Diabetes mellitus

Report of a
WHO Study Group

World Health Organization
Technical Report Series
727

World Health Organization, Geneva 1985
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Geneva, 11–16 February 1985

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DIABETES MELLITUS

Report of a WHO Study Group

A WHO Study Group on Diabetes Mellitus met in Geneva from 11 to 16 February 1985. Dr Lu Rushan, Assistant Director-General, opened the meeting on behalf of the Director-General.

1. INTRODUCTION

Diabetes afflicts large numbers of people of all social conditions throughout the world. The personal and public health problem of diabetes, already of vast proportions, continues to grow despite of exciting advances in the past few years in virtually every field of diabetes research and in patient care (e.g., improved treatment, protection against complications, increased self-care, and even primary prevention of some forms of diabetes).

The main aims of the Study Group were: to review the advances in the understanding of diabetes mellitus and its treatment; to seek ways to use the increased scientific and technical knowledge of the disease to benefit diabetics; and to update the second report of the WHO Expert Committee on Diabetes Mellitus published in 1980 (7).

The underlying cause of diabetes is the defective production or action of the hormone insulin. A major scientific advance has been the identification and mapping of the gene in man that codes for the production of insulin. The human insulin gene can be synthesized in the laboratory; its insertion into a bacterial host by ingenious techniques is now the basis of an entirely novel industrial process for the manufacture of the hormone. The great majority of the world’s insulin is still extracted from animal pancreas, but increasing amounts, theoretically limitless, are now being produced by biotechnology. Yet, despite this new source of supply, diabetics still die for want of insulin in many countries of the world.

A major step towards the prevention of the insulin-dependent form of diabetes is the ability to identify people who are genetically susceptible to the disease. Such people appear to have defective immunological mechanisms and, under the influence of some environmental “trigger”, attack their own insulin-producing cells.
With further research, it should be possible to prevent such attacks or to control the self-damaging process before the disease is irreversibly established.

It is misleading to think of diabetes as a single disease with a single cause. Epidemiological, clinical, and laboratory investigations have revealed evidence of several possible causal mechanisms. Recent studies have highlighted contrasts in the disease between and even within communities. This heterogeneity is illustrated in a section of this report dealing with malnutrition-related diabetes. Characteristically occurring in poor communities in tropical developing countries, malnutrition-related diabetes affects large numbers of young people, causing chronic ill-health and early death. Evidence suggests that this variant of diabetes is generated against a background of protein malnutrition and triggered by dietary and other pancreatic toxins. It should therefore be possible to prevent it. In contrast, the “epidemic” of diabetes among the inhabitants of some Pacific islands is strongly associated with altered life-style, particularly changed nutritional patterns, widespread obesity, and reduced physical activity. Prevention of this type of diabetes will require the effective nutritional counselling of whole populations.

Prevention of diabetes still lies in the future and, until then, tens of millions will continue to suffer from the disease. Every effort must be made to cure as many as possible or, failing that, to alleviate the associated disabilities and to prevent premature death, so that the diabetic can play a productive and fulfilling role in society. Priorities in finding solutions to these problems depend upon the level of technical and economic development in different societies, but some immediate action could be taken by all. A prime requirement is the provision of the means of diagnosing the disease, closely linked with the application of the knowledge and skills necessary for its management and supervision. The development of simple methods for measuring glucose and estimating glycated haemoglobin offers new opportunities for diagnosis and control of the disease. Suitable instruction on how to use new diagnostic methods can be integrated into existing or evolving programmes of community disease control. Such programmes should encourage the patient to play the central role in diagnosis and control of the disease. However, these basic services are unavailable to the great majority of diabetics. A group of experts can propose strategies and schemes for diagnosis and care but their implementation is a matter for national governments and health agencies.
The second report of the WHO Expert Committee on Diabetes Mellitus (1) called attention to the need to improve the prospects for diabetics as regards health and the quality of life, and recommended how this could be achieved. Subsequently, in association with the International Diabetes Federation (IDF), WHO has sponsored a growing range of activities, including international, regional, and national educational courses, seminars, scientific meetings, and workshops on the clinical, technological, epidemiological, and public health aspects of diabetes. A network of WHO Collaborating Centres in Diabetes Mellitus has been established covering many aspects of diabetes, and future plans and priorities have been formulated in a WHO/IDF Programme for diabetes,\(^1\) elements of which are included in this report. The Programme for diabetes is a guide for action not only for WHO and IDF but also for regional, national, and even local health authorities who wish to tackle the enormous health problems of diabetes.

Globally, there are at least 30 million diabetics, the great majority of whom lack even the rudiments of care. All of these could be helped. Lives could be saved and chronic disability prevented. This report aims to review current knowledge of the problems and to define programmes of action that could be immediately undertaken in a highly profitable commitment of human skills and resources.

2. DEFINITION, DIAGNOSIS, AND CLASSIFICATION

2.1 Definition of diabetes mellitus

In the untreated state, diabetes mellitus is recognized by chronic elevation of the concentration of glucose in the blood (hyperglycaemia). This is sometimes accompanied by symptoms of severe thirst, profuse urination, weight loss, and stupor, culminating in coma and death in the absence of effective treatment. More often, presenting symptoms are much less severe without disturbance of consciousness; occasionally symptoms are totally absent. The high concentration of blood glucose and other biochemical abnormalities result from deficient production or action of insulin, a hormone that controls glucose, fat, and amino acid metabolism. Several processes

can cause the diabetic state. The severity of its symptoms is largely determined by the degree to which the insulin action is deficient (see section 5). Characteristically, the diabetic has a long-term risk of developing progressive disease of the retina and kidney, damage to peripheral nerves, and aggravated atherosclerotic disease of the heart, legs, and brain (see section 8).

2.2 Diagnosis and diagnostic criteria

2.2.1 Clinical diagnosis

The clinical diagnosis of diabetes is often prompted by symptoms such as increased thirst and urine volume, unexplained weight loss and, in severe cases, drowsiness and coma; high levels of glycosuria are usually present. A single blood glucose estimation in excess of the diagnostic values indicated in Fig. 1 (black zone) establishes the diagnosis in such cases, as it may also do when symptoms are trivial or absent. Fig. 1 also defines levels of blood glucose below which a diagnosis of diabetes is unlikely. Only if blood glucose values lie in the uncertain range (i.e., between the levels that establish or exclude diabetes) need an oral glucose tolerance test (OGTT) be considered in order to establish diagnostic status (see Annexes 1 and 2). It is often sufficient to measure the blood glucose values only after fasting and at 2 hours after a 75 g oral glucose load. The other values measured in the full OGTT are not required to establish a diagnosis but may serve to confirm it. Diagnostic interpretation of the OGTT response is shown in Table 1.

The clinician must always feel confident that the diagnosis of diabetes is fully established since the consequences for the patient are considerable and lifelong. The requirements for diagnostic confirmation for a patient presenting with severe symptoms and gross hyperglycaemia will differ from those for the asymptomatic patient with blood glucose values found to be just above the diagnostic cut-off values. For the asymptomatic patient, at least one additional test result with a value in the diabetic range is desirable, either from a random sample or from the OGTT. If such samples fail to confirm the diagnosis of diabetes mellitus it will usually be advisable to maintain surveillance with periodic retesting until the diagnostic situation becomes clear. In these circumstances the clinician should take into consideration such additional factors as
Fig. 1. Unstandardized (casual, random) blood glucose values*

<table>
<thead>
<tr>
<th>Glucose concentration (mmol/litre)</th>
<th>Whole blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>Capillary</td>
<td>Venous</td>
</tr>
<tr>
<td>Venous</td>
<td></td>
<td>Venous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.1 (200)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.8 (120)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (180)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 (80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 (80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (20)</td>
</tr>
</tbody>
</table>

*Blood glucose values in the second report of the WHO Expert Committee on Diabetes Mellitus (1) were rounded to the nearest mmol/litre. This decision was challenged on the grounds that it created comparatively large differences between the SI unit and the traditional unit (mg/dl) which could introduce potentially serious biases in diagnostic categories. For this reason, SI units have now been rounded to the nearest tenth of a mmol.

Table 1. Diagnostic values for the oral glucose tolerance test (see Annex 1)*

<table>
<thead>
<tr>
<th>Glucose concentration, mmol/litre (mg/dl)</th>
<th>Whole blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>Capillary</td>
<td>Venous</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>6.7 (120)</td>
<td>7.8 (140)</td>
</tr>
<tr>
<td>Capillary</td>
<td>6.7 (120)</td>
<td>7.8 (140)</td>
</tr>
<tr>
<td>2 hrs after glucose load</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>10.0 (180)</td>
<td>11.1 (200)</td>
</tr>
<tr>
<td>Capillary</td>
<td>10.0 (180)</td>
<td>11.1 (200)</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>6.7 (120)</td>
<td>7.8 (140)</td>
</tr>
<tr>
<td>Capillary</td>
<td>6.7 (120)</td>
<td>7.8 (140)</td>
</tr>
<tr>
<td>2 hrs after glucose load</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>8.7–10.0 (120–180)</td>
<td>8.9–12.2 (160–220)</td>
</tr>
<tr>
<td>Capillary</td>
<td>7.9–11.1 (140–200)</td>
<td>8.9–12.2 (160–220)</td>
</tr>
</tbody>
</table>

*See footnote to Fig. 1.

*For epidemiological or population screening purposes the 2-hour value after 75 g oral glucose 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.
family history, age, adiposity, and concomitant disorders before
deciding on a diagnostic or therapeutic course of action.

2.2.2 Epidemiological studies

For studies of the prevalence of glucose intolerance and diabetes,
individuals may be classified by their blood glucose concentration
measured after an overnight fast, then 2 hours after a 75 g oral
glucose load. Since the fasting state can rarely be assured, and
because of the strong correlation between fasting and 2-hour values
(2), epidemiological studies or diagnostic screening may be restricted
to the 2-hour values only (Table 1). Three recent studies showed that,
of those with fasting plasma glucose values ≥ 7.8 mmol/litre, 97%
also exhibited 2-hour plasma glucose ≥ 11.1 mmol/litre (3, 4).1

2.2.3 Diagnosis of diabetes in children

Diabetes in children usually presents with severe symptoms, very
high blood glucose levels, heavy glycosuria, and ketonuria. In most
children the diagnosis is confirmed without delay by blood glucose
measurements, and treatment (including insulin injection) is initiated
immediately (section 7), often as a life-saving measure. OGTT is
neither necessary nor appropriate.

A small proportion of children and adolescents, however, present
with less severe symptoms and may require an OGTT for diagnosis.
The oral glucose load is related to body weight (Annex 1). In general,
the diagnostic criteria in children, as regards glycaemia, are the same
as those recommended for adults; the interpretation and
management of states of glucose intolerance short of diabetes
mellitus (DM) remain the subject of research. It is within this group
that early pre-diabetic processes may be detected and measures of
prevention studied.

2.2.4 Impaired glucose tolerance

The state of impaired glucose tolerance (IGT) is defined as a
glycaemic response to a standard glucose challenge intermediate

Bethesda, National Institutes of Health, 1985 (administrative document).
between normal and diabetic and can therefore only be determined by an OGTT. The defining limits at 2 hours after challenge are given in Table 1; the fasting value must not be diagnostic for diabetes. For epidemiological studies, the 2-hour value alone may be adequate for diagnosis.

The definition of IGT in 1979–80 (1, 5) replaced terms such as borderline diabetes, pre-diabetes, and chemical diabetes that had been used to describe mild degrees of glucose intolerance; these terms were considered unjustifiable in the light of the natural history of IGT. At present, IGT is rarely diagnosed in the clinical setting, perhaps because of its recent introduction as a glucose tolerance class and lack of knowledge of its clinical significance. IGT is still the subject of research to determine its mechanisms and prognostic implications. Since certain individuals with IGT progress to diabetes, some centres are developing risk-reduction programmes for such people (section 6).

2.2.5 Gestational diabetes

The category of gestational diabetes should be applied only to women in whom glucose intolerance is first detected during pregnancy. Reclassification is necessary post partum.

The report of the second meeting of the WHO Expert Committee on Diabetes Mellitus (1) recommended that the diagnostic procedures and criteria for pregnant women should be the same as those proposed for all adults. It was also recommended that the management of impaired glucose tolerance during pregnancy should be the same as for diabetes. In this, the recommendation differed from that of the National Diabetes Data Group (NDDG) in the United States of America (5), which proposed that the procedures and criteria of O'Sullivan (6) be continued, a recommendation recently confirmed by an Expert Committee of the National Diabetes Data Group.¹

A number of countries have already adopted the 1980 WHO Expert Committee recommendations (1). Further international standardization of diagnostic criteria for gestational diabetes can form the basis for prospective studies of the health of mothers and their infants. The use of the WHO Expert Committee criteria makes

¹ See footnote on page 12.
it possible to determine more specifically the effect of lesser degrees of glucose intolerance upon maternal and child health.

There is no evidence, as yet, that glycated haemoglobin has any special role in the detection of gestational diabetes.

2.2.6 Other diagnostic measurements and indices

The diagnostic definition of the diabetic state (and impaired glucose tolerance) depends upon blood glucose measurement. Certain "non-glycaemic" measurements and tests may be of value in defining subclasses and, in epidemiological studies, in determining the mechanisms and natural history of diabetes.

In the context of diagnosis and classification, such additional indices fall into two groups.

1. Indices of the degree of beta-cell damage. These include measurements of insulin, pro-insulin, and C-peptide secretion. Values of glycated haemoglobin, the degree of glucosylation of other proteins, and the actual degree of glucose intolerance may also be valuable.

2. Indices of the diabetogenic process. These currently include: characterization of HLA types and subtypes; the presence, type, and titre of circulating antibodies directed against the islets of the pancreas and other endocrine cells; evidence of pancreas-directed cell-mediated immunity; demonstration of specific DNA sequences in the human genome; and demonstration of pancreatic or other endocrine disease.

Several other variables qualify the diabetic state and define subclasses of it, e.g., obesity, liability to ketosis, family history of the disease, and age of onset, but these have all been subsumed by, or appear explicitly in, the classification of diabetes mellitus and allied categories of glucose intolerance on page 18. The list of additional measurements and tests is not exhaustive and will undoubtedly increase with time. Properly defined and ascertained, these indices are valuable for identifying homogeneous subclasses of diabetes (section 5).

2.3 Screening

Screening for diabetes is routine wherever urine testing for glucose is an integral part of the clinical examination of a patient.
Systematic urine testing is also commonly used in some countries at military recruitment, in pre-employment examinations, and as a requirement for life insurance, etc. Technological advances in the methods for measurement of blood and urine glucose have made mass population screening possible.

The underlying assumption that justifies screening programmes for diabetes is that early detection and effective control of hyperglycaemia in asymptomatic (or oligosymptomatic) diabetes reduces morbidity. Screening programmes of appropriate design have also yielded valuable information about the prevalence of diabetes and its natural history; in addition, studies of lesser degrees of glucose intolerance have led to the revision of diagnostic criteria.

In the past, population screening for diabetes was often poorly organized and used variable diagnostic criteria and standards for follow-up and patient care. Well-planned community screening programmes that use methods and criteria developed over recent years are important both in developing countries, where epidemiological information is lacking, and in developed countries, where the value of early diagnosis needs to be re-evaluated in the light of the new standardized diagnostic criteria.

Apart from possible benefits to the individual and the acquisition of information of public health relevance, screening programmes for diabetes provide opportunities for creating public awareness and for educating health professionals. Important considerations for screening programmes include:

- the sensitivity, specificity, and cost of screening methods;
- definition of target populations; and
- provision of adequate and effective care for those found to have diabetes.

2.3.1 Screening methods (7)

In the past, the commonest approach to diabetes screening was a preliminary, semi-quantitative test for glucose in a urine sample, followed by an oral glucose tolerance test for those found to have glycosuria.

Many studies now confirm that, although glucose is found in the urine in the most severe cases of diabetes, it is often absent in milder forms of the disease. However, glycosuria may be found in perfectly
normal people. The usefulness of an initial urine screen depends upon the age, sex, ethnic structure, and diet of the target population. While routine urine testing remains an essential part of clinical examination of a patient, it is not appropriate for case-finding or epidemiological surveys of populations. More recent mass-screening programmes have used glucose measurements of a fasting, post-prandial, or random blood sample because of the inadequacies of the urine test; individuals with levels of blood glucose that exceed a predetermined cut-off value are asked to complete a test of glucose tolerance.

Blood samples should ideally be collected under standard conditions, but this may be difficult to achieve and to check.

**Fasting samples.** It is important that true fasting conditions are maintained since comparatively small elevations of blood glucose concentration raise the diagnostic suspicion of diabetes; however, such conditions are difficult to ensure.

**Random samples.** While these may strongly indicate or exclude the diagnosis of diabetes (Fig. 1), a high proportion of measurements fall into the "uncertain zone" and need to be confirmed by the expensive and time-consuming oral glucose tolerance test. Details of the time and nature of the last meal eaten before the random test have little effect on improving the interpretation of results. The measurement of glucose levels in random blood samples is unsatisfactory for epidemiological use; at the most, it can give only a crude estimate of the frequency of diabetes in a population.

**Post-load samples.** Many epidemiological surveys and diagnostic screening studies now attempt to obtain a single blood sample 2 hours after a standard oral glucose load (75 g). This is comparatively expensive and time-consuming if the subject tested has to be kept under observation for 2 hours after the glucose load. Specified meals would seem desirable as test loads but no such meal-load has been adequately validated.

Because of these problems, there have been a number of attempts to evaluate other techniques of screening, e.g., the estimation of glycated haemoglobin (4, 8, 9) and serum glycosamines (10). These newer methods are costly, inadequately standardized, and are unable to give an immediate diagnosis; they also present difficulties in storage of samples, and give rise to substantial misclassification when results are compared with the OGTT as a standard reference.
However, they do have the advantage that little or no preparation of the subject is required. Considerable improvement is needed, however, before these methods can be used for mass-screening programmes.

2.3.2 Target populations

The prevalence of unsuspected diabetes in children and adolescents is so low that screening other than for research purposes has little to offer in case-finding.

In European populations, the prevalence of non-insulin-dependent diabetes mellitus begins to rise at about 45 years of age, but in some populations prevalence rates increase earlier. In countries where epidemiological information is lacking, children in the second decade of life, or younger, should be included in community screening programmes. Target groups should also include those at high risk of glucose intolerance, e.g., the obese and those with close relatives with diabetes, and those in whom even mild glucose intolerance might be a risk factor, e.g., in pregnant women and patients with premature atherosclerosis.

2.4 Revised classification

There has been general acceptance of the classification adopted by the WHO Expert Committee on Diabetes Mellitus in 1980 (I); however, a number of valuable comments and suggestions have since been made. These have now been incorporated into the classification, and the revised version is given in Table 2.

The most important change from the previous classification is the appearance of malnutrition-related diabetes mellitus as a major clinical subclass, ranking with insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus.

2.4.1 Malnutrition-related diabetes mellitus

The introduction of this clinical class of diabetes is in recognition of its clinical distinctiveness and severity, and its high prevalence in some tropical countries. Though more information is now available than in 1980, further epidemiological, clinical, and basic
Table 2. Classification of diabetes mellitus and allied categories of glucose intolerance

A. Clinical classes

Diabetes mellitus (DM)
Insulin-dependent diabetes mellitus (IDDM)
Non-insulin-dependent diabetes mellitus (NIDDM)
  (a) Non-obese
  (b) Obese
Mainnutrition-related diabetes mellitus (MRDM)
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 (IGT)
  (a) Non-obese
  (b) Obese
  (c) Associated with certain conditions and syndromes
Gestational diabetes mellitus (GDM)

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

investigations are still urgently required. The present state of knowledge of malnutrition-related diabetes mellitus and its suggested etiology is briefly reviewed in section 3.

2.4.2 Terminology

There is some lack of agreement and danger of confusion over the use of the terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), and Type 1 DM and Type 2 DM. IDDM and NIDDM are clinically descriptive subclasses; and Type 1 and Type 2 DM (terms given as alternatives to IDDM and NIDDM, respectively, in the earlier classification) represent different pathogenic mechanisms. The definition of IDDM is based only upon clinical observations and simple investigations. The current use of the term Type 1 implies the demonstration of certain immunological phenomena and genetic markers using methods that are rarely available and that lack standardization.
However, these phenomena and markers may also be found in some persons with NIDDM, impaired glucose tolerance, or normal glucose tolerance. There is no definition of the term Type 2 (other than the absence of Type 1 or other known causes of diabetes mellitus). Therefore, the designations Type 1 and Type 2 have not been included in Table 2. Since the terms Type 1 and Type 2 are widely used at present, it is recommended that, in order to avoid confusion, they should be regarded as completely synonymous with IDDM and NIDDM, respectively (i.e., carrying no etiopathogenic implications).

2.4.3 Insulin dependency

The basis for the distinction between the major subclasses of diabetes mellitus is the patient’s dependence for survival on insulin. Such dependence is judged to be present when the “classical” symptoms of diabetes (increased thirst, polyuria, wasting, and ultimately stupor and coma) are associated with greatly raised concentrations of glucose and ketone bodies in the blood and urine.

All other patients meeting the glycaemic criteria for diabetes fall into the non-insulin-dependent (NIDDM) class unless they have malnutrition-related or gestational diabetes or are among the small number who qualify for one of the other special categories.

In diabetic patients of European origin, the clinical distinction of IDDM from NIDDM is often obvious. It is usually easier to distinguish between the different subclasses of diabetes at the time of diagnosis rather than in retrospect when classification may depend upon questionable historical recall and inadequate clinical records. Classification is particularly difficult in middle-aged, non-obese patients receiving insulin after responding inadequately to other treatment, but who may not be dependent on the hormone for survival.

In some non-Europeans, the question of insulin dependency is more difficult to settle. It is estimated that classification difficulties arise in 20-30% of patients, often in those with comparatively youthful onset, without obesity, and with a tendency to develop ketosis under traumatic, infective, or other stress; such patients may have been treated (perhaps unsatisfactorily) for long periods without insulin. Similar classification and treatment difficulties are sometimes found in Europeans. In some patients, non-insulin-dependent diabetes progresses to a clear state of insulin dependency, but in
many it does not. A separate class of "questionable insulin dependency" may be used but it is not included in the classification (Table 2) because it cannot be clearly defined.

2.4.4 Insulin/receptor abnormalities

The new classification recognizes that, in addition to abnormalities of the insulin receptor, genetically-mediated structural abnormalities of the insulin molecule itself (II) are a rare but scientifically important cause of diabetes.

2.4.5 Impaired glucose tolerance (IGT)

It has been recognized by both the National Diabetes Data Group and the World Health Organization that the category of impaired glucose tolerance includes a wide variety of subclasses. In most populations, progressive impairment of oral glucose tolerance is associated with aging, obesity, certain medications, and prolonged physical inactivity. Individuals who develop diabetes mellitus may pass through a phase of impaired glucose tolerance. The presence of glucose intolerance during pregnancy may adversely affect fetal development and maternal health. In some populations, people with IGT have a greater risk of developing arterial disease than those with normal glucose tolerance.

A recent study by Kadowaki et al. (12) suggested that Japanese patients with IGT have a higher risk of developing diabetes mellitus if they have a low plasma insulin level 30 min after the administration of a glucose load (using the same test conditions as for the OGGT). This is independent of the two other positive predictive factors, i.e., high fasting and/or high post-load blood glucose concentrations and the degree of adiposity. Further studies of the mechanisms and natural history of IGT are needed to distinguish its various subclasses and to determine their pathogenesis and prognostic importance.

3. MALNUTRITION-RELATED DIABETES MELLITUS

In tropical developing countries, young diabetics often present with a history of nutritional deficiency and a constellation of symptoms, signs, and metabolic characteristics which fail to meet the
criteria used to classify the two main clinical subclasses of diabetes — IDDM and NIDDM. The distinctive clinical features and course, the uncertain etiology and pathophysiology, and the great number of such cases in some regions justify the creation of a new, major clinical class of diabetes, namely malnutrition-related diabetes mellitus (MRDM). This new category of diabetes includes the variety of types known in the past as tropical diabetes, pancreatic diabetes, parenchymatous diabetes, endocrine pancreatic syndrome, and ketosis-resistant diabetes of the young. These types of diabetes have been extensively reviewed (13–15). A recent monograph has summarized the considerable body of epidemiological, clinical, and biochemical information on MRDM and has suggested the existence of at least two subclasses (16): fibrocalculous pancreatic diabetes, and protein-deficient pancreatic diabetes.

3.1 Fibrocalculous pancreatic diabetes

The characteristic feature of stone formation in the main pancreatic duct and its branches, together with extensive fibrosis of the pancreas supports the use of the descriptive name fibrocalculous pancreatic diabetes (FCPD) in preference to the term fibrocalcific pancreatic diabetes (17).

3.1.1 Epidemiological and clinical features

Cases of fibrocalculous pancreatic diabetes have been described in several countries, including Bangladesh, Brazil, India, Indonesia, Jamaica, Madagascar, Nigeria, Sri Lanka, Thailand, Uganda, Zaire, and Zambia. In several of these countries an estimated 20–70% of diabetics first present below the age of 30 years, many during childhood with recurrent attacks of abdominal pain; men outnumber women by 3 to 1. Patients are grossly underweight, and other stigmata of past or present malnutrition may be present (15). The key metabolic features are moderate to severe hyperglycaemia that requires insulin for control, sometimes in high doses, and the absence of ketosis. Despite extensive damage to pancreatic islets, the residual insulin production, though greatly diminished, probably explains the characteristic, though not invariable, absence of ketosis, especially as it is associated with concomitant glucagon deficiency.
3.1.2 Pathology and diagnosis

Diagnosis is based upon the characteristic clinical features and supported by radiographic demonstration of calculi in the pancreatic ducts. Pancreatic calcification can be detected in 75% of patients with FCPD. In the remainder, ultrasonography may indicate obstruction, dilatation, and calcification of the pancreatic ducts. Other supporting investigations include computerized tomographic imaging and endoscopic retrograde cholangiopancreatography. Abnormalities of exocrine pancreatic function are also present.

Microscopically, the most typical features are diffuse interlobular and periductular pancreatic fibrosis with progressive acinar and islet replacement by fibrofatty tissue; there is little or no evidence of inflammatory reaction. Although the viscid material in the main pancreatic duct and its branches is almost always bacteriologically sterile, this does not entirely exclude the possibility of fibrocalculous pancreatic diabetes being initiated by a non-bacterial infective process.

3.1.3 Causative factors

There is no association between FCPD and gall-bladder disease, or, in most cases, excessive alcohol intake, and no indication that the characteristic pancreatic fibrosis is post-inflammatory in nature.

Epidemiological observations strongly suggest an association between the global distribution of fibrocalculous pancreatic diabetes and the consumption of cassava root (tapioca, manioc). Cassava is the main source of food energy for more than 400 million people living in developing countries, particularly those in the tropics; it is also a major source of cattle fodder in several regions. Cassava root contains several cyanogenic glucosides, but linamarin, which liberates hydrocyanic acid on hydrolysis, is the most important. Cyanide is detoxified by several pathways, mainly those involving sulfur containing amino acids; the main end-product is thiocyanate which is excreted in the urine. High cassava intake combined with inadequate intake of protein, particularly if deficient in sulfur-containing amino acids, creates conditions for the accumulation of cyanide in the body.

Studies indicate that protein intake is low in cassava consuming populations, and this has been suggested as an explanation for the high prevalence of fibrocalculous pancreatic diabetes in parts of Indonesia and Kerala state in India. The hypothesis that cassava
intake and protein malnutrition are causally related to FCPD requires further detailed nutritional and epidemiological studies in the developing countries where this form of diabetes is found.

Other foods such as sorghum, yam, millet, and some varieties of beans may also be sources of dietary cyanide, and high intake of other toxic food factors such as nitrosamines (18) may act similarly when combined with malnutrition. Malnutrition may also enhance susceptibility to certain infective agents.

3.1.4 Prevention

Food preparation and processing significantly alter the cyanide content of cassava, and possibly other cyanogenic foods; for example, the estimated hydrocyanic acid content of fresh cassava leaves is reduced from 167.4 mg/kg to 1.0 mg/kg after frying the leaves in oil (19). Prolonged drying of the tuberous portion of cassava used for making flour may significantly, although not consistently, reduce the cyanide content and the consequent health hazards.

3.2 Protein-deficient pancreatic diabetes

3.2.1 Epidemiological and clinical features

The key features of this type of malnutrition-related diabetes mellitus include resistance to the development of ketosis, partial resistance to the action of insulin, extreme degrees of wasting and emaciation, and an onset of symptoms before the age of 35 years, commonly between 15 and 25 years of age. Pancreatic calcification and fibrosis are absent.

The disease is commonly seen in, and has been reported from, Bangladesh, Brunei Darussalam, Fiji, Ghana, India, Indonesia, Jamaica, Kenya, Malawi, Malaysia, Nigeria, Papua New Guinea, South Africa, Uganda, United Republic of Tanzania, and Zaire. It has been described previously as J-type diabetes, M-type diabetes, malnutrition diabetes, and ketosis-resistant youth-onset diabetes.

The sex incidence varies considerably in different parts of the world. In Asia, men are predominately affected (2:3:1), whereas in African countries such as Nigeria the sexes are equally affected; a female preponderance has been reported from the West Indies.
Patients with both types of malnutrition-related diabetes mellitus are characteristically underweight and have clinical stigmata of present or past malnutrition and of other deficiency states, but three features appear to distinguish the protein-deficient type: (i) absence of a history of recurrent bouts of abdominal pain; (ii) absence of radiographic or other evidence of intraductal pancreatic calcification or dilatation of the ducts; and (iii) absence of demonstrable malabsorption of nutrients caused by exocrine pancreatic insufficiency.

3.2.2 Pathogenesis and laboratory investigations

Measurements of insulin secretion in patients with protein-deficient pancreatic diabetes demonstrated a decreased (but non-delayed) response to an oral glucose load, whereas, in carefully matched IDDM patients, the insulin response was virtually absent (15). It is the residual insulin secretion which probably explains the absence of ketosis in PDPD patients.

3.2.3 Relation to clinical and experimental protein malnutrition

The decreased insulin response after oral glucose loading is similar to that observed in kwashiorkor, and contrasts with the nearly normal response in marasmus (20) (kwashiorkor and marasmus are both syndromes of infantile and early childhood malnutrition). Damage to the beta cells in kwashiorkor may well explain the associated impaired carbohydrate tolerance. The experimental induction of protein malnutrition in the rhesus monkey (Macaca mulatta) produces a pattern of endocrine and metabolic features that resemble those of kwashiorkor and protein-deficient pancreatic diabetes (21).

3.3 Research needs

1. There is an urgent need for epidemiological surveys to define the prevalence of malnutrition-related diabetes mellitus and its patterns of clinical manifestation.

2. The relation between fibrocalculus protein-deficient diabetes and high levels of cassava consumption, when combined with malnutrition, needs to be firmly established.

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3. A search for other food toxins and causative factors is an essential prerequisite for the development of intervention strategies and should therefore be encouraged.

4. The mechanism whereby malnutrition in early infancy and childhood results in partial failure of beta-cell function and clinical onset of protein-deficient diabetes mellitus should be elucidated.

4. EPIDEMIOLOGY

Epidemiological studies of diabetes in many populations have cast light on the definition and classification of the disease, its early detection, its genetic and environmental background, its social and economic impact, and the effect of the disease on health and the quality of life. The epidemiological approach has considerable implications for the planning and provision of economic health services. New methods of clinical diagnosis have been developed and evaluated in epidemiological field studies, and controlled clinical trials have been used to assess diabetes management. Use of the diagnostic criteria and classification recommended in the second report of the WHO Expert Committee on Diabetes Mellitus (I) is leading to standardization of data collected throughout the world and a more accurate picture of the natural history of diabetes.

The prevalence of known cases of diabetes (i.e., the number of diabetics in a population at a specific time) can be ascertained from reports of self-diagnosis of diabetes or from data provided by health care workers. The number of previously undiagnosed cases can be determined by screening.

The incidence of diabetes (i.e., the number of new cases occurring in a population during a specified period of time, often one year) can be calculated by ascertaining all the prevalent cases of diabetes and prospectively determining the occurrence of new cases among the non-diabetics. The diabetes registration system is a valuable tool in incidence studies, and a number of diabetes registers have been started since the second report of the Expert Committee on Diabetes Mellitus was published in 1980 (I). In some countries, registers of drug prescriptions are used in incidence studies.

4.1 Natural history of diabetes and impaired glucose tolerance

The natural history of diabetes is affected by many factors, including the type of diabetes, its complications, and the availability...
and effectiveness of treatment. Improvement in the management of diabetes could well affect the natural history of the condition over the next decade.

4.1.1 *Insulin-dependent diabetes mellitus*

The clinical onset of insulin-dependent diabetes mellitus (IDDM) is typically abrupt, although recent data indicate that an autoimmune process may operate and lesser degrees of glucose intolerance may be present for months, or even years, before clinical onset (22). There may be temporary remission after clinical onset of IDDM. Complications of the eye, kidney, and nervous system occur many years after onset of the disease (section 8). Survival depends on the provision of daily injections of insulin, and the insulin-dependent diabetic has a shortened life span compared with the non-diabetic. However, possibly because of improved management of the disease, increased longevity has recently been noted in some countries.

4.1.2 *Non-insulin-dependent diabetes mellitus*

Non-insulin-dependent diabetes mellitus (NIDDM) usually comes to light in the middle years of life, but earlier in Asians than Europeans. Symptoms of diabetes are often not prominent and diagnosis may be incidental. Hyperglycaemia is often present for several years before diagnosis. With time, some patients with NIDDM may require insulin injections to control blood sugar levels (23); this deterioration may be caused by patients failing to comply with long-term management programmes, but in most cases it probably represents the progressive natural history of NIDDM. Weight reduction in obese patients with recently diagnosed NIDDM may result in remission. All the complications typical of diabetes occur in the NIDDM patient, though their evolution and ultimate form generally differ from patients with IDDM. Life expectancy of NIDDM patients is less than that of non-diabetics; cardiovascular disease accounts for much of the excess mortality in Europeans, but chronic renal failure is more important in the Oriental races.

4.1.3 *Impaired glucose tolerance*

Individuals with degrees of glucose intolerance that are insufficient to classify them as diabetics nevertheless appear to be at
increased risk from coronary heart disease, peripheral vascular disease, and thrombotic stroke. Although the risk of developing diabetes appears to be greater in those with impaired glucose tolerance than in normal subjects, approximately one-third of people with IGT revert apparently spontaneously to normal glucose tolerance (24). The degree of glucose intolerance and, to a lesser extent, the fasting blood glucose value are the strongest predictors of progression to diabetes (12, 25, 26); obesity and an early insulin response in the oral glucose tolerance test have been found to be additional independent predictors in some studies. Studies to date support the recognition of IGT as an independent category of glucose intolerance, though highly heterogeneous in composition. Much work is still required to determine the full significance of IGT and to identify the subclasses which may progress to overt diabetes or to vascular disease.

4.2 Prevalence, incidence, and risk factors

4.2.1 Insulin-dependent diabetes mellitus

Prevalence. Major geographic and ethnic differences exist in the prevalence of IDDM (13). It is unknown or rare in certain groups and the highest rates occur in Caucasian populations. Annex 3 shows the result of several studies of the prevalence of IDDM, but comparisons should be made with caution because of the different age groups studied and the various methods of case assessment used. As a result of the relatively low prevalence of IDDM, large population samples are necessary to obtain reliable data.

Incidence. Population-based studies of the incidence of IDDM using comparable methods of assessment are summarized in Annex 4. There is a 15-fold difference in incidence between countries with the highest and lowest rates. No male-female differences in incidence are evident. The majority of population studies have demonstrated age peaks in the clinical presentation of IDDM, one of particular magnitude occurring at 10–13 years of age (27). There is some year-by-year variation in incidence with limited data suggesting rising trends in some countries. There is little systematic data about IDDM diagnosed for the first time after the age of 20 years.

Risk factors. In Europeans, possession of the HLA-DR3 and/or HLA-DR4 alleles of the major histocompatibility complex is a
marker of genetic susceptibility to IDDM; and the appearance of islet cell antibodies probably indicates the occurrence of beta-cell damage (section 5). Factors that precipitate IDDM in genetically susceptible individuals still need elucidation, but viral infections are thought to play a leading role (26). Further studies are necessary to assess the significance of secular trends, age, seasonal incidence peaks, the protective effect of breast-feeding (29), ingestion of smoked mutton on fetal beta-cell development (18), and possible effects of other toxic substances (section 5).

4.2.2 Non-insulin-dependent diabetes mellitus

Prevalence. Annex 5 presents population-based prevalence estimates of NIDDM using the standard criteria proposed by WHO. Rates vary from zero in the highland population of Papua New Guinea that has retained its traditional lifestyle, to 25% in the populations of the Pima Indians and Nauruans. Prevalence increases with age. In some developing countries, the prevalence of NIDDM is lower in men than in women, but in others the sex ratio is reversed; in the United States of America, rates are equal for the sexes. Within the same ethnic group, urban residents and migrants to urban areas have a higher prevalence of NIDDM than their rural counterparts.

The prevalence of NIDDM and IDDM in different countries is shown in Annex 6.

Incidence. The incidence of NIDDM (based on WHO criteria) in Pima Indians and Nauruans is shown in Annex 5. Incidence rates are difficult to interpret and can only be considered valid if they are based on serial systematic diagnostic studies. So large is the potential pool of undiagnosed NIDDM in many populations that incidence rates may be as much an index of awareness and methods of assessment as of the frequency of diabetes. There are no studies of NIDDM incidence in Caucasian populations using WHO criteria. In the Pima Indians, incidence rises with age until about 50 years and then declines. In most industrially advanced societies, the incidence of NIDDM reported by physicians rises throughout adult life and is usually highest in old age. It is widely believed that incidence is higher in women than men but this lacks documentation.

Risk factors. No specific genetic marker has been found for NIDDM. While the search continues, the important role of genetic factors in NIDDM is underlined by the high rates of concordance
in monozygotic twins (30), and by studies of genetic admixture in
certain American Indian and Micronesian populations, where people
with ancestral "foreign" genes have a lower rate of NIDDM (31).

The changing age structure of developing populations, with
people living longer as a result of improved nutrition and control of
infectious diseases, is an important factor that contributes to the
increasing prevalence of diabetes in these countries. However, this
alone does not explain the emergence of NIDDM as a major health
problem. Obesity has long been accepted as a risk factor for
NIDDM, and the risk is related to both the duration and the degree
of obesity (section 5). Susceptibility to diabetes appears to be
unmasked by a number of environmental factors such as sedentary
life-style, dietary factors, stress, urbanization, and acculturation.
High and low rates of diabetes have been linked to a number of
social factors including occupation, marital status, religion,
economic status, and level of education. Although diabetes is
frequently discovered during pregnancy, most evidence suggests that
parity is not a risk factor for diabetes.

4.2.3 Malnutrition-related diabetes

Aspects of the epidemiology of malnutrition-related diabetes are
discussed in section 3, but systematic community-based studies of
the prevalence and incidence of this type of diabetes are needed. The
reported occurrence of malnutrition-related diabetes is shown in
Annex 7.

4.3 Mortality from diabetes

The role of diabetes as a cause of premature or high mortality
varies with the level of development and the prevalence of disease
in different countries. In some advanced countries, it is of major
importance. For example, when individual causes of death in the
United States of America are considered, more deaths are attributed
to diabetes than to lung cancer, breast cancer, motor vehicle
accidents, cirrhosis of the liver, or infant mortality.1

In most developed countries, diabetes ranks between fourth and
eighth as a cause of death. However, this relatively low ranking is

Publication No. 85-1468).
primarily because many related diseases are grouped together in international death statistics (e.g., cardiovascular diseases, cancers, lung diseases) and, collectively, these rank higher than deaths from IDDM and NIDDM.

4.3.1 Life expectancy of diabetics

In developing countries where insulin and medical resources are scarce, IDDM patients are known to die young for want of treatment, although evidence to support this claim is poor. In advanced countries, about 1% of patients with IDDM die within 1 year of diagnosis (32), and about 33% are dead 30 years after diagnosis; the risk of death is similar to that of non-diabetics before the age of 20 years, but after 20 it is 20-times greater. Death soon after diagnosis indicates an inadequate supply of insulin or lack of understanding of its use; later excess mortality reflects the impact of long-term complications and the success of self-management.

In developed countries, the life expectancy of patients with IDDM of childhood onset is approximately 75% that of non-diabetics; there is some evidence of a decline in life-threatening renal failure. In developing countries, the average life expectancy of an IDDM patient may be only 20–30 years, compared with 50 years for non-diabetics. Patients with NIDDM can have a normal life expectancy but on average their life span is several years shorter in developed countries and many years shorter in developing countries.

4.3.2 Causes of death

The majority of people with IDDM in developing countries die early of infections (e.g., pulmonary tuberculosis) and acute metabolic complications; they do not live long enough to develop life-threatening vascular complications. In developed countries, the major cause of death in diabetics below the age of 20 is also acute metabolic complications, but after this age diabetic renal disease predominates, contributing to 50% of deaths (33). Although cardiovascular diseases account for only 10% of deaths among IDDM patients, this proportion is 12-times higher than in non-diabetics of comparable age (32).

Among NIDDM patients in developing countries, stroke as a complication of hypertension accounts for a large proportion of deaths; gangrene, infections, and metabolic complications are also
major causes of death. In developed countries, cardiovascular diseases are outstandingly the leading cause of death among diabetics. In Caucasians, ischaemic heart disease accounts for 50% of deaths, stroke for 15%, other cardiovascular conditions for 10%, and renal failure for about 8%.\(^1\) In Japan, renal failure is more prominent and accounts for about 15% of deaths in NIDDM patients. In American Indian diabetics, the rates of cardiovascular disease are lower than in Caucasian populations, but coronary heart disease and renal failure are the leading causes of death.

4.3.3 International classification of causes of death

Mortality is the only indicator of the scope and impact of diabetes that has a degree of international standardization, if the coding system given in the WHO International classification of disease (ICD) is followed (34). The “underlying cause” statistic has been used to assess trends in mortality from diabetes within a country and to make cautious comparisons of the mortality rates attributed to diabetes in different countries. Annex 8 shows diabetes mortality rates that have been calculated using ICD coded death certificate data. Unfortunately, the ICD does not distinguish types of diabetes, but it is strongly recommended that future editions should do so.

Certification of death has major limitations in assessing the impact of diabetes. Diabetes, though present, is often not entered at all on death certificates. When it is, only 25% of certificates in the United States of America and the United Kingdom list diabetes as the underlying cause of death (35); thus 75% of the cases of diabetes listed on death certificates may not be counted in international data. Rules for coding given in the International classification of diseases preferentially select cardiovascular diseases and cancer as causes of death. Health policy makers may thus be led to underestimate grossly the contribution of diabetes and should consider multiple-cause coding wherever possible.

4.4 Methods for studying the complications of diabetes

Standard methods must be used to assess the complications of diabetes if international comparisons are to be made. Some standard methods were developed for the WHO Multinational Study of Vascular Disease in Diabetics (36, 37). The standard epidemiological

\(^1\) See footnote on page 29.
methods include: timed ophthalmoscopic inspection with standardized recording of lesions to assess retinopathy; \( ^1 \) semi-quantitative measurements of raised urinary protein concentration to characterize diabetic nephropathy; timed urinary albumin excretion rates for early detection of high-risk patients; and the measurement of elevated plasma creatinine levels to detect serious loss of renal function. The well-validated questionnaire produced by WHO to record details of patients' symptoms, and Minnesota coded (38) electrocardiograms, are used to study coronary heart disease and peripheral vascular disease. Methods for assessing cerebrovascular disease and peripheral neuropathy have yet to be fully validated.

5. CAUSES AND MECHANISMS

It is now apparent that diabetes mellitus is not a single clinical entity, but rather a heterogeneous group of disorders with different underlying causes. This group of disorders has two characteristic features in common: elevated blood glucose concentrations in the fasting state or in response to a glucose challenge; and a widespread pattern of damage (complications) in almost every tissue of the body. Several key factors have been identified in the etiopathogenesis of insulin-dependent diabetes mellitus; these include genetic constitution, immune function, and the environment. Genetic and environmental factors also contribute to the development of non-insulin-dependent diabetes. Specific local factors, possibly interacting with genetic make-up, are suspected of causing other forms of diabetes (e.g., malnutrition-related diabetes). It is believed that an individual inherits a susceptibility to develop either IDDM or NIDDM and that one or more non-genetic, presumably environmental, factors can eventually precipitate overt clinical disease. Genetic and environmental mechanisms also contribute to the appearance and severity of diabetic complications. Major research efforts are necessary to define the genetic components and identify the environmental factors so that the disease can be contained and its morbidity and mortality reduced and ultimately prevented.

\(^1\) Retinal photography is likely to become the method of choice once film-reading techniques have been fully developed.
5.1 Pancreatic beta-cell function and insulin action in diabetes mellitus

The beta cells of the islets of Langerhans in the pancreas are the site of insulin production. Beta cells are long-lived and their rate of cell division is low. Little is known about the life-cycle of the beta cell in man and a better understanding is needed of the mechanisms that control beta-cell viability and regenerative capacity.

5.1.1 Insulin-dependent diabetes mellitus

Individuals who develop IDDM are thought to be born with normal beta cells in normal numbers. The typical lesion in the islets of Langerhans at the time of diagnosis is lymphocytic infiltration and selective destruction of the beta cells (39). At the time of acute clinical presentation, probably 85–90% of the beta cells have been destroyed. Shortly after the start of insulin therapy, improved beta-cell function, and probably increased beta-cell mass, is demonstrable in most patients. This so-called “honeymoon” or remission period may last several months, but usually residual beta-cell function is again in progressive decline 6–9 months after diagnosis of diabetes. IDDM may result from a disturbed balance between beta-cell destruction and a, genetically determined, limited capacity for beta-cell regeneration.

5.1.2 Non-insulin-dependent diabetes mellitus

The non-insulin-dependent diabetic state is characterized by a combination of inadequate insulin secretion and resistance of peripheral tissues to its actions (40). For unknown reasons, beta-cell mass in patients with NIDDM may be reduced at the time of diagnosis. Furthermore, the insulin response to a glucose challenge is diminished in many individuals.

The synthesis of an abnormal, biologically less-active, insulin molecule as a result of mutation of the insulin gene (mutant insulin) has been demonstrated to be the cause of NIDDM in a few patients (11).

5.2 Genetic factors and markers

Family studies have shown the existence of strong genetic components in IDDM as well as in NIDDM (30). The concordance
rate for IDDM in identical twins is about 50%. The hereditary component in NIDDM may be even stronger since its concordance rate in identical twins is approximately 90%. The risk for siblings and children of NIDDM probands is less well defined, but is higher than the risk of developing IDDM in families with a history of insulin-dependent diabetes mellitus.

The existence of a raised genetic susceptibility to NIDDM in certain Pacific and American Indian populations with a high prevalence of diabetes is demonstrated by the fact that admixture of Caucasian genes appears to reduce the risk of the disease (31).

Non-insulin-dependent diabetes of young people, i.e., maturity onset diabetes mellitus of the young, is inherited as a dominant trait and evidence is accumulating to suggest that NIDDM susceptibility may also be conferred by a dominant gene (41). Many reports have been published of genetic syndromes and disorders in which the diabetic state, usually the non-insulin-dependent form, plays a part (42). These reports suggest that several genetic loci may influence glucose metabolism. It is also possible that some cases of diabetes may not have a genetic basis.

5.2.1 Genetic markers

Susceptibility to IDDM is conferred by genes in the HLA-D region of the major histocompatibility complex (MHC) on chromosome 6. Genes in this complex control immune responses. The HLA-D region comprises three loci, DP, DQ, and DR. The HLA-DR allele, HLA-DR4, is strongly associated with IDDM in all ethnic groups, whereas the HLA-DR3 allele shows IDDM association only in Caucasian and some black populations (43). In the Japanese and other populations, other HLA-DR alleles may substitute for HLA-DR3. The highest risk of IDDM is carried by individuals with both HLA-DR3 and HLA-DR4 alleles, i.e., HLA-DR3/4 heterozygous individuals. This and other evidence suggest that the two IDDM associated genes in the HLA-D region may predispose individuals to IDDM by different mechanisms.

Approximately 95% of all Caucasians with IDDM are HLA-DR3 and/or HLA-DR4 positive. However, 50–60% of the normal Caucasian population have HLA-DR3 and/or HLA-DR4 alleles, but only 0.25–0.35% of the population develops IDDM. This observation may be explained in several ways: IDDM susceptibility is not conferred by genes at the HLA-DR locus per se but by
unknown genes in strong linkage disequilibrium with the HLA-DR alleles 3 and 4; or the primary association may be with genes on the HLA-DQ (or DP) locus or with genes in linkage disequilibrium with it. Alternatively, the HLA-DR genes of IDDM patients and non-diabetics may differ at the DNA level.

New investigative methods, e.g., allele-specific DNA probes for genes in the HLA-D region, and MHC-restricted, disease-specific T-lymphocyte clones, will be needed to identify and characterize the genes (or those portions of them that confer susceptibility to IDDM). The predictive risk of developing IDDM by the age of 20 years for a child with a sibling affected by IDDM is approximately 15% if the child is HLA-identical (i.e., sharing both HLA haplotypes) with the proband. The risk of IDDM in siblings sharing one HLA-haplotype with the proband is 4-5%. If no haplotype is shared with the diabetic sibling the risk is &lt;1%. It should be recognized that, at present, HLA-typing cannot be used as a routine method in clinical practice.

NIDDM is not HLA-associated. In the search for a genetic marker of NIDDM susceptibility, restriction fragment length analysis has revealed a large DNA fragment flanking the insulin gene on chromosome 11; this has been found to be associated with NIDDM or a form of NIDDM by some researchers (44). This association is, however, still equivocal and, so far, no specific genetic marker of NIDDM is available. Evidence is accumulating that the insulin response to glucose is genetically controlled and may serve as one of the markers for NIDDM susceptibility.

5.2.2 Immunological associations and markers

The clinical and subclinical associations between IDDM and autoimmune endocrinopathies (mainly thyroid) together with the pathoanatomical findings in the islets of Langerhans at the time of diagnosis suggest that autoimmune mechanisms may be concerned with the pathogenesis of IDDM (45).

Cell-mediated autoimmunity directed against, as yet, unidentified antigenic components of the endocrine pancreas has been demonstrated in IDDM. In addition, a variety of autoantibodies reacting with antigens in the islets of Langerhans have been identified; these include islet-cell cytoplasmic antibodies that react with all endocrine cell-types in the islets, islet-cell surface antibodies that react predominantly with beta cells, complement-dependent
cytotoxic antibodies, and an antibody that immuno-precipitates a 64 k protein present in islet cells.

Islet-cell cytoplasmic antibodies are the most extensively studied; they can be demonstrated in 60–85% of patients with IDDM at the time of diagnosis and in 4–5% of their first-degree relatives, but in only 1% of patients with NIDDM and non-diabetic controls. Furthermore, islet-cell cytoplasmic antibodies, and the other antibodies, may be present for years in a pre-diabetic phase of IDDM, in some NIDDM patients developing insulin dependency (46), and in individuals showing no clinical abnormality of metabolism.

The pathogenic role of islet-cell cytoplasmic antibodies and the other IDDM specific antibodies remains to be elucidated. However, when they occur in individuals with a diminished early insulin response to intravenous glucose stimulation and an IDDM associated HLA-DR allele, they may signal current beta-cell destruction that may eventually lead to IDDM. Methods for the determination of islet-cell antibodies vary between laboratories and standardization is needed. Antibodies to the insulin receptor have been identified in a rare form of diabetes associated with severe insulin resistance and acanthosis nigricans.

It should be recognized that determination of islet-cell and receptor antibodies cannot be used as a routine method in clinical practice at the present time.

5.3 Acquired and environmental factors

5.3.1 Infection

Epidemiological studies provide circumstantial evidence for a possible causative role of viral infections in IDDM (28). Among the viruses that have been implicated are rubella, mumps, and human coxsackievirus B4. Experiments using animal models support the possible etiological role of certain viruses in the genetically susceptible host. At present, the role of viral infection in the etiology of IDDM in man has not been fully documented, and further epidemiological and biological research is required.

Infections, either viral or bacterial, may also precipitate overt clinical disease in both the insulin-dependent and non-insulin-dependent diabetic, acting through non-specific stress mechanisms.
5.3.2 Direct beta-cell cytotoxicity

Toxic substances such as alloxan may damage the beta cells directly. The recognition of diabetic ketoacidosis after the ingestion of pyriminur, a rodenticide, is of note, particularly as an indicator of other possible toxic hazards and as a potential public health problem (47). Experimentally, streptozocin, a product of fungal origin, produces diabetes in a large number of animal species, although marked differences in susceptibility exist among species, presumably because of genetic factors.

5.3.3 Damaged beta-cell function through other mechanisms

The special form of malnutrition-related diabetes seen in some tropical countries appears to be associated with damage of the pancreas caused by toxic substances and a background of inadequate protein intake (section 3).

Intake of certain nitrosamines in foods, e.g., in smoked and cured mutton, by pregnant women has been implicated as a cause of IDDM in their offspring (18). More needs to be known about the potentially harmful effects of nitrosamines on the development and differentiation of pancreatic beta cells and their possible diabetogenic effects in various populations.

5.4 Changes in life-style

Epidemiological studies have shown that the prevalence of diabetes is low in certain populations that have retained their traditional life-style, and that modernization of life-style and diet, and migration to urban areas, are associated with an increase in the prevalence of NIDDM (section 4).

5.4.1 Overnutrition and obesity

Obesity can induce resistance to the action of insulin in several ways. In some instances, it reduces the number of insulin receptors on target cells, but in most cases it produces insulin resistance through postreceptor changes, e.g., decreasing glucose transport or impeding intracellular glucose metabolism (48). The factors associated with obesity that are responsible for these cellular defects may include increased storage of fat, increased energy intake, the composition of the diet (especially high fat-intake), and physical
inactivity. Insulin resistance can be reduced by dietary restriction leading to weight loss, physical training, and by obtaining control of blood sugar levels through the use of insulin or sulfonyureas. If remedial measures are not adopted, the beta cells of genetically predisposed individuals may not be able to meet the chronic challenge of insulin resistance and diabetes mellitus will result. There is no sound evidence that diabetes is specially associated with high intake of any of the major nutrients.

5.4.2 Physical inactivity

Physical inactivity appears to be an important risk factor for the development of NIDDM. Lack of exercise may alter the interaction between insulin and its receptors and subsequently lead to NIDDM.

5.4.3 Malnutrition

It is difficult to isolate the individual contribution of a change in total food intake to the increased prevalence of NIDDM associated with modern life-styles from that of physical inactivity, possible diabetogenic effects of specific dietary constituents, and other factors. There is a need for additional studies on the potential role of specific dietary components as causative or contributory factors. Protein deficiency may be involved in the pathogenesis of some forms of diabetes (section 3). Excessive consumption of alcohol can increase the risk of diabetes by damaging the pancreas and liver and by promoting obesity. In some countries, the fermentation practices used in the manufacture of alcoholic drinks produce large amounts of iron which may cause pancreatic damage and diabetes.

It has been suggested that deficiencies of trace elements such as chromium, copper, and zinc play a role in the pathogenesis of diabetes mellitus, but convincing evidence is lacking. The role of trace elements in glucose intolerance needs further elucidation.

5.4.4 Severe or prolonged stress

Several states of physical stress such as acute myocardial infarction, surgery, infections, and severe burns and trauma are associated with glucose intolerance induced by hormonal effects on glucose metabolism and insulin secretion and action. Whether they can lead to permanent diabetes is not established. The role of
emotional and social stress as contributory factors in diabetes mellitus remains unproven.

5.4.5 Drugs and hormones

Long lists of drugs that affect carbohydrate metabolism have been compiled (5). Among commonly used drugs, phenytoin, diuretics (particularly of the thiazide type), corticosteroids, steroids used in oral contraceptives, and beta-adrenergic blocking agents may cause glucose intolerance and, in susceptible individuals, may induce diabetes. This usually resolves after withdrawal of the drug.

Several endocrine disorders may be associated with the diabetic state, but in some cases, diabetes resolves when the primary disease is treated.

5.4.6 Pancreatic disorders

Inflammatory, neoplastic, and other disorders of the pancreas, such as cystic fibrosis and haemochromatosis, as well as pancreatectomy, may lead to different degrees of insulin deficiency and hence, in some cases, to diabetes mellitus. Damage to the islets of Langerhans appears to be the basis of malnutrition-related diabetes mellitus (section 3).

5.5 Metabolic and endocrine disturbance

The underlying cause of diabetes is insulin deficiency, which is absolute in IDDM and partial in NIDDM. Disorders of the interaction between insulin and its receptors may play an important role in the etiology of NIDDM. The overall effect of these disorders is reduced utilization of glucose which leads to hyperglycaemia accompanied by glycosuria.

When glucose cannot be used effectively as a metabolic fuel, the mobilization of energy reserves from fat stores is enhanced, leading to elevated concentrations of fatty acids, glycerol, and ketones in the blood. Severe ketosis with accompanying acidosis contributes to coma and death in untreated IDDM.

Insulin deficiency also causes loss of body protein which impairs growth and repair of tissues, and reduces the body’s immune defences against bacterial and fungal invasion. Glucagon and growth hormone are released in response to cellular deprivation of
glucose, and these hormones aggravate and accelerate the breakdown of tissue. Chronic hyperglycaemia induces changes in the polyol and sorbitol pathways which may damage vulnerable tissues (49). Increased glucosylation occurs in the connective tissues, the lens of the eye, and in other important structural proteins which may impair their function (50). Most of these metabolic and endocrine changes can be reversed by insulin therapy.

6. STATUS OF PREVENTION

Increased morbidity and premature mortality caused by diabetes have resulted in escalating costs, both in terms of increased medical care and the loss of manpower resources (see Annexes 9 and 13). There is therefore a major financial incentive for developing effective prevention programmes and for their integration into control programmes for other noncommunicable diseases. The improved understanding of the causes and mechanisms of the major types of diabetes now provides some indication of how they could be prevented. At present, the prevention of NIDDM would appear to offer the greatest promise of success.

6.1 Preventive strategies

Two strategies for primary prevention and one for secondary prevention deserve consideration.

*Primary prevention*

1. A population strategy to alter the life-style and environmental characteristics, and their social and economic determinants, that are the underlying cause of the different types of diabetes.
2. A high-risk strategy to provide preventive care for those individuals who can be identified as being at special risk of developing diabetes.

*Secondary prevention*

The main aims of secondary prevention are to avert recurrences in patients that have achieved a remission, and progression in those already irreversibly affected.

Prevention of the long-term complications of diabetes (tertiary prevention) is discussed in section 8.
6.2 Insulin-dependent diabetes mellitus

6.2.1 Population strategy

Primary prevention of IDDM aimed at an entire population is not feasible and, on the basis of current knowledge, is probably not appropriate.

6.2.2 High-risk strategy

Until the degree of susceptibility of an individual can be determined with greater precision and more effective means are available to slow or arrest the pathogenic process, a specific high-risk strategy cannot be recommended. However, current advances in knowledge make it important to keep this question under review. At present, there is no practical justification for genetic counselling as a method of primary prevention.

6.2.3 Secondary prevention

This forms the basis of attempts to arrest the pathogenic process of autoimmune beta-cell destruction. Although this mechanism is not proven in man, there is strong presumptive evidence that, in genetically predisposed individuals, self-damaging immunological mechanisms are involved. These are triggered by some as yet unidentified environmental agent(s), and effective primary prevention awaits their identification. As a form of "post-primary" prevention, several centres are undertaking studies of the effect of immune suppression using cyclosporin in new cases of insulin-dependent diabetes (51). Widespread use of cyclosporin as a preventive measure should await the result of prospective studies.

6.3 Non-insulin-dependent diabetes mellitus

Environmental factors appear to induce NIDDM in genetically susceptible individuals (52). The reduction of environmental risk factors has contributed to a dramatic fall in the level of mortality caused by coronary disease in many countries (53), and it now seems appropriate to establish whether non-insulin-dependent diabetes can be prevented in a similar manner.
6.3.1 Population strategy

Many areas of the world, including a few developed countries, have not yet adopted the pattern of life associated with a high incidence of NIDDM. In these countries, risk factors such as obesity and physical inactivity have not yet increased to critical levels, but economic advance and changing life-styles threaten to undermine this situation. There is therefore a pressing need to consider primordial prevention—that is, prevention of the emergence of predisposing conditions in countries in which they have not yet appeared. Other less well-defined risk factors such as protein deficiency and food toxins may also be important causal factors for diabetes in some populations.

The striking emergence of NIDDM as a major health problem in populations undergoing modernization of life-style strongly suggests that factors associated with acculturation may be of major importance (52). Many environmental changes are likely to occur simultaneously with modernization and it is not certain which of these is responsible for the increased prevalence of NIDDM.

Programmes for prevention. The development of prevention programmes for NIDDM depends upon accurate data on the environmental risk factors in a given community. In many populations, there is a strong association between obesity and NIDDM (54, 55); thus programmes to prevent and control obesity are likely to reduce the frequency of NIDDM in these communities and should therefore be incorporated into strategies for disease control.

Recent evidence suggests that obesity is not necessarily the most important risk factor for NIDDM (31, 56), and that physical inactivity and diet may also be important determinants.

An improvement in glucose tolerance has been noted after exercise training in subjects with NIDDM (57). The preventive role of increased physical activity should therefore be investigated in communities where sedentary life-style is associated with NIDDM.

Reversion to traditional life-style has been shown to improve or normalize major metabolic abnormalities of NIDDM in a group of Australian Aboriginals (38). At least three factors known to improve sensitivity to insulin were involved in this study—weight loss, a low fat diet, and increased physical activity. If the results of this study can be confirmed in other populations, the incorporation of these “healthy” changes of life-style into prevention programmes could reduce the incidence of NIDDM in target communities.
Before such programmes are implemented, proper community assessment is essential and this includes not only a knowledge of the relevant risk factors for NIDDM, but also data on prevalence, incidence, morbidity, and mortality. It also involves an assessment of the attitudes and behaviour of the community and its willingness to comply with prevention strategies. The prevention of NIDDM will involve action by many sectors of society—government, the media, industry, agriculture, educational and health services, and the general community. Public health policies should encourage good nutrition in schools and other government-supported food programmes. Schools may represent a major opportunity to promote healthy life-styles that include plenty of exercise and good nutrition.

An integrated approach to prevention. Prevention programmes will need to be integrated into existing health services (e.g., the primary health care system) and comprehensive programmes of disease control (e.g., those for prevention of coronary heart disease and hypertension). Private health service programmes should also incorporate preventive methods.

6.3.2 High-risk strategy

Sufficient data have accumulated to initiate community-based prevention programmes for NIDDM. In many communities, the disease appears to be linked with a sedentary life-style, overnutrition, and obesity, correction of which may reduce the risk both of diabetes and its complications (32, 34). Prevention programmes may most effectively be directed at those people who are genetically susceptible to diabetes (i.e., those with a close family member with NIDDM, or evidence of ethnic susceptibility). Possible methods of prevention include modification of diet to avoid or correct obesity and an increase in physical activity. More research is needed to identify effective methods of influencing those at risk to change their eating and exercise habits.

7. MANAGEMENT OF DIABETES

In severe cases, the life of the recently diagnosed diabetic depends on regular injections of insulin, a regular pattern of meals, and a suitably adjusted life-style. At the other extreme, a weight-reducing
diet may suffice to correct the metabolic disturbance completely. Diabetes may be discovered in many ways—by a routine medical examination during pregnancy; when a patient presents with an infection; after a myocardial infarction; in children with weight loss and slowing of growth; or by the sudden emergence of ketoacidotic coma. Each situation requires its own individual management plan, but certain general aspects of management are considered below, together with some specific problems such as pregnancy.

7.1 The objectives of diabetes management

There are four main objectives of the management of diabetes:

1. to preserve the life of the diabetic patient and relieve the symptoms of the disease;
2. to enable the patient to have as normal a social life as possible;
3. to establish and maintain good metabolic control; and
4. to avoid the complications of diabetes mellitus.

The degree of metabolic control is primarily assessed by determining the concentration of glucose in the blood, although the measurement of glycated haemoglobin and plasma lipids is also important. The range of glucose concentrations aimed for in treatment is similar to normal and falls within the following limits: 3.3–5.6 mmol glucose/litre (60–100 mg/dl) of venous whole blood under fasting conditions and not exceeding 10 mmol/litre (180 mg/dl) after meals; blood glucose concentrations should not be allowed to fall below 3 mmol/litre (55 mg/dl). Concentrations of glycated haemoglobin should reflect mean blood glucose concentrations of less than 8.6 mmol/litre (155 mg/dl); this is usually expressed as a percentage of total haemoglobin with the reference range varying with the method of estimation used (59) (Annex 10).

The principal means of achieving the objectives of diabetes management are adjustment of diet, reduction and avoidance of obesity, adequate physical activity, use of oral hypoglycaemic agents, and administration of insulin if necessary. Education and motivation of the patient to play an active part in the antidiabetic programme and maintenance of general physical and emotional health is essential if the therapeutic measures are to be effective (Section 11).
7.2 Food

Some form of advice on dietary adjustment will be needed by all types of diabetic, though it differs for the two main types. In many NIDDM patients, suitable restriction of food intake often combined with a programme of increased physical activity will initially be the only "treatment" required. Patients who need insulin injections have to learn the basic facts about the composition of foods and mealtime strategies. Dietary information and advice must be simple, clear, realistic, and geared to the individual's cultural, educational, and economic status. It is best given by a person trained in dietetics and skilled in communication. It is difficult to change dietary patterns, and it should not be supposed that this can be achieved by giving the patient a printed sheet and a cursory explanation.

Patients with NIDDM who need to reduce food intake to lose weight should not disproportionately restrict carbohydrates. Excessive consumption of refined carbohydrate should be avoided and sources rich in energy such as fats and alcohol should be restricted. The food energy requirements of diabetics of normal weight are best assessed from their habitual intake. Diets explained on the basis of energy intake alone are unrealistic and usually disregarded. Dietary advice should take into account locally available foods, as far as possible, habitual types of food and mealtimes should be retained.

Since atherosclerosis is a major cause of disability and death among diabetics, many authoritative bodies have reviewed the NIDDM advice for diabetics, largely bringing it into line with the "prudent diets" being recommended to the general population to reduce the risk of arterial disease (60). Where the prevailing pattern of food intake requires it, dietary fat should be limited to approximately 30% of total daily energy intake, and foods containing polyunsaturated vegetable oils (e.g., margarines and cooking oils) should be substituted for those containing saturated fats (e.g., dairy products). Protein should account for approximately 15–20% of the daily intake, and carbohydrates rich in natural fibre should constitute the remaining food energy. The same general principles of good nutrition apply to both diabetics and non-diabetics. The fat content of the normal diet in some populations may be as low or lower than that recommended above, and intake of unrefined carbohydrates may be as high or higher; diabetics in these populations can be well controlled with such diets.
There may be conditions under which the above recommendations for daily food intake do not apply. For example, diet should be adapted to the special needs of growth, pregnancy, lactation, physical activity, and medical disorders. Special “diabetic foods” are neither desirable nor necessary, though artificial sweeteners may be safely used by diabetic patients. The emphasis in the insulin-treated diabetic should be on regularity in timing and intake of food, with mealtimes planned, as far as possible, to fit the diabetic’s normal way of life. A common pattern for insulin-dependent diabetics is to eat three “main” meals, with small intervening snacks to balance the lowering action of insulin on blood glucose levels.

7.3 Use of insulin

Diabetics who need insulin injections should aim to maintain the concentration of blood glucose as closely within the normal range as is practicable and safe. Good control of this sort requires a flexible regimen that matches insulin action to food intake and physical activity. This is usually best achieved by taking multiple (two or more) small injections a day rather than a single larger injection. In principle, the diabetic should attempt to mimic the normal situation—a stable continuous background of insulin in the basal fasting state with peaks of insulin to cover the special needs of meals (61). Good control has been obtained over long periods in some patients by continuous subcutaneous insulin infusion from small portable insulin pumps that can also deliver extra boosts of insulin on demand before meals. Adequate blood glucose self-monitoring by the patient is essential for all of these intensified insulin regimens (see Annex 2). It is therefore vital that patients are taught to take the major role in their own diabetes management by trained and experienced health care personnel. Whenever possible, injections should be self-administered. The patient should also be taught how to make adjustments to insulin dosage to improve control. The diabetic must be equipped with insulin, syringe, and needles, and taught the principles of antisepsis. With adequate equipment, training, and motivation, patients can develop high levels of expertise and success in their own management.
7.3.1 Insulin types

Insulin is usually injected under the skin; its action depends on the rate at which it disperses, via the bloodstream, to the tissues of the body. Absorption of unmodified insulin solution (soluble, crystalline, regular) is comparatively rapid but can be moderately or considerably delayed by suitable crystallization or complexing of the insulin solution. Mixtures of unmodified and modified preparations should be selected to fit the individual needs and life-style of each diabetic. A patient's life-style may change and the insulin regimen should be flexible enough to adapt accordingly. Skilled and well-informed use of the different types of insulin by the patient is the key to a virtually unrestricted range of life activities and is indispensable to good diabetes management (Annex 11).

7.3.2 Insulin concentration and purification

Historically, insulin solutions have been produced in several concentrations, usually expressed in international units per millilitre (e.g., 20, 40, 80, 100 IU/ml). The availability of so many concentrations leads to confusion and dosage errors, and restriction to a single concentration is highly desirable. Many countries have now adopted 100 IU/ml (U-100) as the single standardized concentration with appropriate modification of syringe design.

Most insulin is extracted from animal pancreas and consequently its structure differs slightly from that of human insulin; therefore only the most purified form should be used since this is least likely to induce immune reactions in the patient. Beef and pork insulin have similar antidiabetic potency but the former is more likely to evoke an immunological response. Insulin with identical structure to the human hormone, prepared by either biosynthetic techniques using recombinant DNA or chemical modification of pork insulin, is now commercially available. It is fully effective clinically, but its therapeutic superiority has yet to be demonstrated.

7.3.3 Identification and administration of insulin

The continuing lack of uniformity in methods of identification of type, concentration, degree of purification, and species of origin of insulin preparations is potentially hazardous and confusing for both patients and health care personnel. Agreement and standardization are strongly recommended. Specially designed syringes are available
for insulin injection that are calibrated for a specific concentration of insulin and made from glass or plastic. With suitable precautions, a diabetic patient may reuse a plastic syringe on several occasions (62).

7.3.4 Potency, storage, and availability

In hot climates, unrefrigerated insulin loses its potency after a few weeks. It should be stored away from sunlight in a cool place.

Once the commitment to insulin therapy has been made, continued supplies of the correct types should be ensured. High cost may restrict the availability of insulin in some developing countries, often with disastrous effects on the health and life of diabetics.

7.3.5 Implantable insulin-delivery devices and pancreatic transplantation

New therapeutic approaches such as implantable insulin-delivery devices and transplantation of the whole or part of the pancreas or of the pancreatic islets have been attempted in a limited number of patients. These procedures are still in the experimental stage and their use should be restricted to specialized centres for the time being.

7.4 Oral hypoglycaemic agents

Some patients with NIDDM do not respond adequately to restricted food intake and dietary advice. In many of them, reinforcement of diet with oral sulfonylurea and biguanide preparations will reduce hyperglycaemia and relieve symptoms, but some endogenous secretion of insulin is necessary for these drugs to work. There are many types of sulfonylurea with varying degrees of hypoglycaemic potency (63). Generally speaking, they can be divided into those with long, intermediate, or short half-lives of activity. The choice of preparation is determined by the need to avoid hypoglycaemia, especially in the elderly; by the possibility of kidney or liver disease interfering with their excretion or metabolism; and by the patient’s reaction to the drugs. Doses should be reduced after attaining blood glucose control, and the drug discontinued if control can be maintained by diet alone.

The use of the biguanide phenformin has declined because of its contribution to the rare but often lethal condition of lactic acidosis;
in some countries it has been totally withdrawn from use. Metformin, another biguanide, is associated much less frequently with lactic acidosis. Buformin may occupy an intermediate position between these two drugs with respect to lactic acidosis. Low doses of metformin or buformin may be useful for treating patients under 65 years of age without kidney, liver, or cardiovascular disease or history of alcoholism.

7.5 Exercise

Planned physical activity, according to age and physical status, is considered a useful part of treatment (57). Exercise improves metabolism and increases wellbeing in the patient, and it has been shown to enhance insulin action on target tissues. When physical activity is a normal part of the pattern of life, diabetes should not restrict it.

7.6 Resources required for treatment

Therapeutic agents, the means of administering them (syringes, needles, etc.) and methods of monitoring glucose concentration in urine and blood that can be used by the patient (i.e., self-monitoring techniques) are essential to diabetes care (see Annexes 2 and 12). The supply of these basic requirements is inadequate or non-existent in some developing countries. In all social and cultural contexts, teaching patients about diabetes, how to control and correct it, and how to prevent complications are of central importance.

7.7 Acute metabolic problems

Diabetic ketoacidosis and insulin-induced hypoglycaemia account for significant morbidity and mortality among patients with IDDM; non-ketotic hyperosmolar hyperglycaemic coma and lactic acidosis occur less frequently but are dangerous.

7.7.1 Hypoglycaemia

Hypoglycaemia is a common side-effect of insulin therapy. Its symptoms include weakness, profuse sweating, irritability, confusion, unconsciousness, and convulsions. It is feared by the
patients and their relatives, is potentially dangerous, and may cause 
permanent neurological damage. If frequent and severe, it is 
incompatible with normal life.
Hypoglycaemia may be defined biochemically, i.e., as a blood 
glucose concentration of less than 2.5 mmol/litre (45 mg/dl) but, in 
practice, the term is used to describe the symptoms and signs of the 
condition. The relation between these symptoms and signs and the 
blood glucose concentration may be variable. Awareness of 
biochemical hypoglycaemia varies between patients and, from time 
to time, in individuals. Hypoglycaemia at night may fail to rouse the 
patient from sleep. Some of the warning symptoms may be masked 
by beta-adrenergic blocking drugs used in the treatment of 
hypertension and angina. Frequent blood glucose monitoring is 
necessary to detect and prevent low blood glucose levels.
Mild hypoglycaemic symptoms should not be a cause of alarm if 
they occur infrequently, at expected times (e.g., just before lunch), 
and in circumstances that do not expose the patient or others to 
danger. Repeated or severe hypoglycaemia is, however, a signal for 
urgent enquiry and correction as it can be associated with serious 
consequences. Hypoglycaemia is usually caused by over-treatment 
with insulin, delayed meals, unexpected vigorous exertion, 
consumption of alcohol, or diminished awareness. Furthermore, in 
most patients with IDDM, the body's normal counter-regulatory 
hormonal defence against hypoglycaemia is impaired. When there 
is inadequate counter-regulation, the variable absorption of 
subcutaneously injected insulin imposes an additional 
hypoglycaemic hazard.
Recognized early, hypoglycaemia is easy to treat. The patient 
should correct "mild" episodes promptly by ingesting rapidly 
absorbed carbohydrate (sugar lumps or glucose tablets) followed by 
food. If self-treatment is not possible persistent attempts to give 
sugar drinks by mouth should be made while the patient remains 
conscious. However, this is dangerous once consciousness is 
impaired and intravenous injections of 50 ml of 20% glucose 
solution or intramuscular injections of glucagon (1 mg) should be 
given without delay. It is essential that food is taken by mouth after 
consciousness is restored and that the patient is kept under 
observation since relapse can occur.
Patients, relatives, all health workers, teachers, and fellow 
employees in contact with diabetics should be aware of the 
symptoms of hypoglycaemia and know what action to take.
Factitious hypoglycaemia, i.e., hypoglycaemia produced by deliberate injection of an overdose of insulin may be difficult to diagnose and treat. Possible deleterious effects of repeated episodes of hypoglycaemia, especially on the central nervous system, are not well elucidated and research in this area is needed.

7.7.2 Hypoglycaemia in patients treated with oral hypoglycaemic agents

A few patients taking oral hypoglycaemic drugs, especially the elderly and patients with impaired hepatic and renal function, may be at risk of developing severe and protracted hypoglycaemia in special circumstances such as alcohol consumption, insufficient food intake, and interaction with other drugs. Severe hypoglycaemia is rare and is seen mainly in patients taking oral hypoglycaemic drugs with prolonged action.

7.7.3 Severe hyperglycaemic ketoacidosis (diabetic coma)

Diabetes may first present with coma caused by severe insulin deficiency. In diabetics already under treatment, ketoacidosis most often results from failure to take adequate insulin and may point to poor education, psychological factors, and inadequate provision of health care. Severe stresses like heart attack and trauma may precipitate ketoacidosis even in mild diabetics through the increased secretion of hormones that oppose insulin action. Early recognition and vigorous treatment by the patient, relatives, or medical personnel can prevent otherwise serious deterioration in physical condition (64).

Mortality rates, especially in the elderly, can be high. Education of health care personnel and patients is therefore crucial and, at present, often inadequate. Rapid and early access to adequate health care facilities is necessary and insulin must be available. Infections must be treated promptly and patients made aware of the increased insulin requirements associated with illness, infection, and trauma. Patients with IDDM must be instructed never to omit insulin injections, especially during intercurrent illness.

The diagnosis of severe diabetic ketoacidosis can be made from the patient's history, clinical examination, urine tests for sugar and ketones, and simple bedside blood tests for glucose and plasma
ketone bodies. Sometimes the patient’s breath may smell of ketone or acetone. Portable meters that measure blood glucose concentrations quickly and accurately are valuable in diagnosis and monitoring of treatment.

Where possible, blood should also be sent to a laboratory for estimation of glucose, urea, electrolytes, and acid/base status.

Ketoacidotic coma should be treated with low-dose, intramuscular or intravenous insulin injections (5-10 IU/h) combined with adequate rehydration and electrolyte replacement. If a blood glucose response is not seen within 4 hours, larger doses of insulin are necessary. Precipitating infections should be treated, potassium salts administered as required, and acidosis corrected if severe. Further general measures include gastric intubation to relieve gastric dilatation, monitoring of central venous pressure in the elderly or those with cardiovascular disease, and blood or plasma infusion in patients with persistent peripheral circulatory failure.

Partial correction of ketoacidosis and hyperglycaemia will often occur with rehydration and restoration of the circulation alone. Where insulin is unavailable or facilities for patient care are poor, fluid replacement with saline will be useful while the patient is being moved to a special centre. If facilities for intravenous fluid administration are not available, then saline (if necessary made from table salt and boiled water) can be given rectally.

7.7.4 Other metabolic comas

Coma associated with severe hyperglycaemia may occur without ketoacidosis (non-ketotic hyperosmolar coma) (65). Hyperventilation is absent and plasma and urine show little or no evidence of ketone bodies. Patients should be treated with intravenous saline solutions (e.g., 0.45 g/100 ml saline solution) and insulin regimens similar to those described for ketoacidotic coma.

Lactic acidosis (66) in diabetics is particularly associated with biguanide therapy (especially phenformin; see section 7.4) but may also result from shock, sepsicaemia, or anoxia. The degree of acidosis is more severe than ketone body measurements indicate, and mortality is high. Circulatory support and correction of metabolic acidosis is necessary.
7.8 Pregnancy

Better control of maternal metabolism and improved fetal surveillance have dramatically decreased perinatal morbidity and mortality in diabetic pregnancies over the past 25 years. However, congenital malformations still occur more frequently in the offspring of diabetic women. The first weeks of pregnancy are critical for normal organogenesis. Diabetic women of childbearing age should receive systematic counselling and, whenever feasible, conception should be postponed until optimum glycaemia has been achieved; optimum glycaemia should be maintained throughout pregnancy.

7.8.1 Management

Coordination of diabetic, obstetric, and paediatric skills is necessary for the management of the pregnant diabetic. Blood glucose concentrations should be maintained within the normal physiological range by intensive dietary and insulin therapy, careful surveillance of the diabetic, obstetric and general health of the expectant mother, and regular monitoring of fetal size and function by the most effective means available.1 Improvement in the outcome of pregnancy can be achieved even under difficult conditions; at centres with good facilities for antenatal care, outcome now approaches that of non-diabetic pregnancy. Normal principles of dietary management in pregnancy apply in the diabetic. Daily food intake should contain approximately 126 kJ (30 kcal) per kg desirable body weight during the first trimester and 147 kJ (35 kcal) per kg desirable body weight during the second and third trimesters; throughout pregnancy food intake should contain 1.5–2.5 g of protein per kilogram of desirable body weight. Total weight gain during pregnancy should not exceed 12 kg.

Every effort should be made to achieve optimal levels of glycaemia with fasting values between 3.3 and 5.6 mmol/litre (60–100 mg/dl) of venous whole blood and two-hour post-prandial values of less than 7.8 mmol/litre (140 mg/dl). Insulin therapy must be designed to suit the specific needs of individual patients; this usually requires the use of a combination of short and intermediate

acting preparations. Insulin requirement doubles on average during pregnancy, but after delivery it drops precipitously to pregravid levels. Severe hypoglycaemia should be avoided but lesser degrees are probably unavoidable. Urine tests for glucose are unreliable during pregnancy because the renal threshold for glucose falls. Ketonuria can, however, be reliably detected and should be avoided.

Patients should be seen every two weeks until week 30, then weekly. Diabetic control is best achieved by frequent self-monitoring of blood glucose concentrations and a daily test for urinary ketones, with fasting and post-prandial blood glucose estimations at each visit to the clinic. Hypertension, hydramnios, pre-eclampsia, toxemia, urinary tract infection, retinopathy, and renal disease should be systematically and repeatedly sought, and appropriate therapy instituted if an abnormality is detected. Rapidly progressive renal or retinal complications may be an indication to terminate the pregnancy.

Routine fetal monitoring includes regular measurements of fetal heart rate and fetal ultrasonography in the first or second trimester to estimate the size of the fetus, to detect certain malformations, and to assess cephalic versus somatic growth. Estriol measurements and amniocentesis may be required. All of these procedures can be performed on an outpatient basis. Where resources are limited, the pregnant diabetic should be given priority access to centres where suitable facilities are available.

Gestation should be allowed to proceed to a normal delivery unless fetal distress is suspected; Caesarean section should be performed solely for obstetric indications. Intravenous infusion of glucose and insulin is valuable for controlling diabetes during labour (section 7.9).

The neonate requires special care so that the risks of hypoglycaemia, hypocalcaemia, hyperbilirubinaemia, or respiratory distress syndrome can be detected and dealt with early.

Diabetes mellitus first diagnosed in pregnancy (gestational diabetes) and lesser degrees of maternal glucose intolerance may be associated with increased perinatal morbidity and should be managed according to the above guidelines.

7.8.2 Puerperium

After delivery, insulin dose requirements drop precipitously to pregravid levels. Return to the pre-pregnancy regimen of food and
insulin should therefore not be delayed. Breast-feeding is normally possible, but food intake and insulin dosage will need to be raised.

7.8.3 Contraception

The diabetic woman should have her family while she is young. Pregnancy with the renal or vascular complications of diabetes carries a poor fetal prognosis, and termination and sterilization may be advisable. Any of the contraceptive methods that are currently available can be used, although physical methods (intra-uterine devices, barrier methods) are preferable to oral contraceptives, which may adversely affect metabolism or accelerate vascular disease. An alternative is surgical sterilization of either partner.

7.9 Surgery and the diabetic

Approximately 50% of diabetics will have at least one operation during their lifetime. The metabolic stress of general anaesthesia and surgery, if untreated, can lead to severe loss of diabetic control. Management should be geared to local facilities.

Few special precautions are required for minor operations under local or general anaesthesia. The simplest method is to postpone therapy (oral hypoglycaemic agents or insulin) on the morning of the operation.

The simplest scheme for treating non-insulin-dependent and insulin-dependent diabetics during a major operation is to use a continuous intravenous infusion of insulin (2-4 IU/h) in glucose (100 ml of 100 g/litre glucose per hour) from the morning of the operation until the first meal is taken, when the usual therapy can be recommenced. Blood glucose should be monitored frequently to avoid hypoglycaemia during anaesthesia. Alternatively, repeated small injections of soluble insulin with careful monitoring of blood glucose will suffice.

7.10 IDDM in children and adolescents

The chief aim of therapy is to obtain normal blood glucose levels and to maintain good control over the years in the hope that a state of euglycaemia, or one approaching it, will reduce the risk of the

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1 See footnote on page 53.
7.10.1 Initiation of treatment

Control of blood glucose concentration is achieved by a combination of insulin therapy and diet (adjusted to the family's customs and child's activities). In a child with severe diabetic ketoacidosis (coma), the approach to initial treatment is similar to that for the adult (see section 7.7.3) with appropriate scaling down of dosages of insulin, fluids, etc. Those that are less severely affected should be treated with an initial daily dosage of soluble (regular) insulin of approximately 0.6-1.0 IU/kg body weight, divided into two or three doses, or a single daily dose of 0.5-0.6 IU/kg of intermediate-acting insulin. Subsequent doses and pattern of insulin administration should be adjusted according to blood and urine glucose levels. Daily food intake should be related to age and physical activity and should be distributed over 6-7 meals, including a bedtime snack.

Provided that specialized premises and trained personnel are available, initial therapy and education can often be given on an outpatient basis (68).

After initiation into the routine of diabetic treatment, during which the child is in frequent contact with the health professionals, repeated routine follow-up visits should be arranged at intervals of not longer than 3 months.

In most children, a significant decline in insulin requirement occurs during the few months after initiation of treatment. This period, referred to as the "remission" or "honeymoon" period, results from a partial recovery of islet-cell function. However, this period is followed by exhaustion of the beta cells and a corresponding increase in the requirement for insulin to approximately 0.6-1.0 IU/kg body weight; the insulin requirement is even greater during puberty.

7.10.2 Long-term management

Long-term management should aim for normal physical and emotional development; slowing of growth or delayed onset of puberty may indicate inadequate treatment.
Education of the child and family members is most important and can be achieved by a variety of methods, e.g., personal instruction, courses, lectures, written material, slides, and films. It should include the need for dietary control, intelligently applied and consonant with good nutrition; adjustment of insulin dose and timing according to physical activity; measures to be taken during illness; and the management of emergency situations. Such systematic instruction should be repeated on a continuous basis and not reserved for special courses or vacation camps.

Psychosocial counselling of the child and the family by skilled personnel from the onset of the disease is an essential aspect of management (section 10).

Diabetes occurring in infancy and very unstable diabetes require special attention because of the many difficulties of management.

7.11 Diabetes in the elderly

Diabetes in the elderly is a major health problem. Its impact is often not fully acknowledged and should attract more attention from health care professionals and planners (69). In the old person, diabetes is often not the sole or even the major health problem. The disease often comes to light incidentally while investigating such problems as heart disease, arterial insufficiency, or failing vision.

7.11.1 Management

Most elderly diabetics are not dependent on insulin, but a few develop diabetes abruptly and are insulin-dependent, and some present with severe non-ketotic hyperglycaemia. An increasing number of patients with early-onset, insulin-dependent diabetes are surviving to old age.

Management in the elderly aims to relieve diabetic symptoms, to correct accompanying disease as far as possible, to initiate preventive measures, and to improve the quality of life.

To promote over-energetically a policy of metabolic normalization in the old is distressing and even dangerous; it is also difficult to justify on the basis of prevention of long-term complications. Hypoglycaemia may have devastating consequences, and insulin and oral hypoglycaemic agents should therefore be used sparingly. Severe dietary restriction is unkind, though advice on better nutrition is valuable.
7.11.2 Other problems in the elderly diabetic

Much can and should be done to remedy accompanying disorders, and the presence of diabetes is not a contraindication. Drug interactions must be considered and episodes of major illness, trauma, or surgery will need carefully supervised insulin support. Individual advice on foot hygiene with early correction of existing foot problems by appropriately trained health personnel may avert a future amputation. The elderly diabetic always needs reassurance that the diagnosis does not spell doom; social services are therefore of great importance.

8. COMPLICATIONS

Progressive damage to the eyes, kidneys, nerves, and arteries represents the major threat to the health and life of diabetics. In recent years, new possibilities have appeared for limiting the progression of these complications, so reducing the risk of blindness, end-stage renal failure, neuropathic tissue damage, ischaemic tissue damage, amputation, heart attack, and stroke. Evidence from clinical observations (70) and experiments on animals (71) strongly suggests that improved control of the diabetic state (i.e., the maintenance of nearly normal levels of blood glucose concentration) will reduce the complication rate and, increasingly, therapeutic effort is being intensified to achieve this objective.

Although complications usually first appear some years after clinical diagnosis, they may be present at the time of diagnosis. Some patients only present because of the complications, undiagnosed diabetes having been present for many years; this is especially true of the elderly. The effectiveness of methods of prevention and treatment of the complications depends upon their timely application; it is therefore crucial to submit the diabetic patient to a regular examination that is specifically designed to detect early abnormalities in the tissues and organs at risk.

8.1 Diabetic eye disease

8.1.1 Prevalence of diabetic retinopathy

Diabetes-associated damage to the retina of the eye is the leading cause of visual disability arising in middle-aged and elderly people.
in economically advanced societies (72). In Denmark, blindness or severe visual handicap developed in about one-third of a cohort of youth-onset insulin-dependent diabetics that was followed for 40 years or more (73). Among non-insulin-dependent diabetics, who are much more numerous than insulin-dependent diabetics, 10% or more developed visual handicap or blindness.

The widespread association between retinopathy and the many forms of diabetes is well recognized. Its frequency in patients with early and late onset diabetes has recently been well documented in a defined population in Wisconsin, United States of America (74, 75). It has also been reported as a complication of the highly prevalent, obesity-associated diabetes in the isolated Pacific population of Nauru (76) and in the Pima Indians of Arizona (77). Retinopathy of different degrees of severity was documented in all 14 national samples commissioned for the WHO Multinational Study of Vascular Disease in Diabetics (78). Most diabetics (and virtually all insulin-dependent patients) will eventually develop some retinopathic manifestation, but only a proportion appear to be at risk of developing the severe sight-threatening forms.

8.1.2 Risk of blindness

Examination of the ocular fundus can detect those patients who have a high risk of going blind. The "high risk" state is indicated by the appearance of fine new blood vessels, particularly on or close to the disc, or elsewhere in the retina when associated with retinal haemorrhages. In older people the risk to vision is predicted by the deposition of white exudate and haemorrhage, or by oedematous swelling of retinal tissues in the region of the macula. Clinical trials (79, 80) have indicated that prompt detection and early treatment with photoocoagulation will arrest the process and conserve vision in about 70% of eyes that would otherwise have become blind. The institution of regular, effective screening for such danger signs and the ready availability of photoocoagulation treatment clearly deserve to be given high priority in the planning of health services.

8.1.3 Prevention and management

The cause of diabetic retinopathy is not known, but animal experiments suggest that it is much more likely to occur when the
control of diabetes is poor (71). Maintenance of optimal degrees of metabolic control may thus be able to prevent retinopathy or slow its progression. The evidence for this in man is largely circumstantial, but clinical trials of the effectiveness of greatly improved diabetic control are in progress. Other measures such as effective treatment of accompanying high blood pressure and the use of “antiplatelet” drugs may also slow the progression of early diabetic retinopathy. If the eye has already been seriously damaged by diabetes, highly specialized surgery may salvage some useful vision.

For many blind diabetics, rehabilitation schemes will preserve a measure of independence. Special syringes that enable the visually handicapped to draw the correct insulin dose, and special devices with audible signals for self-measurement of blood glucose are available. All organized programmes for the general prevention of blindness should include provision for the prevention of diabetic retinopathy.

8.1.4 Cataract and other eye diseases

Cataract occurs earlier and more often in diabetics than in non-diabetics. Vision may be preserved by surgical removal of the diseased lens. A good result depends upon the absence of any substantial degree of accompanying retinopathy. Acute metabolic opacity of the lens may occur in young people soon after diabetes is diagnosed and treatment started. While this may resolve spontaneously, surgical removal is often necessary. The nerve supply to the oculomotor muscles may be affected by diabetic neuropathy but usually recovers with time; the pupillary nerves may also be involved and, rarely, the optic nerve itself. Congestive glaucoma may complicate severe proliferative retinopathy.

8.2 Kidney disease

8.2.1 Prevalence of renal failure

Progressive impairment of renal function, accompanied by urinary protein loss and culminating in end-stage renal failure, threatens the health and life of up to half those patients who develop
IDDVM in youth or adolescence (33), and a smaller, inadequately-defined, but significant, proportion of patients who develop non-insulin-dependent diabetes later in life. Among some population groups where IDDM is very uncommon (e.g., Japanese, Chinese, and American Indians that have retained their traditional life-style) and in whom NIDDM starts in middle age, diabetes causes a substantial amount of renal failure (51). As increasing numbers of diabetics survive the earlier hazards of the disease, more will live long enough to develop renal failure. Chronic renal disease not only robs the sufferer and society of years of vigorous and productive activity, but also puts a heavy burden upon the health services that provide expensive forms of therapy.

8.2.2 Evolution of nephropathy

Until recent years the first indication of diabetic renal failure was the appearance of clinically detectable proteinuria, other probable causes having been excluded. By this time, however, structural damage to the kidney is advanced and within a few years impairment of the filtration and excretory functions of the kidney sets in, with inexorable progression to terminal renal failure. In some patients effective reduction of raised arterial pressure may slow the progress of renal deterioration (82); stringent improvement in diabetic control has little or no effect (83), though the need to maintain adequate metabolic control remains. Renal dialysis or transplantation ultimately become the only options for survival, but these forms of treatment can only be provided by specialized units. The newly transplanted kidney should be protected from re-involvement by the maintenance of the highest possible levels of diabetic control. Renal failure in the diabetic is often complicated by problems such as blindness or coronary and peripheral arterial disease.

8.2.3 Early detection and prevention

In recent years, the use of sensitive assay methods has shown that some diabetics excrete slightly increased amounts of plasma albumin in their urine (microalbuminuria). These patients have a greatly increased risk of developing progressive renal failure (84). Other markers of prospective renal failure, such as high rates of glomerular filtration, kidney enlargement, and minor rises in arterial pressure may also be found. At this early stage, there is some evidence that
intensification of diabetic control will arrest or even reverse the nephropathic process. Pharmacological approaches may also be useful. Clinical trials are in progress to determine the best strategies for early action to prevent the catastrophe of renal failure in susceptible diabetics.

8.2.4 Mechanism of nephropathy

Damage to the delicate filtering capillaries of the renal glomerulus is initiated by inadequate control of the diabetic state. However, once a substantial part of the filtration apparatus is damaged, the extra excretory burden put upon the rest causes progressive deterioration. This process of renal autodestruction may be slowed by dietary restriction of protein and/or phosphate intake, which reduces the excretory burden falling upon the residual kidney tissue. Urinary-tract infections may accelerate kidney damage and should be sought and eradicated. Radiographic contrast-media and potentially nephrotoxic drugs may provoke sudden and severe deterioration in the damaged kidney.

8.2.5 Other problems

Urinary tract infections are more commonly provoked in diabetics than non-diabetics by bladder instrumentation or by urinary stasis because of obstruction or neuropathic bladder weakness. Renal infection and ischaemia contribute to the chronic fibrosis, tissue destruction, and renal failure of pyelonephritis which is frequently encountered in the diabetic. With increased blood viscosity, these factors may also lead to the severe complication of renal medullary necrosis which is sometimes complicated by obstruction of the ureter.

8.3 Diabetic neuropathy

Damage to nerve fibres conducting sensation and supplying muscles, blood vessels, and viscera is the most common complication of diabetes. There are several distinct patterns of neurological disease giving rise to a number of clinical syndromes and disabilities (65).
8.3.1 Patterns of nerve damage

The commonest pattern, usually occurring after many years of diabetes, affects principally the sensory nerves of the lower limbs with loss of the sensation of pain and sometimes severe and progressive destruction of the soft tissues, bone, and joints; paraesthesia is frequent, and painful neuropathy may also occur. When the motor nerves are affected, there is weakness and muscle wasting, often involving the legs and feet, and sometimes the hands and arms. Obstruction of the blood supply may damage individual nerve trunks, and lead to focal loss of nerve function with isolated muscle paralysis or areas of sensory loss. Damage to autonomic nerve fibres may disrupt such functions as blood pressure control and emptying of the stomach and urinary bladder; if the pelvic nerves are involved it may cause erectile and ejaculatory failure. Sudden unexpected cardiorespiratory arrest may occur, particularly if the diabetic is taking drugs to depress respiration or is anaesthetized. Diabetics are more susceptible to other factors that damage nerves, such as alcohol and other neurotoxins, localized pressure, and infection.

8.3.2 Preservation of nerve function

Prevention of nerve damage by maintenance of optimal diabetic control and early detection of neuropathy are of major importance, since established neuropathy may be irreversible. Drugs that protect the nerves by locally blocking the effects of hyperglycaemia (88), or drugs, such as the gangliosides, that affect myelin metabolism and sprouting, may prove useful for preventing neuropathy in diabetics, and are currently being investigated. Even when nerve damage is established, the risk of serious consequences such as soft-tissue and joint destruction can be reduced by appropriate care.

8.3.3 Causal factors

Several mechanisms probably contribute to nerve damage. The biochemistry of the nerve cell itself and its sheath is disordered in diabetics, particularly when control of the disease is poor. Alterations in blood viscosity and circulating platelets, and swelling of the endothelial cells lining the fine blood vessels that supply the nerve trunk, reduce and may arrest blood flow in the nerve.
Intensified research into this comparatively poorly understood and imperfectly treatable complication of diabetes is needed.

8.4 Cardiovascular complications

8.4.1 Coronary heart disease

Coronary heart disease occurs more frequently and has notably more serious consequences in diabetics than in non-diabetics; this is particularly true for women. This increased vulnerability is universally reported and in westernized cultures it is responsible for half or more of the deaths in diabetic patients (87). However, the mortality rate follows national patterns; for example, although in Japan the mortality rate from coronary heart disease is higher for diabetics than non-diabetics, it is still considerably less than for non-diabetics in Europe and North America. The high prevalence of arterial disease in diabetics is only partly explained by the increased frequency of known risk factors such as hypertension and hyperlipidaemia. Arterial disease is also associated with lesser degrees of glucose intolerance (i.e., impaired glucose tolerance). The increased susceptibility to coronary heart disease of Japanese diabetics who migrate to a western environment strongly suggests an adverse effect of changed life-style, with suspicion resting particularly on changed dietary patterns. In recent years, this has prompted revisions in dietary prescriptions for diabetics in the hope of reducing the risk of arterial disease (section 7). Treatment of established coronary artery disease with bypass surgery or angioplasty has been extended to diabetic patients in whom results are comparable with those of the non-diabetic.

8.4.2 Non-coronary cardiopathy

Other disorders of heart muscle associated with the metabolic disorder of diabetes, disturbed nervous control, and perhaps microvascular disease worsen the impact of coronary atherosclerosis and the outcome of myocardial infarction. Even in the absence of significant coronary obstruction, these abnormalities may cause heart disease (diabetic cardiopathy) in their own right.
8.4.3 Peripheral and cerebrovascular arterial disease

Atherosclerotic disease of the small arteries in diabetics is responsible for the high incidence of intermittent claudication and gangrene in the lower limbs, and for cerebral infarction, stroke, and diffuse cerebrovascular disease. General dietary preventive measures should be taken and, as with non-diabetics, the early detection and effective correction of hypertension is of great importance.

8.4.4 Prevention of cardiovascular disease

The preventive measures recommended to the population as a whole—correction of raised blood pressure, lowering of plasma cholesterol, cessation of smoking, and avoidance of physical inactivity—are particularly important for diabetics since they have a higher risk of developing cardiovascular disease. Careful examination for and correction of known risk factors should be an obligatory part of systematic diabetic care. There is some evidence that, if cardiac damage has occurred, diabetics may be protected from sudden and perhaps lethal rhythm abnormalities by long-term treatment with cardioselective beta-adrenergic blocking drugs.

8.5 The diabetic foot

A considerable amount of disability in diabetics is caused by the peculiar susceptibility of the foot to severe tissue-damage (88). The combination of chronic foot ulceration, sepsis, and gangrene is the chief cause of prolonged hospitalization for diabetics, and accounts for more than half of the non-traumatic amputations performed in some developed countries. With correct care, the extent of tissue damage could be limited, and many of the mutilating operations completely avoided.

Three major factors contribute to damage to the diabetic foot: chronic diabetic neuropathy, atherosclerotic obstruction of the arteries that supply the lower limb, and bacterial infection. Any one factor may predominate in an individual case, though usually all are present to some degree.

8.5.1 Predominant neuropathy

Diabetics who have developed neuropathy over many years lose sensation in their feet and are often unaware of progressive damage
caused by pressure, friction, or abrasion. Microorganisms enter the deep tissues of the foot from under compressed callus or through an unsuspected wound, and break down soft tissues, tendons, and bones; this results in a sequestered collection of pus and tissue debris deep in the foot. When tissue destruction is extensive, amputation may be unavoidable but, short of this, wide drainage with removal of damaged tissue and unhurried healing under antibiotic cover may conserve a useful foot. Minor traumas to the ankle in a neuropathic limb may initiate rapid breakdown of intra-articular tissue culminating in an unstable, disorganized joint with Charcot's disease. Early recognition of the abnormal joint response, prohibition of weight-bearing on the affected joint, and the use of anti-inflammatory drugs may arrest this disabling and mutilating arthropathy.

8.5.2 Predominant arterial obstruction

The blackened shrivelled tissue of the gangrenous ischaemic foot is characteristic of the late and irreparable stage of diminished arterial supply. Tissue necrosis may be preceded for many years by a cold foot with dystrophic skin, and sometimes by pain in the calf caused by intermittent claudication. Physical or thermal trauma may precipitate gangrene in such a foot. Bacterial colonization of the necrotic tissue, often by several microorganisms, results in catastrophic spread of infection which may threaten the leg or the life of the patient and usually demands urgent amputation. If possible, amputation is best performed below the knee, since this improves the chance of the patient being satisfactorily rehabilitated with an artificial limb.

8.5.3 Prevention

The foot at risk from neuropathy or vascular disease is easily identified by clinical examination. Instruction in careful cleansing, attention to toenails, avoidance of shoe pressure or thermal trauma, and regular foot inspection will greatly reduce the risk of “diabetic foot”. Tobacco smoking should be strongly discouraged because of its adverse circulatory effects. Organized teamwork and systematic instruction of the patient will dramatically reduce the frequency of amputations among diabetics (88).
8.6 Screening for complications

Even in communities with well-organized facilities for the care of diabetics, the long-term complications of the disease are the major burden to the patient, to family and friends, and to society. Regular screening and early treatment for retinopathy have been shown to reduce the risk of serious visual loss. Screening for subclinical increases in urinary albumin excretion may identify a high-risk group for renal failure in which measures of prevention are appropriate. Screening for raised arterial blood pressure and its effective treatment are very likely to protect vulnerable arteries in the cerebral and coronary circulations and the lower limb, and may also protect renal and perhaps retinal microvasculature. Screening for raised plasma lipids, particularly the cholesterol-rich lipoproteins with low or intermediate density, and their correction by diet or drug therapy are also likely to reduce the risk of arterial disease. Early detection of neuropathic or ischaemic feet by systematic screening enables valuable treatment to be undertaken to prevent further degeneration. While research into the basic causes of the complications remains vital for their ultimate eradication, it is clear that properly-organized screening and preventive action in vulnerable patients can do much to reduce the risk of severe disability.

9. HEALTH CARE SERVICES

9.1 Health care planning

It is both a paradox and a challenge that the understanding of diabetes and the approaches to its management make rapid progress while organized health care services for diabetics in most parts of the world lag far behind. Health planners must be aware of this and should make care of the diabetic patient their prime concern.

9.1.1 An integrated approach to diabetic care

Provision of appropriate health care services for diabetics should take into consideration all the major components of the health care system, including assessment of local needs and resources, consensus on standards of care, mechanisms for translating recent advances in research into community practice, appropriate education and
utilization of all categories of health care professionals, and continuing evaluation of the quality and effectiveness of patient management. Fundamental to the planning and provision of health care services for a community is an understanding of its environmental, social, political, and economic structures. Services must be focused on patient care and must be designed to facilitate their integration into existing systems of national health care delivery and financing.

Concerted efforts should be made to orient comprehensive health care systems towards the following goals:

— identification of high-risk subjects at an early stage and, where possible, provision of health education aimed at primary prevention;  
— early diagnosis of diabetes and institution of management to reduce morbidity and mortality;  
— prevention and early recognition of acute complications such as infections and ketoacidosis, and the institution of effective treatment;  
— prevention or amelioration of neurological, cardiovascular, renal, and ocular complications of diabetes;  
— education of the patient, and the patient’s family, in methods of self-care within the home environment;  
— provision of equal opportunities for fulfilment of educational, physical, psychosocial, and employment potentials; and  
— identification and rehabilitation of diabetics who are partially or totally disabled.

To achieve these objectives, comprehensive health care for diabetics must be organized and delivered. Planning is the keystone of a comprehensive strategic health system that provides appropriate treatment for diabetics at the primary, secondary, and tertiary level.

9.1.2 Primary health care

Primary health care is of great importance to diabetic patients and their families, since most care is obtained at this level. Basic care, screening for complications, and patient education can be provided by a variety of health workers. Health workers must be well-informed of the diagnostic, therapeutic, and preventive aspects of care, and skilled in communication and educational techniques. Education of patients and their families is vital to optimize the effectiveness of primary health care services. Primary health care
facilities must be easily accessible to patients and their families, and compatible with their culture and beliefs. Care may be provided in a variety of settings including the home, health units, or better equipped outpatient clinics.

The components of diabetes health care at primary level include self-care, care at home, education, and care through community health workers. These efforts are supported by a health team consisting of a primary care physician, a nurse, and other allied health professionals. It is important that primary health care be linked with other levels of care. Some of these issues have been highlighted and were discussed in the second report of the WHO Expert Committee on Diabetes Mellitus (1).

9.1.3 Community control programmes

If systems are designed as recommended above, diabetes care can serve as a model for developing control strategies for other noncommunicable diseases. Emphasis on common risk factors, education of the community, patients, and professional health workers, and integration into existing health care systems at all levels is essential if such strategies are to be successful.

9.1.4 Diabetes care at secondary and tertiary levels

The creation of the essential core of skills and manpower needed to provide care for diabetics at the primary level must be coordinated with training of health care workers at secondary and tertiary levels. This calls for review of the undergraduate medical curriculum and of instruction courses for nurses, physicians, and allied health professionals involved in diabetes care.

Referral of the patient from the primary to the secondary level will generally be required when more expert or specialized assistance in the management of the disease or its complications is needed; for example, when an insulin-dependent diabetic needs expert guidance on how to improve control of the disease. Referral will also be necessary for obstetric advice during pregnancy, paediatric advice for an insulin-dependent child, and specialist advice for diabetics with chronic ocular, cardiovascular, and renal complications.

In addition to the availability of specialized physicians and appropriate support from allied health professionals, facilities should exist to provide routine consultations with obstetricians,
paediatricians, and other specialists. Care of the pregnant diabetic, including optimal conditions for the delivery and care of the newborn infant, should be provided at the secondary level of the health care service. Screening for ocular complications of diabetes, with arrangements to record and document any changes, are also necessary.

Laboratory services should include provisions for haematology, clinical chemistry, microbiology, radiography and electrocardiography. The level of these services should be appropriate to the health care setting and its requirements. There should be access to inpatient facilities and day-care centres, which should also serve as educational centres for patients and their families.

The main objective at the tertiary level is to organize specialized clinics and units capable of providing diagnostic and management skills of a high order. Such units are needed for the care of those with diabetic retinopathy, end-stage renal disease, and vascular disease. Specialized care of referred patients belonging to vulnerable groups such as pregnant diabetics and children with diabetes should be ensured. Provision of well-organized rehabilitation services is essential.

Centres for tertiary care should have the special resources, competence, and skills that are needed to prepare educational material for diabetics and for all categories of health workers involved in their care; adequate testing and validation of such learning materials is essential. In view of the considerable variability in the degree of literacy among populations, efforts should be made to develop effective learning aids for the semi-literate and the illiterate.

The tertiary referral level should encourage, emphasize, and be involved in basic, clinical, and epidemiological research. Research centres should aim to meet relevant local or regional needs, to exploit resources of competence, and to collaborate at the national, and regional levels. There should also be a strong component of operational and field research with special focus on the cost-effectiveness of alternative systems of providing health care for diabetics (89), and on the critical evaluation of such systems in terms of various indices of health economics. For such research, there has to be a close interaction between the health planners, health economists, and the various categories of health care personnel who work at the primary, secondary, and tertiary levels.
It is essential that the channels of communication are kept open between the different levels of health care. Patients should continue to receive their basic care at the primary level, but referral to secondary and tertiary care must be available. Coordination of care at the various levels should be built into the health care system.

9.2 Health manpower development

A key element of comprehensive health care for diabetics is health manpower planning. Any system of primary health care that attempts to cover a large population at relatively low cost must depend upon allied health professionals and adequate support from appropriate levels of secondary and tertiary care.

In most of the developed countries, the primary health care system is based upon a trained team of physicians, community nurses, and dieticians. In the developing countries, however, scarcity of trained personnel, and the priority of other health-related demands on their time, means that much of the responsibility of primary care falls upon manpower resources within the community, e.g., village schoolteachers, health volunteers, etc. The treatment and management of diabetes must therefore be included in training programmes for such manpower; this has been fully reported elsewhere (90).

9.3 Health economics

Establishing priorities for the allocation of restricted resources to the health sector in general, and to health services for noncommunicable diseases in particular, is a major dilemma for health planners, especially in developing countries. In order to argue the case for diabetes health care convincingly, there is a need to evaluate and compare available (or proposed) intervention techniques. This can be undertaken on the basis of: (i) the direct and indirect economic cost of diabetes (annex 13); (ii) cost-benefit analysis; and (iii) cost-effectiveness analysis.

The estimates of cost savings as a result of optimal diabetes care generally relate to the potential economic benefits of a programme of prevention, control, treatment, and rehabilitation. It is difficult enough to estimate direct economic costs and benefits of such a programme if it is solely concerned with diabetes, but it is even more so when diabetes care is part of an integrated community health
programme. The direct expenditure on health services, essential hospital care, and physicians is easier to compute. However, health education programmes that are designed to prevent a number of diseases that share common risk factors, e.g., diabetes, hypertension, and other degenerative vascular diseases, cannot be evaluated by conventional techniques. Furthermore, community control programmes aimed at promoting positive health, with improvements in physical efficiency, performance, and quality of life, also need a different system of evaluation. The indirect cost of the morbidity and mortality caused by diabetes or its complications is calculated in terms of lost man-hours and consequent loss of production.

Cost-benefit analysis evaluates health in monetary terms, since benefits and costs are calculated in terms of productivity and earning capacity. In contrast, cost-effectiveness analysis is a measure of the ratio of cost to effectiveness, e.g., cost per year of life saved. Thus, it enables the evaluation and ranking of alternative techniques in terms of the cost of producing different types of health improvement. In diabetes health care, decision makers should use cost-effectiveness analysis to help them choose between alternative intervention strategies (90).

9.4 Research

Health systems research is needed to develop a comprehensive diabetes health care programme that is linked with community control programmes for other noncommunicable diseases and that can be integrated into national health systems, particularly at the primary health care level. Such a programme should be multidisciplinary, with emphasis on social and behavioural aspects of diabetes care, and should aim at improving the delivery of health services, use comparative methods of investigation, help promote the application of existing and advancing biomedical knowledge, and provide a sound foundation for health planning and policy formulation.

9.5 Conclusions

Treatment and management of diabetes mellitus must be included in the framework of planning for the delivery of primary health care
in all countries. Care at the peripheral level should be linked through a network of referral centres to national centres of excellence.

10. THE DIABETIC IN SOCIETY

10.1 Integration and discrimination

With adequate care by the patient and understanding by society, diabetes should impose few real constraints upon life-style, working and recreational activities, and social relationships. Despite significant advances toward this ideal, there remain examples, sometimes glaring ones, of unnecessary and unjustifiable discrimination against diabetics which obstruct their full integration into society. Discrimination may be subtle and difficult to define and expose. It may operate at work and affect opportunities for promotion, at school, or within the family or social group. Irrational barriers can only be removed by challenging them vigorously and dispelling misapprehensions about diabetes; this can be achieved by disseminating simple explanatory information about the condition. Apart from the frustration and unhappiness of the individual patient, discrimination deprives society of the many talents and services that diabetics are able to offer.

10.2 The young diabetic

The impact of diabetes in childhood and adolescence is always great and may be devastating. It is important that the diabetic child should not be made to feel “different”, and that management schemes should interfere as little as possible with normal life. Parental counselling and group discussions help to achieve the difficult balance between over-protectiveness on the one hand and inadequate attention to the child on the other. Diabetic children should attend normal schools but information on their special needs should be given to teachers. Organized holidays for groups of diabetic children foster their self-confidence and reduce their sense of isolation. Helping the child and its family to cope with the emotional burdens of diabetes should be seen as a major part of management and may require skilled and experienced specialist help. Adolescence brings its own problems, not least the choice of occupation in life. The young diabetic is well advised to acquire as
much career-related training and as many qualifications as possible and should be adequately counselled.

10.3 Adulthood

Patients with diabetes of childhood onset should approach the opportunities and responsibilities of adult life with confidence and self-reliance born of enlightened and sympathetic management. However, diabetes may first make its appearance when the pattern of adult life and work is already established. Treatment usually involves insulin injections which may necessitate adjustments in lifestyle or occupation. Such changes should be kept to a minimum by devising appropriate treatment strategies and carefully explaining them to the patient to ensure compliance.

10.3.1 Training and employment

Opportunities for further education, training, and employment may be restricted for diabetics. Where restrictions are due to irrational prejudice or misapprehensions, they should be vigorously challenged. In some countries, educational and employment opportunities for diabetics are protected by legislation. All types of employment should be freely open to the appropriately trained and qualified diabetic, except in the very few instances where insulin treatment may endanger the safety of the patient or of others. Insulin-dependent diabetics should be advised against occupations where driving heavy goods vehicles and public service vehicles may be necessary; in many countries, they may be unable to obtain licenses to drive this category of vehicle. Private car licenses should be issued when diabetic control is good and the patient has adequate understanding of diabetes management.

10.3.2 Parenthood

A commonly expressed anxiety of diabetics wishing to start families is the risk of transmitting the condition to offspring. This risk is low and should not be regarded as a bar to parenthood. More relevant is the presence of severe diabetic complications in women which may deteriorate during pregnancy and hinder parental relationships and responsibilities later. Diabetic neuropathy may cause sexual dysfunction in the male; psychosexual problems may be ameliorated by appropriate counselling.
10.3.3 Insurance and cost of health care

Private insurance schemes may discriminate unselectively and unjustifiably against diabetic applicants and some refuse to accept them altogether. Some companies are sufficiently enlightened to offer terms which reflect the improved outlook for the well-controlled patient, and diabetics should seek these out with the advice of their national associations. All companies should now base their terms upon the revised definition and classification of diabetes (section 2). Impaired glucose tolerance (IGT) and the "statistical risk classes" are associated with demonstrably lower risks to health, and this should be reflected by improved terms for patients in these categories. In many countries, health insurance and the cost of diabetes care are fully covered by national schemes. Where they are not, special consideration, perhaps involving governmental agencies, should be given to providing full coverage for the diabetic. In particular, the free provision of insulin and equipment for its administration, oral hypoglycaemic drugs, monitoring equipment, and facilities for patient education should be given the highest priority. The purchase of new devices for the administration of insulin that have recently been developed could be justified as an investment of public or state resources since they greatly improve the quality of life for diabetics and may reduce the risk of long-term complications.

10.4 Aging with diabetes

In the elderly, the diagnosis of diabetes is likely to be made in association with some other, perhaps unrelated, disability. Visual deterioration, arterial insufficiency, and chronic foot ulceration are common accompaniments and require attention in their own right. Social isolation, financial hardship, and low levels of motivation may also be problems. The management of diabetes remains important, but it is usually not justifiable to press as intensively for the control of blood glucose concentrations as it is in the younger patient. Although diabetes in the elderly can normally be controlled by diet and oral agents, true dependence on insulin may occur. Hypoglycaemia, sometimes unsuspected, may be responsible for behaviour patterns attributed to senility, and should be avoided. Management of diabetes in the elderly has a high supervisory and social content and is greatly facilitated by the activities of nurses specialized in diabetic care.
10.5 Other problems

Adjustment to the “diabetic life” always requires informed reassurance and repeated explanation. Some diabetics adjust more successfully than others, but much depends on the understanding and support of family, friends, employers, and others. Specific attention should be given to personal problem areas such as occupation, social and emotional relationships, and dietary adjustments, and strong reinforcement given to cessation of smoking, moderation with alcohol, and regular physical activity. The insulin-dependent patient should be encouraged to tell colleagues and work associates of his or her condition so that they may recognize the need for assistance in case of hypoglycaemia. It is important for the individual to wear a bracelet or carry a card that indicates that he or she is a diabetic.

Associations and societies for diabetic patients are of proven value in protecting the welfare of, and dispelling popular misconceptions about, people with this condition. They are also the source of valuable information for patients seeking advice on specific subjects such as diet, insurance, travel, and advances in treatment. Most importantly, they can counter unreasonable discriminatory practices in situations where the individual may be powerless to act.

11. EDUCATION

Education and training of patients and their families are the foundations of good diabetic therapy. Education of the general public is an integral part of a prevention-oriented approach to diabetes mellitus. It is also essential because, at present, diabetes is often not perceived by the community or the health services as a public health problem. Accurate and comprehensible information must be provided for populations with a wide variety of cultures, ranging from highly sophisticated, technically attuned societies to those that, at best, may be only semi-literate.

11.1 Why educate?

A formal process of education carries enormous advantages to the health and life of the diabetic patient and consequent social and economic advantages to society.
11.1.1 *The patient*

Medical therapy and the expertise of health care workers are at their most effective in the treatment of acute episodes of diabetes mellitus such as hypoglycaemia, hyperglycaemia, or severe ketoacidosis and comas. However, the majority of these episodes could be prevented by proper education and training of patients. In the daily management of diabetes, active participation of the patient appears to be the only efficient solution for control of the disease and its long-term complications. Patient education and training have been shown to reduce hospital-bed occupancy dramatically. In one hospital, occupancy has fallen from 5.6 days per year in untrained diabetics to 1.4 days in trained patients (91), which is not significantly different from that of non-diabetics. Comprehensive education and training of the patient in self-care has led in certain situations to a 78% decrease of hyperglycaemic coma (92) and to a 75% decrease of below-knee amputations (93).

11.1.2 *Biological, psychological, and social effects of education*

The effectiveness of educating patients in self-care can be observed and evaluated using a number of criteria.

1. Effects on diabetic control include:
   — more efficient short-term and long-term metabolic control which can be evaluated by urinary glucose and ketone tests and by measurement of blood levels of glucose, glycated haemoglobin, triglycerides, and cholesterol;
   — prevention of acute loss of metabolic control as evidenced by a decrease in hypoglycaemic attacks and gross hyperglycaemia, with or without ketosis; and
   — better diabetes control during unusually strenuous physical activities or illness.

2. Effects on long-term complications include:
   — decreased incidence of long-term complications; and
   — reduced frequency of tissue damage caused by ischaemia and/or neuropathy (tertiary prevention). (Patients with loss of sensation in the feet or with impaired vision require special attention.)

3. Effects on psychological wellbeing include:
   — decreased fear of diabetes and its complications;
   — decreased sense of helplessness;
— improved acceptance of diabetes; and
— better participation by the patient in prevention strategies and therapy.

4. Effects on social integration include:
— decreased sense of isolation as the diabetic learns to adapt management to his or her social needs;
— less absence from work as acute and chronic complications lessen; and
— decreased fear of diabetes as information is transmitted to the patient’s family, school teachers, employers, and society in general.

5. Effects on the public health system may include:
— decreased medical and social costs of diabetes (94);
— improved social welfare programmes for diabetics including social security systems, life insurance, retirement plans, and job opportunities; and
— the use of patient education in diabetes care as a model for other programmes for chronic diseases.

11.2 Who to educate

There are five interlinked target groups: patients with diabetes, the patient’s family, health care personnel, the community (which includes people at high risk of developing diabetes), and health policy planners. These groups can be divided into two main types: those that require education in the practical management of diabetes (the patient, the patient’s family, and health care personnel); and those that need to be made more aware of diabetes, especially its economic and preventive aspects (the community and health policy planners).

11.2.1 Patients

All patients need simple basic information about their disease and its possible complications, as well as appropriate education for day-to-day management. Inadequate instruction of certain diabetics is a serious clinical error that may lead to severe hypoglycaemia in insulin-treated patients, and progression of foot infections and gangrene in patients with neuropathy and ischaemia.
Education needs to be directed to specific groups according to age, type of treatment, and presence of long-term complications. There are special requirements for the elderly, the very young and their parents, pregnant diabetics, the blind, and amputees.

1. Patients taking insulin or oral hypoglycaemic agents need to be taught:
   — the facts about their form of diabetes;
   — the skills of self-management;
   — how to adjust to necessary changes in life-style; and
   — how to cope with emergencies, in particular hypoglycaemia.

   Continuous education programmes for children and adolescents, and their families, school teachers, and friends should start immediately diabetes is diagnosed.

2. Patients not requiring insulin therapy need to be taught:
   — the facts about diabetes and its management;
   — the basis of good nutrition, and how to achieve and maintain optimal body weight; and
   — the importance of physical activity.

3. Patients with long-term complications need to be taught:
   — the facts about the complications, and the purpose and procedures of therapy, especially those aspects where their active participation is crucial; and
   — the necessary skills to prevent disabling consequences of the complications (e.g., infection and gangrene of the foot).

11.2.2 The family and the patient’s entourage

The patient’s family and friends need to be given some general information about the disease and its complications. The following topics may require explanation: the importance of correct food intake, the care of the patient during illness, and the recognition and early correction of emergency situations such as hypoglycaemia and hyperglycaemia with or without ketoacidosis.

11.2.3 Health care personnel

The education of health care personnel should cover the practical daily needs of the patient, and also the public health and economic
implications of diabetes. It should emphasize the importance of promoting self-reliance in the patient.

Doctors, nurses, dieticians, social workers, and allied health personnel, such as primary health care workers, should receive adequate training in educational methods and practical experience in teaching (95). Information on diabetes (and other chronic diseases) must be incorporated into basic training courses in medical schools and all levels of training for primary health care workers; the information should be continually updated by in-service training in hospitals or specially-organized courses. Diabetics should be encouraged to associate with and teach other diabetics, since this transmits knowledge gained by first-hand experience and develops self-esteem.

11.2.4 The community

Better understanding of diabetes by the community at large will be of direct benefit by improving the patient's social integration. It should also assist in the formation of national and local policies for providing health care.

The community also needs to be made aware of diabetes as a public health problem and the possibilities of prevention by control of obesity and by increased physical activity, particularly in high risk individuals.

11.2.5 Health policy planners

Policy planners at local and national levels should understand the socioeconomic implications of the disease and the vital importance of education in the management of diabetes, and be motivated to improve and extend health services for diabetics.

Policy planners should realize that diabetes and its complications represent a very large and an increasing public health problem. The long-term dividends from investment in preventive health care and health education need emphasis because they are less well recognized than the short-term benefits of curative medicine. The financial burden of diabetes on society was well illustrated by Jönsson (94) who analysed the cost of diabetes in Sweden (8.5 million inhabitants). He found that there was a total loss of 7955 production years in 1977 as a result of early retirement caused by diabetes; the direct cost attributable to diabetes was 69 million US dollars and the
indirect cost (mainly due to long-term complications) $90 million dollars.

Adequate patient education leading to efficient secondary and tertiary prevention could dramatically cut the cost of diabetes for the individual and for society.

National diabetes organizations, health care personnel, community-based groups, and the mass media all have a major role to play in alerting policy planners to the importance of diabetes, with particular emphasis on the preventive aspects.

11.3 How to educate

Learning is a fundamental part of diabetic management and the resources needed for effective education must be made available (96). These include personnel trained in educational techniques, literature, and equipment (blackboards, slide projectors, films, computerized learning programmes, and games), as well as adequate facilities.

11.3.1 Clinical approach versus patient education

The clinical approach often seems incompatible with patient education. Traditional medical practice is based on diagnosis and cure of pathological conditions, with the patient playing a passive role. This mode of treatment is used extensively, and has become known as the “disease model”. In contrast, patient education in treatment of chronic illness is centred on changing the patient’s behaviour and on self-care, and thus requires the active participation of the patient. The coexistence of both types of treatment is fundamental to good care of chronic illness, but unfortunately traditional practices often predominate. It is therefore important that health care workers are taught the principles of patient education and made aware of its many advantages.

Some specific characteristics of health care providers and of patients have to be taken into account in the teaching/learning process.

11.3.2 Health care workers

Before they can give instruction to patients, health care workers themselves need to be taught about diabetes, its long-term complications, and its treatment. They also need to acquire the
appropriate educational skills in the same way as they do for other forms of therapy. Their training should include instruction on how to prepare and use printed material, since oral information on its own may be misinterpreted. Printed material also helps to foster a consistent approach among the members of the medical team. Printed information should be simple, easy for patients to understand, concise, and presented in large print for patients with visual impairment. Pictorial information should be available for semi-literate or illiterate patients.

Patients with chronic disease are not necessarily willing to participate actively in their treatment straightaway. Learning becomes effective only when the patient is receptive, i.e., when the patient feels the need to learn about diabetes and to develop appropriate skills. In order to assess readiness to learn, health care workers must be capable of estimating the patient’s ability to master any specific skill, prevailing health-beliefs, degree of acceptance of the disease, and expectations of therapy, and how easily and how fast the therapeutic goals can be reached. Particular “entry points” for effective education (e.g., pregnancy, intercurrent illness, episodes of instability) should be recognized and exploited.

Readiness to learn is best assessed by interviews and by informal observation of the patient’s performance by doctors, nurses, or other allied health personnel. Interaction between patients and health care workers is fundamental if efficient treatment of chronic disease is to be combined with satisfactory quality of life.

11.3.3 Patients and their families

The main goal of patient education is to help diabetics and their families to become “active” participants in the control of the disease and the prevention of acute and long-term complications; patient motivation is vital for self-care. Training patients to control their own disease is a difficult task, and several factors must be taken into account.

1. Health beliefs of the patient and his or her family. These vary with ethnic group, age, sex, and socioeconomic status (97). Health beliefs must also be taken into account when planning weight-reduction campaigns.

2. The degree of acceptance of the disease. “Coping with disease” is the state reached when an individual has passed through the
sequence of difficult psychological adaptations that occur when a person becomes ill (98). These difficult psychological adjustments are normal and must be recognized by the members of health care teams. Patients who deny the existence of their condition or who revolt against it will experience difficulties in learning and complying with treatment. Only by listening to the patient’s subjective experiences can the medical team adapt the educational and therapeutic approach to his or her needs.

11.4 Need for evaluation

Each educational programme should be reviewed periodically, and the results used for subsequent programme planning and modification. Evaluation should be a continual process that measures how many of the educational objectives have been attained. An educational programme can only be widely implemented after its effectiveness has been validated.

11.4.1 Educational objectives

The goal of patient education is not to increase general knowledge about diabetes but to improve patient autonomy regarding therapy. The results of educational programmes are therefore defined by what patients can do at the end of a learning period that they could not do before.

11.5 The role of organizations

There are four main types of organization that may be involved in diabetes education:

— patient-oriented associations, both local and national;
— medically-oriented associations, both local and national;
— diabetes clinics and education centres; and
— regional, national, and international organizations such as the International Diabetes Federation and Juvenile Diabetes Foundation International.

It is essential that these groups work together and interact with each other. Organizations can concentrate their resources and energies on areas of special concern such as the social acceptance of
diabetics, welfare entitlement, the adequate distribution of essential
drugs and equipment, lobbying policy planners at governmental and
local authority levels, funding all aspects of research, and protecting
the rights of the individual.

12. RESEARCH AND FUTURE DEVELOPMENTS

Improvement in the health status of the diabetic depends on both
effective health care and related research. The many different types
of research—basic research, clinical research, operational research,
research in health economics, and population studies—need to be
coordinated to optimize their effect upon the health of diabetics.
This requires motivation, organization, appropriate resources at
local, national, and international levels, and good communication
between clinicians and research workers.

There is a major need for: (i) community-based programmes,
particularly in developing nations; (ii) studies of the most cost-
effective ways of delivering health care, including preventive services,
in different socioeconomic environments; and (iii) evaluation of the
methods used in programmes of diabetes education.

The needs of both the developing and the developed world must
be continuously reviewed. Diabetes research, wherever it is
conducted, is likely to have general relevance; collaborative
activities, exploiting the special interests and skills of the WHO
Collaborating Centres in Diabetes Mellitus, are therefore of great
potential value and should be actively fostered.

The purpose of this section is to review areas where promising
research developments are occurring and to draw attention to those
fields of health care provision and health sciences where
investigations and improvement are desirable. Simplification and
standardization of techniques and methods should be sought so that
the results of research programmes can be compared.

12.1 Basic research

— Studies to define the molecular basis of the genetic
susceptibility to IDDM, NIDDM, and other types of diabetes
should be intensified and extended to different population groups.
— Studies are needed to define in detail the role of immune
mechanisms in IDDM. The relevant beta-cell antigen marker(s)
should be identified, isolated, and characterized; these could then possibly be used in specific and quantitative assays to detect the early stages of an attack on the beta cells.

— The environmental factors involved in the development of diabetes should be identified and the mechanisms through which they provoke the diabetic state defined.

— New animal models for the study of diabetes in its various forms, and of its complications, should be developed.

— The abnormalities of insulin secretion and action in the various forms of diabetes should be defined more clearly.

— Studies are needed (i) to identify factors responsible for the specific complications of diabetes and their mechanisms of action; and (ii) to establish similarities and dissimilarities between the arteriopathic mechanisms in IDDM, NIDDM, and non-diabetic subjects.

— The genetic and metabolic factors that are associated with congenital malformations in the offspring of diabetic women should be identified.

12.2 Epidemiological research

— Organized and standardized collection of data, using WHO methods and criteria, is needed to determine the prevalence and incidence of the different forms of diabetes in developing countries; local environmental factors that are thought to be diabetogenic should be investigated.

— Further studies are needed of the heterogeneity of the mechanisms of impaired glucose tolerance.

— Accurate mortality and morbidity data, including age and sex specific information, on the various types of diabetes in different countries should be compiled.

— Studies are needed to elucidate the mechanisms by which overnutrition, malnutrition, individual nutrients, obesity, physical inactivity, stress, and intra-uterine environment interact with genetic susceptibility to produce impaired glucose tolerance and diabetes.

— Prospective studies, case control studies, and population-based surveys are needed to identify risk factors for the development of the complications of diabetes (or factors associated with resistance to their development), to provide insight into their pathogenesis, and to define their impact on public health.
12.3 Clinical research

— Studies are needed to characterize the clinicopathological features and the hormonal patterns of subclasses of malnutrition related diabetes and other special forms of diabetes.
— Improved methods for treating IDDM, e.g., insulin delivery systems, glucose sensors, and pancreatic islet transplantation, should be developed and evaluated.
— Appropriate randomized studies are needed to define more clearly the relation between metabolic control and the complications of diabetes.
— To reduce perinatal mortality and morbidity, studies to determine the optimal conditions for delivery should be encouraged.
— Studies are needed (i) to clarify differences in outcome of pregnancy in women whose glucose intolerance preceded pregnancy and in those in whom it developed during pregnancy; and (ii) to define the true risk (if any) of impaired glucose tolerance to the fetus and mother.

12.4 Research in prevention

— The effects of weight reduction, antidiabetic drugs, dietary manipulation, or an increase in physical activity upon progression from impaired glucose tolerance to NIDDM should be investigated.
— Prospective studies of preventive intervention should be encouraged. Research should be focused on people who have a close family member with NIDDM since they have a high risk of developing the disease.
— Controlled studies of primary prevention should be extended to IDDM as soon as sufficient knowledge of the disease has been gained to make this feasible.

12.5 Social, psychological, and educational research

— Patients and their families should be studied to see how they learn to cope with diabetes, how their motivation changes, and how well they comply with treatment regimens. The prevailing beliefs of the patient on health and disease should be taken into account in such studies.
— Variations in learning ability should be studied and new teaching methods designed to meet the different needs of individuals.

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— Educational programmes should be evaluated, and national standards for patient education developed and implemented.
— Studies are needed to determine the factors that motivate health care workers to implement educational programmes for patients, and those that cause them to resist patient education.
— Studies are needed of (i) the social adaptation to diabetes in the light of the health beliefs of different societies, and (ii) the role of the interdisciplinary team in identifying defective adaptation and facilitating treatment and rehabilitation of the diabetic.
— Resistance to patient education and treatment arising from ethnic and social traditions within a society, and from political opposition, should be investigated.
— The possibilities of applying existing methods of health systems research should be examined and the development of new forms of such research that are appropriate to the economic and social structures of different societies should be investigated.
— Research is needed to evaluate the efficacy of contemporary health systems and to compare it with that of traditional medicine.

12.6 Health services research
— New methods of diagnosing, managing, and preventing diabetes should be systematically explored, and their development encouraged. Developments in the organization of health services for diabetics should be appropriate for the prevailing social, economic, cultural, and geographical conditions.
— New models for the delivery of diabetes health care should be formulated and tested.
— The effectiveness of different ways of integrating diabetes care and research into health services should be evaluated.
— Studies are needed of the management, utilization, and effectiveness of health manpower in the delivery of diabetes health care.

13. CONCLUSIONS

1. Diabetes mellitus is a major and growing cause of prolonged ill-health and premature mortality that affects tens of millions of people in countries at all levels of development. The central mechanism of the diabetic state, the defective action of insulin, is
responsible for derangement of the processes of growth, defence, repair, reproduction, and fuel utilization. The failure to use glucose gives diabetes its most characteristic feature—chronic hyperglycaemia.

2. The diabetic state may be triggered by a wide variety of environmental factors—overnutrition, undernutrition, infection, ingestion of toxic substances, etc. These factors may act directly or, in many cases, indirectly by interacting with inborn susceptibility. The nature of the underlying susceptibility and of the environmental determinants is becoming clearer and opening the way to rational attempts to prevent diabetes.

3. Diabetes occurs at all ages and is to be found in almost all human communities. In some developing countries undergoing rapid changes in life-style, diabetes prevalence is increasing rapidly. Local environmental factors may trigger diabetes if there is a background of genetic or ethnic susceptibility.

4. The range of clinical manifestation of diabetes, broadly similar in all societies, depends upon the degree of damage of the insulin-secretory tissue. The most severe form of the disease, insulin-dependent diabetes mellitus (IDDM), is lethal unless promptly diagnosed and treated with insulin injections. In people of European origin, it is possible to identify some genetically susceptible individuals in whom blood glucose control is normal. Although the environmental factors that initiate the diabetogenic process are not yet clear, it may be possible to slow or arrest the immunological attack upon insulin-producing cells that ultimately causes the disease. Even after the insulin-dependent state is established, it may be possible to cure the condition by grafting normal insulin-producing tissue. Although they are still at the experimental stage, these efforts at prevention and cure deserve generous research support.

5. Non-insulin-dependent diabetes mellitus (NIDDM) is much more common than IDDM, is less severe at presentation, and usually occurs later in life. This form of the diabetic state also appears to be caused by a number of environmental factors acting on genetically susceptible individuals. Obesity, long considered to be the major provocative factor, is inadequate to account for all, or even most, cases of NIDDM; physical inactivity and/or deficiencies of specific nutrients may also be involved.

6. High intake of cyanide producing foods (e.g., cassava and certain beans) combined with protein malnutrition may cause
damage to pancreatic islets and lead to malnutrition-related diabetes mellitus (MRDM). Intensive education in nutrition and methods of food preparation may reduce the risk of this form of diabetes which is prevalent in tropical developing countries.

7. The glycaemic criteria for diagnosis of diabetes and impaired glucose tolerance proposed by the WHO Expert Committee on Diabetes Mellitus in 1980 have found general acceptance (1). With some minor modifications of presentation, these criteria were endorsed by this Study Group. Glycated haemoglobin estimation, of proven value in the management of diabetes, has at present no place in screening or diagnosis.

8. The term impaired glucose tolerance (IGT), introduced in 1980 to describe a state intermediate between diabetes mellitus and normality, has been largely accepted though comparatively little used. It can only be defined by the oral glucose tolerance test, and this test is rarely used for purposes other than epidemiological studies or screening (e.g., during pregnancy). Those people with impaired glucose tolerance who have high glucose levels and low insulin responses early in the test (and who are not pregnant) appear to be more likely to progress with time from impaired glucose tolerance to diabetes mellitus.

9. Standardization of terms and procedures related to diabetes should be extended so that comparisons can be made between patients, and of the same patient at different times. This applies to the prevalence for forms of diabetes when recorded in population studies or in death certification, to the criteria and terms for the various types and grades of diabetic complications, to the therapeutic products such as insulin, syringes, needles, and oral anti-diabetic preparations, and to the nutritional policies for diabetics.

10. There is encouraging evidence that the risk of blindness caused by diabetic retinopathy may be reduced by early screening and photocoagulation treatment. Early indications suggest that diabetics “at risk” of renal failure may be identifiable at a stage when prevention is still possible, but this remains to be demonstrated. Diabetic disease of somatic and autonomic nerves may be preventable by improved diabetic control, and there is hope that enzyme inhibitors may protect nerves from damage by abnormal metabolites. The risk of atherosclerosis in diabetics may be reduced by a low-fat diet with a high content of unrefined carbohydrate.

11. Primary prevention of diabetes in any of its forms has yet to be clearly demonstrated. A number of strategies have been
suggested, applicable particularly to the populations of developing countries that are undergoing major changes in life-style. In such populations, preventive measures for diabetes, involving improved nutrition and avoidance of physical inactivity, should be fully integrated into other community-based programmes for the prevention of noncommunicable diseases.

12. There remains much unrealized potential for improving the care of the diabetic. Health planners and policy makers should address themselves to meeting the needs of diabetics by integrating diabetes care into national, regional, and local health care structures. Effective care will generate better health for the patient and enormous savings for society.

13. It is overwhelmingly evident that the patient should take the major role in applying diabetes care and undertaking management schemes. The patient's role should extend far beyond control of diet and medication, and requires understanding of the disease, motivation, and willingness to accept responsibility. Education and training of the patient are of primary importance, and this should be reflected in the allocation of resources.

14. Only by the effective prevention of the complications of diabetes or the disease itself can the enormous cost of the condition to the individual and to society be reduced. A vigorous programme of research into diabetes, its causes, its course, and its complications is therefore essential. Research must be stimulated at all levels — basic, epidemiological, clinical, preventive, psychosocial, and educational; research into improving the organization of health services is also important.

15. Global activities against diabetes have been significantly fostered by the joint activities of WHO and nongovernmental agencies concerned with diabetes, supported by a growing number of WHO collaborating centres that cover various aspects of diabetes care and research. The Programme for diabetes that has been formulated as a result of this conjoint activity has been accepted by WHO and the International Diabetes Federation.1 The programme represents a significant step in the coordination and direction of world-wide efforts to solve the problems of diabetes, and is a suitable blueprint for future activities.

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1 See footnote on page 9.
14. RECOMMENDATIONS

The following recommendations were formulated by the Study Group, taking into account those of the WHO Expert Committee on Diabetes Mellitus that were published in 1980 (1) and the knowledge gained since then.

1. Health systems planning for, and research into, diabetes must be adaptable to the wide variation in social, economic, and medical conditions and structures. Community-based primary health care schemes should be linked to specialized levels to optimize the quality of care, depending upon the requirements of the patient and the availability of resources. A group of experts should review alternative strategies and make specific proposals for health systems planning, and for the integration of diabetes care into national health services.

2. In certain types of diabetes, survival depends upon the adequate and continuing availability of insulin. This is listed as an essential drug by WHO, and national health departments should give the highest priority to the provision of insulin and the means for its efficient administration.

3. Special centres should be established in developing countries that are concerned with the promotion of health care and the education of diabetic patients and people involved in their care; they should also initiate research into the epidemiology and prevention of diabetes that is appropriate for local conditions. Such centres should draw support from the growing international network of WHO Collaborating Centres in Diabetes Mellitus and constitute important focal points for the development of local diabetes programmes.

4. Systematic education of the diabetic patient as well as of health care personnel is vital to improve the health and welfare of diabetics. At present, its importance is not sufficiently recognized. A group of experts should review the field of education and, on the basis of their findings, recommend strategies that can be adapted to meet local needs. At national levels, those agencies funding health care should make adequate financial provision for systematic and organized educational activity.

5. International standardization should be extended to include: the universal adoption of the updated recommendations for methods and criteria for diagnosing diabetes given in this report; use of the revised classification of types of diabetes, especially in national
morbidity and mortality reports; clinical and epidemiological methods and criteria for recording diabetic complications; production of information and learning material for diabetes education; and identification of insulin preparations, purity, and strength.

6. Since it seems likely that certain common types of diabetes can be prevented by the avoidance of obesity and the promotion of physical activity, information on such preventive measures should be widely disseminated through health care agencies and the mass media. The growth of knowledge relevant to the prevention of other types of diabetes (e.g., insulin-dependent and malnutrition-related types) makes it timely for a group of experts to review the whole field of primordial and primary prevention of diabetes.

7. Health care planning and diabetes prevention both require accurate information on the distribution of diabetes within populations and on its environmental and genetic associations. Further population-based studies of the epidemiology of diabetes are necessary, and are of particular importance in the case of malnutrition-related diabetes. Surveys to establish the true prevalence of malnutrition-related diabetes, its environmental and nutritional background, and its clinical course should be organized, perhaps through a multidisciplinary, internationally-based task force.

8. The long-term complications of diabetes impose a very heavy burden on the individual and on society. This burden can be reduced by better control of the diabetic state using new approaches to treatment and patient self-monitoring. Regular screening should be carried out to detect early markers of retinal and renal complications, and resources committed to provide facilities for appropriate treatment. The high risk of coronary and peripheral vascular disease in diabetics could be reduced by a vigorous campaign against the known major risk factors (i.e., smoking, high levels of blood cholesterol, raised arterial pressure) as well as by the improvement of diabetes control.

9. Traditional methods of treatment and management of diabetes require further investigation.

10. National and local registries for diabetes should be established; these registers should use the system of classification given in this report so that comparisons can be made. The classification should also be used in death certification; this should be strongly encouraged by the allocation of specific codes to the
different classes of diabetes in the forthcoming revision of the *International classification of diseases*.

11. Activities undertaken to implement the recommendations of the second report of the WHO Expert Committee on Diabetes Mellitus (e.g., the joint activities of WHO and the International Diabetes Federation, the establishment of the WHO Collaborating Centres in Diabetes Mellitus, and the various national and international meetings, seminars, and courses promoted or sponsored by WHO) should be continued and intensified. The *Programme for diabetes*,\(^1\) formulated jointly by WHO and the International Diabetes Federation should serve as a blueprint for future activities.

12. Active collaboration between WHO and the International Diabetes Federation at regional, as well as international level, is feasible now that the IDF has been restructured on a regional basis; this collaboration should be vigorously pursued.

**ACKNOWLEDGEMENTS**

The Study Group is indebted to the following colleagues who prepared working papers and other material for the use of members of the group.

Dr P. H. Bennett, Epidemiology and Field Studies Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, Phoenix, AZ, USA

Dr T. Deckert, Steno Memorial Hospital, Gentofte, Denmark

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Dr E. Eschwege, Unité de Recherches Statistiques, INSERM, Villejuif, France

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\(^1\) See footnote on page 9.
REFERENCES


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 three days of unrestricted diet (greater 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, etc.).

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 body weight up to a total of 75 g of glucose. Blood samples must be collected 2 hours after the test load; if appropriate, samples may also be taken every half an hour during this period (see section 2.2).

Unless the glucose concentration can be determined immediately, the blood sample should be collected in a tube containing sodium fluoride (6 mg per ml 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 1 on page 11.

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1 The International Study Group for Diabetes in Children (ISGID) recommend a test load for children of 45 g/m² body surface area (Wanner, B. Standardization of the oral glucose tolerance test. International study group for diabetes bulletin, 2: 23–26, 1978).
Annex 2

METHODS FOR MEASURING SUBSTANCES IN BLOOD AND URINE

Measurement of glucose in blood

The 2-toluidine method remains in use for blood glucose measurement but enzyme-based methods are increasingly available, particularly in test-strip form. Reductometric methods (the Somogyi-Nelson, the ferricyanide and neocuprine autoanalyser methods) are also still in use. Highly accurate and rapid (1–2 min) devices are now available based on immobilized glucose oxidase electrodes. Hexokinase and glucose dehydrogenase methods are used for reference.

Whole blood samples preserved with fluoride show an initial rapid fall in glucose of up to 10% at room temperature, but subsequent decline is slow; centrifugation prevents the initial fall. Whole blood glucose values are 15% lower than corresponding plasma values in patients with a normal haematocrit reading, and arterial values are about 7% higher than corresponding venous values.

The use of test-strip glucose oxidase methods has made bedside estimation of blood glucose very popular. However, despite the great increase in their use, the cost of the test-strips remains high. Punctilious technique and accuracy of timing are critical, and the strips must be stored in airtight containers. The method gives reasonably quantitative results with visual colour-matching techniques. Used with reflectance meters, results can have a coefficient of variation of less than 8%. Battery-operated meters are now widely available and test-strip methods have been validated under tropical, field conditions. Diabetes may be strongly suspected from the results of strip-based glucose estimation, but the diagnosis cannot be confidently excluded by the use of this method. Confirmation of diagnosis requires estimation by chemical methods.

Patients can easily be taught to collect small blood samples themselves (either in specially prepared plastic or glass capillary tubes or on filter-paper), and self-monitoring using glucose test-strips with direct colour-matching or reflectance meters is now widely practised. Patients should be properly trained in the appropriate techniques to avoid inaccurate or misleading results.
The insulin-treated patient is commonly requested to build up a “glycaemic profile” by self-measurement of blood glucose at specific times of the day (and night). A “7-point profile” is useful, with samples taken before and 90 min after breakfast, before and 90 min after lunch, before and 90 min after an evening meal, and just before going to bed. Occasionally, patients may arrange to wake at 03h00 to collect and measure a nocturnal sample. The complete profile rarely needs to be collected within a single 24-hour period, and it may be compiled from samples collected at different times over several days.

**Measurement of glucose in urine**

Insulin-treated patients who do not have access to facilities for self-measurement of blood glucose should test urine samples passed after rising, before main meals, and before going to bed. Non-insulin-dependent patients do not need to monitor their urine so frequently. Urine tests are of somewhat limited value, however, because of the great variation in urine glucose concentration for given levels of blood glucose. The correlation between blood and urine glucose may be improved a little by collecting short-term fractions (15–30 min) of the urine output. Benedict’s quantitative solution or self-boiling, caustic soda/copper sulphate tablets may be used or the more convenient, but costly, semi-quantitative enzyme-based test-strips.

**Ketone bodies in urine and blood**

The appearance of persistent ketonuria associated with hyperglycaemia or high levels of glycosuria in the diabetic points to an unacceptably severe level of metabolic disturbance and indicates an urgent need for corrective action. The patient should be advised to test for ketone bodies (acetone and aceto-acetic acid) when tests for glucose are repeatedly positive, or when there is substantial disturbance of health, particularly with infections. Rothera’s sodium nitroprusside test may be used or, alternatively, test-strips that are sensitive to ketones. In emergency situations such as diabetic precoma or coma, a greatly raised concentration of plasma ketones can be detected with a test-strip and roughly quantified by serial 1 in 2 dilution of plasma with water.
Protein in urine

The urine should be regularly screened for the presence of clinical proteinuria (i.e., > 500 mg/day) by either adding sulfosalicylic acid or, more conveniently, using semi-quantitative test-strips. Urinary protein can also be demonstrated in the dense precipitate that is produced when acidified urine is boiled.

Urinary protein excretion must be increased several fold before clinical tests become positive. Measurement of slight increases in urinary albumin concentration is important as an early indication of diabetic renal disease, but at present this requires complex radioimmunoassays or enzyme-linked immunosorbent assays (ELISA). However, simpler methods for detecting subclinical albuminuria are becoming available for routine use.
Annex 3


<table>
<thead>
<tr>
<th>Location</th>
<th>Age group studied (years)</th>
<th>Method of ascertainment</th>
<th>Prevalence (per 1000)</th>
</tr>
</thead>
<tbody>
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<td>China</td>
<td>10–19</td>
<td>Survey</td>
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</tr>
<tr>
<td>Cuba</td>
<td>0–15</td>
<td>National registry</td>
<td>0.14</td>
</tr>
<tr>
<td>France</td>
<td>0–19</td>
<td>Central registry</td>
<td>0.14</td>
</tr>
<tr>
<td>Japan</td>
<td>7–15</td>
<td>School records</td>
<td>0.07</td>
</tr>
<tr>
<td>Scandinavian countries</td>
<td>0–14</td>
<td>National registry and hospital records</td>
<td>0.63–2.23</td>
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<tr>
<td>United Kingdom</td>
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<td>National survey of health and development</td>
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<td>School records</td>
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Annex 4

ESTIMATES OF INCIDENCE OF INSULIN-DEPENDENT DIABETES MELLITUS

<table>
<thead>
<tr>
<th>Location</th>
<th>Period of study</th>
<th>Age group studied (years)</th>
<th>Incidence (per 100,000 person-years at risk)</th>
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<td>Finland</td>
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<tr>
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<td>Israel</td>
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<tr>
<td>Ashkenazim</td>
<td>1975–80</td>
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<td>6.3</td>
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<tr>
<td>Non-Ashkenazim</td>
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</tr>
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<td>Netherlands</td>
<td>1978–80</td>
<td>0–14</td>
<td>11</td>
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<tr>
<td>Netherlands</td>
<td>1978–80</td>
<td>0–19</td>
<td>11</td>
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<tr>
<td>Rhode Island, USA</td>
<td>1978–80</td>
<td>0–29</td>
<td>14</td>
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<tr>
<td>Scotland</td>
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<tr>
<td>Sweden (north)</td>
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<td>Toronto, Canada</td>
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### Annex 5

**PREVALENCE AND INCIDENCE OF NON-INSULIN-DEPENDENT DIABETES MELLITUS IN CERTAIN POPULATIONS, USING THE CRITERIA PROPOSED BY WHO**

<table>
<thead>
<tr>
<th>Location/population</th>
<th>Age group (years)</th>
<th>Rate (%)</th>
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</thead>
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<td>Mexican Americans (USA)</td>
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<tr>
<td>Papua New Guinea (highlands)</td>
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</tr>
<tr>
<td>Pima Indians (USA)</td>
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</tr>
<tr>
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<tr>
<td>Incidence</td>
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<tr>
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<td>Pima Indians (USA)</td>
<td>20+</td>
<td>1.6 per annum</td>
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</table>

*Prevalence of diabetes ascertained either from medical records and use of antidiabetic preparations or from records of newly diagnosed diabetics with venous plasma glucose $\geq$ 11.1 mmol/litre two hours after a standard 75 g oral glucose load (see reference 2 on page 94).*
Annex 6

PREVALENCE OF DIABETES MELLITUS IN SOME COUNTRIES

The rates shown include both NIDDM and IDDM, though the latter represents a small proportion of the total. Rates are derived from many sources, principally national and regional surveys but also hospital statistics in some developing countries. In most cases WHO standardized diagnostic criteria have not been used.
It should be noted that prevalence of this type of diabetes is largely unknown.
### Annex 8

**RATE OF DIABETES MORTALITY (PER 100 000), BY AGE GROUP, IN DIFFERENT LOCATIONS**

<table>
<thead>
<tr>
<th>Location</th>
<th>Year recorded</th>
<th>Age group (years)</th>
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<th>65-74</th>
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<th>Trend ratio*</th>
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<td>109.1</td>
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<td>5.6</td>
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<td>71.1</td>
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</tbody>
</table>

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*The trend ratio is calculated by dividing the overall mortality rate (i.e., the rate for all ages) for each country by the corresponding rate recorded at least 4 years earlier; the earlier mortality rates were published in Canada 3 of the second report of the WHO Expert Committee on Diabetes Mellitus (see reference 7 on page 84). The trend ratios indicate that there is little or no systematic trend of diabetes mortality with time. Variability in death registration practices makes comparison between countries uncertain; however, comparisons within countries are probably more valid.*

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## Annex 8 (continued)

### RATE OF DIABETES MORTALITY (PER 100 000), BY AGE GROUP, IN DIFFERENT LOCATIONS

<table>
<thead>
<tr>
<th>Location</th>
<th>Year recorded</th>
<th>All ages</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>65–74</th>
<th>75+</th>
<th>Trend ratio*</th>
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*See footnote on page 107.
IMPACT OF DIABETES ON LIFE AND HEALTH

The prevalence of diabetes in most adult populations is 2–5%; in some populations the rate is considerably higher. Insulin-dependent diabetes affects between 1 in 500 and 1 in 200 children and adolescents, respectively.

The expected life span in insulin-dependent diabetics is shortened by as much as one-third. Diabetic kidney disease is present in 1 diabetic in 6 and directly causes or contributes to premature death in 50% of youthful onset IDDM patients.

The risk of blindness in diabetics in advanced societies is up to 10-times that of non-diabetics, and is the leading cause of blindness in the middle-aged. Visual disability occurs in more than 10% of diabetics surviving for 20 years or more.

In some advanced countries, diabetic ketoacidosis accounts for 1 in 20 admissions of diabetics to hospital, and is the cause of 1 in 10 deaths attributed to diabetes.

Half or more of all non-traumatic amputations are performed on diabetics. About 5% of diabetics have chronic foot problems, and the annual incidence of gangrene is 1 per 200 diabetics.

The risk of coronary heart disease is 2–3 times higher in diabetics than non-diabetics. It is responsible for 30–50% of deaths in diabetics over the age of 40 years in industrialized countries.
Annex 10

GLYCATED HAEMOGLOBIN ESTIMATION

Glycated haemoglobin measurement (HbA₁,ᵢ) usually expressed as a percentage of the total haemoglobin, is now widely used as a cumulative estimate of the mean blood glucose concentration over the preceding 6–8 weeks. The rate of glucosylation is related to blood glucose concentration by an irreversible non-enzymatic process. Several methods are available for its measurement including chromatographic techniques, colorimetric methods, and electrophoretic separation. The most accurate method employs affinity chromatography columns but, with a large workload, the use of one of the electrophoretic techniques is recommended. Methods are now becoming available for collecting blood samples on filter-paper which can then be sent elsewhere for analysis. Where possible, the major glycohaemoglobin subfraction, HbA¹₅₀, should be measured as this gives a more valid estimate of glucosylation. Severe anaemia, pregnancy, renal failure, and haemoglobinopathies influence the estimate. Reference ranges of values should be established by testing a selected sample of the normal population. The “calibration” of raised HbA₁ values against the corresponding degrees of hyperglycaemia should be established in selected diabetic individuals who are prepared to make repeated measurements of blood glucose and record the results. With most methods of measurement, proportions of glycated haemoglobin exceeding 8–9% of the total HbA are abnormal; an excess of 12% or more indicates severe and sustained hyperglycaemia.

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2 Glycated haemoglobin refers to the products of the chemical reaction between glucose and haemoglobin. It is a special case of glycosylation that describes the general reaction between sugars and proteins. It is also referred to as glucosylated haemoglobin, but glycated haemoglobin is now the preferred term.
### Annex 11

**MAIN TYPES OF INSULIN AVAILABLE**

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<td>Neutral</td>
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<td>Human</td>
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<td><strong>Intermediate action</strong></td>
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<tr>
<td>Insulin zinc suspension, crystalline plus amorphous (lente)</td>
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<td>Beef</td>
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<tr>
<td></td>
<td>Human</td>
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<tr>
<td>Isophane, insulin protamine complex (NPH)</td>
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<tr>
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<td>Pig</td>
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<td>Human</td>
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<td><strong>Slow action</strong></td>
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<td>Protamine zinc insulin</td>
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<td>Pig</td>
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<td>Human</td>
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All insulin preparations are now available in "highly purified" form, though there is no universally agreed definition of the description.

Insulins are available at strengths of 10, 20, 40, 60, and 100 U/ml. In case of special need they may also be supplied at strengths of 320 and 900 U/ml.

*Beef* these preparations, unless clearly labeled to the contrary, may contain a variable proportion of pig insulin.

*Human, semisynthetic or biosynthetic insulin. The human insulin zinc suspension (crystalline) has a shorter duration of action than similar beef or pig insulin preparations.
Annex 12

BASIC EQUIPMENT FOR SELF-CARE BY DIABETICS

Items required for self-management by:

Non-insulin-dependent diabetics
1. Urine-testing materials for:
   (i) glucose, and
   (ii) ketone bodies.
2. Book (or chart) and pencil for recording results of tests and body weight.
3. When applicable, oral hypoglycaemic agents.
4. Sugar lumps or other readily absorbed carbohydrate.

Insulin-dependent diabetics
1. Urine-testing materials as above and/or blood-glucose-testing material.
2. Book (or chart) and pencil for recording results.
3. Insulin as prescribed (plus cool place for storage).
4. Syringe (with carrying case) and needles.
5. Sterilization facilities.
7. Cleansing agent.
8. Sugar lumps or readily absorbed carbohydrate.

Facilities required for a primary health care centre:
1. All the items required for self-management, as above; plus materials for testing the presence of protein in urine.
2. Weighing machine.
4. Glucose for intravenous use—glucagon, if available.
5. Simple printed educational material and teaching aids.
6. Place for storing patients’ records.
Annex 13

ESTIMATED COST OF DIABETES IN THE UNITED STATES OF AMERICA DURING 1980

A. Estimated direct costs

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<td>Nursing-home care</td>
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<td>Insulin and oral hypoglycaemic agents</td>
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B. Estimated indirect costs

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