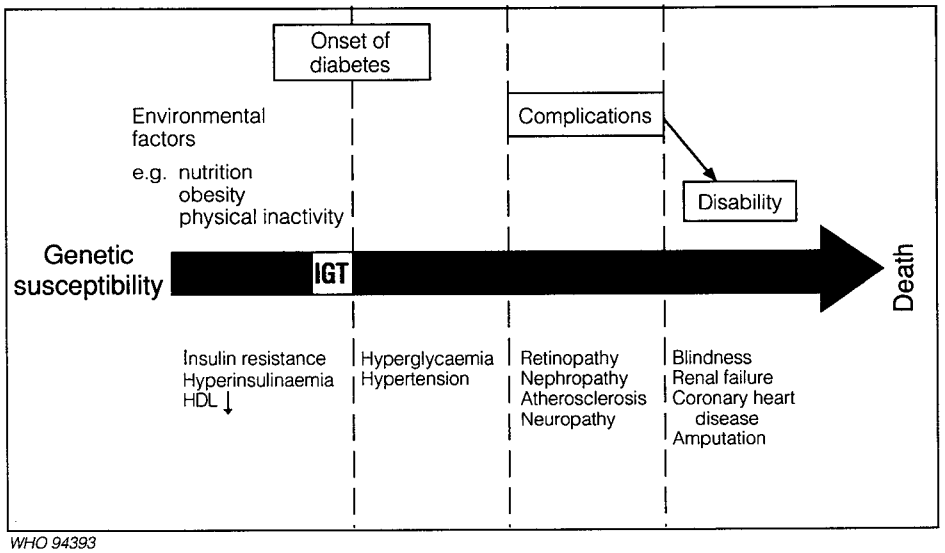
NIDDM and IGT detected only during pregnancy, gestational NIDDM (GDM) and gestational IGT (GIGT) tend to recur with subsequent pregnancies; GDM carries a very high risk of the ultimate development of permanent NIDDM (see section 4.5).

The OGTT is likely to be the major tool for assessing the efficacy of measures to prevent NIDDM and IGT. Consideration must be given to its high degree of variability in the planning of intervention studies, and it may be necessary to repeat the test before firm conclusions can be drawn about individual responses to preventive measures.

## 4.2 Pathogenesis of non-insulin-dependent diabetes mellitus and impaired glucose tolerance

Although the pathogenesis of the different forms of NIDDM is not fully understood, there are at least three factors of importance: (1) individual or ethnic genetic factors leading to susceptibility; (2) defects in pancreatic beta-cell function; and (3) decreased action of insulin in insulin-sensitive tissues (insulin resistance), including skeletal muscle, liver and adipose tissue (*19, 67*). The natural history of NIDDM is depicted in Fig. 7.

Figure 7
**The natural history of non-insulin-dependent diabetes mellitus**[a]




*WHO 94393*

[a] HDL, high-density lipoprotein; IGT, impaired glucose tolerance.

Several suggestions have been made regarding the cellular mechanisms responsible for increased insulin resistance, including decreased activation of enzymes (e.g. glucokinase and glycogen synthase), reduced levels of cell-membrane glucose transporters and increased levels of circulating fatty acids (*43, 67, 68*). Insulin resistance is accentuated in those with generalized and/or central obesity and in the physically inactive, and it is probably of importance in the genesis of IGT (*11, 68*).

Insulin resistance and the associated hyperinsulinaemia in IGT and NIDDM are closely associated with various constellations of putative cardiovascular risk factors including arterial hypertension, dyslipoproteinaemia (raised triglycerides and low high-density lipoprotein (HDL) cholesterol), generalized and central obesity, and physical inactivity (*19, 43*) as well as hyperuricaemia, microalbuminuria and raised plasminogen-activator inhibitor 1 and fibrinogen. A pathogenic role for insulin resistance/hyperinsulinaemia remains to be proved (*19*).

A proportion (5-15%) of middle-aged and elderly people with NIDDM (in particular those who are not obese) show genetic and immune markers similar to these seen in the Type 1 diabetes process, but may go for many years without becoming insulin-dependent (*46*). These subjects require further study to determine whether some of them should be reclassified in a new category – latent autoimmune diabetes in adults (*54*).

IGT is a heterogeneous state, including several groups of individuals: those at the upper end of the normal glucose tolerance distribution, those at the lower end of the NIDDM distribution, those in transition from normal to NIDDM and those who are stable in the IGT category (*49*). It shares putative etiological factors with NIDDM (see Fig. 7), the main distinction being better preserved insulin secretion.

Prevalence increases with age, and may reach high levels, particularly in populations undergoing epidemiological transition – a high IGT prevalence may be a prelude to "epidemic" levels of NIDDM in these communities (*69*).

Several studies have shown people with IGT to be at increased risk of developing diabetes (*70-75*), although if their glucose tolerance does not deteriorate, they are not at risk of specific diabetic microvascular complications (*3*). In studies using WHO criteria, such as the studies in Malmöhus County, Sweden (*70*), Nauru (*71*), Malmö, Sweden (*72*), San Antonio, Texas (*74*) and Pima Indians in Arizona (*75*), the incidence of diabetes was 19-61% in 5-10 years. An initial OGTT result diagnostic of IGT was consistently a strong predictor of future diabetes in all studies. Hyperinsulinaemia is also a predictor, but, paradoxically, some people with IGT with a lower insulin response to a glucose load are more likely than those with normal or high insulin levels to progress to diabetes (*19, 76*).

People with IGT are a prime target group for prevention. Limited intervention studies to date have given variable results, although

progression to diabetes was halved in a Swedish study (*72*) and was only 2% in 6 years in Indians living in East Africa (K.G.M.M. Alberti, personal communication 1992) where lifestyle modification was used with the major emphasis on physical activity and diet.

### 4.2.1 *Genetic factors*

NIDDM shows strong familial aggregation. Twin and family studies have provided firm evidence that the role of the genetic component is relatively strong (*41*). NIDDM appears to be the consequence of an interaction between this genetic susceptibility and exposure to environmental factors. In certain populations in which there is evidence of a major genetic component, a "thrifty genotype" has been proposed (*77*). By conferring metabolic efficiency, this offers advantages in times of prolonged food deprivation but becomes disadvantageous when food is plentiful.

Several genes have been suggested as markers for NIDDM but to date, apart from evidence for abnormalities in the adenosine deaminase (*36*) and glucokinase genes (*35*) in some families affected by maturity-onset diabetes of the young, no other consistent abnormalities have yet been found.

### 4.2.2 *Environmental factors*

Several environmental factors have been proposed as being associated with an increased risk of NIDDM. Major putative factors are shown in Fig. 7, page 25.

*Physical activity*

It has been demonstrated that regular physical activity increases insulin sensitivity and improves glucose tolerance (*19*). Several cross-sectional studies have shown 2- to 4-fold differences in NIDDM prevalence between the least active and the most active individuals. This finding seems to hold among a range of ethnic groups including those of European origin, Indigenous Americans, Asian Indians, Chinese, Mauritian Creoles, Polynesians, Micronesians and Melanesians (*19*). Recently, prospective studies have also shown that physical activity is associated with a reduced risk of NIDDM (*73, 78*). These studies have further suggested that there is a gradient in risk with increasing physical activity. Furthermore, physical activity has beneficial effects on blood lipids, blood pressure and body weight/fat distribution, i.e. on multiple aspects of the "chronic metabolic syndrome" (*79*) so that it may also prevent cardiovascular disease.

The association between physical inactivity and the risk of diabetes seems to remain even when adjusted for obesity, hypertension and family history of NIDDM. Thus, exercise appears to have a protective effect against NIDDM, possibly through improved insulin sensitivity, which can be accentuated by weight loss achieved through increased physical activity.

*Body weight and fat distribution*

Obesity has been implicated as a risk factor for NIDDM in cross-sectional and longitudinal studies (*80–82*). Body mass index is positively associated with increased risk of NIDDM in both sexes in many ethnic groups. Centralized distribution of body fat (variously measured and referred to as abdominal, upper body, truncal, or central obesity) has been implicated as a risk factor for NIDDM in those of European origin, Hispanics living in the United States, Indigenous Americans, Asian Indians, Chinese and Mauritian Creoles in both cross-sectional and longitudinal studies (*19, 80–82*). An association between the risk of IGT and abdominal obesity, indicating that fat distribution is important in determining the risk of lesser degrees of glucose intolerance (*80, 82*), has also been demonstrated in cross-sectional and longitudinal studies.

The mechanisms by which abdominal obesity and overall body mass may independently influence the risk of glucose intolerance are poorly understood. Weight loss is notoriously difficult to achieve in obese individuals (*83*), and the extent to which abdominal distribution of body fat is reversible is unclear. However, early evidence indicates that weight loss in individuals with abdominal obesity leads to improvements in the waist-to-hip ratio (*84*), and it has been suggested that the metabolic abnormalities associated with abdominal obesity including blood lipid changes may be improved by physical training (*85*).

*Nutritional factors*

In the early stages of human evolution food supply may often have been precarious. The agricultural revolution brought profound changes in food production and storage. The industrial revolution in developed countries introduced radical changes in methods of food production, processing, storage and distribution (*86*). Recent technological innovations, along with increased material well-being and lifestyles that have allowed the exercise of dietary preferences (amplified by modern marketing techniques), have led to major changes in the nutritional composition of the diet in developed countries. The long-term adverse health effects of the "affluent" diet prevailing in the developed and also in many developing countries, which is characterized by an excess of energy-dense foods rich in fats (particularly saturated fats), refined and simple sugars and a deficiency of complex carbohydrate foods (fibre), have only become apparent over recent decades (*86*).

It would be an over-simplification to propose that any single nutrient is specifically diabetogenic. However, there is evidence from both laboratory and epidemiological studies in various populations to suggest that increased dietary intake of saturated fats and decreased intake of dietary fibre can result in decreased insulin sensitivity and abnormal glucose tolerance (*19*). Individuals differ in their susceptibility to the adverse effects of specific dietary factors. The "affluent" diet is also accompanied by other changes such as arterial hypertension, dyslipidaemia and obesity (*19, 87*).

Although there is general agreement that dietary modification and exercise should serve as the cornerstones in the prevention of diabetes and the treatment of people with the disease, the exact nature of the diet remains controversial. Experimental and epidemiological studies suggest that adoption of the Westernized diet (low carbohydrate, low fibre, high fat) leads to a deterioration in glucose tolerance, and Australian Aborigines with NIDDM, moving back from such a diet to a traditional one, showed a dramatic improvement in glucose tolerance (*88*).

Dietary manipulations such as decreased intake of saturated fats, increased intake of some unsaturated fatty acids, and increased soluble fibre content of the food may also be beneficial. A decrease in daily food energy intake at the expense of fats and carbohydrates, especially starch and refined sugars, has been shown to produce a decrease in fasting plasma insulin concentrations, glycaemia and the atherogenic fractions of circulating lipoproteins. Definitive evidence that such dietary changes can prevent the development of NIDDM is, however, lacking.

Recently it has been suggested that malnutrition during early life may predispose to later metabolic abnormalities and increase the chance of development of IGT and NIDDM (*89, 90*). In recent studies, low-birth-weight babies were found to be more likely to develop diabetes in adulthood than those of higher birth weight (*89*). Maternal malnutrition (or placental inadequacy) may hinder pancreatic beta-cell development in the fetus. If confirmed, these findings may help to explain the greatly increased frequency of diabetes in some populations which move rapidly from nutritional want to adequacy or surfeit, e.g. Jews who have recently migrated from Ethiopia to Israel (*91*).

*Other factors*

- *Severe or prolonged stress.* Several states of physical stress or trauma are associated with glucose intolerance induced by hormonal effects on glucose metabolism and insulin secretion and action. It has not yet been established whether they can lead to permanent diabetes. The role of emotional and social stress as contributory factors in diabetes mellitus remains unproved.

- *Drugs and hormones.* Long lists of drugs that impair glucose metabolism have been compiled (*29*). Among commonly used drugs, phenytoin, diuretics (particularly of the thiazide type), corticosteroids, some contraceptive steroids and β-adrenoceptor-blocking agents may cause glucose intolerance and, in susceptible individuals, may induce diabetes. This usually resolves after withdrawal of the drug.

## 4.3 Strategies for the prevention of non-insulin-dependent diabetes mellitus and impaired glucose tolerance

### 4.3.1 *Current approaches*

There are few published studies that have examined the effect of interventions on the development of NIDDM. Most current advice is therefore based on knowledge gained from epidemiological and pathophysiological studies and experience gained from the prevention of cardiovascular disease (*25*). Intervention strategies to prevent NIDDM are based on efforts to decrease insulin resistance and to promote and sustain pancreatic beta-cell function (e.g. by programmes of obesity reduction and the promotion of physical activity).

These measures are probably most usefully applied to high-risk individuals (*28*) who include:

- those with a strong family history of NIDDM including that with onset during youth;
- those changing from traditional to Westernized lifestyles, from rural to urban societies, or from active to sedentary lifestyles;
- those with a history of GDM, GIGT or large-birth-weight babies; and
- those with other elements of the chronic metabolic syndrome, e.g. hypertension, dyslipoproteinaemia and obesity, particularly central.

The main lifestyle changes that reduce insulin resistance are:

- correction and prevention of obesity;
- avoidance of a high-fat diet (which leads to a reduction in energy consumption and increased insulin sensitivity);
- derivation of a high proportion of the carbohydrate content of the diet from unrefined sources – soluble fibre should be included;
- avoidance of, or cautious use of, diabetogenic drugs; and
- increased physical activity, which has a major beneficial effect on insulin sensitivity independent of its effect on weight.

In addition to directing efforts towards those at high risk, public education with respect to lifestyle modification should be advocated on a wider scale, particularly in societies with a high susceptibility to NIDDM.

### 4.3.2 *Evaluation*

No prevention programme should be commenced without a properly constituted evaluation component. This means making baseline measurements to establish the prevalence in the community of NIDDM and risk factors including IGT and general and central obesity, and to determine levels of physical activity and fitness and of other factors related to insulin resistance such as blood lipids and blood pressure. If possible, fasting plasma insulin concentration and/or insulin sensitivity should also be assessed. All these factors should be reassessed at the predetermined end of the study, e.g. after 5–10 years. Guidelines for undertaking an epidemiological survey are given in Annex 2.

The key outcome indicator will be the prevalence of diabetes in the community, or the number of new cases of diabetes that have occurred in a cohort during the study period, giving an estimate of the incidence of NIDDM. The rate of progression of people with IGT to diabetes and their reversion to normal glucose tolerance, together with the fall in morbidity and mortality of those established as diabetic or as having IGT at baseline, may also be determined in longitudinal follow-up. If interventions are implemented in an attempt to prevent the development of NIDDM, the study design needs to include a reference population.

A major problem is that the OGTT, conventionally used as the main diagnostic test for diabetes, gives highly variable results in any one individual (*3*). This makes it difficult to define outcome parameters accurately, particularly in cohort studies. The guidelines for diagnosis of NIDDM and IGT outlined by the 1985 WHO Study Group (*3*) are as follows: if a subject becomes symptomatic during the intervention period a single abnormal blood glucose measurement or OGTT is diagnostic, but if a subject is asymptomatic, two abnormal OGTTs are needed to confirm the diagnosis of NIDDM or IGT.

When evaluating community intervention programmes, repeated surveys using independent population samples each time are recommended. In such serial cross-sectional surveys, diagnostic classification can be based on one OGTT only, because prevalence estimates are needed for populations, not for individuals.

The interventions themselves also require evaluation. Thus if dietary change in both qualitative and quantitative terms is attempted, both the composition and the amount of food should be measured and anthropometric parameters included. Similarly, if physical activity is the target of the intervention, the type and amount of physical activity need to be assessed; physical fitness should preferably also be assessed. Acceptability and feasibility of the interventions should also be examined, together with their interaction with other aspects of lifestyle and well-being.

The overall size of the community or sample needed depends on whether the impact of the whole intervention package only is to be assessed or individual components are to be examined. In the latter case, a much larger sample is required. To obtain accurate information on subgroups (e.g. according to age, sex, ethnic origin), an even larger sample is needed. The sample size also depends on the expected change in determinants to be covered and the precision with which they can be measured. The number of subjects included determines the "power" of such studies, i.e. the size of an effect which is unlikely to be due to chance that the study can detect. It is important to select the most appropriate size of sample for the method used, particularly in research studies.

## 4.4 Malnutrition-related diabetes mellitus

### 4.4.1 *Pathogenesis*

There is no association between fibrocalculous pancreatic diabetes and gall-bladder disease or, in most cases, excessive alcohol intake, and no indication that the characteristic pancreatic fibrosis is post-inflammatory in nature (*47*). The underlying causative mechanism(s) may relate to the effect of dietary toxins against a background of long-standing malnutrition (*47, 48*), as suggested by the association between the global distribution of fibrocalculous pancreatic diabetes and the consumption of dietary toxins in foods such as cassava root (manioc, tapioca). Further investigation is needed of the possible role of cyanogenic glucosides (e.g. linamarin) in initiating cellular injury and causing this form of diabetes when detoxifying mechanisms are inadequate because of insufficient intake of dietary protein rich in sulfur-containing amino acids. Other food toxins may play a similar role.

In contrast to fibrocalculous pancreatic diabetes, where interaction of malnutrition and dietary toxins constitutes a possible causative mechanism (*47*), severe protein malnutrition during infancy and early childhood may itself affect the development of pancreatic beta-cell function. This has been shown in kwashiorkor, and is further supported by data from experimental animal models (*47*). In industrialized societies, the effects of early malnutrition – even during intrauterine fetal development – can be demonstrated by the relationship between low birth weight, weight at 1 year of age and the later appearance of NIDDM and other disorders (*89*).

### 4.4.2 *Prevention strategies*

Integrated strategies to improve nutritional intake during pregnancy and infancy, especially at the time of weaning, are obviously beneficial in countries where malnutrition-related diabetes mellitus is seen. Similarly, as cyanogenic glucosides in cassava have been implicated in the causation of tropical ataxic neuropathy and endemic goitre as well as fibrocalculous pancreatic diabetes, diminishing levels in food to within safe limits ($< 50$ mg of such glucosides per kg of freshly grated cassava) constitutes an important public health strategy. A large proportion of the cyanogenic glucosides can be eliminated by peeling and washing the tuber, sun-drying tapioca slices, and cooking and frying foods prepared from cassava. Mixing cassava with wheat and groundnut flour has also been advocated. Finally, horticultural research to develop varieties of cassava rich in protein and low in cyanogenic glucosides should be intensified.

## 4.5 Gestational diabetes mellitus and gestational impaired glucose tolerance

GDM can be of metabolic significance for both mother and fetus. For the fetus, it is associated with macrosomia, perinatal risk and the possibility of

developmental abnormality (*50*). In the mother, it carries some increase in obstetric risk, is likely to recur in subsequent pregnancies, and indicates a greatly increased likelihood of diabetes later in life.

There is general agreement that, in pregnancy, the diabetic state as defined by the 1985 WHO Study Group's criteria carries increased risk. However, the degree of risk associated with lesser degrees of glucose intolerance, essentially within the IGT range, remains uncertain (*92*); an apparent relationship with adverse outcome may be due to confounding effects of advanced maternal age, maternal obesity or multiparity, which themselves constitute risks. This uncertainty is reflected in the different diagnostic recommendations for GDM made by WHO expert groups (*2, 3*) and by the United States National Diabetes Data Group (*29*). Previous WHO expert groups have drawn a distinction between the categories of GDM and GIGT in order that they may be separately reviewed as risk indicators, a position reaffirmed in this report. The United States National Diabetes Data Group essentially establishes one category of GDM encompassing both grades of glucose intolerance. The uncertainty will be resolved only by appropriately designed studies that relate pregnancy outcome, maternal metabolic fate, and effects in the offspring to glucose tolerance during pregnancy.

### 4.5.1 *Pathogenesis*

It has been inferred that the glucose intolerance of GDM and GIGT actually starts during pregnancy and is in some way caused by it. However, doubt has been cast upon this by the demonstration of relatively high rates of glucose intolerance in non-pregnant women in the child-bearing years of life (*93*). It will not be possible to resolve this question completely without prospective studies, although the result may have little influence on the management of glucose intolerance in pregnancy. The possibility of coincidental coexistence of glucose intolerance and pregnancy must be considered in relation to pathophysiology.

There is evidence for increased insulin resistance (*94*), including enhanced placental degradation of insulin (*95*), as the dominant mechanism resulting in gestational hyperglycaemia. Impaired insulin secretion, in some due to immune islet beta-cell damage (*96*), may play a part. Placental hormones and "accelerated starvation" (rapid weight loss with lipolysis) in pregnancy may also contribute (*97, 98*).

Fetal macrosomia has been attributed to the stimulatory effects of maternal hyperglycaemia. Resulting fetal hyperinsulinaemia may stimulate growth and adipogenesis *in utero* and cause neonatal hypoglycaemia. Other materno-fetal substrates (metabolic substrates passing from mother to fetus) and growth factors may also be implicated (*98*).

Longer-term effects of exposure to this intrauterine environment may include increased liability to adult obesity and glucose intolerance in the offspring (*99*), which may introduce the potential for prolonged familial

transmission of susceptibility to the diabetic state. Disturbed development of intellectual function has also been suggested (*90*). These possible sequelae underscore the importance of extending teratological studies of GDM into postnatal and adult life.

Animal data suggest that glucose intolerance induced in the mother during pregnancy may be transmitted to her offspring (*100*). In humans, the offspring of IDDM parents are more likely to be diabetic themselves when it is the father who has IDDM rather than the mother (*101*), although the converse may be the case for NIDDM (*102*).

### 4.5.2 *Management*

Blood glucose concentrations should be maintained as close to normal as possible by dietary therapy and insulin injections if necessary. Insulin requirement may rise during the pregnancy. Severe hypoglycaemia should be avoided. Urine tests to assess glycaemic control are unreliable during pregnancy because the renal threshold for glucose reabsorption falls, and blood glucose measurements should be used with care.

Hypertension, hydramnios, pre-eclampsia, toxaemia and urinary tract infection should be sought and treated if present. Fetal monitoring includes periodic measurement of heart rate and ultrasonography to estimate size, detect certain malformations and assess cephalic versus somatic growth. Where resources are limited, pregnant women with diabetes should be given priority access to health care facilities. Gestation should be allowed to proceed to a normal delivery unless macrosomia, fetal distress or other indications for intervention are detected. Caesarean section should be performed solely for obstetric indications. The neonate may require special intensive care so that the risks of hypoglycaemia and other metabolic disturbances can be detected and dealt with early.

### 4.5.3 *Prevention strategies*

For the woman found to have glucose intolerance during pregnancy, the high risk of the later development of diabetes (*103*) offers the important possibility of preventive intervention. It has been claimed that the vigorous treatment of GDM with insulin during pregnancy will reduce the risk for the fetus and of overt diabetes later in life in the mother. This requires confirmation by controlled clinical trials. After pregnancy, dietary intervention to prevent obesity and physical exercise (as for prevention of NIDDM) are rational measures, but should also be the subject of planned clinical trials.

Repeated pregnancy may also increase the risk of diabetes in the mother. To prevent further pregnancies, the widely available oral contraceptives can be used. However, these may adversely affect metabolism or accelerate vascular disease, so that physical methods of contraception may be preferred.

In populations undergoing rapid improvement in nutritional status, the risk of diabetes may be reduced by wide dissemination of the advice to avoid obesity and increase physical activity.

#### 4.5.4 *Recommendations*

The diagnostic criteria for diabetes and IGT recommended by the 1980 WHO Expert Committee on Diabetes Mellitus (*2*), as adapted by the 1985 WHO Study Group on Diabetes Mellitus (*3*), are the same for both pregnant and non-pregnant women. The criteria for diabetes are set at a higher concentration of blood glucose than those of the United States National Diabetes Data Group for GDM (*29*), and this has been misinterpreted as an indication to exclude women with lesser degrees of glucose intolerance, e.g. IGT, from consideration for GDM management protocols. In fact, the two previous WHO expert groups recommended similar care and management for GDM and GIGT (*2, 3*), and the present Study Group endorsed these recommendations. There is a need for global standardization and consensus on diagnostic criteria for these conditions.

Depending on local health priorities, resources and facilities, serious consideration should be given to screening all pregnant women for glucose intolerance at the beginning of the third trimester of pregnancy. An OGTT is recommended for both screening and diagnosis. Results are interpreted according to the criteria for diabetes and IGT presented in Table 2, page 17.

# 5. Secondary prevention

The primary purpose of secondary prevention activities such as screening is to identify individuals without symptoms who either already have a disease or are clearly at high risk of developing it, and where intervention could have a beneficial effect (*104*). The desirable characteristics of such a programme are shown in Annex 3. It is often worth while to combine screening for diabetes with screening for other noncommunicable diseases as recommended in the WHO INTERHEALTH Programme (*9*). A summary of current screening methods is presented in Table 3.

## 5.1 Screening for non-insulin-dependent diabetes mellitus

The question of mass community screening for NIDDM remains controversial. The underlying philosophy has been that detection of diabetes in asymptomatic or minimally symptomatic individuals will result in effective treatment that may retard its progression and reduce the risk or the severity of complications, thus diminishing premature morbidity and mortality. This is brought into focus by the frequent presence of specific complications at the time of clinical diagnosis and the estimate that on average subjects had had NIDDM for 4 to 7 years prior to diagnosis (*105*).

Table 3
**Summary of screening methods for diabetes**

| Diabetes type | Method | Specificity | Sensitivity | Cost |
|---|---|---|---|---|
| NIDDM[a] | Glycated Hb $A_{1c}$ or proteins | + + + | + /− | + + + |
| | Urine glucose | + /− | + /− | + |
| | Casual blood glucose | + + | + | + |
| | Fasting blood glucose | + + + | + | + |
| | Oral glucose tolerance test | + + + | + + | + + |
| IDDM[b] | HLA type | + /− | − | + + + |
| | ICA | + | + | + + + |
| | Anti-GAD | + | + | + + + |
| | Early insulin secretion | + /− | + | + + |

Key: − none; + /− none or minimal; + low; + + intermediate; + + + high.

[a] At present screening can be recommended only for high-risk individuals or for epidemiological studies.

[b] HLA, human leukocyte antigen; ICA, islet-cell cytoplasmic antibodies; anti-GAD, antibodies to glutamate decarboxylase.

Over the years opinions have changed frequently on the value of mass screening. Initially it was widely recommended. However, the diabetes screening workshop held in Atlanta, Georgia, in 1978 (*106*) reversed this trend. The consensus at that time was that screening to detect diabetes should not be encouraged, except during pregnancy, as evidence for benefit did not outweigh the evidence of deleterious effects, and the cost of screening was not justified. This is still the position adopted by many.

Well designed, epidemiologically based screening programmes can, however, provide valuable information about the prevalence of diabetes and IGT and their natural history in different populations. Such data are essential for public health planning and provide information for continued evaluation of the current diagnostic criteria (see Table 2, page 17) regarding the status of abnormal glucose tolerance. Screening programmes may also improve community awareness and pave the way for education about diabetes. There are three different approaches to screening – population, selective and opportunistic – which are described further in section 5.1.1.

A positive result in a screening test indicates only a high probability of the individual having the disease. Confirmatory tests are always necessary in the case of individual diagnosis.

Important considerations in the design of an appropriate screening programme include:

- the sensitivity, specificity and predictive value of the screening test;
- the cost-effectiveness and resource requirements of the screening

methodology and any necessary follow-up in the context of the anticipated positive detection rate;
- the definition of the target population to be screened;
- the provision of adequate and effective follow-up and care for individuals having positive test results.

There are also potential adverse effects of screening:

- psychological stress, socioeconomic disadvantage and additional costs resulting from a false-positive test result;
- false reassurance of a false-negative test result;
- medical complications of the screening test;
- medical complications of the intervention in people diagnosed as having diabetes.

Appropriate explanations and procedures should be incorporated into the screening protocol and programme design to minimize adverse effects and to address them when they do occur.

It must be emphasized that screening is only worth while if an effective intervention can be introduced to decrease the burden of the already existing disease or prevent diabetes developing. The current state of knowledge suggests that definitive proof of the value of screening is lacking, but evidence in its favour is steadily accumulating. The approach to screening adopted will depend on: (a) the resources available; (b) the potential disease burden; and (c) the risk factor distribution.

### 5.1.1 *Screening approaches*

*Population screening*

This is worth while only for health care planning or epidemiological research purposes or in high-prevalence populations. It can be used to identify individuals with IGT provided the OGTT is employed. In most societies it is ineffective in terms of cost and effort to screen children and young adults for NIDDM.

*Selective screening*

This is undertaken in selected groups known to have risk factors indicative of a high risk of having or developing NIDDM (*104*). These include:

- ethnicity – certain groups such as Pacific islanders, Australian Aborigines, Mauritians, migrant Asian Indians and Chinese, and Indigenous Americans show high diabetes prevalence;
- a positive family history of NIDDM in first-degree relatives (parents, siblings or children);
- obesity, e.g. body mass index equal to or greater than 27, especially in women with a history of GDM or large babies;
- age greater than 50 years in those of European origin, or greater than 30–40 years in high-prevalence communities;

- history of previous abnormality of glucose tolerance, particularly in pregnancy (e.g. GIGT or GDM);
- hypertension, macrovascular disease or dyslipoproteinaemia (raised triglycerides).

In low-prevalence communities an even more selective approach should be adopted.

*Opportunistic screening*
This occurs when high-risk individuals present themselves to some sector of the health care system. It is the most employed method and is highly cost-effective in that no resources are needed to organize the screening or call for subjects.

### 5.1.2 *Screening strategies*

*Risk assessment*
A screening programme should identify individuals with one or more diabetes risk factors as described above. This can be done by means of a written or verbal questionnaire. Individuals with more than one risk factor should be referred for evaluation and testing.

*Glucose measurement*
At present there is no satisfactory substitute; alternatives, such as measurements of glycated haemoglobin, glycated proteins and 1,5-anhydroglucitol, although specific, are too insensitive to detect lesser degrees of glycaemic disturbance reliably (*107, 108*).

- *Urine glucose measurement.* This is both insensitive and relatively non-specific for the detection of diabetes. However, it may be used if reliable blood glucose measurements are not available. Sensitivity is improved by using post-prandial urine samples. A positive urine test result indicates the need for confirmatory blood glucose testing.
- *Casual blood glucose measurement.* A value of $\geq 10.0$ mmol/l in venous whole blood or 11.1 mmol/l in venous plasma is suggestive of diabetes. Levels greater than 7-8 mmol/l should be followed by further testing.
- *Fasting blood glucose.* Fasting is defined as avoiding the consumption of any food or beverage other than water for at least 10 to 16 hours before testing. Fasting blood and plasma glucose levels are interpreted as follows:

| *Fasting blood (plasma) glucose* | *Interpretation* |
|---|---|
| <4.4 (<5.6) mmol/l; <79 (<100) mg/dl | Excludes diabetes (probably) |
| 4.4-5.5 (5.6-6.4) mmol/l; 79-99 (100-116) mg/dl | Low probability, not an indication for diagnostic testing |
| 5.6-6.6 (6.5-7.7) mmol/l; 100-119 (117-139) mg/dl | Indication for diagnostic testing (OGTT) |

≥ 6.7 (≥ 7.8) mmol/l; ≥ 120 (≥ 140) mg/dl — Indicates diabetes

- *Oral glucose tolerance test.* This remains the definitive confirmatory diagnostic test for diabetes. Diagnostic glucose levels 2 hours after a 75-g oral glucose load are shown in Table 2 (page 17) and the method for performing the OGTT is decribed in Annex 1. The OGTT also allows screening for IGT.

As stated in the 1985 WHO Study Group report (*3*), the diagnosis of diabetes cannot be made on the basis of a single abnormal blood glucose value in an asymptomatic individual. Repeat testing is required for definitive diagnosis.

There are many methods available for measuring blood glucose, ranging from visually read test-strips to sophisticated automated methods. Precision and accuracy are required for screening. If portable meters are to be used, they should be checked under a full quality assurance programme, and a coefficient of variation of > 5% should not be accepted. When automated procedures are used, care must be taken to minimize the risk of errors in sample identification.

Every screening programme must have an established mechanism for follow-up and further evaluation of those with a positive result. It is important to ensure that these people maintain contact with the health services. A written record of the screening information must be maintained, with due care for confidentiality, and the information should be communicated to all individuals tested (*104*).

### 5.1.3 *Potential obstacles*

Screening programmes should not be embarked upon without full recognition of the cost implications, both for screening and for follow-up and clinical care of individuals in whom diabetes is detected. Proper training is required for those conducting the screening, and the importance and relevance of the diagnostic programme to health care should be made explicit.

### 5.1.4 *Evaluation*

Screening programmes should be evaluated in terms of:

- numbers of new cases detected
- cost per new case detected
- actions taken for individuals with positive test results
- long-term benefits of early detection.

### 5.1.5 *Conclusions*

- Screening for diabetes is justified on the grounds that early detection allows effective early intervention, and hence diminishes the likelihood of the development of complications.

- Population screening is not justified other than for health care planning and research purposes, and in high-prevalence populations.
- Selective high-risk and opportunistic screening must be accompanied by confirmatory diagnosis and appropriate follow-up of new cases.
- Screening for IGT may be justified in high-risk populations but requires an OGTT for identification and a lifestyle intervention programme. Evidence for the value of the latter is still circumstantial.

### 5.2 Screening for insulin-dependent diabetes mellitus

Given current knowledge, screening can be recommended only for research purposes related to the prevention of IDDM (see section 3). Different screening approaches can be applied depending on the particular research question. The four parameters available for use are: (1) family history; (2) genetic markers (HLA); (3) immunological risk markers, e.g. islet-cell cytoplasmic antibodies, insulin autoantibodies and antibodies to glutamate decarboxylase; and (4) metabolic risk markers.

Screening for presymptomatic IDDM and individuals at risk remains purely experimental at this time, but there is intense research activity in this area.

## 6. Tertiary prevention

Tertiary prevention of diabetes includes every action taken to prevent or delay the development of acute or chronic complications. Acute complications, including hypoglycaemia, ketoacidosis and infections, can all be life-threatening. Chronic complications can be life-threatening, but they can also have deleterious effects on the lifestyle of the diabetic patient. Strategies for tertiary prevention involve prevention of the development of complications by strict metabolic control, education and effective treatment. They also involve screening for early stages of complications, when intervention and treatment are generally more effective. Such screening for complications aimed at early intervention and treatment has proved successful and may be even more effective than strategies aimed at preventing the development of complications.

### 6.1 Acute complications

#### 6.1.1 *Hypoglycaemia*

*Background*

The development of hypoglycaemia is an ever-present possibility in all patients with diabetes treated with insulin or oral hypoglycaemic medications (*109*). The serious consequences of hypoglycaemia relate to its effects on the brain, including loss of cognitive function, seizures and coma. Prolonged or repeated episodes of hypoglycaemia may produce permanent brain damage, and the adrenergic response to the condition may be dangerous in people with cardiovascular disease.

The risk of hypoglycaemia is particularly high when meticulous glycaemic control is sought. In the Diabetes Control and Complications Trial (*110*) there was a 3-fold increase in the risk of severe hypoglycaemia, including coma and/or seizures, when intensive insulin therapy was used. These episodes occur with disproportionate frequency at night.

The risk of hypoglycaemia is magnified in patients:

- who have difficulty perceiving hypoglycaemic symptoms (hypoglycaemia unawareness);
- who do not spontaneously recover from hypoglycaemia (counter-regulatory unresponsiveness); or
- in whom hypoglycaemia might be particularly dangerous (e.g. patients with angina pectoris or transient cerebral ischaemic attacks, and infants and young children).

It should be appreciated that meticulous glycaemic control may reduce the ability to perceive hypoglycaemic symptoms and to recover from hypoglycaemia (*111*). Moreover, patients with autonomic neuropathy may have greater difficulty in detecting hypoglycaemic symptoms and/or of spontaneously recovering from hypoglycaemia. β-Adrenoceptor blockers may also impair detection of symptoms and/or recovery, and alcohol consumption may aggravate the risk of hypoglycaemia and impair recovery (*112*). Delayed or missed meals and increased physical activity increase the risk of hypoglycaemia. Moreover, moderately intensive exercise carries potential risk well after exercise is conducted. Oral hypoglycaemic agents, particularly sulfonylureas, may induce hypoglycaemia. These factors represent a particularly important problem in elderly people with NIDDM (*112*).

There is no evidence that the species of insulin commonly used for treatment of diabetes *per se* influences the ability of patients either to perceive hypoglycaemic symptoms or to recover from hypoglycaemia.

### *Prevention strategies*

*Patient assessment.* Education of patients and their families about the prevention, recognition and treatment of hypoglycaemia is essential for survival and is, therefore, the most important approach.

Health care workers, particularly emergency medical personnel, should be familiar with the recognition and treatment of hypoglycaemia. To facilitate prompt assessment, patients receiving insulin treatment should wear or carry appropriate identification.

Blood glucose targets must be individualized for each patient. If meticulous glycaemic control is to be considered, patients should be able to recognize hypoglycaemic symptoms readily and to recover from hypoglycaemia spontaneously. Higher blood glucose targets should be selected for patients who are elderly, who have difficulty in perceiving hypoglycaemic symptoms, who do not spontaneously recover from

hypoglycaemia, or in whom hypoglycaemia might be particularly dangerous (e.g. patients with angina pectoris or transient ischaemic attacks). Patients who no longer experience the usual warning symptoms should be carefully instructed in subtle clues to hypoglycaemia (e.g. minor changes in mental function, perioral paraesthesia) besides having their glycaemic targets raised. There should be a careful balance of food intake, activity and insulin dosage in both quantity and timing, taking into consideration the eating and other lifestyle habits of the individual. Energy intake should meet the needs of usual daily activity. Meals should be consumed on time, and appropriate changes made in insulin dosage if meals have been omitted. Between-meal and bedtime snacks may be necessary to reduce the risk of hypoglycaemia. Bedtime administration of intermediate-acting insulin may eliminate nocturnal peaks in insulin action, thus reducing the risk of nocturnal hypoglycaemia.

*Exercise.* For sporadic physical activity departing from the patient's usual daily routine, action needs to be taken to avert hypoglycaemia. Such action might include consumption of extra carbohydrate food to cover the increased activity. Initially, this may be 10–15 grams of carbohydrate every 30–45 minutes during increased activity. Blood glucose should be monitored before, during and after exercise to determine the effectiveness of this intervention. Another option is to reduce the dose of insulin either in addition to or instead of giving dietary carbohydrate supplements. All patients should have quick-acting, rapidly absorbed carbohydrate available during exercise in case of hypoglycaemia. Patients should realize that moderately intensive exercise may deplete glycogen stores, resulting in a sustained food requirement to replace the glycogen. As a consequence, hypoglycaemia may occur well after exercise (e.g. 12 hours after jogging). For this reason, patients should be cautious when planning vigorous physical activity in the evening hours.

Patients should carry rapidly absorbable carbohydrate with them at all times. It may be desirable to measure blood glucose before driving a motor vehicle or operating potentially dangerous equipment, both at leisure and in the workplace.

*Glucagon for emergency use.* Glucagon should be available in the home (and possibly in the school, day care centre or workplace) of insulin-treated patients, especially those at particular risk of hypoglycaemia, where economically feasible. Family members, teachers and colleagues should be aware of the proper use of glucagon.

Glucagon should be available in emergency rooms, in emergency vehicles and in first-aid kits in all aircraft used in commercial aviation throughout the world. Personnel should be familiar with its use.

*Therapy changes.* When hypoglycaemia arises in patients treated with sulfonylureas, it should be recognized that these agents persist in the circulation for a long time, and that hypoglycaemia may recur after its initial correction (*112*). Such patients should be monitored for an

appropriate period after therapy is changed, depending on the sulfonylurea originally used.

Any change of insulin preparation, formulation, concentration or species should be accompanied by appropriate education of individuals with diabetes, health professionals and all other people involved in diabetes health care.

### 6.1.2 *Diabetic ketoacidosis*

Diabetic ketoacidosis remains a potentially lethal condition with mortality as high as 10-15%, with 21 life-years lost per death in some countries. At least 50% of cases are avoidable (*113*). Many new patients with IDDM present with ketoacidosis so that early recognition and diagnosis are obviously of importance.

It is crucial to educate patients and health care personnel about precipitating factors and actions to be taken to avoid ketoacidosis. Major precipitating factors include infection and other acute illnesses (*113*). In such situations, insulin requirements are likely to increase. Insufficient insulin therapy is also a major cause of diabetic ketoacidosis in some parts of the world (*114*). With proper instruction on monitoring of blood glucose and urine ketones, insulin dose adjustment and maintenance of fluid intake, many potential cases of diabetic ketoacidosis can be prevented (*113*). If vomiting occurs, early referral for intravenous therapy is required. It should be stressed that people with NIDDM may also develop ketoacidosis (as well as hyperosmolar non-ketotic coma and lactic acidosis) in the face of severe infection or other major intercurrent illness (*113*).

It is essential that insulin should be readily available for the treatment of all people who require it in all parts of the world.

### 6.1.3 *Infections*

People with poorly controlled diabetes are more prone to develop bacterial (in particular mycobacterial and anaerobic) and fungal infections (*115*). Tuberculosis of respiratory and other organ systems, fungal infections of skin and mucous membranes, bacterial infections of the urinary tract, and anaerobic infections of deep tissues pose serious health threats, particularly in poor hygienic surroundings (*116*). If not treated promptly and effectively, advancing infections may directly threaten life besides precipitating diabetic ketoacidosis (*113*).

Urinary tract infections are more commonly provoked in people with diabetes than in non-diabetics by bladder instrumentation, and may also result from urinary tract problems such as obstruction and neuropathic bladder. Pyelitis and pyelonephritis aggravate diabetic nephropathy. Chronic painless infection may destroy a neuropathic and/or ischaemic foot.

The differential susceptibility of people with diabetes in different parts of the world to a variety of infections may, in addition, depend upon level of environmental sanitation, nutritional status and degree of individual immunity.

## 6.2 Chronic complications

### 6.2.1 *Atherosclerosis*

*Background*

Atherosclerosis is the most common complication of diabetes mellitus among those of European origin. It accounts for 75% of their deaths, a figure that is two to three times as high as that in people without diabetes. Coronary and cerebrovascular disease are also two to three times more common in those with diabetes, and post-infarction mortality is higher. The assessment of clinical events in coronary artery disease is made more difficult because of the frequency with which cardiac ischaemia is asymptomatic in diabetes. Peripheral arterial disease is even more accentuated in those with diabetes, being four times more common. Because of the frequent coexistence of neuropathy and vascular problems, the diagnosis of diabetic foot problems is also difficult. One feature unique to women with diabetes is the loss of the usual relative protection from atherosclerosis prior to menopause (*117-120*). These increases in atherosclerosis in diabetic individuals are seen in all populations, whether the general incidence of atherosclerosis is low or high. In developing and rural societies, changes in lifestyle to those of more developed and urban societies are often associated with a general increase in atherosclerosis, including that associated with diabetes. The largest numbers of ischaemic events occur in people with NIDDM. However, the risk of atherosclerosis is also extremely high in IDDM and may be manifest at a young age.

*Atherogenic factors*

Many factors that predispose non-diabetic individuals to atherosclerosis are also associated with atherosclerosis in people with diabetes. These include factors:

- relating to the artery wall;
- affecting thrombogenesis;
- affecting lipoproteins;
- affecting vascular injury (*117, 121*).

Smoking, hypertension and hypercholesterolaemia also increase the risk of coronary artery disease in people with diabetes mellitus in a manner that parallels that seen in those without diabetes. However, the risk of developing coronary disease is still higher in diabetes, even after adjustment for these factors.

Some, but not all, studies suggest that hyperglycaemia itself may be associated with the risk of atherosclerosis. The differences may result from

the ways in which, and the frequency with which, glycaemia is determined (*122-124*). Hyperglycaemia may act by:

- inducing modifications of lipoproteins (e.g. glycation of low-density-lipoprotein (LDL));
- glycation of artery wall proteins;
- inducing advanced glycation end-products;
- stimulating insulin secretion.

There is a vast body of evidence to show that smoking greatly increases atherosclerosis, particularly in those with diabetes (*125*). There is also a great increase in the risk of macrovascular disease in people with urinary albumin excretion exceeding 30 mg/24 hours (*126*) and in those with clinical nephropathy (*21*). People with these characteristics are therefore important targets for prevention.

Hyperinsulinaemia has been shown in prospective studies of general populations to be independently associated with coronary disease in men (*127-129*). It has also been shown in cross-sectional studies to be associated with coronary disease in both men and women (*130*). Whether these links reflect the effects of the high level of insulin itself, or of proinsulin and its split products, remains to be clarified. The associations may be mediated through the effects of hyperinsulinaemia on blood pressure, blood triglyceride and plasminogen-activator inhibitor 1 levels or arterial wall metabolism.

Obesity, particularly abdominal obesity, is another factor closely linked with a liability both to atherosclerosis and to diabetes. Its impact may be mediated, at least in part, through increased insulin resistance and hyperinsulinaemia, dyslipoproteinaemia and hypertension, or a combination of these factors.

Hyperinsulinaemia and hypertriglyceridaemia are often associated (*43, 131*). The importance of this to the diabetic person is emphasized by the demonstration of an independent coronary risk effect of hypertriglyceridaemia in those with diabetes and IGT (*132, 133*). Studies in non-diabetic people have shown the greatest risks associated with hypertriglyceridaemia to be in those in whom it is combined with low levels of HDLs. In NIDDM, HDL levels may be reduced or normal whereas in IDDM they may be normal or increased. LDL levels in those with diabetes generally do not differ from those in non-diabetic people. However, LDL structure may be modified in diabetes (changes in composition, oxidation or glycation) to make the LDLs much more atherogenic. A variety of thrombotic factors are also altered in diabetes and in hyperinsulinaemic states. These may also be important in producing atherosclerosis and vascular occlusion (*134-137*).

### *Screening*

People should be screened for risk factors for macrovascular (cardiovascular, cerebrovascular and peripheral vascular) disease and for

the presence of existing macrovascular disease when their diabetes is first diagnosed, and periodically as indicated thereafter, in order to plan management to prevent or delay the disease and its complications (*138*).

Screening for risk factors should include determination of:

- lipid profile including total cholesterol, triglyceride and HDL and calculated LDL concentrations (these determinations should preferably be done on fasting blood samples, but if this is not possible, non-fasting samples should be used to check the need for a follow-up fasting determination);
- arterial blood pressure;
- heigh, weight and waist-to-hip ratio;
- smoking history;
- urinary albumin excretion rate (rates above 20 μg/minute or 30 mg/24 hours indicate risk); and
- family history of macrovascular disease.

Recognition and appropriate management of one or more such risk factors may delay or prevent future vascular events.

The presence or absence of existing vascular disease should be ascertained by:

- completing a clinical history or standard questionnaire and physical examination for the presence of coronary heart disease or cerebrovascular or peripheral vascular disease, including questions relating to previous myocardial infarction, transient ischaemic attacks, stroke and intermittent claudication, and physical examination for cardiac function, presence of bruits, presence/absence of peripheral pulses and evidence of peripheral and/or cerebral ischaemia; and
- obtaining a standard resting 12-lead electrocardiogram.

The sensitivity and specificity of these methods are only moderate and they cannot exclude the possibility of the presence of clinically important disease. Suspicion on clinical grounds should lead to more extensive characterization of the suspected abnormality using appropriate methods. Diagnostic criteria for ischaemia, end-organ disease and arterial hypertension for people with diabetes are the same as for those who do not have the disease.

Recognition of the presence of these risk factors and/or existing vascular disease may influence management decisions designed to improve prognosis (*138*).

*Setting targets*

In the absence of studies specifically addressing the effects of risk modification in people with diabetes it is not possible to set specific lipoprotein or blood pressure targets for those with the disease. Targets for the general population currently set by various national bodies are therefore recommended.

*Intervention strategies*

There are currently no trials studying the effects of intervening to modify risk factors specifically in diabetes. In one limited trial (Diabetes Intervention Study, *139*) intervention did not alter the incidence of ischaemic heart disease. Hence, the present recommendations are based on those formulated for non-diabetic people.

- *Smoking.* Every effort should be made to discourage people from starting smoking and to encourage smokers to stop.
- *Diet.* Dietary intervention should have five aims: (1) correction of obesity; (2) optimization of glycaemic control; (3) control of dyslipoproteinaemia; (4) salt restriction in those prone to hypertension; and (5) protein restriction in those with nephropathy. In general this means: controlling energy intake; limiting fat intake to 30-35% of energy (saturated fat intake to < 10% of energy; the use of $n-3$ ($\omega 3$) polyunsaturated fatty acids may be beneficial in hypertriglyceridaemia but their effect on glycaemia must be monitored); restricting daily cholesterol intake to < 300 mg; limiting simple sugars and emphasizing unrefined carbohydrates; restricting alcohol intake by those with hypertriglyceridaemia; using soluble fibre; and where indicated, restricting salt and/or protein intake.
- *Physical activity.* Regular physical activity has been shown to reduce a number of atherogenic risk factors. For example, it increases HDL levels, assists in reducing obesity and blood pressure and improves insulin sensitivity (*140*). It should therefore be encouraged.
- *Hypoglycaemic drugs.* People with diabetes who are not restored to desirable glycaemia by diet alone will need the addition of a hypoglycaemic drug. It is important to clarify the relationship between insulin and atherosclerosis in order to recommend the most appropriate hypoglycaemic drug.
- *Hypolipidaemic drugs.* Where optimal lipoprotein levels are not achieved by diet and exercise, drugs may be used (*141*):
  - The clofibrate derivatives are effective in reducing triglycerides and raising HDLs; some also reduce LDLs. In addition, they may reduce fibrinogen and perhaps improve glycaemic control. However, they may increase the risk of cholelithiasis.
  - HMG-CoA (hydroxymethylglutaryl-CoA) reductase inhibitors primarily reduce LDL cholesterol and have weaker effects on triglycerides. They do not affect glycaemia.
  - Bile-acid-binding resins reduce LDLs but may increase triglycerides. They may cause problems in those with disorders of gastrointestinal motility.
  - Nicotinic acid is an effective and cheap drug that reduces both triglycerides and LDLs, and increases HDLs. It may, however, aggravate insulin resistance, hyperglycaemia and hyperuricaemia.
  - Antioxidants such as probucol and, possibly, large doses of vitamin

E and nicotinamide may prevent LDL oxidation, potentially reducing its atherogenicity.

- *Antihypertensive drugs:*
  - Thiazides are the least expensive and are often effective. They may, however, aggravate hyperlipoproteinaemia, hyperglycaemia and hyperuricaemia and induce hypokalaemia. They should therefore be used only in low doses.
  - β-Adrenoceptor blockers may be useful, but they may induce dyslipoproteinaemia and mask hypoglycaemic warning symptoms.
  - Inhibitors of angiotensin converting enzyme are potentially very useful but may have two adverse effects: hyperkalaemia and hypotension. The latter necessitates caution in patients with autonomic neuropathy.
  - Calcium channel blockers are also potentially very useful.

### *Challenges*

The epidemiology of macrovascular disease in diabetes has still not been fully defined or explained, although the WHO Multinational Study (*5, 133*) has shed some light on the situation. This is mainly because of the inaccuracies that still exist in the diagnosis of macrovascular disease in both large populations in general and diabetic populations in particular.

In studies of mortality, difficulties arise because of inaccuracies in death certificates, where these are used as the method of establishing the cause of death. As an underlying cause, diabetes often fails to be mentioned and is therefore systematically under-reported. In morbidity studies, the diagnosis of coronary artery disease in diabetes is made difficult by the frequency with which myocardial ischaemia is clinically silent. In addition, a number of the candidate risk factors are not easy to measure. For example, hypertriglyceridaemia comprises a constellation of lipoprotein disorders and cannot be regarded as a single entity. It is therefore necessary to consider characterizing individuals according to the subfractions of their lipoproteins. This may require complex separation methods that are not even available to all lipid clinics and are certainly not applicable to large populations. Lipoprotein (a) is another potentially important risk-related lipoprotein whose impact needs to be evaluated in those with diabetes.

The heterogeneity of diabetes mellitus itself and the inadequacies, because of variability, of single blood glucose measurements are further complications. It is necessary to analyse results for people with NIDDM and IDDM separately and to distinguish those treated by dietary control and oral agents from those treated with insulin. The effect of glycaemic control on atherogenesis must be determined more precisely.

From the therapeutic standpoint, there are also a number of questions:

- What is the most appropriate diet for people with diabetes?
- What are the optimal relative proportions of fat and carbohydrate?

- How far should simple sugars, etc. be restricted?
- How effective is reduction of raised arterial blood pressure in diabetes, and what is an appropriate target level?
- Should agents that might reduce proteinuria be used?
- How can people with diabetes be deterred from smoking?
- What is the effect of stringent blood glucose control on macrovascular complications?
- Does normalization of blood glucose prevent atherosclerosis or is hyperinsulinaemia a more important factor?
- What is the effect of lipid reduction on macrovascular disease in people with diabetes?
- Is the effect similar to that in non-diabetic people?
- Is it important to aim for even lower lipid levels in those with diabetes than in those without the disease?

At the moment, the main approach to preventing macrovascular disease in diabetes is the same as that used in non-diabetic people. However, there is no evidence that this is justified. Clearly more studies are required. Because of the difficulties outlined above and others, studies in large populations may not be possible; future studies will probably address well defined questions and be conducted in small, well selected populations. It is essential, for example, to study the effect of plasma lipid correction on coronary artery disease in diabetic people since all previous studies have excluded diabetic patients.

### 6.2.2 *Diabetic eye disease*

*Background*

Diabetes mellitus is associated with damage to the small blood vessels in the retina, resulting in loss of vision. In economically developed societies, it is a major cause of visual disability in people aged 25 years or older. In Wisconsin, United States of America, in 1980–1982, after 15 years of diabetes, 21% of diabetic people had visual impairment and 6% were legally classified as blind (*142*). In Denmark, blindness or severe visual handicap developed in about 33% of a cohort of younger-onset insulin-dependent people with diabetes followed for 40 or more years (*21*).

More recently, the overall 4-year incidence of visual impairment (9%) and blindness (2%) was estimated in IDDM patients in Wisconsin (*143*). The 4-year incidence of blindness was higher (3%) in older-onset than in younger-onset IDDM patients (1.5%). As the former are more numerous, they made up a higher proportion (89%) of those who became blind than did the younger-onset group (11%). In the younger-onset group, diabetic retinopathy was the underlying cause of blindness in 86% of eyes; in the older-onset group, blindness was due to diabetic retinopathy in 35% of eyes while in the remainder the causes included cataract, glaucoma and age-related macular degeneration.

Almost everyone with younger-onset diabetes will develop diabetic retinopathy after 20 years of the disease (*144*). At some time during their lives, 75% will develop the most severe stage, proliferative diabetic retinopathy; in older-onset NIDDM, almost 60% will develop diabetic retinopathy and at some time during their lives about 10% will develop proliferative retinopathy. Both younger- and older-onset diabetic people are at risk of developing another sight-threatening manifestation of diabetic retinopathy, namely macular oedema, a swelling of the central part of the retina. These findings are consistent from study to study, whether in the isolated Pacific population of Nauru, Pima Indians in Arizona or Hispanic Americans in San Antonio, Texas, or in Colorado (*145*).

Epidemiological data also suggest that loss of vision due to open-angle glaucoma and cataract may be more common in people with diabetes than in non-diabetics.

*Rationale for screening and intervention*

Clinical trials have demonstrated the benefit of laser photocoagulation for severe proliferative retinopathy and clinically significant macular oedema. Recent findings from one study, the Early Treatment Diabetic Retinopathy Study, suggest that timely treatment may prevent up to 90% of severe visual loss associated with proliferative retinopathy. Guidelines for ophthalmological care have been developed to implement these findings (*145*). However, recent epidemiological studies in the United States of America and Europe show that a significant proportion of the population may not be receiving such care (*145*). The reasons for this include:

- physician factors
  - failure to dilate pupils on examination
  - poor ophthalmoscopy skills
  - lack of knowledge of benefits of photocoagulation
- patient factors
  - lack of awareness of the presence of vision-threatening retinopathy because it is often asymptomatic
  - lack of knowledge of, access to and availability of such care.

Recent studies suggest that screening and the timely treatment of vision-threatening retinopathy with photocoagulation are of economic benefit (*146, 147*).

*Screening strategies*

A number of screening strategies have been recommended for the detection of diabetic retinopathy (e.g. *10*).

Examination should include:

- a history of the onset of visual symptoms;
- a history of glaucoma and cataract;
- measurement of visual acuity unaided and, if necessary, with glasses

and/or a pinhole to obtain an estimate of best-corrected visual acuity;
- pupil dilatation with 2.5-10% phenylephrine, 1% tropicamide or 1% cyclopentolate eyedrops;
- lens examination for cataract with a +10 lens in the ophthalmoscope or red reflex photography;
- fundus examination by direct ophthalmoscopy (which is inexpensive, widely available and reasonably sensitive and specific in the hands of well trained observers);
- where feasible, retinal photography using either a standard or a non-mydriatic camera.

Although fundus photography is more expensive than ophthalmoscopy, its advantages include a more permanent objective record which can be produced by technical personnel. These images can be assessed at a later time by a specialist.

Standard protocols for retinal photography have been developed. Photographs should be obtained on colour-free or red-colour-free transparencies because they are cheaper, provide better definition and do not fade with prolonged storage as do instant prints.

If the screening is performed by an ophthalmologist, fluorescein angiography, slit-lamp biomicroscopy and other more specialized techniques may be considered, but these are not usually standard screening methods.

Findings indicating the need for referral as soon as possible to an ophthalmologist for further assessment are:

- preproliferative retinopathy;
- venous irregularities (beading, reduplication, etc.), multiple retinal haemorrhages, multiple cotton-wool spots, or intraretinal microvascular abnormalities;
- non-proliferative retinopathy with macular involvement, leading to reduced visual acuity not corrected by pinhole, or haemorrhages;
- hard exudates within one disc diameter of the macula, with or without visual loss;
- non-proliferative retinopathy without macular involvement but with large circinate hard exudate material;
- proliferative retinopathy.

Screening should be done by an individual adequately trained to detect retinopathy by ophthalmoscopy, such as an ophthalmologist with an interest in diabetic eye disease; where this is not feasible and the patient is not under the care of an ophthalmologist, it is recommended that the screening be the primary responsibility of the doctor or organization responsible for the health care of diabetic patients. It should be done in close collaboration with the nearest ophthalmic facilities adequately equipped for further assessment and treatment of diabetic retinopathy, glaucoma and cataract. Non-physician screeners should be properly trained and qualified.

There should be established channels for rapid referral of patients with sight-threatening retinopathy. If screening is carried out using retinal photography, the pictures should be taken by medical photographers and evaluated by experienced readers who should then report back to the organization responsible for the screening and the patient.

People with diabetes should be encouraged to report any significant changes in visual acuity not related to changes in blood glucose to their primary care providers or their eye doctors.

All post-pubertal children with IDDM should be screened, usually 5 years after diagnosis; it is rare to observe vision-threatening diabetic retinopathy in people who have had IDDM for less than 5 years (*144, 145*). The eyes should then be examined yearly if no retinopathy is found, or more frequently if retinopathy is found, especially in the case of very poor glycaemic control, initiation of good control after periods of prolonged poor control, intercurrent illness or renal impairment. Eyes should be examined when pregnancy is being considered, at confirmation of pregnancy, and then every three months or more frequently if necessary.

Patients with NIDDM should be examined at the time of diagnosis because of the relatively high levels of retinopathy (10–28%) present at diagnosis (*105, 144, 145*). This high level of retinopathy has been suggested as a rationale for screening for diabetes in high-risk populations. The schedule of examinations thereafter should depend on the presence of retinopathy. Recent data suggest that, if no retinopathy is present, it may be safe to wait 4 years until further retinal examination in people with NIDDM. If retinopathy is found, yearly or more frequent examinations are recommended.

The American Diabetes Association has recently made the following recommendations for screening (*148*):

- Patients with NIDDM should have an initial examination for retinopathy shortly after the diagnosis of diabetes is made.
- If ophthalmoscopy of the dilated pupil is used, then examinations should be repeated annually.
- If skilled readers of 7-field stereo-photographs are available and no retinopathy is revealed at the initial screening, the patient need not be re-examined for 4 years. Care should be taken not to lose these patients to follow-up. After the 4-year examination, subsequent screening with stereo-photography or ophthalmoscopy of the dilated pupil should be performed annually.
- Patients with persistent, very high plasma glucose concentrations (e.g. mean >280 mg/dl) or proteinuria should have yearly examinations regardless of screening technique.

In people with NIDDM, measurement of intraocular pressure, examination of the optic nerve and visual field testing may be needed to determine whether open-angle glaucoma is present. There is a need to

detect glaucoma because, if left untreated, it can lead to significant visual impairment. Examination of the lens by slit-lamp will permit assessment for cataract.

*Intervention strategies*

Clinical trials have demonstrated the efficacy of pan-retinal laser photocoagulation for eyes with advanced proliferative retinopathy, and focal laser photocoagulation for eyes with clinically significant vision-threatening macular oedema, and these surgical treatments can be used to prevent visual loss where indicated (*149, 150*).

There are no drugs available to prevent the development or progression of retinopathy in humans. Neither aspirin nor aldose reductase inhibitors have proved beneficial.

Animal experiments and epidemiological studies in humans strongly suggest a higher incidence and further progression of retinopathy and visual loss in diabetic people with higher blood glucose concentrations (*145, 151, 152*). However, to date, lowering of blood glucose in clinical trials has not altered the progression of retinopathy. It is hoped that the results of the United States Diabetes Control and Complications Trial (*110*) will provide a better understanding of this relationship.[1]

There is less consistent evidence of an association between blood pressure and the incidence and progression of retinopathy (*145, 154*). While there are no data to indicate that intervention with antihypertensive drugs will prevent retinopathy in people with hypertension, it is important to treat hypertension when present because of its association with cardiovascular and renal disease.

Most epidemiological evidence does not support a relation between smoking and retinopathy (*145*). However, smoking should be discouraged because of its association with increased morbidity and mortality.

*Potential obstacles to prevention*

Potential obstacles to prevention include:

- lack of awareness of sight-threatening retinopathy because it is often asymptomatic (an important reason why patients are not necessarily examined for retinopathy);
- lack of awareness by primary care physicians of the benefits of timely detection and treatment with photocoagulation;
- lack of the necessary ophthalmoscopic skills by primary care physicians;
- lack of lasers to treat retinopathy;

[1] *Chairmen's note:* Since the meeting of the Study Group, the Diabetes Control and Complications Trial has convincingly demonstrated that lowering of blood glucose both delays the onset and slows the progression of retinopathy in people with IDDM (*153*).

- lack of skilled ophthalmologists to treat retinopathy when lasers are available;
- lack of economic resources to seek and secure care.

*Setting goals*

The major goal is to reduce blindness. This can be achieved by:

- educating patients about the need for ophthalmological care with examination of the retina through dilated pupils;
- educating primary care providers about the benefits of detection and referral of their patients for appropriate eye care;
- developing methods of achieving good glycaemic control in an attempt to prevent the development of retinopathy, and promoting good glycaemic control as a possible approach to the reduction of diabetic retinopathy once it occurs;
- reducing the economic barriers that prevent patients from seeking ophthalmological care when needed;
- ensuring that facilities (with lasers) are available for photocoagulation treatment of retinopathy.

*Evaluation and monitoring*

There is a need to collect data on the current prevalence of blindness and visual impairment and, after the initiation of any screening or intervention programme, to monitor the effectiveness of retinal photocoagulation and other interventions in reducing visual impairment. Educational programmes must be evaluated by testing the knowledge of primary care physicians, other health professionals and patients about diabetic eye disease and recommended care both before and after the programme is introduced, and by monitoring changes in behaviour (consultation of ophthalmologists, etc.). Costs should also be monitored.

*Conclusions*

The highest priority at present is the education of patients, their physicians and health care decision-makers about the benefits of timely detection of vision-threatening diabetic retinopathy and prompt treatment with laser photocoagulation. The screening methods used will depend on available resources but should include assessment of the ocular fundus by appropriately trained individuals and referral to specialists when vision-threatening retinopathy is detected.

If the Diabetes Control and Complications Trial (*110*) demonstrates that glycaemic control is beneficial in reducing blindness secondary to diabetic retinopathy,[1] there will be a need to achieve tighter control of blood glucose in those at risk. A clinical trial may be required to determine whether reduction of arterial pressure in normotensive people with IDDM will reduce the incidence and progression of diabetic retinopathy.

[1] See footnote, page 53.

The likelihood of success in preventing and reducing the consequences of diabetic eye disease will depend on the availability of resources to implement educational programmes and on the continuous monitoring of these programmes.

### 6.2.3 *Diabetic kidney disease*

*Background*

Diabetic kidney disease is a major cause of premature death in diabetic patients, largely through uraemia and cardiovascular disease (*21*). It is a multistage condition that requires several years to become clinically overt. At the time of diagnosis of IDDM, there may be changes in renal function, e.g. glomerular hyperfiltration, increased renal blood flow and increased renal size (*155*). Some of these early changes may be reversible. Persistence of these changes may have prognostic significance for future development of overt kidney disease. Otherwise, these early kidney manifestations are not part of the syndrome of diabetic nephropathy.

Diabetic nephropathy can be divided into several stages:

- incipient (subclinical) nephropathy;
- clinical (or overt) nephropathy;
- advanced nephropathy; and
- end-stage renal disease.

Incipient nephropathy is defined by a persistent increase in albumin excretion rate, also called microalbuminuria, without frank proteinuria. This coincides with an albumin excretion rate of 20–200 µg/minute (30–300 mg/24 h) (*155*). Microalbuminuria may be accompanied by a rise in blood pressure. Clinical nephropathy is defined by the presence of persistent proteinuria, i.e. > 200 µg/min (> 300 mg/24 h) (*155*). It is usually accompanied by hypertension. In advanced nephropathy there is a significant decline in glomerular filtration rate and the appearance of symptoms of uraemia and/or nephrotic syndrome. End-stage renal disease necessitates renal dialysis or renal transplantation.

Diabetic patients are 17 times as prone to kidney disease as non-diabetic people, and diabetes is now the leading known cause of end-stage renal disease in the United States of America (*156*). The cumulative risk of diabetic nephropathy in IDDM is about 30–40% after 25–30 years of disease (*157*). The cumulative risk of diabetic nephropathy in NIDDM varies considerably with ethnic origin. In some groups of European origin, it is as low as 15% after 25 years of disease (*10*). On the other hand, much higher cumulative risks (up to 50% after 25 years) have been reported in Japanese, Pima Indians (Arizona), Zuni Indians (New Mexico) and Hispanic Americans (*155*).

*Rationale for prevention*

The frequency, severity and progression of diabetic nephropathy are related to the degree of hyperglycaemia and associated metabolic

derangements, as well as the duration of diabetes.[1] The progression and severity of kidney disease are also associated with blood pressure elevation and haemodynamic conditions, and are profoundly influenced by the effectiveness of control of coexisting hypertension (*155*). However, diabetic nephropathy itself results in blood pressure elevation.

A number of factors may slow the progression of damage. These include:

- careful control of hyperglycaemia (since moderate hyperglycaemia results in increased renal perfusion);
- meticulous control of hypertension, with particular attention to antihypertensive strategies that prevent increases of intracapillary pressure within the kidney; and
- dietary protein restriction (since protein is also vasodilatory in the kidney and leads to increased renal perfusion).

The cost of renal replacement therapy (either dialysis or transplantation) is enormous. For example, in the United States of America in 1989, the costs for renal replacement in diabetic patients exceeded US$ 1 billion (*156*). The costs in diabetic patients amounted to more than 60% of the total costs for end-stage renal disease in that country, although diabetic patients account for only 30% of the patients; this is because coexisting conditions in those with diabetes increase the costs of treatment.

Clinical trials have demonstrated the benefits of programmes designed to reduce morbidity and mortality resulting from diabetic nephropathy. These include meticulous glycaemic control, dietary protein limitation and vigorous control of blood pressure (*155, 158*). For these reasons, guidelines for screening and intervention have been developed.

*Screening strategies*

Blood pressure should be monitored at least annually in all patients with diabetes mellitus. All those who have had IDDM for more than 5 years and are above the age of 12 years and all patients with NIDDM should have their urinary albumin excretion measured at least once a year until the age of 70 years. It should be appreciated that albumin excretion rate is increased by:

- heavy exercise
- urinary tract infection
- acute illness
- high protein intake
- decompensation of metabolic control, including recent ketoacidosis
- cardiac failure.

An elevated albumin excretion rate should be confirmed by repeated testing. The urinary microalbumin test is a convenient method. It has been demonstrated that the onset of nephropathy in IDDM patients can be

[1] *Chairmen's note:* Since the meeting of the Study Group, this has been convincingly confirmed for IDDM by the United States Diabetes Control and Complications Trial (*153*).

detected many years earlier using this method than by screening for proteinuria (*158*). Patients with an elevated albumin excretion rate should be monitored at least every 6 months, and more often if required by clinical conditions and/or treatment strategies. Such monitoring should also include regular assessment of glycated haemoglobin, blood pressure, serum creatinine and serum lipids. If overt nephropathy appears, creatinine clearance should be measured at least annually, or more often if indicated by clinical conditions.

*Intervention strategies*

Several randomized studies have demonstrated that incipient nephropathy (microalbuminuria) can be stabilized by meticulous glycaemic control (*155, 158*), and there is evidence that such control may slow or even stop the progression to overt nephropathy (*159*). In NIDDM, insulin therapy should be seriously considered if satisfactory glycaemic control is not otherwise achieved.

Arterial hypertension should be treated vigorously. For patients below the age of 60 years, antihypertensive treatment should be started once systolic blood pressure reaches 140 mmHg (18.7 kPa) and/or diastolic blood pressure reaches 90 mmHg (12.0 kPa), or if diastolic blood pressure increases by 5 mmHg (0.67 kPa) or more within a year (two or more readings should be averaged on each occasion). Treatment should be considered at these thresholds for those older than 60 years depending on clinical conditions and available resources (*10*), but in any case should be offered to all patients fulfilling the criteria for hypertension recommended by a WHO Expert Committee on Arterial Hypertension (*160*). Non-pharmacological therapies should be attempted first. If satisfactory blood pressure control is not otherwise achieved, antihypertensive drugs should be used. Agents that do not adversely influence carbohydrate or lipid metabolism are preferable, with special consideration given to those that reduce glomerular hyperfiltration.

Progression from overt nephropathy to end-stage renal disease may be slowed by vigorous correction of raised arterial blood pressure, but there is no convincing evidence that meticulous glycaemic control will influence its course. A reduction in dietary protein intake, particularly animal protein, should be seriously considered for diabetic patients with overt nephropathy.

Symptomatic and supportive treatments are necessary to reduce the impact of diabetic nephropathy. Associated lipid abnormalities should be appropriately treated. Interventions based on clinical indications should be used to limit metabolic bone disease and anaemia. If fluid retention occurs, loop rather than thiazide diuretics should be given.

As end-stage renal disease evolves, there should be early referral for consideration for renal replacement therapy (dialysis or transplantation) as appropriate, depending on clinical judgement and local facilities.

In order to decrease renal damage from any cause, other precautions should be taken. Patients should be checked for urinary tract infections, which should be treated vigorously. Radiographic contrast media may provoke sudden and severe deterioration in the damaged kidney, so appropriate precautions should be taken before radiography. Potentially nephrotoxic drugs should be avoided, if possible, in patients with diabetes and particularly those with any stage of nephropathy.

*Potential obstacles to prevention*

Potential obstacles to prevention include:

- lack of awareness by primary care physicians about the benefits of careful glycaemic control in preventing renal disease and of timely detection and treatment, particularly of incipient nephropathy;
- lack of economic resources to provide care;
- lack of donated kidneys for transplantation;
- feelings of hopelessness on the part of patients and health care providers.

*Needs*

There is a need:

- for continued collection of data to monitor the effectiveness of interventions;
- to educate patients and primary care physicians about the value of detection and the benefits of treatment of nephropathy;
- to achieve good glycaemic control in an attempt to minimize the development of nephropathy; and
- to reduce the economic barriers preventing patients from seeking appropriate care when necessary.

*Evaluation and monitoring*

In the case of end-stage renal disease, there are many national and regional databases available to provide valuable information on:

- the identity of patients requiring renal replacement therapy;
- objective programmes for educating and testing the knowledge of primary care physicians;
- how to evaluate patients' knowledge about diabetic nephropathy and recommended care both before and after educational programmes;
- how to evaluate the success of programmes by monitoring changes in behaviour; and
- how to evaluate the cost-effectiveness of programmes.

*Conclusions*

Vigorous treatment of clinical nephropathy may delay the development of end-stage renal disease (*155*, *158*). One of the highest priorities at present is the education of patients and their physicians about the potential for early detection and prevention of diabetic kidney disease. There is a need to

achieve tighter glycaemic control in patients at risk, and to educate physicians about criteria for the initiation of blood pressure reduction and the appropriate choice of antihypertensive agents.

The likelihood of success in preventing and reducing the consequences of diabetic kidney disease will depend on the availability of resources to implement educational programmes and to monitor them continuously.

### 6.2.4 *Diabetic neuropathy*

*Background*

Diabetic neuropathy is a demonstrable disorder, either subclinical or clinically evident, that occurs in diabetes mellitus without other evident cause. Manifestations may occur in both the peripheral and the autonomic nervous systems (*161*). Peripheral neuropathies include (*162*):

- polyneuropathies, e.g. distal sensorimotor neuropathy and proximal motor neuropathy;
- focal neuropathies, e.g. mononeuropathies (including cranial) and entrapment neuropathies; and
- multifocal neuropathies.

Autonomic neuropathies may involve the cardiovascular, gastrointestinal, genitourinary and sudomotor (integumentary) systems.

The most common form of neuropathy is distal symmetrical sensorimotor polyneuropathy (*162*), which can be divided into three stages: early, symptomatic and severe. Early distal sensorimotor neuropathy is usually asymptomatic, but sensory loss may be detectable; neurophysiological abnormalities are demonstrable. Symptomatic distal sensorimotor neuropathy is manifested by sensory loss, often with frank numbness, and may be accompanied by paraesthesia and/or pain. Severe distal sensorimotor neuropathy is manifested by motor involvement, and may be accompanied by disabling symptoms and the potential for ulceration, which can lead to infection, necrosis, gangrene and loss of the limb.

Diabetic neuropathy may be the commonest complication of diabetes mellitus. In a prospective study of 4400 outpatients in a diabetic clinic in Belgium, approximately 10% of patients had neuropathy at the time of diagnosis of their diabetes, and the incidence of neuropathy increased with the duration of diabetes (*163*). In a cohort of 278 IDDM patients in the United States Diabetes Control and Complications Trial, 39% had clinically detectable neuropathy (*164*). In a population-based study of IDDM in Pittsburgh, Pennsylvania, United States of America, 34% had neuropathy (*165*); among those aged 18 years or older, longer duration of diabetes, higher levels of glycated haemoglobin, positive smoking history, and cardiovascular disease were associated with an increased prevalence of the disorder. In a study in Colorado, United States of America, distal sensorimotor neuropathy was present in 27% of Hispanic and 30% of non-Hispanic whites with NIDDM (*166*). In a population-based study in Rochester, Minnesota, United States of America, 66% of diabetic patients

had objective evidence of neuropathy (decline in vibratory sensation in the feet), although only 20% had symptoms (*167*).

Hyperglycaemia associated with diabetes is thought to be central to the effect on nerve structure through a number of possible mechanisms (*168*), including increased activity in the polyol pathway, altered *myo*-inositol metabolism and non-enzymic glycation. Other mechanisms may also be involved, for example alterations in nerve growth factor activity, blood viscosity, circulating platelets and the rate of synthesis and transport of intra-axonal protein. There may be interactions between these pathways.

*Rationale for prevention*

The presence of neuropathy is associated with significant morbidity, including: recurrent foot infections and ulceration, necessitating amputation; impotence in diabetic men; and sudden death in individuals with cardiovascular autonomic neuropathy (*162, 169*). More hospital beds are occupied by diabetic patients with foot problems than by those with all other consequences of diabetes. In the United States of America, 50–70% of all non-traumatic amputations of the lower extremity are secondary to diabetes, and in 1987, there were 56 000 hospital discharges for amputation among individuals with diabetes (*170*).

*Screening strategy*

The bare feet should be routinely examined. A simple screening procedure for distal sensorimotor neuropathy, developed at the University of Michigan, United States of America, in collaboration with the Royal Free Hospital, London, England, involves:

- inspection of the feet for evidence of dry skin, hair or nail abnormalities, callus or infection;
- the grading of vibratory sensation at the dorsum of the great toe as normal, reduced or absent; and
- the grading of ankle reflexes as normal, reduced or absent.

Patients with abnormalities should undergo a more complete neurological assessment. Cardiovascular autonomic neuropathy may be detected by testing heart rate control in response to deep breathing (paced respiration) or after standing from the lying position, and/or the circulatory response to the Valsalva manoeuvre. This may be important as a screen before a patient undergoes general anaesthesia, since those with cardiovascular autonomic neuropathy have an increased mortality risk from such anaesthesia.

*Intervention strategies*

The frequency, severity and progression of neuropathy are related to the degree and duration of hyperglycaemia, and are also a function of age (*165, 166*). Several small randomized studies have suggested that manifestations of neuropathy may be stabilized or improved by improved glucose control (*162*). A large, randomized, prospective, controlled clinical trial (the

Diabetes Control and Complications Trial) is currently being conducted in an effort to provide firm evidence that would confirm or refute this (*164*).[1] In the interim, efforts to improve glycaemic control seem warranted, particularly in asymptomatic patients. However, as noted in section 6.1.1, there is an increased risk of severe hypoglycaemia with intensive insulin therapy. Patients with autonomic neuropathy may have greater difficulty detecting hypoglycaemic symptoms and/or spontaneously recovering from hypoglycaemia. Thus, treatment goals must be carefully selected and individualized.

Aldose reductase inhibitors are now available in an increasing number of countries. They offer the potential for inhibiting the polyol pathway, one of the important pathways thought to lead to diabetic neuropathy, without incurring the risks of hypoglycaemia (*171*). Other interventions aimed at altering the pathophysiology of neuropathy are under evaluation.

Symptomatic and supportive treatments are necessary to reduce the burden imposed by diabetic neuropathy.

There should be early identification of those at risk of developing neuropathic foot problems and appropriate education of patients (see also section 6.2.5).

*Setting goals*

Realistic objectives must be chosen for any programme designed to prevent the onset or progression of diabetic neuropathy. In the early stage of distal sensorimotor neuropathy, the goals are early detection, halting disease progress and minimizing further deterioration. In the symptomatic stage, they include symptom assessment, halting disease progression, allowing nerve repair and regeneration, relief of symptoms and preventing further deterioration. In the severe stage, they include management of clinical symptoms, helping patients to overcome disability and to learn to have a limited expectation of full return of function, and preventing further deterioration and ulceration. (The prevention of disability is discussed in more detail in section 6.2.5).

*Potential obstacles to prevention*

Potential obstacles to prevention include:

- lack of awareness of the limb-threatening and disabling nature of diabetic neuropathy because the disorder is asymptomatic in its early stages;
- lack of awareness among primary care physicians of the benefits of timely detection and treatment;
- lack of the necessary skills in primary care physicians for detecting neuropathy;

[1] *Chairmen's note:* Since the meeting of the Study Group, the Diabetes Control and Complications Trial has clearly demonstrated that meticulous glycaemic control can decrease the rate of appearance of clinically significant neuropathy in people with IDDM (*153*).

- lack of economic resources to seek care;
- lack of neurologists to evaluate neuropathy quantitatively, e.g. by neurophysiological testing;
- lack of a realistic appreciation that interventions may halt progression but not necessarily reduce symptoms;
- feelings of hopelessness on the part of patients and health care providers.

*Needs*

There is a need:

- for data on the current prevalence of neuropathy and continued collection of such data for monitoring the effectiveness of interventions;
- to ensure the training of those who will educate patients and primary care physicians and the availability of neurologists to evaluate neuropathy;
- to educate patients and primary care physicians about the benefits and need for detection and treatment of neuropathy;
- to achieve good glycaemic control in an attempt to minimize the development of neuropathy;
- to reduce the economic barriers preventing patients from seeking appropriate care when needed.

*Evaluation and monitoring*

Evaluation and monitoring should include:

- objective programmes for educating and testing the knowledge of primary care physicians;
- evaluation of patients' knowledge about diabetic neuropathy and recommended care both before and after educational programmes;
- evaluation of the success of programmes by monitoring changes in behaviour;
- monitoring the cost-effectiveness of programmes.

*Conclusions*

The highest priority at present is the education of patients and their physicians about the potential for detection and treatment of early neuropathy. If the Diabetes Control and Complications Trial demonstrates that glycaemic control is beneficial in reducing the frequency or progression of neuropathy,[1] there will be a need to achieve tighter glycaemic control in those at risk, without increasing the risk of hypoglycaemia. Further studies to investigate the usefulness of therapeutic agents such as aldose reductase inhibitors should be encouraged, given that other current modes of therapy, apart from improved metabolic control, are purely symptomatic and do not influence the cause of the neuropathy.

[1] See footnote, page 61.

The likelihood of success in preventing and reducing the consequences of diabetic neuropathy will depend on the availability of resources to implement educational programmes and to monitor them continuously.

### 6.2.5 *Foot ulceration and amputation*

The problem of limb amputation in people with diabetes is of such a serious and global nature that a special section giving guidelines for prevention was felt to be warranted in this report.

*Background*

Diabetes is associated with increased frequency of lower-limb amputations, many of which are potentially preventable (*172*). Epidemiological data from the United States of America suggest that > 50% of the 120 000 non-traumatic lower-limb amputations in that country are associated with diabetes and that the overall risk of amputation in people with diabetes is 15 times that in people without diabetes (*170, 171*).

In Wisconsin, United States of America, the 4-year incidence of lower-extremity amputations varies from 2.4% in people with younger-onset IDDM to 4.4% in older-onset cases (*173*). The incidence is positively associated with duration of diabetes, glycaemia, blood pressure and cigarette smoking. In a study in Switzerland, 6% of lower-extremity amputations were performed in people below 44 years of age and 72% in those aged 65 years or older (*174*). In younger people, the direct cost of a below-knee amputation is about US$ 25 000 in Switzerland. In the elderly the cost may be higher because of the longer rehabilitation period. The costs associated with hospital treatment of foot lesions in people with diabetes were estimated to have exceeded US$ 200 million in the United States of America in 1980 (*170, 172*). Although the lower extremities are at high risk, upper limbs may also be affected, particularly in developing countries.

*Rationale for screening and intervention*

The underlying lesions that often result in chronic ulceration and amputation have been termed the "diabetic foot". This is defined as infection, ulceration and destruction of deep tissues, associated with neurological abnormalities (loss of pain sensation) and various degrees of peripheral vascular disease in the lower limb. A number of preventive strategies (careful self-examination, specially fitted shoes, minimization of trauma, etc.), earlier detection and more aggressive management of foot ulcer (e.g. local débridement, provision of special supports and early antibiotic therapy) will prevent or delay lower-limb amputations. In developing countries, lack of proper footwear and inadequate hygiene, together with poorly controlled diabetes, are a major cause of lower-limb amputations.

Although the control of neuropathy and arteriopathy in a given patient represents a long-term objective (years), the control of plantar ulcers and

lesions that could lead to amputation may be achieved in the short term (weeks). Studies have shown the financial benefit of prevention of amputation. Hospitalization for treatment of infection and/or amputation may often last several weeks. Ambulatory care and education may therefore save substantial amounts of money.

*Screening strategies*

The key to success in managing the diabetic foot is to organize a regular screening programme to identify all patients at risk of developing foot ulcers. Physicians should examine the feet of diabetic patients on a regular basis. In some situations it may be helpful to create a registry, if possible adapted to the local health care system, of all people with diabetes so that they may be called for regular screening and identified if they are at risk. Patients at risk should be seen regularly. Patients themselves should expect their physician to perform regular foot examinations.

Screening can be carried out by adequately trained observers, without complex technology. Simple classification schemes may be of value in identifying risk. One such system suggests four risk categories based on the presence of sensitivity to a standard monofilament or Riedel-Siefert graduated tuning fork, the presence of foot deformities, the presence of ulceration, and a past history of lower-extremity ulceration or amputation (*175*). Specialized centres are needed to make a precise diagnosis of leg and foot problems in diabetes, but the bulk of the preventive work should be carried out at the primary care level.

Patients at particular risk will exhibit one or more of the following features, assessed by simple inquiry and clinical examinations:

- a past history of foot ulcer;
- symptoms of neuropathy (tingling and decrease or loss of the sense of pain and touch) and/or ischaemic vascular disease (exercise-induced calf pain or icy foot);
- signs of neuropathy (hot feet, non-sweating skin, wasted muscles, clawed toes, hard skin over pressure points, bounding pulses or venous distension) and/or peripheral vascular disease (cold feet, shiny and thinned skin, absent pulses or atrophy of subcutaneous tissue);
- severe foot deformities in the presence of less severe neuropathy and/or peripheral vascular disease;
- other long-term complications of diabetes (renal failure, significant ocular involvement);
- other risk factors (decreased visual acuity, orthopaedic problems interfering with the correct care of the feet (*5*), such as arthritis of knee, hip or spine, poor footwear);
- personal factors (low socioeconomic status, being elderly or socially isolated, psychological attitudes of denial).

For the neuropathic foot, facilities for electrophysiological study and the quantitative assessment of vibration and thermal threshold are important

in research and differential diagnosis, but *not* in routine clinical management. Simple tools such as the graduated tuning fork (*175*) and standard monofilaments are useful for the semi-quantitative diagnostic evaluation of neuropathy. Diabetic patients who have significant vascular disease and ischaemia of the foot should have access to the modern investigative techniques of Doppler ultrasonography and arteriography where possible. Non-invasive angioplasty or surgical arterial reconstruction should be performed if indicated. In angiography, special attention should be paid to patients with nephropathy, even in its early stages, since radiopaque dye administration can provoke renal deterioration.

*Intervention strategies*

Diabetes is the major cause of non-traumatic amputation (*172*). Integrated health care (*10*) can contribute greatly to patients' quality of life and to reducing the cost of the disease (*176*). Such an approach can:

- prevent, or minimize, foot ulceration in patients with neuropathy;
- prevent, or minimize, ischaemic gangrene in patients with vascular disease; and thus
- prevent at least 75% of amputations of any part of a neuropathic foot or leg.

Every member of the diabetes care team should understand and practise the principles of foot protection. This is also valid for other health care providers, particularly those caring for the elderly. A specialist *foot care team* should be part of every comprehensive diabetes care service. In the treatment of established foot ulcers, early local débridement and aggressive antibiotic therapy should be considered. For resistant foot ulcers, special plantar supports or castings should be provided. Patients need to understand the importance of adhering strictly to the prescribed antibiotic regimen.

Since the majority of patients with foot problems also suffer from other diabetic complications, health care providers involved in foot care have to be fully aware of this situation and be able to take specific action.

The foot care team should consist of a physician, a nurse specialist or educator, and a chiropodist or podiatrist. In addition, the team should ideally have easy access to:

- an orthotist;
- a vascular radiologist with facilities for non-invasive intra-arterial angioplasty;
- a vascular surgeon to offer reconstruction;
- an orthopaedic surgeon to correct severe structural abnormalities; and
- physiotherapists for the rehabilitation of patients after amputation; because of their age, usually greater than 55 years, and associated long-term complications (visual problems, postural hypotension, etc.) the rehabilitation period is often several months long.

If no specialists are available, experienced general practitioners and home visiting nurses can manage at least two-thirds of cases, providing they have received 1 or 2 days formal training.

Many of the above health professionals and services will not be available in developing countries, where they are most needed. In this event, training of non-specialist health workers and simple direct instructions to patients themselves are likely to reduce the risk of serious tissue destruction.

As with other diabetic complications, the frequency of *follow-up* of foot complications will depend on their type and severity. For instance, patients with plantar ulcers should be seen at short intervals (1-3 weeks); those with loss of pain sensation but without local lesions may be seen every 3 months.

*Education* is the most important contribution to the prevention of foot lesions in diabetes. The first objective should be to increase the knowledge of all those who care for diabetic patients concerning the dangers inherent in the development of diabetic foot lesions and the different skills needed to examine feet and to treat lesions.

Another primary goal is to establish an educational programme for patients at special risk of developing foot ulcers. The programme should include:

- regular attendance by patients for the reinforcement of knowledge and of motivation for continuing to care for their feet;
- formal teaching sessions to explain the reasons for the vulnerability of the diabetic foot, and the importance of everyday matters such as suitable footwear and foot hygiene;
- the provision of appropriate written and/or audiovisual material.

Education of patients has to be centred on appropriate skills aimed at preventing foot lesions. Patients should learn:

- not to walk bare-footed;
- to examine shoes daily and look for foreign bodies;
- to avoid "bathroom surgery" (no scissors, no razor blades, no chemical skin loosener for hyperkeratosis);
- to treat fungus disease and apparently minor cuts early;
- to use a mirror to observe the plantar surface of the foot;
- to test the degree to which pain sensation has been lost;
- to prevent burns (no hot water or electric heaters).

Specific educational approaches are needed to help patients to compensate for the lack of pain sensation.

*Potential obstacles to prevention*

- Diabetic foot complications often require the attention of several specialists.
- Foot lesions are frequently not detected early enough, mainly because of lack of symptoms and signs. Once established, lesions may be

beyond the surgical capabilities of the general practitioner but not dramatic enough to receive timely attention by a surgeon, so that proper care may be delayed.

- Hospital care is often not oriented towards tertiary prevention of diabetic foot complications, which may not be curable and are often self-perpetuating.
- Medical teams often lack the elementary skills for diagnosis, follow-up and management of chronic foot lesions.
- Education of patients and their families has been shown to be helpful, but lack of signs and symptoms hinders early diagnosis and intervention.

*Needs*

There is a need for:

- a standard classification scheme for foot lesions associated with diabetes;
- epidemiological data obtained using standard techniques to detect and define lesions associated with the diabetic foot;
- accurate data on the prevalence, incidence and progression of lesions leading to lower-limb amputation;
- determination of the causes and pathophysiological mechanisms (neuropathy, ischaemia, infection, wound-healing failure) leading to diabetic foot problems;
- well controlled clinical trials on therapeutic approaches currently being advocated; and
- assessment of the knowledge of diabetic patients and primary care physicians regarding the detection and management of foot problems.

*Evaluation and monitoring*

Evaluation and monitoring should include:

- assessment of current screening methods and medical intervention strategies used to prevent lower-limb amputation;
- surveys of diabetic patients to evaluate post-intervention changes in knowledge, behaviour and outcomes regarding diabetic foot problems;
- assessment of the quality of diabetes control at the time of foot infection;
- assessment of quality of life after amputation and its social and economic consequences.

*Further studies*

Since education and training are major tools for initiating and pursuing tertiary prevention of diabetic complications, studies on the following would be useful:

- methods for teaching appropriate skills to health care teams;
- management of an interdisciplinary team;

- how to structure and manage the follow-up of patients at high risk of amputation;
- specific educational approaches for patients having lost pain sensation; and
- ways of reducing the high frequency of above-knee amputation by making surgeons more aware of the alternatives and through appropriate training.

# 7. Diabetes prevention and control programmes

## 7.1 Socioeconomic impact

The primary goal of preventive programmes is the reduction of human suffering. Few reliable data are available on the economic costs of diabetes, particularly from the developed world, and more information is urgently needed.

Costs can be divided into direct and indirect costs as shown in Table 4. *Direct costs* include emergency care, hospitalization, medical services, outpatient care, surgery, drugs, laboratory tests and equipment. *Indirect costs* include premature mortality, loss of working days resulting in loss of production and earnings, insurance payments, personal costs and intangibles such as pain and suffering (*22*). Many of these costs could be averted by adequate prevention programmes.

Recent data suggest that in the United States of America the costs of diabetes care are rising rapidly (*22, 177, 178*); in 1986 the direct costs were US$ 12 billion (US$ 7 billion for care and US$ 5 billion for complications) (*177, 178*). The proportion of estimated total health care costs related to diabetes is 3.6% in the United States of America and 4–5% in the United Kingdom (US$ 1.7 billion) (*179*). In Sweden, the estimated costs for 1978 were US$ 0.5 billion (at 1992 prices) for all diabetic people (*180*), and in

Table 4
**Elements of direct and indirect costs of diabetes**[a]

| Direct costs | Indirect costs | Intangibles |
|---|---|---|
| Emergency assistance | Premature mortality (years of life lost) | Pain |
| Hospitalization | Disability: | Suffering of family |
| Physicians' services: | — working days lost | Insurance |
| — long-term care | — leisure time lost | Personal costs |
| — surgery | — regular activity foregone | Income assistance |
| Laboratory tests | | |
| Drugs | | |
| Equipment | | |

[a] Adapted, with permission, from reference *177*.

Denmark, US$0.4 billion for elderly diabetic people alone. Recent estimates for the United Republic of Tanzania, where diabetes prevalence is only 0.9%, show that diabetes-related costs (one-third of which are related to IDDM) consume 9% of the national health budget; the absolute cost is nevertheless low since total health expenditure amounts to less than US$2 per person per year (A.B.M. Swai & K.G.M.M. Alberti, personal communication 1992). In 1992, estimated expenditure per diabetic patient per year was > US$3000 in the United States of America (*181*), US$2000 in Germany and US$156 in the United Republic of Tanzania (A.B.M. Swai & K.G.M.M. Alberti, personal communication 1992) and, in 1989, < US$100 in Bangladesh (M. Ibrahim, personal communication 1989). The amount spent naturally depends on the economic resources of the country, the proportion allocated to health care, and the competition for these resources.

Several studies have examined the costs of the specific complications of diabetes and the potential benefits of prevention. It has been estimated that screening for and prompt treatment of diabetic retinopathy in patients with IDDM in the United States of America can save US$60–1000 million annually, or US$10000 per diabetic person, as a result of prevented or delayed blindness (*146, 182, 183*). Similarly, foot care programmes offer major potential savings in hospital costs for amputation and rehabilitation. Thus in 1990, 9000 amputations in United States Veterans Administration hospitals, mostly preventable, cost US$225 million (G. Reiber, personal communication 1992). In 1985, there were 56000 below-knee amputations attributable to diabetes in that country (*156*).

Few cost estimates are available for primary and secondary prevention programmes aimed at changing people's lifestyles (*177*). In the United States of America, it has been estimated that these programmes cost US$11000 per "well-year" gained in established NIDDM. It is likely, however, that such programmes will be much cheaper in many other countries.

Could prevention pay for itself? Primary prevention of diabetes mellitus is likely to be both cost- and health-effective. Disease is prevented; therefore the costs of treating that disease are saved. Evaluations of the efficacy of secondary prevention programmes will probably show that they are not cheap. However, they will reduce human suffering and improve quality of life. Programme costs might be no greater than for other disorders, but precise data are urgently required so that the most cost-effective programmes can be adopted.

## 7.2 Goals and guidelines

The main goals for national diabetes prevention and control programmes are:

- to prevent as far as possible the development of diabetes in susceptible individuals and communities;

- to provide diabetes education to health care professionals;
- to maintain the health and quality of life of individuals with diabetes through effective patient care and education;
- to prevent and treat diabetes complications and thereby decrease morbidity, mortality and the cost of diabetes mellitus;
- to support research to prevent and control diabetes mellitus.

The support and understanding of national/local policy-makers and national organizations representing health care providers, health insurers, educators, diabetes patients, etc. are essential if diabetes prevention and control programmes are to be successful. It is also important to ensure strong leadership and to evaluate programmes at all stages.

Useful information on the development of such programmes is provided in the 1991 WHO document *Guidelines for the development of a national programme for diabetes mellitus* (*11*). A suggested outline for the development of a national programme is provided in Annex 4 of this report.

Needs and problems vary greatly between WHO regions and at the country and local level within regions, and these differences have to be taken into account when using the WHO guidelines in preparing specific national or local programmes.

The approaches adopted in the planning and implementation phases, the scale of operations and the targets set should be based on a careful analysis of the situation prevailing in a particular country. For example, it may be advisable to integrate diabetes prevention and control into existing services for other chronic diseases (see section 7.7).

It is recommended that, as part of its national programme, each country should establish special centres concerned with diabetes prevention and care to act as focal points for leadership, education, logistics and research relevant to the country.

Although research is desirable, it may not be feasible, nor a priority, in many developing countries. However, even small-scale research at the local level using carefully standardized methodology can make a valuable contribution, particularly in the fields of epidemiology and provision of health services. In many countries, improved application of available research findings could improve patient welfare considerably (see Annex 4).

## 7.3 Monitoring and evaluation

Monitoring and evaluation are essential to determine the feasibility and effectiveness of programmes (*11*). Policy-makers need to know whether a programme results in a change in the health status of the population, what kind of cost-effectiveness is attained and what reprogramming is indicated. Managers need to know whether the provision of services is adequate and whether the resources are adequate and appropriately deployed. The

evaluation process can be simplified by the use of measurable performance objectives at predetermined points in time. It is important to answer several questions regarding programme focus:

- Are the goals the same as when the programme started?
- Are the objectives still appropriate for the stated problems?
- Has the order of priorities changed?
- Have the strategies and activities collectively reduced or eliminated the problem addressed?
- Are there exceptional care providers in the country? Can their performance be used as a model in improving the performance of others?
- Is the responsible authority committed to the programme?
- Are the resources allocated to the programme sufficient?
- Are patients and patient organizations actively involved?
- Are patients able to exercise their rights and roles adequately?

An annual review of programme surveillance and management data at local, provincial and national levels will help to compare the actual and projected process and readily measured outcomes of the programme. Less frequent evaluation may be indicated for other outcomes such as blindness, amputation, chronic renal failure and diabetic ketoacidosis. Approaches for monitoring IDDM and NIDDM in the community are outlined in section 7.6.

Careful data analysis and evaluation are also essential for improving the quality of care. Reporting of both programme successes and failures to members of the diabetes professional community through regular publication channels or professional meetings will foster movement towards more effective approaches and so save time and resources.

## 7.4 Major obstacles

There are a number of potential obstacles that may be encountered during the implementation of diabetes prevention and control programmes. Difficulties may stem from the different partners involved as well as from the type of prevention undertaken (primary, secondary or tertiary). A summary of these variables is given in Table 5.

Many obstacles are common to different partners, while each specific group may encounter its own difficulties.

### 7.4.1 *Common difficulties*

*Lack of data*

Information about the disease and its prevention and control and data on the baseline situation and on the progress and quality assessment of prevention and control programmes are often inadequate. Data are needed by all parties involved but in particular by politicians, purchasers and providers, so that they are aware of the problems and take appropriate action.

Table 5
**Interest and skill of the partners involved in diabetes prevention in terms of the difficulties encountered in their respective roles**

| Partners | Primary prevention | Secondary prevention | Tertiary prevention |
|---|---|---|---|
| Community | ☹ | ☺ + | ☺ + + |
| Politicians | ⚠ | ⚠ | ⚠ |
| | (lack of facts, knowledge, motivation) | | |
| Purchasers: | | | |
| — private | ☹ | ☺ + | ☺ + |
| — national programme | ☹ | ☺ + | ☺ + |
| Media: television, radio, press | ☹ ⚠ | ☹ ⚠ | ☹ ⚠ |
| | (lack of facts, little progress reportable, little public interest, limited media interest) | | |
| Providers: | | | |
| — planners | ☺ + | ☺ + | ☺ + |
| — doctors | ☹ | ☺ + + | ☺ + |
| | (doctors often have poor skills in interdisciplinary management of chronic care) | | |
| — nurses | ☹ | ☺ + | ☺ + + |
| — others (e.g. podiatrists) | ☹ | ☺ + | ☺ + + |
| Patients | ☹ | ☺ + | ☺ + + |

*Key*

☹ Little or no interest or skill

☺ + Interested and/or skilled

☺ + + Very interested and/or skilled

⚠ Interest is stimulated only by hard facts and by external motivation

The situation can be improved by training in data collection and quality assessment, building up banks of specific data, improving feedback, and adapting communication strategies to different target groups.

*Lack of knowledge*

Appropriate knowledge is needed by all partners, in particular health care providers and patients. It is therefore essential to provide suitable

continuing education to all partners. There is also a need to develop, evaluate and promote new, interactive educational strategies.

*Lack of specific skills*

Health care providers and patients require appropriate skills for the management of diabetes and its acute and long-term complications. Training frequently gives greater emphasis to the acquisition of knowledge than to the acquisition of specific skills. Training curricula should be improved to ensure that health care providers acquire the necessary skills and learn how to communicate better with patients.

### 7.4.2 *Obstacles within specific groups*

*Patients*

In addition to a lack of knowledge and skills, many patients have difficulty in coming to terms with the implications of a lifelong disease and the self-awareness and commitment it will require. Further, patients' needs may be in conflict with traditional beliefs in the community, and modern approaches to diabetes care may clash with those of alternative medical systems.

Patients need constant guidance and psychosocial support. Health care providers need to be aware of local beliefs and, where necessary, to encourage changes.

*Health care providers*

Experience shows that health care providers are not always motivated to evaluate their own performance or to try to improve. Often, health care providers are not aware that their care is mediocre, and they neither establish close links with centres of excellent practice nor attempt to analyse such practice. These centres themselves may not actively promote their methods.

Training of health care teams to apply quality development schemes in their daily practice will lead to improvements in care.

## 7.5 Continuous quality development

In many countries, health care services are inadequate and of poor quality. Even in the industrialized countries, objective data on the quality of health care systems are limited. Registers are mainly local, not always comparable, and cover only few aspects of the diseases recorded. This is a major obstacle to all efforts to improve the quality of health care.

Although data are available from epidemiological studies on the prevalence and incidence of diabetes, and some countries have registers of varying completeness on IDDM and some of the complications of diabetes, the picture is usually incomplete. A major requirement of any diabetes prevention and control programme is, therefore, a quality

development scheme which includes the setting of goals for improvements in quality of care and continuous monitoring (*184, 185*).

The scheme should operate at all levels of health services and should include health care managers and providers and patients. It should be based on self-assessment and self-regulation rather than on external control and legislation. Some countries have already included quality development in their health policies and remuneration schemes.

Instruments for monitoring quality development, based on patient information sheets and subsequent computer analysis, have been developed by various groups. Some have been broadly evaluated for practicability and usefulness, and several have proved successful in local or regional use for some time. Further efforts are needed to develop standard methods for application worldwide at national and local level.

## 7.6 Monitoring insulin-dependent and non-insulin-dependent diabetes mellitus in the community

Monitoring of IDDM and NIDDM is critical for understanding the etiology and natural history of these conditions and for evaluating preventive actions. Standard monitoring procedures include registries for IDDM and diabetes surveys for NIDDM. These approaches require unbiased case ascertainment that is as complete as possible in order to determine accurately the number of cases or rate of diabetes in the community. Where existing methods are inadequate and are assumed to give a point estimate not close enough to the truth, methods such as "capture-recapture" (see section 7.6.1 and Fig. 8) can be very helpful and are recommended. However, there are limitations to the capture-recapture method in situations where the primary and secondary sources are strongly interrelated or the quality of the basic data is very poor.

### 7.6.1 *Insulin-dependent diabetes mellitus*

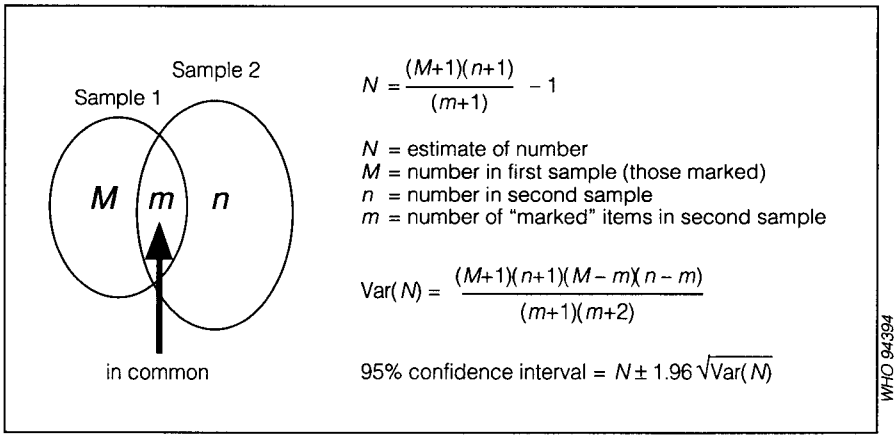
IDDM registries are surveillance systems through which new cases are actively identified (*5*). The goal is to identify and count as close to 100% of actual cases of IDDM as possible, with at least 90% ascertainment from the primary source. In addition a secondary source for case ascertainment is needed, which should be independent of the primary source. It is usually much less costly to employ two or more incomplete sources for case ascertainment than to try to count all cases from a single source.

When two sources are available for case ascertainment, the capture-recapture approach can be applied (see Fig. 8). With this approach the proportion of cases not counted can be estimated and the correct frequency of the disease can be calculated (*186*).

For adults, as opposed to children and adolescents, internationally accepted criteria for monitoring IDDM incidence have not yet been developed. IDDM registries are operating for adults in only a few countries

Figure 8

**The capture–recapture method for case ascertainment in surveillance studies**[a]




[a] Adapted, with permission, from reference *186*. In the context of diabetes epidemiology, *N* would be the final estimate of the number of people with diabetes in the total population, *M* the number ascertained from the primary source of information, *n* the number ascertained from the secondary source, and *m* the number common to both sources. A key assumption of the technique is that the two sources of information are truly independent.

at present. They initially register all insulin-treated cases of diabetes; a certain period (e.g. about one year) after diagnosis, insulin-dependency is assessed and cases are classified accordingly.

### 7.6.2 *Non-insulin-dependent diabetes mellitus*

For estimating the prevalence of NIDDM and IGT, standardized surveys are the method of choice. To monitor changes in prevalence, repeated surveys at regular, for instance 5-year, intervals are needed (see Annex 2). It is better to base such surveys on independent, randomly selected population samples each time, rather than on longitudinal follow-up of a single cohort. Careful attention should be paid to sample selection, size and representativeness of the population and subgroups under study, participation rate and the consistency of survey methods. A model protocol for a diabetes survey has been described elsewhere (*187*). Usually a diabetes survey should be part of a more comprehensive survey of risk factors for cardiovascular and other noncommunicable diseases.

Because of costs, sample sizes will be relatively small. Typically, 60–80% of the people in a selected sample will actually be tested. People with known diabetes may differ in their response from people without diabetes to an invitation to participate in a diabetes survey. Moreover, it may sometimes be inadvisable to undertake an OGTT in those with known diabetes who participate in the survey. Therefore, the inclusion of readily obtainable information about known (treated) diabetes from another source (e.g. diabetes clinics, physicians, pharmacies) in prevalence surveys and

application of the capture–recapture method may be useful. Routinely collected information can serve as a secondary source of ascertainment of diabetic cases in the community, and can be used to estimate accurately the degree to which people in the study sample fulfil the criteria for diabetes.

## 7.7 Integrating diabetes prevention and control programmes with programmes for other noncommunicable diseases

WHO and national health authorities recognize two approaches to the prevention and control of noncommunicable diseases: "vertical" programmes for single diseases or single groups of conditions, such as cardiovascular diseases, cancer and diabetes; and integrated "horizontal" programmes for the control of several different noncommunicable diseases, epitomized by WHO's integrated programme for community health (INTERHEALTH) (*9*).

The two approaches are complementary, and the decision as to their relative importance in a given community will depend on a variety of local circumstances (Table 6). Generally, the integrated approach is most effective at the primary level of prevention and care, whereas the vertical approach is most useful at the secondary and tertiary levels. However, both approaches have relevance at all levels of health care.

Integrated programmes are particularly suitable for communities at the early stages of the epidemiological transition from infectious to non-infectious diseases, and in those in which resources are limited, in which the majority of care is given at the primary level, and in which a variety of noncommunicable diseases coexist, so that common therapeutic and preventive approaches are feasible. Specific consideration of the problem of diabetes is recommended at all levels of the health system in any community in which the disease has assumed public health

Table 6
**Factors favouring vertical and integrated approaches to diabetes care programming**

| Vertical approach: disease-oriented | Integrated approach: health-directed |
|---|---|
| Optimal health care delivery system at primary, secondary and tertiary levels | Organized and functional primary health care system |
| Diabetes as the predominant noncommunicable disease | Many coexisting noncommunicable diseases with clustering of risk factors |
| High health expenditure as a proportion of gross national product | Low health expenditure as proportion of gross national product |
| Optimal referral and linkage services to secondary and tertiary care | Referral services in the process of development |
| Political support and leadership available for programme development | Political support and leadership available for intersectoral coordination and programme development |

prominence, in particular where diabetes has emerged as the major chronic disease, where diabetic people are normally referred to diabetes centres and other centralized institutions, and where resources are available for the specialist services that have been developed for diabetes care. In some communities, diabetes (particularly NIDDM), hypertension and obesity have emerged as major, coexistent health problems, and the simultaneous development of parallel programmes for these conditions may be the most efficient approach (*9, 188*).

The development of a successful community-based diabetes programme with strong political support and leadership can provide an excellent model for the later development of allied programmes for other noncommunicable diseases. Features that recommend diabetes programmes as models include: the relatively clearly defined classification of the disease, the availability of process and outcome indicators, the wide range of specialists and services required for successful management of diabetes, and the opportunities for cost-saving during its chronic course.

# 8. Research needs

## 8.1 Basic research

1. Exciting developments are occurring in molecular biology which have allowed the identification of genetic markers for many diseases. Current efforts to identify markers and the gene(s) responsible for susceptibility to both IDDM and NIDDM should be intensified. This will allow precise identification of those at risk and the focused implementation of primary prevention strategies. It will also allow more precise definition of the various types of diabetes.
2. The cellular mechanisms underlying insulin resistance and impaired beta-cell secretion require identification. This will allow rational drug design for affected individuals.
3. The immune and other mechanisms responsible for beta-cell destruction in IDDM and the environmental triggers need to be identified, and potential mechanisms of beta-cell regeneration investigated.
4. The precise mechanisms whereby diet and physical activity influence NIDDM and IGT require further elucidation.

## 8.2 Epidemiological research

1. Studies of the natural history of diabetes, using standardized methods, are still needed in diverse ethnic groups.
2. More detailed information is needed on the role of environmental factors (e.g. nutrition, viruses, chemicals) in the genesis of IDDM.

3. More detailed information is required on the role of different nutritional factors in the genesis of NIDDM and malnutrition-related diabetes mellitus, in particular during pregnancy and early life.
4. Studies are needed to elucidate the mechanisms whereby specific complications develop, and to identify genetic markers and other factors influencing the risk of complications.
5. Further studies are needed to establish the causes of heterogeneity of IGT.
6. The nature of the increased susceptibility to cardiovascular disease in diabetes requires further exploration through careful study of risk factors in societies with high and low prevalences of cardiovascular disease.
7. There is a need to establish the precise glucose levels or the range of levels at which the risk of specific complications becomes significant.
8. The level of glucose intolerance that puts the fetus and mother at risk during pregnancy needs further definition in different ethnic groups.
9. There is an urgent need to develop better diagnostic tools than the oral glucose tolerance test and determination of fasting glucose levels.
10. To facilitate future epidemiological research, consensus is needed on appropriate standardized methods for the ascertainment and staging of diabetic complications.
11. Simple, robust, sensitive and specific methods of measuring insulin resistance in individuals and in population studies should be developed.

## 8.3 Intervention research

1. Major collaborative long-term studies, using different preventive strategies, are essential for progress in the primary and secondary prevention of diabetes.
2. There is a need to develop and evaluate better pharmacological agents for improving insulin secretion, enhancing insulin sensitivity, preventing beta-cell destruction, promoting beta-cell regeneration or repair, and interrupting pathways leading to the various complications of diabetes.
3. The usefulness of insulin sensitivity enhancers in treating IGT needs to be investigated.
4. Different models of care for diabetes should be compared and evaluated in different societies.
5. Studies of interventions to prevent atherosclerosis have not specifically included diabetic men and women. However, since there is a greatly increased relative risk of atherosclerosis in people with diabetes, there

is a need to study whether intervention to reduce atherogenic risk factors can lower this risk.

6. Studies to evaluate the efficacy of traditional medicine and non-pharmacological methods in preventing NIDDM are needed.

### 8.4 Health services research

1. More effective means are required of altering, through the population approach, aspects of lifestyle that affect health.
2. The place of diabetes within an integrated noncommunicable disease programme in community care should be evaluated.
3. Studies are needed of the most effective use of health care personnel in diabetes care at primary, secondary and tertiary levels.
4. The role of and need for tertiary referral centres for diabetes in every country should be evaluated.
5. Studies are needed to evaluate community-based programmes for diabetes prevention and control that have been integrated with national primary health care programmes.
6. The role of diabetes educators, dieticians and diabetes nurses in the care of people with diabetes should be examined, in particular to assess the potential for involving diabetes nurses in regular treatment.
7. Studies are needed to examine ways of ensuring that the rights of people with diabetes are respected and that they can play a full role in their own care.

## 9. Recommendations

The heavy burden of morbidity and premature mortality now caused by diabetes mellitus has resulted in high costs all over the world, in terms of both medical care and loss of human resources. Improved understanding of the causes and mechanisms of the major types of diabetes mellitus provides a basis for prevention. National health departments, diabetic patients' associations and health professionals should be informed of the existing potential for preventing diabetic complications and urged to implement comprehensive prevention strategies. Adequate financial and other resources should be allocated for developing preventive programmes and, where appropriate, for their integration with prevention and control programmes for other noncommunicable diseases within primary health care.

The Study Group made the following specific recommendations:

1. All countries should establish the magnitude and costs of diabetes mellitus and its consequences in their societies.

2. Governments are urged to initiate primary prevention studies on non-insulin-dependent diabetes mellitus, in particular in high-prevalence populations and populations undergoing major lifestyle changes.
3. Governments should establish national diabetes programmes encompassing primary, secondary and tertiary prevention components, where possible integrated with other noncommunicable disease programmes.
4. Studies should be initiated: (a) to develop more effective programmes to sustain lifelong behavioural changes in relation to physical activity, nutrition, weight control and smoking reduction; and (b) to identify and remove obstacles to the prevention of diabetes mellitus.
5. National targets and programmes should be established for reducing the rates of acute hospitalization, loss of vision, kidney failure, amputation, heart attack, stroke and adverse outcome of pregnancy in people with diabetes.
6. Pregnant women should be screened at the beginning of the third trimester of pregnancy by means of an oral glucose tolerance test, so that gestational diabetes mellitus and gestational impaired glucose tolerance can be identified and management initiated.
7. Women with impaired glucose tolerance detected during pregnancy are a high-risk group, and active measures should be taken to prevent their subsequent development of diabetes mellitus.
8. People with impaired glucose tolerance are at high risk of developing diabetes mellitus. Further research on the prevention of diabetes in this group is recommended.
9. More special centres should be established, particularly in developing countries, to promote appropriate health care in diabetes and education of both diabetic patients and those involved in their care.
10. In all countries, the availability of insulin as an essential life-saving drug should be ensured, without imposition of taxes or restrictions regarding the transfer of technology for its manufacture.
11. Technologies necessary for the secondary and tertiary prevention of diabetes mellitus and its consequences, e.g. laser therapy, should be available in all countries.
12. The classification and diagnostic criteria for diabetes mellitus should be reviewed in the light of increasing knowledge of its causes.
13. Methods and criteria for ascertaining and staging diabetic complications should be standardized.
14. The possible use of genetic and other predictive markers in the prevention of diabetes mellitus should be investigated.

15. The roles of members of the health care team at primary, secondary and tertiary levels of care should be evaluated.
16. The potential for involving diabetes nurses in the treatment and counselling of people with diabetes should be investigated.
17. Research should be conducted to develop strategies for the prevention of diabetes and its consequences that are appropriate to local conditions.
18. Research should be undertaken to determine how the effects of home blood-glucose monitoring and self-care in general can be measured and integrated in national plans.
19. Specific research studies should be conducted on the prevention of insulin-dependent diabetes mellitus.
20. Diabetes registers should be established in the most cost-effective way.

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Annex 1

# The oral glucose tolerance test

The oral glucose tolerance test (OGTT) is principally used for diagnosis when blood glucose levels are equivocal, during pregnancy, or in an epidemiological setting to screen for diabetes and impaired glucose tolerance.

The OGTT should be administered in the morning after at least 3 days of unrestricted diet (more than 150 g of carbohydrate daily) and usual physical activity. The test should be preceded by an overnight fast of 10–16 hours, during which water may be drunk. Smoking is not permitted during the test. The presence of factors that influence interpretation of the results of the test must be recorded (e.g. medications, inactivity, infection).

After collection of the fasting blood sample, the subject should drink 75 g of glucose (or partial hydrolysates of starch of the equivalent carbohydrate content) in 250–300 ml of water over the course of 5 minutes. For children, the test load should be 1.75 g of glucose per kg of body weight up to a total of 75 g of glucose.[1] Blood samples must be collected 2 hours after the test load; additional samples may be taken during the test for clinical or research purposes, but are not necessary for diagnosis.

Unless the glucose concentration can be determined immediately, the blood should be collected in a tube containing sodium fluoride (6 mg per ml of whole blood) and centrifuged to separate the plasma; the plasma should be frozen until the glucose concentration can be estimated. For interpretation of results, refer to Table 2 on page 17 of the main report.

[1] The International Study Group for Diabetes in Children has recommended a test load for children of 45 g/m$^3$ body surface area (Weber B. Standardization of the oral glucose tolerance test. *International Study Group for Diabetes bulletin,* 1978, 2:23–26).

Annex 2

# Planning and carrying out an epidemiological survey[1]

## Planning a study

Specify:
- data to be collected
- survey procedures
- statistical methods
- laboratory methods.

Prepare a written protocol.

Obtain:
- permission
- funds.

Select:
- survey sample
- team leader.

Estimate costs:
- preparation of protocol
- training
- printing and stationery
- equipment and consumables
- staff salaries and travel
- local assistance and expenses
- local transport
- shipping of samples
- laboratory analysis
- data analysis
- preparation of report
- publication
- inflation
- contingencies.

## Conducting a study

### *Selecting the survey sample*

Many practical considerations dictate the choice of the sample. Two common approaches are simple random sampling and cluster sampling. For diabetes surveys, which are generally performed at a central survey site, the cluster sampling approach has many practical advantages.

### *Sample size determination*

Information is provided in a set of tables in Lwanga SK, Lemeshow S. *Sample size determination in health studies: a practical manual* (Geneva, World Health Organization, 1991).

[1] Adapted, with permission, from King H. Further epidemiology. In: *Proceedings of the Japan–US diabetes epidemiology training course*. Tokyo, Shinohara Publishers, 1992: 17–20 (Japan Diabetes Foundation Publication Series no. 1).

Armitage has shown that, for a prevalence of 4%, even a sample of only 500 will give a 95% confidence interval of 2.3-5.7%; on the other hand, for a prevalence of 1%, a sample size of 500 would be insufficient to estimate the prevalence in the population (Armitage P. *Statistical methods in medical research,* 2nd ed. Oxford, Blackwell, 1987). This illustrates the general point that the rarer the condition the greater the sample size required, but that for moderate- or high-prevalence populations, relatively small samples can give useful results providing that the samples are unbiased and appropriate survey methods are used.

### *Preparing the community*

Always take plenty of time to explain the purpose of the study and what is expected of participants.

### *Training*

This is essential for those conducting the study, and a formal assessment of operator accuracy is recommended for all measurement procedures.

### *Selecting the survey site*

This should take into account the need for running water, privacy, quiet and light control.

### *The survey form*

This should be carefully designed and preferably "self-coding", with numerical choices provided for answers for direct transfer to the computer.

### *The oral glucose tolerance test and other examinations*

These are of prime importance in diabetes surveys and should be accurate and repeatable.

### *The survey procedural flow chart*

It is important to determine the rate-limiting steps in the survey.

### *Non-response*

No matter how carefully a community has been prepared for a field survey, there will always be some people who are unable, or unwilling, to participate. In order to identify possible bias, the characteristics of non-responders should be compared with those of responders with respect to key variables (age, family history of diabetes, etc.).

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For a more detailed description of field survey methods for diabetes and related noncommunicable diseases, see: Dowse GK, Zimmet P. A model protocol for a diabetes and other noncommunicable disease field survey. *World health statistics quarterly,* 1992, 45:360-372.

Annex 3

# Screening for diabetes mellitus [1]

## General principles

| | |
|---|---|
| Purpose: | To detect cases of disease earlier than they would normally come to the attention of health care providers, with a view to improving outcome. |
| Choice of population: | – Volunteers<br>– General population<br>– High-risk subgroups<br>– High-risk individuals. |
| Choice of tactic: | – Routine or "campaign"<br>– Single- or multiple-disease strategy. |
| Choice of test: | – Sensitive (i.e. few false-negatives) if missing a case would have serious consequences<br>– Specific (i.e. few false-positives) if a mistaken diagnosis would have serious consequences. |
| Questions to be answered: | 1. Can health services cope with the load?<br>2. Does earlier treatment improve prognosis? (Note that earlier diagnosis may lead to apparently longer survival, without truly improving prognosis.)<br>3. Is the test acceptable?<br>4. Is uptake seen in at-risk sectors of the community?<br>5. What is the cost:<br>– to health services?<br>– to respondents?<br>6. What is the yield in terms of:<br>– reduction in costs?<br>– improvement in survival?<br>– improvement in quality of life? |

## Desirable characteristics of disease-screening programmes

### *Disease characteristics*

- The disease should be an important public health problem in terms of prevalence, severity (attributable morbidity and mortality), and economic and social cost to the community in question.
- The natural history of the condition should be adequately understood, particularly the rate and determinants of progression from inapparent to symptomatic disease.
- There should be a detectable preclinical phase to the condition.
- A safe, accessible and effective form of treatment should be available.

[1] Adapted, with permission, from King H. Further epidemiology. In: *Proceedings of the Japan–US diabetes epidemiology training course*. Tokyo, Shinohara Publishers, 1992:17–20 (Japan Diabetes Foundation Publication Series no. 1).

- There should be clear indications of when, how and in whom to use the treatment – it should necessarily improve the course and prognosis of the condition in presymptomatic individuals.

***Test characteristics***

- The test should be safe and acceptable.
- It should detect presymptomatic disease with appropriate validity (sensitivity and specificity) and reproducibility.

***Programme and health system characteristics***

- Facilities and staff should be available for definitive diagnostic testing and subsequent treatment of individuals whose test results are positive.
- Costs of screening, subsequent diagnostic testing and resultant treatment should be acceptable in comparison with the costs that would have been incurred in the absence of the programme, and/or in the face of alternative use of such resources.
- Screening should be a continuing process; there is therefore a need for some form of systematic integration into health care services and training of appropriate personnel. Moreover, the programme should reach its target population.

Annex 4

# Suggested outline for the development of a national programme for diabetes prevention and control

1. An officer responsible for national liaison and for liaison between WHO and government is appointed.

2. The national liaison officer acquires knowledge of major diabetic care activities in his or her country and identifies local representatives (professional, political, lay) willing to participate actively in the programme (i.e. to champion the cause). Activity will be concentrated around diabetes centres that collaborate closely with providers of primary health care to treat and educate patients.

3. The national liaison officer convinces the government health authorities to invite and pay for 5–10 of these representatives to attend a national meeting to prepare a proposal for a national diabetes programme.

   Attendance:
   - national liaison officer (chairman)
   - 2–4 health authority representatives
   - 5–10 local representatives
   - 1–2 representatives of WHO and the International Diabetes Federation (if required).

   Goals:
   - to set preliminary targets for the country
   - to develop a proposal for a national action plan
   - to assign responsibilities for work on the different parts of the proposal
   - to nominate a task force for the completion of the proposal
   - to prepare nominations for a national steering committee.

   Suggested parts of the proposal:
   (a) Situation analysis
   (b) Objectives and targets
   (c) Role of/links with the government health authority
   (d) Strategies for:
      - primary prevention (public awareness, lifestyles)
      - secondary prevention (special risk groups)
      - tertiary prevention (prevention of complications)
   (e) Actions: again for primary, secondary and tertiary prevention
   (f) Monitoring and evaluation:
      - process/outcome indicators
      - development of a diabetes registry
   (g) Time frame
   (h) Organization, management, responsibilities
   (i) Role of patients and patients' organizations

(j) Budget

For further details readers are referred to *Diabetes care and research in Europe: the St Vincent Declaration action programme* (unpublished document EUR/ICP/CLR 055/3; available on request from the WHO Regional Office for Europe, Copenhagen, Denmark) and *Guidelines for the development of a national programme for diabetes mellitus* (unpublished document WHO/DB/DM91.1; available on request from Division of Noncommunicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland).

4. The task force completes the proposal, specifically checking the availability of resources, identifying critical resources and re-calculating the budget.

   The task force discusses with the health authority the cost of the next steps and the whole programme in relation to the benefits expected and how the programme can be funded.

   The following steps take place after approval of funding.

5. The proposal is mailed, with a request for comments, to all parties interested in diabetes care in the country, namely:
   - health authorities
   - diabetologists and their associations
   - patients' organizations
   - nursing associations
   - health educators
   - health insurers
   - industry
   - WHO and the International Diabetes Federation.

6. The comments are condensed by the task force and included in a revised proposal which is again mailed to all parties.

7. The health authorities invite 30–100 representatives of the interested parties to a national consensus meeting where the proposal is discussed in depth.

8. The task force condenses the discussions of this meeting into the proposal, which is now called the national diabetes action plan. This is again circulated for comment.

9. The task force includes only important additions, and finalizes and publishes the national diabetes action plan as the national implementation document.

10. Implementation of the programme, according to the phases of the action plan, is organized by the task force and supervised by the steering committee.

11. Outcome analysis and evaluation indicate the progress of the programme. Follow-up should be continued and results should be compared at the international level. Intermediate reports can be given at appropriate regional, national and international meetings.