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PRINTED IN SWITZERLAND

804695 — La Concorde — 10 000
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WHO EXPERT COMMITTEE ON DIABETES MELLITUS

Geneva, 25 September – 1 October 1979

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WHO EXPERT COMMITTEE
ON DIABETES MELLITUS

Second Report

The WHO Expert Committee on Diabetes Mellitus met in Geneva from 25 September to 1 October 1979. Dr D. Tejada-de-Rivero, Assistant Director-General, opened the meeting on behalf of the Director-General.

1. INTRODUCTION

Diabetes mellitus is a universal health problem affecting human societies at all stages of development. At least 30 million people are involved throughout the world, and the numbers of cases reported are increasing rapidly with the aging of populations, changes in lifestyle, and improvement in ascertainment. Although a more prominent health problem in developed countries, it is erroneous to consider diabetes a disease of affluent societies. Epidemiological studies indicate high rates universally, but little is known of the real extent of diabetes and its sequelae in developing countries. Mortality data grossly underestimate the real magnitude of the problem.

In some societies obesity is a major association of diabetes; in others malnutrition is probably an important determinant; infection and toxic conditions are also believed to play a part, through mechanisms that are now being elucidated. Environmental determinants of diabetes interact with varying degrees and types of inherent susceptibility. Observation and research have shown that the state of diabetes mellitus may be arrived at by divers routes. Once established, environmental influences and genetic constitution again interact to determine the course and the complications of the disease. With increasing knowledge of the nature of susceptibility and better identification of pathogenic factors, the exciting possibility arises of preventing the disease.

Fundamental to improved health for the diabetic is the coordination and integration of many social and medical skills for the provision of health care, research, and education. Diabetes is an example of a chronic disorder in which the affected person must take
major responsibility for his own health with the support of the medical profession and the community—every diabetic his own doctor. Countries that already have health care systems with the major emphasis on the community lend themselves naturally to the care of the diabetic. However, in addition to the basic structure of self-care and community services, the diabetic must also have access to diagnostic and therapeutic specialties.

Research and development are an integral part of diabetic care. They need not—and indeed should not—be divorced from health care itself.

This report outlines the present position and the prospects for the future. The health authority in each country must decide what resources it will make available and what activities it will undertake to reduce the incidence of diabetes and to lessen the heavy toll exacted by its complications.

2. DEFINITION, DIAGNOSIS AND CLASSIFICATION

2.1 Definition

Diabetes mellitus is a state of chronic hyperglycaemia (i.e., the state of having an excessive concentration of glucose in the blood), which may result from many environmental and genetic factors, often acting jointly. The major regulator of glucose concentration in the blood is insulin, a hormone synthesized in and secreted by the B cells of the islets of Langerhans in the pancreas (sometimes called beta cells). Hyperglycaemia may be due to a lack of insulin or to an excess of factors that oppose its action. This imbalance leads to abnormalities of carbohydrate, protein, and lipid metabolism. The major effects of diabetes include characteristic symptoms, keto-acidosis (diabetic “coma”), the progressive development of disease of the capillaries of the kidney and retina, damage to the peripheral nerves, and excessive arteriosclerosis (see sections 5 and 6).

2.2 Diagnosis and diagnostic criteria

2.2.1 General considerations

Diabetes may present with severe thirst, increased urine volume, rapid weight loss, and sometimes coma. Blood glucose concentration is grossly elevated. Glucose will be excreted in the urine, usually in
large amounts. In this situation diagnosis is simply confirmed from
blood glucose estimation without formal provocative tests. Random
plasma glucose concentrations exceeding 2 g/l are diagnostic. The
presence of specific microvascular disease, usually retinopathy, also
establishes the diagnosis. When such symptoms and signs are absent
and blood glucose levels less markedly elevated, measurements made
under standard conditions, such as fasting or after a carbohydrate
challenge, may be necessary to confirm or refute the diagnosis.
Commonly the oral glucose tolerance test is performed (see Annex 1).
The importance of this test as a clinical diagnostic tool has been
grossly overemphasized. It is useful only in clearly defined
situations.

The interpretation of diagnostic tests is hindered by a lack of
uniformity in procedures and in the criteria of abnormality. There is
little agreement on the dosage of glucose and its relation to age and
weight, the time of day at which tests are carried out, prior period of
fasting, frequency of blood sampling, nature of the fraction of blood
used (capillary or venous, plasma or whole blood), method of
expressing results, or criteria of interpretation. Furthermore, results in
an individual are variable from day to day despite standardization of
methods and conditions (1). Methods of glucose analysis are shown
in Annex 2.

The glycaemic response to ordinary meals has been recom-
mended as a more physiological metabolic test for diabetes, but the
meals are difficult to standardize. Furthermore, there are few valid
data to serve as a basis for diagnostic standards. It has been argued
that the diagnosis of diabetes should not be made in the absence of
fasting hyperglycaemia. However, the evidence suggests that a
diagnosis of diabetes is justifiable even when fasting glucose levels
are normal, if the impairment of glucose tolerance is substantial.

2.2.2 The oral glucose tolerance test

There is a developing consensus on a more uniform approach to
the performance and interpretation of the oral glucose tolerance test,
and this forms the basis of the Committee's recommendations. A
standard glucose load of 75 g has been proposed for adults; fasting
and 2-hour post-glucose values are considered to be of major
diagnostic value; diagnostic values for diabetes have been raised
from those recommended in the first report of the WHO Expert
Committee (2). The suggested amendments to diagnostic criteria are based on epidemiological studies of populations following the proposals of that Expert Committee. The new 2-hour value is based on several findings: (1) subjects with 2-hour glucose values below the new cut-off point rarely show development of the specific complications of diabetes; (2) only a small proportion show metabolic deterioration "worsening to diabetes"; (3) many show spontaneous reversion to normal glucose values. The new criteria (see Table 1) are closely similar to those recommended by the Diabetes Epidemiology Study Group of the European Association for the Study of Diabetes (3) and to those proposed by the National Institutes of Health Diabetes Data Group in the USA (4). A clinical diagnosis of diabetes mellitus should not be made on the basis of only one abnormal blood glucose concentration. Further diagnostic values from the same test, or repeated tests, are required. In Table 1 and elsewhere in this report, glucose values are rounded to the nearest whole mmol/l.

Table 1: Diagnostic values for oral glucose tolerance test under standard conditions. Load 75 g glucose in 250-300 ml of water for adults or 1.75 g/kg body weight (to a maximum of 75 g) for children, using specific enzymatic glucose assay. Two classes of response are identified—diabetes mellitus and impaired glucose tolerance.

<table>
<thead>
<tr>
<th>Glucose concentration</th>
<th>Venous whole blood</th>
<th>Capillary whole blood</th>
<th>Venous plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>&gt; 7.0 mmol/l</td>
<td>&gt; 7.0 mmol/l</td>
<td>&gt; 8.0 mmol/l</td>
</tr>
<tr>
<td>(&gt; 1.2 g/l)</td>
<td>(&gt; 1.2 g/l)</td>
<td>(&gt; 1.4 g/l)</td>
<td></td>
</tr>
<tr>
<td>and/or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hours after glucose load</td>
<td>&gt; 10.0 mmol/l</td>
<td>&gt; 11.0 mmol/l</td>
<td>&gt; 11.0 mmol/l</td>
</tr>
<tr>
<td>(&gt; 1.8 g/l)</td>
<td>(&gt; 2.0 g/l)</td>
<td>(&gt; 2.0 g/l)</td>
<td></td>
</tr>
</tbody>
</table>

| Impaired glucose tolerance    |                    |                       |               |
| Fasting                       | < 7.0 mmol/l       | < 7.0 mmol/l          | < 8.0 mmol/l  |
| (< 1.2 g/l)                   | (< 1.2 g/l)        | (< 1.4 g/l)           |               |
| and                           |                    |                       |               |
| 2 hours after glucose load    | > 7.0--< 10.0 mmol/l| > 8.0--< 11.0 mmol/l | > 10.0--< 11.0 mmol/l |
| (> 1.2--< 1.8 g/l)            | (> 1.4--< 2.0 g/l) | (> 1.4--< 2.0 g/l)    |               |

2.2.3 Proposed diagnostic procedure and criteria

The Expert Committee recommended the following procedure for diagnosis.
(1) If symptoms of diabetes are present, perform random or fasting blood glucose measurement. In adults, random venous plasma values of 11 mmol/l (2.0 g/l) or more or fasting values of 8 mmol/l (1.4 g/l) or more are diagnostic. Random values below 8 mmol/l and fasting values below 6 mmol/l (100 g/l) exclude the diagnosis.

(2) If results are equivocal, measure blood glucose concentration 2 hours after 75 g of glucose taken orally after an overnight fast (Annex 2). Two-hour venous plasma glucose values of 11 mmol/l (2.0 g/l) or more are diagnostic of diabetes. Values below 8 mmol/l (1.4 g/l) are normal and those in the range 8-11 mmol/l (1.4-2.0 g/l) are termed "impaired glucose tolerance".

(3) In the absence of symptoms of diabetes at least one additional abnormal blood glucose value is needed to confirm the clinical diagnosis (e.g., a 1-hour post glucose value of 11 mmol/l (2.0 g/l) or more during the first test or an elevated 2-hour or fasting glucose value on a subsequent occasion).

The criteria described above may be used for pregnant women as well as for all other patients with suspected diabetes, though obviously different clinical action is necessary. It should be noted that the National Institutes of Health Diabetes Data Group has suggested (4) that a separate set of criteria be used for pregnant women.

The cut-off points suggested above may not be universally applicable. The pathogenic significance of the substantial interpopulation differences observed in the frequency distribution of plasma glucose values needs further investigation. Age is sometimes taken into account when classifying (5). Particular emphasis needs to be placed on local diagnostic values. In Pima Indians, two glycaemic populations may be described with an intersection of the two distributions for fasting plasma glucose values at 8 mmol/l (1.36 g/l) (6). Support for these values also comes from other populations. One problem is that overlap would place some diabetics below the cut-off level. Fasting venous plasma values in the range 7-8 mmol/l (1.20-1.39 g/l) may be considered abnormal in certain situations. It must also be noted that many drugs, diseases, and states other than diabetes affect glucose tolerance. Even though the new criteria are more soundly based than earlier values, the cut-off levels remain somewhat arbitrary. Action to be taken in the case of individuals with values near the limits may be influenced by individual circumstances.
Extrapolations from data on differences in response to 50 and 100 g oral glucose loads suggest that 2-hour values after 75 g would be about 1 mmol/l (0.15 g/l) higher than after 50 g and about the same amount lower than after 100 g.

The Expert Committee recommended that the criteria outlined above be used as a guide to diagnosis until more detailed information becomes available on different populations, other diagnostic indices, and the development of complications. In the interim it is crucial that subjects with impaired glucose tolerance are not labelled “normal” and returned to the community by default. They have an increased risk of worsening to diabetes and of developing atherosclerosis. Different courses of action will be necessary depending on age, obesity, and the presence of other diseases. During pregnancy, the treatment for impaired glucose tolerance should be the same as for diabetes.

2.3 Classification

The first report of the WHO Expert Committee on Diabetes Mellitus, published 15 years ago, contained a classification of patients according to age of recognized onset (2). Since that time research has brought to light several pathogenic mechanisms leading to diabetes mellitus (7), and long-term studies have provided evidence of differing courses and outcomes. This new information has led several groups to review the classification of the disease. Since many of the reclassifications proposed reflect the special interest of particular groups it has become increasingly difficult to construct a simple classification that is useful to all. Such a classification needs to include all possible forms of diabetes mellitus and should be mutually exclusive, i.e., not allow a case to occupy more than one class, though individuals might move from class to class or out of a category. All present classifications are inadequate in these terms—diabetes of different types (e.g., primary or secondary) may, for example, be either insulin-dependent or non-insulin-dependent. A new approach to classification is required.

2.3.1 An interim classification

As an interim measure, the classification scheme prepared by the Diabetes Data Group of the National Institutes of Health, USA, (4) will meet many needs and is recommended for use. A simplified version is given in Table 2.
Table 2. Classification of diabetes mellitus and other categories of glucose intolerance

A. Clinical classes

Diabetes mellitus
- Insulin-dependent type — Type 1
- Non-insulin-dependent type — Type 2
  (a) non-obese
  (b) obese

Other types including diabetes mellitus associated with certain conditions and syndromes: (1) pancreatic disease, (2) disease of hormonal atrophy, (3) drug or chemical-induced condition, (4) insulin receptor abnormalities, (5) certain genetic syndromes, (6) miscellaneous.

Impaired glucose tolerance
  (a) Non-obese
  (b) Obese
  (c) Impaired glucose tolerance associated with certain conditions and syndromes

Gestational diabetes

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

2.3.2 Different approaches to diabetes classification

Many recognizable “constellations” of characteristics are emerging.

Insulin-dependent diabetes (sometimes termed Type 1) often has particular HLA tissue types (8, 9), usually has, early in its course, circulating antibodies to islet cells, and may be marked by a family history of diabetes or autoimmune disease (10). At present, there are few diabetics for whom this information is available, but they appear to show geographical and ethnic variations in distribution. The relevance of this information to clinical management and disease prevention is unclear, but it is highly relevant to research and could eventually become important to clinicians and public health workers.

2.3.3 Classification based on data

Groupings based on clinical features (e.g., proneness to ketosis, age at presentation, insulin treatment and degree of obesity) are of
special clinical and epidemiological value. Etiological features such as HLA, islet cell antibody, and blood insulin values are of value in research and epidemiology. All such data need to be collected and documented in a standard way, as does information on the course and complications of the disease. Attempts should be made to create descriptive classifications based on these characteristics; they should be usable even when the information is incomplete. Such classifications would be of use to clinicians, epidemiologists, and research workers, who could select their required groupings of characteristics from the available information. It is urged that cases in clinical or epidemiological reports be described by certain readily available indices that are, in a sense, classifying terms. They include age, sex, proneness to ketosis, type of treatment (insulin or non-insulin), age group at onset, fatness as appropriately defined, and familial tendency.

3. EPIDEMIOLOGY

The epidemiological approach to diabetes has cast light on the definition and classification of the disease, its early detection, the genetic and environmental associations, its social and economic importance, and the effects of the disease on health and life. Examination methods of clinical value have been developed and evaluated, and the techniques of the controlled clinical trial have been applied.

3.1 Natural history

The natural history of diabetes is affected by many factors, including the type of diabetes and the effectiveness of treatment. When obesity is present at diagnosis, diabetes may remit if the weight returns to normal early in the disease. In poor societies, where insulin is difficult to obtain, a substantial proportion of insulin-dependent diabetics die within a few years of diagnosis, but, with reasonable access to resources, life expectancy of typical childhood-onset cases averages about 30 years (50% normal), although considerably shorter and longer survivals are common. There is some evidence that life can be prolonged if the metabolic state of severely diabetic patients is well controlled (11). In later-onset non-insulin-dependent diabetics, life expectancy averages about 70% of normal. Ordinarily, the
symptoms of diabetes can be promptly relieved with appropriate treatment.

The onset of insulin-dependent diabetes is typically abrupt and there may be temporary remission. Non-insulin-dependent diabetes, typically gradual in onset, usually occurs in late middle age and is often discovered by chance. Mild hyperglycaemia is often present for several years before diagnosis. Hyperglycaemia in the obese tends to worsen gradually unless there is mitigation of obesity. In the first 10 years of diabetes only a few such patients require insulin injections but this treatment becomes necessary in increasing numbers of patients after 15 years.

In western Europe and North America diabetic kidney disease is the leading cause of death in childhood-onset cases, usually occurring 17–25 years after the onset of diabetes. After more than 25 years of diabetes, coronary disease predominates. In adult-onset diabetics of Japan, the leading cause of death is glomerulosclerosis. In adult-onset cases of Europe and North America the leading cause of death is coronary disease, responsible for about half the mortality. Ischaemic heart disease, glomerulosclerosis, retinopathy, gangrene of a lower extremity, neuropathy, stroke, and cataract are major causes of prolonged ill health. Rates of disability are in general about 2–3 times as great in diabetics as in non-diabetics, but blindness is about 10 times commoner and gangrene 20–30 times (12). However, some diabetics live long lives with little disability.

In many societies (e.g., Japan, Hong Kong), rates of atherosclerosis are low, even in diabetics. In all societies ketoacidosis is a significant cause of death in diabetics, and in some developing countries it is a leading cause of diabetes-related death. Severe hypoglycaemia also figures as a cause of death and disability.

3.1.1 The concept of susceptibility

Genetic markers have recently been described (see section 4) that indicate increased susceptibility to insulin-dependent diabetes, and genetic markers may also exist for subtypes of non-insulin-dependent diabetes. Epidemiological study of these and other factors is required, along with the study of the environmental determinants.

3.2 Prevalence, incidence and risk factors

The prevalence of diabetes varies greatly among countries and populations (Annex 2). In some communities more than one-third of
older adults have diabetes and a majority will eventually develop the disease. In other societies, in contrast, rates of diabetes are as low as 2% in the elderly.

The rate of occult diabetes is strongly affected by the definition of "diabetes". When conservative diagnostic criteria are used, the rates of undiagnosed diabetes in the USA are roughly the same as those cited above for clinically diagnosed diabetes. Thus, about 6% of all adults have diabetes (including both diagnosed and undiscovered cases), the prevalence rising to about 16% in those aged 65 and over (both known and occult). Rates are roughly comparable in European countries and indeed diabetes is a common problem in every affluent society.

Although rates are thought to be lower in the developing countries, ascertainment is often difficult; it appears, however, that the disease is becoming an increasingly significant problem. In urban areas particularly, diabetes rates tend to be moderate to high in Asia, Africa, and Latin America. In Oceania, rates vary from low to extremely high. Mortality rates, a very crude indicator of diabetes prevalence (i.e., total number of cases at a given time), are presented in Annex 3.

Studies of incidence (the number of new cases per year per 100,000 population) have been few but, in general, have yielded results that parallel the observations cited above.

3.2.1 **Age and sex**

In most industrially advanced societies the incidence of diabetes gradually rises during adult life (13). Both incidence and prevalence are usually highest in old age. However, these typical relationships may be altered by environmental circumstances. In very corpulent populations incidence is considerably higher in the fourth and fifth decades than in the elderly. In insulin-dependent cases, there are peaks of incidence, one of particular importance occurring at 10-13 years of age.

In societies in which the food supply is not limited, diabetes is usually somewhat more common in women than in men. In Europe and North America, a female to male ratio of 1.4 is typical. However, this ratio varies widely by age and circumstance and has changed towards unity in the United Kingdom in the past 30 years (14). In a few societies, particularly in South-East Asia, an excess of male diabetics has been observed.
3.2.2 Geography, race, and obesity

Differences by race and geography in the frequency of insulin-dependent diabetes are summarized in section 3.2.4. Profound differences of prevalence of non-insulin-dependent cases by race and geography have been described. There may be interracial differences in susceptibility to non-insulin-dependent diabetes, but differences in degree and duration of fatness and in exercise levels appear to be responsible for many cases.

In general, diabetes is common in all corpulent, physically inactive populations, irrespective of race. It is rare in all lean populations, irrespective of race. Environmental and social factors are clearly more powerful than race in determining susceptibility to non-insulin-dependent diabetes.

The most powerful risk factor for adult-onset diabetes is obesity. The incidence of diabetes is increased about fourfold in persons with moderate obesity and thirtyfold in those with very severe obesity (13). The risk of diabetes is related to the duration as well as the degree of obesity.

3.2.3 Other factors associated with excessive rates of diabetes

Genetic factors play important roles in both insulin-dependent and non-insulin-dependent diabetes (see section 4). Much of the family aggregation of non-insulin-dependent diabetes is secondary to the family aggregation of obesity; the disease probably occurs in families with an obesity-sensitive genetic susceptibility to diabetes.

It is widely believed that childbearing increases the risk of diabetes. Although diabetes is frequently discovered during pregnancy, most evidence suggests that parity is not a risk factor for diabetes.

High and low rates of diabetes have been linked to a number of social factors including occupation, marital status, religion, economic status, level of education, and rural or urban status. These associations are usually explained by the confounding effects of links with obesity, physical inactivity, and undernutrition.

3.2.4 Prevalence of special types of diabetes

Substantial interpopulation differences have been observed in rates of typical insulin-dependent diabetes (12). The genetic susceptibility to this type of diabetes differs among races. In subpopulations
of Europe and North America the risk of developing diabetes in the first two decades of life is 0.1–0.3%. In Japan it is probably less than 0.02%. It is also possible that environmental factors account for some of these interpopulation differences. Such factors may include nutritional status and the timing, dosage, or frequency of exposure to certain viruses.

It is not clear whether the malnutrition-related syndrome of severe non-ketotic diabetes in children in the tropics is a peculiar manifestation of ordinary childhood-onset diabetes or whether it is etiologically distinct. This type, known also as J (for Jamaica) diabetes, had been found in many tropical developing countries, where it sometimes constitutes a majority of childhood-onset cases. The syndrome also occurs in young adults. These cases nearly all have a history of severe malnutrition in childhood. Annex 4 lists countries in which malnutrition-related diabetes has been reported.

In a few populations, the most common type of diabetes, with fibrosis and calcification of the pancreas and a history of severe childhood malnutrition, has been associated with excessive consumption of cyanide, especially from cassava (16). Further epidemiological information is required.

There are few numerical data in any population on the prevalence of certain subtypes of diabetes. This includes insulin-dependent diabetes with onset in older adults, the non-insulin-dependent diabetes of the lean, and the non-insulin-dependent diabetes or impaired glucose tolerance that has its onset during youth. In a very few societies, haemochromatosis is a major cause of diabetes. This occurs when iron consumption is very high. In certain Bantu communities, for example, alcoholic drinks stored in iron receptacles lead to very high levels of iron consumption (17).

3.3 Mortality and cost of diabetes

Diabetes is one of the leading health problems in the world. Excess mortality attributable to diabetes has, in the past decade, caused more deaths than all wars combined. In the USA it is the fourth leading cause of death, and in at least 30 other developed countries it is also a leading cause of death. It is also a major cause of morbidity and mortality in many developing countries. In communities in which it is difficult to provide insulin therapy, diabetes is
3.4 Screening

Most diabetes specialists believe that the early discovery of diabetes and the effective control of hyperglycaemia reduces morbidity. There is, however, considerable disagreement on the usefulness of community screening programmes for early diagnosis. As previously performed, the results have sometimes not justified the costs. Selective community screening is still justified in some circumstances, subject to careful planning and evaluation.

3.4.1 Cost-effectiveness, priorities, and strategies

It is generally agreed that in the past bad screening programmes were common, the indirect costs of screening were ignored, and the benefits were poorly evaluated in relation to costs. Well designed population screening gives useful epidemiological data. For clinical reasons, screening is desirable as a routine in pregnancy and in adults admitted to hospitals. Clinical and epidemiological studies suggest that subjects with raised blood glucose values have increased morbidity and mortality. The achievement and maintenance of normoglycaemia in early diabetes often improves and may preserve B-cell function. Diabetes in the obese can often be reversed with weight loss. Earlier detection could reduce the proportion (about 10–20%) of all cases of gangrene and ketoacidosis found at diabetes diagnosis. Symptoms of diabetes, usually easily reversible with treatment, often go undiagnosed. Public education combined with screening could reduce this and disseminate awareness of the disease in professionals as well. Screening has several disadvantages, such as under- and over-diagnosis and the economic exploitation of screening campaigns, but with good planning it is possible to avoid them. The more conservative diagnostic standards now recommended will greatly reduce the numbers of people with lesser degrees of impaired glucose tolerance labelled as diabetic. The practice of detecting new cases without providing adequate and effective clinical care is irresponsible.

Groups at high risk of diabetes include the obese and adults with a strong family history of diabetes. Periodic screening may be justified for all adults over 35 years old. Mass screening of children is
not justified. Screening for diabetes could accompany general screening programmes. For economy and efficiency, screening should when possible be associated with confirmatory procedures for positively identified individuals. An important part of a screening programme will be conducted in clinics, hospitals, health departments, and whenever care is provided. Screening should always be accompanied by cost-benefit analysis.

3.4.2 Methods and techniques

**Urine tests.** Urine tests (see Annex 1) are convenient and cheap. With previous diagnostic criteria, the method had low sensitivity and only moderate specificity, but few subjects meeting the suggested new criteria for diabetes mellitus will fail to have postprandial (though not necessarily fasting) glycosuria. There will be many false positives, however, especially with lesser glycosuria. These would include pregnant women, younger males, and subjects with mildly impaired glucose tolerance. Urine glucose testing remains a screening technique appropriate to some circumstances and deservedly retains an important place in clinical routine.

**Blood tests.** The low cost and higher diagnostic specificity of blood glucose determination (Annex 1) usually make this the method of choice, particularly when large numbers of people are to be examined. Screening blood glucose measurements are usually made at any time of day without special preparation, but fasting samples are sometimes used and occasionally samples are collected at a fixed time after a meal or a glucose (or glucose equivalent) load. There are advantages in confirmatory tests being carried out by the screening agency as soon as possible, preferably on the same day.

3.4.3 Screening levels

A positive screening test indicates only that the probability of diabetes is sufficient to warrant a confirmatory diagnostic test. However, a screening blood glucose level (see Table 1) may be so high as to make the diagnosis virtually certain. If this is not the case, a fasting venous plasma glucose concentration in excess of 7 mmol/l (1.20 g/l) or a non-fasting value exceeding 8 mmol/l (1.50 g/l) merits further attention. Whole-blood screening values are 15% lower. Fasting capillary samples give similar glucose values to venous blood but, postprandially, capillary values are typically about 1 mmol/l

20
higher (0.1-0.25 g/l higher). Recommended diagnostic values after standard glucose loads are given in Table 1.

4. CAUSES AND MECHANISMS

It is being increasingly recognized that the syndrome of diabetes mellitus includes a number of clinically and genetically heterogeneous disorders, with the common denominator of elevated blood glucose concentrations, either in the fasting state or in response to a glucose challenge. Major and concerted efforts are necessary to elucidate the fundamental causes of diabetes so that ultimately the disease can be contained, morbidity and mortality avoided, and in the long term, the disease prevented.

4.1 Natural history of the B cell

The B cell of the pancreas is responsible for the production of insulin. More knowledge of the natural history of the B cell in man is required in order to understand the pathological effects of various genetic and environmental influences. B cells are long-lived and the rate of cell division is slow; the signal for B-cell replication remains unknown. Genetic susceptibility of the B cell to destructive environmental factors will therefore result in diabetes mellitus when it is also associated with a lack of replication of these cells. There is thus a need for an understanding of the mechanisms that control the number of B cells and their longevity, viability, and replicability. Fibroblasts and smooth muscle cells obtained from subjects with a strong genetic background for diabetes age more rapidly than those from subjects without this genetic background. Similarly, collagen in diabetics shows premature ageing. This could be a general factor that also affects the B cell, making it more vulnerable to environmental influences (18, 19).

4.2 Genetic mechanisms and specific markers

4.2.1 Twin studies

In both insulin-dependent and non-insulin-dependent diabetes, studies of identical twins have shown a strong genetic influence. In half of the pairs with insulin-dependent diabetes, both twins had
diabetes, while in 88% of the pairs with non-insulin-dependent diabetes both twins had the disease (20). Bias due to the method of ascertainment will certainly have caused a false elevation of the concordance rate, but none the less these studies indicate the importance of genetic factors.

4.2.2 HLA types: immune interactions and associations

In all Caucasian populations studied it has been shown that there is an increased risk of insulin-dependent diabetes in subjects with certain HLA haplotypes. The highest risk is incurred by subjects with DRw3 and DRw4 specificities (8, 21). Different associations have been found for Japanese and other population groups. The predictive risk for a child in a family with an insulin-dependent diabetic sibling is 50-60% if their HLA types are identical but much lower if they are not. In Caucasians a rare genetic type (Bf F1) of properdin factor B has recently been found in the blood in 23% of patients with insulin-dependent diabetes, but in only 2% of the general population (24); individuals carrying this factor thus have a greatly increased risk of developing diabetes (relative risk 15). It is important to emphasize the low order of magnitude of HLA association in an individual.

No evidence of HLA association has been reported in non-insulin-dependent diabetes, but this does not mean that other markers of these forms of diabetes do not exist, such as decreased early insulin response (22) to a glucose challenge. Islet cell antibodies are present in some patients with insulin-dependent diabetes of recent onset, in those with HLA-B8 antigens and/or in those with autoimmune disease (23). Islet cell antibodies can also be detected in non-diabetics (1%) and in non-insulin-dependent diabetics (6-8%). The presence of islet cell antibodies may prove useful as a subsequent indicator of insulin need. The destruction of B cells and their failure to regenerate could be the result of an HLA-linked genetically controlled immune response to environmental factors—e.g., to viruses that have an affinity for pancreatic B cells.

4.3 Acquired and environmental factors

4.3.1 Infection

Animal models, most notably encephalomyocarditis-induced murine diabetes mellitus, have demonstrated the development of
severe diabetes in the genetically susceptible host. Several viruses have been implicated as causal factors of insulin-dependent diabetes in man (25). They include enterovirus coxsackie B 4, mumps, and rubella. Further evidence is needed on mild viral infections to delineate the relationship between genetic susceptibility and virus infection.

4.3.2 Toxicity

Direct B-cell cytotoxicity. Toxic substances may directly damage the B cells. The recent recognition of diabetic ketoacidosis following the ingestion of rodenticide is of note (26), particularly as a potential public health problem. Streptozocin, a product of bacterial origin, produces diabetes in a large number of animal species. Nitrosamines (to which streptozocin is related) have been detected in foods.

Altered B-cell function through multifactorial mechanisms. Pancreatic diabetes (calcific-fibrosis of pancreas) is common in some developing countries, notably Brazil, India (Kerala), Indonesia, Nigeria, Uganda, and Zaire (see Annex 4). An association between pancreatic damage and the consumption of tapioca (cassava) has been suggested. Tapioca, a tuberous root, is a major source of dietary cyanide, although other foods like yams, sorghum, and millet also contain small quantities. Lack of sulfur-containing amino acids in the diet or in the body reduces the formation of thiocyanate, a major pathway of cyanide detoxification. Thus, consumption of tapioca or cyanide-containing foods by populations with marginal nutrition, may lead to excessive accumulation of cyanide, resulting presumably in pancreatic damage (27).

4.3.3 Nutrition

Overnutrition. Hyperinsulinaemia, both in the basal state and in response to a glucose challenge, is a feature of obesity and is often associated with glucose intolerance. Obesity induces peripheral resistance to the action of insulin owing mainly to a reduction in the number of insulin receptors in the target tissues (28). This can be corrected by dietary restriction leading to weight reduction. If remedial measures are not adopted, however, the B cells of individuals genetically predisposed to diabetes may not be able to withstand glucose challenge, and the failure will lead to diabetes mellitus.
Protein malnutrition. Basal normoglycaemia or hypoglycaemia with carbohydrate intolerance following glucose challenge is a feature of kwashiorkor, one of the major manifestations of protein-energy malnutrition during the early years of life. The main cause of glucose intolerance seems to be a low insulin output in response to glucose challenge, indicating either a reduction in the number of B cells or the functional impairment of those cells. Whether continued protein deprivation would ultimately result in irreparable damage to B cells, or would increase their vulnerability to harmful (noxious) environmental influences, needs further study as it may provide useful insights into the understanding of both the J type and the pancreatic diabetes seen in the tropics. Indeed, the J type of diabetes is characterized by malnutrition (29).

Alcohol. Alcohol can indirectly increase the risk of diabetes by producing acute, chronic, or relapsing pancreatitis, by enhancing obesity, and by producing hepatic cirrhosis (hepatogenous diabetes). Furthermore, in certain communities in Africa, some alcoholic drinks contain large amounts of iron, and may thus lead to haemochromatosis. Deficiency of chromium and zinc may also be important, but data are scanty.

Nutritional imbalance. Deficiency of dietary fibre has been related to the prevalence of diabetes mellitus. Many factors may, however, be involved and no causal relationship has been established. Similarly the suggested specific relationship between sucrose consumption and diabetes prevalence has not been confirmed in recent studies in human populations (30).

4.3.4 Severe or prolonged stress

Several stress states such as acute myocardial infarction, surgery, and severe burns are associated with carbohydrate intolerance. Whether they can lead to permanent diabetes is not established. Similarly the role of emotional stress and anxiety as causative or precipitating factors in diabetes mellitus and in gestational diabetes remains inconclusive.

4.3.5 Drugs and hormones

Long lists of drugs affecting carbohydrate metabolism are available (4). Among commonly used drugs, phenytoin, diuretics (particularly of the thiazide type), oral contraceptive steroids, and
beta-adrenergic agonists may all cause glucose intolerance, and in
susceptible individuals may trigger diabetes. Administration of corti-
cotrophin or corticosteroids in pharmacological dosage over a
prolonged period may also precipitate diabetes.

Lists of endocrine disorders associated with diabetes mellitus may
be found in standard textbooks. Several are associated with reversible
glucose intolerance.

4.3.6 Pancreatic disorders

Inflammatory and neoplastic disorders of the pancreas, as well as
total or subtotal pancreatectomy, lead to absolute insulin deficiency,
and hence diabetes mellitus. The metabolic response of such cases
may differ from that of other clinical types of diabetes mellitus owing
to the absence of pancreatic glucagon.

4.3.7 Physical inactivity

It is believed that physical inactivity is an important risk factor
for diabetes. Insensitivity to insulin, the number of insulin receptor
sites in muscle, and adiposity are related to physical fitness.

4.4 Relationship between genetic and environmental factors

It is abundantly clear that interactions between genetic and envi-
ronmental factors provide the basis of the multifactorial causes of
diabetes. In any given subject it is the relative proportion of these
factors that determines the eventual development of the disease.

4.4.1 Identification of people at high risk

People who have a relative with insulin-dependent diabetes are
themselves at increased risk of the disease. The histocompatibility
haplotypes and islet cell antibodies are the main biological
markers.

The following factors indicate an increased risk to an individual
of non-insulin-dependent diabetes: being a first-degree relative of a
non-insulin-dependent diabetic or being a member of a family with a
strong history of the condition; giving birth to a baby weighing more
than 4 kg (or 3.5 kg in constitutionally small populations); being a
member of an ethnic group with a high prevalence of diabetes;
having excess body weight; taking of oral contraceptives; and being
subjected to stress (e.g., infection, trauma, and emotional disturbance).

Biological markers include transient abnormalities in glucose tolerance during pregnancy and low insulin response to a glucose challenge.

4.4.2 Action to be taken

In these high-risk subjects it is unwise to await the full development of diabetes before taking action. If blood glucose values reach levels indicating impaired glucose tolerance, advice regarding diet, exercise, and maintenance of normal weight should be given. Subjects at risk of diabetes should be informed about the importance of controlling weight and avoiding diabetogenic drugs, such as oral contraceptives. It is wise to reduce factors that promote atherosclerosis, i.e., smoking, high blood pressure, high serum cholesterol, and high triglyceride levels. Abnormalities of glucose tolerance during pregnancy require special action, as discussed in section 5.8.1.

4.5 Metabolic and endocrine disturbances

The diabetic syndrome results from a disturbance of the metabolic regulatory system responsible for the storage and/or utilization of the chemical energy released from food (31). Insulin is a key controlling point in this system. The disturbance of diabetes, although made clinically evident by the high blood glucose level, will also affect the pathways of fat and protein metabolism.

4.5.1 Carbohydrate metabolism

Hyperglycaemia, which characterizes the diabetic syndrome, reflects the loss of the regulatory hormonal balance between insulin, which induces glucose consumption, and several "anti-insulin" hormones, which lead to glucose production. Absolute or relative hypoinsulinaemia is the most widely accepted direct endocrine cause of hyperglycaemia. Even when insulin levels are raised they tend to be lower than in matched non-diabetic subjects rendered equally hyperglycaemic.

There is a close functional relationship between insulin and the other peptide hormones produced by the pancreas and neighbouring gastrointestinal tract. These include glucagon, somatostatin, and
gastric inhibitory polypeptide. Glucagon and insulin act as an important opposing pair in controlling glucose metabolism by the liver. Insulin stops production of glucose by the liver and drives glucose into many cells of the body, while glucagon increases liver glucose production. In diabetes, glucagon levels are often raised, causing a further increase in blood glucose levels, and other hormones such as adrenaline, noradrenaline, glucocorticoids, and growth hormone also oppose the effects of insulin. Growth hormone levels are often raised as well, although the significance of this is uncertain. The brain, too, has important effects on metabolism. Nervous impulses, mainly from the hypothalamus, can both modulate insulin secretion and directly affect the metabolic action of certain organs (74).

Many hormones, including insulin, act by combining with specific receptors. Insulin controls its own receptor concentration, so that high levels of insulin are associated with low levels of receptors and therefore decreased insulin action. This may explain the apparent paradox in obesity of high insulin levels with mild glucose intolerance.

4.5.2 Fat metabolism

Insulin deficiency leads to accelerated mobilization of energy reserves from fat stores, fatty acids, and glycerol. This is because glucose can no longer be used efficiently as a fuel. The fatty acids travel to the liver where they are oxidized to ketone bodies. If this happens in excess then “ketosis” or “ketoacidosis” occurs and ketone bodies appear in the urine. If this process continues, the accumulation of ketone bodies leads to severe ketoacidosis and diabetic coma.

Some of the excess fatty acids are also converted in the liver to triglycerides, and, with insulin deficiency, fewer circulating fats are removed. In diabetes these may accumulate in the blood as lipoproteins, giving rise to hyperlipoproteinaemia or hypertriglyceridaemia.

4.5.3 Protein metabolism

Insulin is as important for the synthesis of proteins as for storing other large molecules. If insulin is deficient, proteins break down, and this process leads to the classical protein depletion and muscle wasting seen in untreated insulin-dependent diabetes.
5. MANAGEMENT OF DIABETES

At one extreme of severity, 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, weight reduction by dietary restriction may suffice to correct the metabolic disturbance completely. Diabetes may be discovered in many ways—e.g., as the result of a routine medical examination, in pregnancy, after a myocardial infarction, or in a ketoacidotic, comatose patient. Each situation will require its own individual management plan, but certain general aspects of management are considered below, together with some specific problems such as pregnancy.

5.1 Food

Some form of dietary advice will be needed by all types of diabetic, though it differs for the two main types. In many non-insulin-dependent patients, dietary restriction will be the only “treatment” required. In all insulin-takers it will involve learning basic facts about the composition of foods and mealtime strategy, previously taken for granted. Dietary advice must be simple, clear, realistic and repeated. It is best given by a person trained both in dietetics and in communication. The changing of existing dietary patterns is difficult: and it should not be supposed that this can be done with a printed sheet and a cursory explanation.

In the obese, a disproportionate limitation of carbohydrate will not be necessary, although consumption of sugars will be decreased. Total energy intake should be decreased with as much attention paid to fat and alcohol as to carbohydrate. The requirements of normal-weight diabetics are best assessed from their habitual intake. Diets explained on the basis of energy intake only (i.e., joules or calories) are unrealistic and usually disregarded. Dietary advice should be translated into locally familiar food. As far as possible habitual types of food and meal times should be retained.

Selective carbohydrate restriction in rarely necessary but rapidly absorbed sugars are best avoided. Fat intake should be reduced with some substitution of dairy products by polyunsaturated vegetable and marine oils in margarines and for cooking. A high fibre intake should be advised. Otherwise the general principles of good nutrition—an
adequate intake of protein, vitamins and minerals—apply as in the non-diabetic. Diet may need adaptation for growth, pregnancy, lactation, or medical disorders. Diabetics should not assume that special diabetic foods are desirable or necessary.

The emphasis in the insulin-dependent diabetic should be on regularity both in timing and in intake. Timing of meals should vary little from day to day and, so far as possible, fit the diabetic's normal way of life. Planned between-meal snacks are usually necessary to prevent hypoglycaemia. Insulin treatment can be adapted to this.

5.2 Insulin

Insulin-dependent diabetics should inject insulin to try to maintain their blood glucose concentration as closely within the normal physiological limits as is practicable and safe. It is of great importance to the independence of the diabetic that, whenever possible, the insulin injection be self-administered. Good control can usually be best achieved by taking more than a single injection each day: usually two, sometimes three. The patient must not only learn correct injection technique but also how to monitor his response to insulin. He should learn how to improve blood glucose control and will need to understand the basic facts about diabetes. To prevent cross-infection, in particular viral hepatitis, the diabetic should never receive an injection from a syringe that has been used by others.

5.2.1 Insulin types, strength, and purity

Insulin may be used in simple solution or modified in various ways to delay absorption and prolong its action (see Annex 6). The present profusion of preparations could profitably be simplified. When there are different strengths (concentrations) of insulin preparations, confusion may cause dosage errors with potentially serious consequences. It is felt increasingly that the hazards outweigh the advantages and that a single standard strength within a country is advisable. This standard strength should be decided locally, although there would be clear advantages in international agreement. Highly purified insulins are widely available: average doses are lower and there are theoretical advantages in their use together with some practical benefits. These must be weighed against higher production costs and sometimes lower production yields. Differences between
insulins from the pancreas of different animals do not affect their antidiabetic potency but may excite different immune responses in the diabetic.

5.2.2 Identification

The continuing absence of uniformity in ways of identifying type, strength, degree of purification, and species of origin of insulin preparations requires agreement and standardization to reduce confusion and danger.

5.2.3 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. Its high cost may restrict the availability of insulin in less economically developed countries, often with disastrous effects on the health and life of diabetics. Once the commitment to insulin therapy has been made, continued supplies of the correct types of insulin should be ensured.

5.3 Oral hypoglycaemic agents

Some non-insulin-dependent diabetics respond inadequately to restricted food intake and dietary advice. In these patients the oral sulfonylurea and biguanide preparations often reduce hyperglycaemia and relieve symptoms. Some endogenous insulin secretory activity is necessary for both groups of drugs to be effective. Longer-term protective effects against diabetic complications (see section 6) have not been conclusively demonstrated. In a prospective multicentre trial in the USA (32), “maturity-onset” diabetics were divided randomly into various groups and given the following kinds of treatment: fixed doses of tolbutamide (a sulfonylurea), fixed doses of phenformin (a biguanide), a low fixed dose of insulin, a clinically varied dose of insulin, and an inactive placebo. No advantages of any active treatments over placebo were found. The study has been subjected to intense criticism not least because, contrary to expectations, it showed greatly increased mortality attributed to cardiovascular causes in patients treated with tolbutamide and phenformin compared with those receiving placebo (33). In the case of tolbutamide this was not reflected by increased total mortality. No supporting evidence has come from four other prospective, random
allocation, double-blind trials, some of which indeed suggested benefits of tolbutamide in respect of cardiovascular morbidity (34). This unresolved conflict of evidence suggests that chance factors and classification problems may have been responsible for some of the findings. Many new sulfonylurea preparations have since been introduced, and it is questionable whether conclusions should be extrapolated from one drug to another for an effect unrelated to their common action of lowering blood glucose. Phenformin has been used diminishingly (and in some countries totally withdrawn from use) because of its contribution to the rare but often lethal condition of lactic acidosis (35). At low dose-levels, in the absence of contraindications and in patients less than 60 years of age, the drug may have some restricted value. Metformin, another biguanide, is associated much less frequently with lactic acidosis, and buformin may occupy an intermediate position. The main indications for biguanides are in the treatment of obese diabetics and as an adjunct to inadequate sulfonylurea response. Used selectively, oral drugs occupy a place in diabetes therapy.

5.4 Other antidiabetic treatment

Exercise improves metabolism and also increases well-being in the well-controlled diabetic. Graded exercise suited to the age and physical status of the diabetic should be encouraged as part of treatment. In developing countries, physical exertion is a natural accompaniment of life and should remain so. Yoga is recognized in some parts of the world as a form of antidiabetic treatment; preliminary data are encouraging.

5.5 Resources required

Therapeutic agents, the means of administering them (syringes, needles), and the means of monitoring and self-monitoring of urine and blood glucose are essential to diabetes care (see Annex 7). They are in inadequate supply in some of the developing nations. In all social and cultural contexts, the means of learning about diabetes, its correction and control, are of central importance for the patient and for those responsible for providing care.
5.6 Acute metabolic problems

Hyperglycaemia with ketoacidosis and hypoglycaemia account for significant morbidity and mortality. Non-ketotic hyperosmolar hyperglycaemic coma and lactic acidosis occur less frequently, but they are more likely to kill.

5.6.1 Hypoglycaemia

Hypoglycaemia most commonly occurs as a side-effect in diabetics injecting insulin. It may also result from the overaction of oral antidiabetic agents, usually because of interaction with other drugs, if the antidiabetic preparation has not been properly excreted or if its use was unwarranted. Early warning symptoms of hypoglycaemia just before a meal are not unusual in the well-controlled patient but should be carefully monitored. Severe hypoglycaemia is normally due to imperfect understanding of the treatment, to change or irregularity in habit, to consumption of alcohol, or to loss of warning signals owing to nerve damage. Self-monitoring of blood glucose supported by adequate advice and instruction helps the diabetic to understand his own metabolic patterns of response, and to minimize the risk of hyperglycaemia.

Patients, their relatives and all health workers involved in diabetic care should learn the early symptoms and signs of hypoglycaemia and know what action to take. Action must be prompt and, if consciousness is unimpaired, consists of giving the patient carbohydrate food or sugar or glucose in suitable form. Attempts to feed the unconscious patient are dangerous, and intravenous glucose or intramuscular glucagon should be given. The latter can be injected by a family member after suitable training.

5.6.2 Severe hyperglycaemic ketoacidosis (diabetic coma)

Diabetes may first present with coma, caused by lack of insulin action. In diabetics already under treatment, ketoacidosis most often results from failure to take adequate insulin and may point to poor educational and health care facilities. Severe stresses like heart attack and trauma may precipitate ketoacidosis even in mild diabetics through the release of hormones opposing insulin action.

Prevention is essential. Mortality rates, especially in the elderly, can be as high as 50% (36). Education of health-care personnel and patients is crucial and at present often defective. Rapid access to
adequate health-care facilities is necessary and insulin must be
available. Infections must be treated promptly and patients made
aware of increased insulin requirements associated with illness,
infection, and trauma.

The diagnosis of severe ketoacidosis can be made from the
history, clinical examination, urine tests for sugar and ketones, and
simple bedside blood tests for glucose and plasma ketone bodies.
Sometimes the ketone, acetone, may be smelled on the patient's
breath. Portable meters that give blood glucose results rapidly and
with adequate accuracy are valuable in diagnosis and treatment.

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

Treatment is with modern, low-dose, intramuscular or intra-
venous regimes (36). Adequate fluid and electrolyte replacement is
required to make good the fluid and salt lost before treatment begins.
Precipitating infections should be treated, acidosis corrected if severe,
and potassium salts administered as required. Further general
measures include gastric intubation to relieve gastric dilatation,
heparinization in the severely hyperosmolar, central venous pressure
monitoring in the elderly or those with cardiovascular disease, and
blood or plasma infusion in cases of persistent peripheral circulatory
failure.

Partial correction of the metabolic disturbance will often occur
with rehydration alone. Where insulin is unavailable or facilities for
patient care are poor, fluid replacement with saline may usefully start
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 intra-
rectally.

5.7 Other metabolic problems

Coma associated with severe hyperglycaemia may occur without
ketoacidosis. Hyperventilation is absent and plasma and urine show
little or no evidence of ketone bodies. Intravenous fluids, frequently
hypotonic, should be given.

Lactic acidosis in diabetes is particularly associated with
biguanide therapy (especially phenformin; see section 5.3) but may
also result from shock, septicaemia, or anoxia. The degree of acidosis
is more severe than ketone body measurements indicate, and
mortality is high.
5.8 Pregnancy

Better metabolic and obstetric management have dramatically improved prognosis for pregnancy in the diabetic woman over the past 25 years. Congenital malformations still occur, however, and their frequency is increasing. The first 12 weeks of pregnancy are critical for normal organogenesis, and poor control may be responsible for damage then. Ideally, conception should be postponed until optimum glycaemia has been obtained, and this should be maintained throughout pregnancy. The cost of this kind of management is high in both effort and resources. Wherever possible, the conduct of pregnancy and the care of the mother and newborn should be carried out in properly appointed centres.

5.8.1 Management

The coordination of diabetic, obstetric, and paediatric skills is necessary. Blood glucose concentrations in the physiological range can be achieved with intensive application of the measures described above. Early admission to hospital may be desirable for diabetic or obstetric reasons. Insulin requirement doubles on average during pregnancy but drops precipitously to previous levels after delivery. Urine tests for glucose become unreliable in pregnancy as the renal threshold for glucose falls. Ketonuria with glucose loss does not necessarily mean bad glycaemic control. Antenatal monitoring for urinary tract infection, pre-eclampic toxaemia, fetal maturation, and placental function should be carried out by the most effective means locally available. Adequate nutrition with vitamin and iron supplements should be ensured.

Vaginal delivery at term is becoming the norm if excellent metabolic control has been maintained throughout pregnancy. If not, or if there are other indications, earlier induction is indicated, provided fetal maturity allows. Continuous intravenous glucose and insulin infusion is a satisfactory method of controlling metabolism during labour. Caesarean section is performed if labour is prolonged or for other feto-maternal indications.

Women with impaired glucose tolerance in pregnancy require equally careful surveillance. If adequate normalization of blood glucose cannot be achieved by dietary means, the use of insulin, even in small doses, is strongly indicated.
Rapidly progressive renal or retinal complications during pregnancy are an indication for termination. Retinopathy has been successfully treated during pregnancy by photocoagulation (37).

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

5.8.2 Puerperium

Return to the pre-pregnancy regime of food and insulin should not be delayed. Lactation and adequate breast feeding are practicable, but food intake and insulin dose may need to be raised. For the gestational diabetic, insulin treatment can generally be stopped immediately after delivery.

5.8.3 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 (38), and termination and sterilization may be advisable. Contraception can be obtained by any currently available methods, though physical methods (intrauterine 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.

5.9 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 surgery under local anaesthesia or for minor surgery under general anaesthesia. The simplest method is to postpone therapy (oral agents or insulin) on the morning of the operation.

The simplest scheme for treating non-insulin-dependent and insulin-dependent diabetics during major surgery is to use a continuous intravenous infusion of insulin (3–4 IU/h) in glucose (100 ml of 100 g/l glucose per hour) from the morning of surgery until the first meal is taken, when the usual therapy can be recommenced. Alternatively, repeated small injections of soluble insulin
with careful monitoring of blood glucose will suffice. Blood glucose and potassium should be measured when possible.

5.10 Diabetes in children

Diabetes usually appears abruptly in children; if unrecognized, coma and death ensue. Insulin is life-saving, and dependency on it is permanent and absolute. Early recognition of the disease and the provision of treatment are therefore central requirements.

Adequate growth, both physical and emotional, is the chief aim. The first depends on sufficient nutrition supported by an appropriate provision of insulin, individually administered to meet changing requirements and varying patterns of activity.

Emotional development may be threatened both by parental rejection and overprotectiveness, and by the child’s resentment of regulation. Independence must be fostered from the first and self-confidence built securely on a sound understanding that grows with age. Responsibility for injections, insulin measurement, dietary decisions and self-monitoring must be handed to the child as soon as it is safe to do so. Informed discussions in depth with child and parents supported by adequate literature are highly desirable.

Children are often admitted to hospital to begin with, mainly to start treatment and the long process of education. Both may be better done in the home environment, but this requires adequate trained staff. Continued medical care should be as closely integrated with normal life as possible. Later emergency admissions to hospital for diabetes often indicate failure of understanding in patients, parents, or health-care team. Parents and child must have ready access to reliable medical advice. Special clinics for young diabetics may be desirable to centralize skills and protect children from exposure to major diabetic disabilities. Clinical responsibility can properly be taken by a physician or paediatrician trained in diabetes.

5.11 Diabetes in the elderly

In the old person diabetes is not usually the sole or even the major health problem. The disease often comes to light while investigating such problems as heart disease, arterial insufficiency, or failing vision due to cataract. The great majority are of the non-insulin-requiring type, but a few old people will develop diabetes abruptly and be insulin-dependent. Some will present with severe non-ketotic
hyperglycaemia. A few will be survivors of early-onset insulin-dependent diabetes.

The management of diabetes in the elderly aims to relieve diabetic symptoms, to correct accompanying disease so far as possible (e.g., cataract extraction), to initiate preventive measures, and to improve the quality of life.

To promote overenergetically a policy of metabolic normalization in the old is distressing and even dangerous. Hypoglycaemia may have devastating consequences. Insulin and oral agents should be used sparingly. Severe dietary restriction is unkind, though advice on better nutrition is valuable. This is not a policy of therapeutic nihilism but of commonsense.

By contrast, much can and should be done to remedy accompanying disorders. Of itself, coexisting diabetes is no contraindication of the treatment of other disorders, though drug interactions must be considered, and there is a need for carefully supervised insulin support during surgery or during infective or traumatic stress. Detailed personal advice on foot hygiene with skilled assistance from health personnel may avert a future amputation. The elderly diabetic always needs reassurance that the diagnosis does not spell doom. Social services are of prime importance.

6. COMPLICATIONS

The clinical course of diabetes and the prognosis for health and life of the diabetic are now largely determined by the so-called complications of the disease. The characteristic progressive damage to the eyes, kidneys, and nerves and the heightened susceptibility to heart disease, gangrene, and stroke are most probably a direct consequence of inadequate control of the metabolic disorder, but it is not yet settled to what extent they evolve independently. This important question requires an answer in that it influences the nature and intensity of diabetic treatment. The value of improved control in reducing fetal loss in diabetic pregnancy is, however, unquestionable.

The acute metabolic complications of diabetes are discussed in the preceding section.
6.1 Pathogenic processes

Several processes combine to cause the distinctive patterns of structural and functional disorder known collectively as “complications”. These processes include diabetic microangiopathy, arterial disease, metabolic factors, neuropathy, and infection.

*Diabetic microangiopathy.* This term describes a specific progressive change in the capillaries, characteristically contributing to retinal and renal disease in diabetics of long duration. The capillary abnormalities vary in form and effect but have the common feature of thickening of the glycoprotein basement membrane, accepted by many as a fundamental pathological change in microangiopathy.

*Arterial disease in the diabetic.* Atherosclerosis in the diabetic closely resembles that in the non-diabetic but is more severe, more widespread, begins earlier, and involves smaller arteries. It is the major contributory cause of heart disease, stroke, intermittent claudication, and gangrene, as shown by the high values for these conditions found in the WHO multinational study of vascular disease in diabetics (Annex 8). Arterial disease is significantly more common in diabetic than non-diabetic women, approaching or equaling the rates in men (39). It is influenced by the same major risk factors in the diabetic as in the general population.

*Metabolic factors.* Abnormalities of the tissue environment in the diabetic may provoke direct local damage, as in neuropathy or cataract, or may complicate the response to other pathological processes such as infection or arterial occlusion. Metabolic abnormalities may themselves initiate microvascular disease.

*Diabetic neuropathy.* Damage to peripheral nerves is both a manifestation of, and a contributory factor to, the complications. It is often a main contributor to the chronic destructive process affecting soft and bony tissues of the foot of the diabetic. Disease of the autonomic nerve supply to the viscera causes disorders of alimentary, cardiovascular, respiratory, urinary, and sexual function.

*Infection.* The inadequately controlled diabetic is unduly prone to certain infections. Tuberculosis, fungal infections of skin and urinary tract, and anaerobic infections of deep tissues are serious threats, particularly in poor hygienic surroundings. Urinary tract infection is particularly likely if the diabetic has a neuropathic bladder. Pyelitis and pyelonephritis aggravate diabetic nephropathy. Chronic painless sepsis may destroy the neuropathic and/or ischaemic foot.
6.2 Suggested causal mechanisms

The differences in susceptibility to complications among diabetics cannot be completely explained by differences in the degree of metabolic "control". Other factors clearly modify progress and severity but are poorly understood.

Diabetic control. Many clinical studies, most of them retrospective and unplanned, strongly suggest that diabetics with less severe degrees of metabolic disorder are less liable to develop the microvascular and neuropathic complications (40). However, it is also possible that this relative freedom from complications may be due to the effectiveness of the treatment rather than the lesser severity of the metabolic abnormality, and it is difficult to assess the degree to which each factor is responsible. In animals rendered experimentally diabetic and maintained at different levels of control, changes analogous to human complications are directly related to the degree of control (41), but only cautious extrapolation to man is permissible. Rapid restoration of disturbed microvascular function can be achieved by improved metabolic control, but the relevance of reversible functional change to later morphological abnormalities is as yet unclear. Apart from sustained hyperglycaemia, many abnormalities of hormones and metabolites are associated with poor control, and any or all of them could be pathogenic.

Genetic factors. Genetic factors influence the frequency and severity of diabetic retinopathy. When both members of identical twin pairs have diabetes with retinopathy it is closely similar in degree. In one study of identical twins, the retinopathy was less severe in diabetics whose twin siblings did not have diabetes (42). By contrast, some families with strongly inherited early-onset non-insulin-dependent diabetes have a reduced risk of retinopathy, as perhaps do other genetically defined groups (43). Slow acetylators may be more prone to neuropathy than fast acetylators. The drug isoniazid, used in the treatment of tuberculosis and itself a cause of neuropathy, depends on acetylation for biotransformation and could worsen diabetic neuropathy in slow acetylators.

Hormonal factors. Growth hormone excess has been implicated in diabetic retinopathy, and some studies suggest that microvascular complications are closely associated with low insulin production. On the other hand, increased local insulin concentration may favour development of arterial wall disease in the diabetic.
**Circulatory factors.** Focal ischaemia and local abnormal tissue metabolism have been blamed for the complications, as have raised blood viscosity, high plasma glycoproteins and lipoproteins, and impaired neuroregulation. Retinopathy probably occurs more often and evolves faster when arterial blood pressure is raised.

**Other factors.** Altered blood platelet function, circulating metabolites and macromolecules, immune complexes, and clotting factors are associated with microvascular disease. It is difficult to determine whether they result from the vascular disease, whether they cause it, or whether they are parallel but unrelated phenomena.

### 6.3 Prevention of complications

Specific measures for the prevention of diabetic complications are not yet available. However, some measures may exercise a general effect on several of the manifestations, as described below.

#### 6.3.1 Improvement of metabolic control

The strong indications of the preventive or retarding effects of better blood glucose control on certain of the complications, although as yet scientifically unproven, justify clinical attempts to achieve metabolic normoglycaemia. Blood glucose control should be pursued so far as is safe and practicable. There are limits, however, to the currently available therapy, and improved methods are required. Prolonged and severe hypoglycaemia may cause neurological damage, a risk that can be greatly reduced by adequate patient education.

#### 6.3.2 Prevention of vascular disease

The susceptibility of the diabetic to arterial disease of heart, leg, and brain is in part related to the risk factors operating in the general population (44). Effective control of hypertension in the diabetic is of great importance, for this may also protect the renal and retinal circulation (45). Cessation of cigarette smoking and reduction of hyperlipidaemia are important to the diabetic: physical fitness and correction of adiposity are desirable. The standard diabetic dietary policies should be reviewed, with the aim of reducing dietary fat intake, replacing saturated by polyunsaturated fatty acids, increasing the proportion of food energy from carbohydrate, and providing
more dietary fibre (46). Much further investigation of optimum dietary policy for diabetics is required. The effectiveness of the systematic and widespread use of medications for lower plasma lipids (for effects on platelets or vessel walls) has not yet been established.

6.3.3 Prevention of infection

Urinary tract infection in diabetic females should be guarded against by ensuring adequate perineal toilet and sex hygiene. Infection should be sought routinely and treated by appropriate methods. Fungal infection of the interdigital clefts of the foot should be eradicated before it allows entry of other organisms into vulnerable tissues.

6.3.4 Preservation of organ function

Even after complications are established, slowing or arrest of the progression to organ failure may be achieved. This is the case in retinopathic blindness, renal failure, gangrene, and the sequelae of myocardial infarction. Early and active measures of rehabilitation will reduce chronic invalidism.

6.4 Diabetic complications of organs and systems

Diabetic damage is usually due to a combination of pathogenic processes, though one or another may predominate. Several systems are usually affected together. It is most useful to consider each organ or system separately.

6.4.1 The eyes

Blindness due to diabetic retinopathy and cataract is a major long-term risk for the diabetic. Retinopathy is the commonest single cause of blindness registration in the middle-aged in most economically advanced communities. The extraocular nerves, the optic nerve, and the uveal tract are also affected with increased frequency in the diabetic.

Retinopathy increases in frequency and severity with duration of diabetes, and few diabetics escape the specific pattern of damage to the retina and its microcirculation. This can be readily detected by
simple direct examination of the optic fundus, though it is more completely displayed by techniques such as fluorescein angiography. Scattered capillary microaneurysms, haemorrhages, and exudates (the so-called "background retinopathy") commonly appear after some years of diabetes and often persist for very long periods without significant effects on vision. Vision is threatened when new vessels form, particularly at the optic disc, or when bleeding, protein deposits, and excess fluid passing through abnormally permeable blood-vessel walls affect the macular region.

Regular examination of the optic fundus permits early recognition of threatening lesions. Prompt treatment by retinal light coagulation has been shown to reduce by two-thirds the risk of blindness associated with disc new vessels and maculopathy. Adequately sited diagnostic and therapeutic facilities should be made available as a priority in diabetic care wherever possible. There is no drug treatment of proven worth, and other therapeutic measures such as pituitary ablation are now rarely to be recommended. Operations to salvage some vision in the blind (vitrectomy, banding, etc.) are not firmly established as helpful and require further evaluation. Survival after blindness is sometimes relatively short, but active measures of rehabilitation, development of special apparatus and appropriate employment of the diabetic blind is highly desirable.

Cataract of the so-called senile type occurs earlier in life and progresses faster in diabetics than non-diabetics. It may be surgically extracted as with non-diabetics, but postoperative complications are more common and severe underlying retinopathy may restrict recovery of vision. The rare metabolic ("snowstorm") cataract of diabetes responds well to surgery.

There is little valid epidemiological information about regional variations in the frequency of eye disease in diabetics, owing largely to inadequately standardized methods of examination and documentation. The WHO multinational study of vascular disease in diabetics (47), which used a simple clinical protocol, showed unexpectedly large variations in reported eye and kidney disease among participating national centres (Annex 9).

6.4.2 The kidneys and urinary tract

Progressive renal disease is a major threat to life and health, particularly when diabetes is diagnosed in childhood. In one study half the diabetics diagnosed before the age of 15 years were dead by the
age of 40, with renal failure as the major causal or contributory factor (12). Disease specifically affects the glomerular capillaries, the basement membrane of which thickens, becomes nodular, progressively closes the vessel, and finally replaces the vascular tuft. This process, usually combined with arterial and arteriolar disease and chronic pyelonephritis, leads progressively to renal failure. Renal medullary tissue may necrose, blocking the ureter and reducing renal substance. Recognized clinically by proteinuria, there is no specific treatment for diabetic nephropathy, though progression may be delayed by effective treatment of accompanying hypertension and treatment of urinary tract infection. Renal failure management, including repeated haemodialysis or peritoneal dialysis and renal transplantation, is achieving increasing success in specialized centres, but accompanying retinal microvascular and coronary artery disease at present restrict the number of patients suitable for such treatment. Urinary tract infection is a particular risk to diabetics, especially when bladder emptying is impaired. Urinary catheterization should be avoided when possible.

6.4.3 Neuropathy

Somatic and autonomic peripheral nerves are frequently damaged by diabetes. Clinical manifestations depend on the site and the severity. Metabolic abnormalities affect the nerves, and damage is probably initiated by departures from good diabetic control. The nerves of the diabetic are “sensitized” to other insults—e.g., pressure, alcohol, drugs, and toxins. Clinically, sensation is lost (usually in the feet) so that unrecognized trauma, chronic infection, and tissue destruction may ensue, and sometimes Charcot’s joints. Obstruction of blood vessels to the nerves causes focal loss of function, and motor weakness may occur through vascular occlusion or local pressure. Asymmetrical muscle weakness and wasting, with pain in buttocks and thighs is part of the syndrome of diabetic amyotrophy and usually carries a good prognosis.

When disordered autonomic function affects the bowel it causes diarrhea or constipation; involvement of the bladder causes chronic urinary retention; and involvement of the pelvic nerves results in erectile or ejaculatory failure. Cardiac, respiratory, and peripheral vascular denervation causes abnormalities of reflex control, sometimes with disabling symptoms.
Apart from general and symptomatic treatment, scrupulous protection of nerve-damaged feet is vital to prevent progressive and disabling tissue destruction.

6.4.4 The heart

Heart disease (cardiopathy) in several forms is typically 2-3 times more common in diabetic men and 5-6 times more common in diabetic women than in corresponding non-diabetics (12). It may manifest as angina pectoris, myocardial infarction, ventricular failure, syncope, and sudden death. Although coronary artery disease affects diabetics excessively, it fails to account for all the cardiopathy. Disease of small intramural arteries and arterioles, neurological dysfunction, and disturbed metabolic milieu of heart muscle and conducting tissues may all contribute to the disordered cardiac function. Simple assumptions that all heart disease in the diabetic is secondary to coronary insufficiency may be misplaced, and the relative contributions of other factors and their control require investigation.

Myocardial infarction is twice as likely to kill the diabetic as the non-diabetic (48). Careful metabolic correction, often requiring insulin, and antidysrhythmic measures may help. Hypoglycaemia should be avoided. Sudden death in neuropathic diabetics may result from cardiac or respiratory arrest. In other respects, medical and surgical treatment of ischaemic heart disease in the diabetic is the same as in the non-diabetic. The considerable difference in susceptibility to ischaemic heart disease between western diabetics and those indigenous to Japan and Hong Kong (Annex 10) strongly suggests environmental and potentially avoidable factors, probably dietary. This demands further exploration.

6.4.5 The foot

The triad of ischaemia, neuropathy, and infection contributes to the chronic disabling complication known as “diabetic foot” or “neuropathic gangrene”. Chronic discharging skin ulceration usually overlies a region of infected necrotic tissue deep in the foot, often involving bone. Frequently painless because of denervation, damage may progress to the degree that amputation or major reconstructive surgery is necessary. As much limb function as possible should be conserved.
This condition must be distinguished from true ischaemic gangrene (20 times commoner in diabetics than in non-diabetics), in which arterial obstruction dominates, causing blackened, mummified extremities. Amputation is usually necessary with provision of an adequate prosthesis and training for rehabilitation.

Arterial supply to the leg and foot is commonly restricted in diabetics and is sometimes accompanied by intermittent claudication. The disaster of gangrene and amputation can be delayed or averted by simple, systematic hygienic activities carried out by the patient and by his health attendants. Certain diabetic populations (e.g., in Japan and Hong Kong) are remarkably free of peripheral vascular disease.

6.4.6 Other complications

Cerebrovascular disease, mainly thrombotic, resulting in hemiplegic stroke and lesser impairments of brain function also occurs more commonly in the diabetic. Coexisting hypertension is a contributory factor and should be adequately treated. The alimentary, vesical, sexual, and cardiovascular effects of autonomic neuropathy present with a diversity of symptoms. The adverse effects of poorly controlled maternal diabetes on fetal outcome is referred to elsewhere; it provides clear evidence of the advantage to be obtained from the improved control of a “diabetic complication”. The skin lesions associated with diabetes may arise from metabolic or microvascular abnormalities. Necrobiosis lipoidica diabeticorum is rare. Denervation, dryness, and cracking of the skin of the feet increase vulnerability to infection.

7. HEALTH SERVICES FOR THE DIABETIC

The major goals in diabetic health care include: rapid identification of new cases; access to adequate therapy; early diagnosis and efficient therapeutic control to relieve symptoms and help prevent complications; prevention of social discrimination and promotion of social adaptation; rehabilitation for those suffering from handicaps secondary to diabetes; prevention of the disease.

7.1 Primary health care

Primary health care is of first importance to the diabetic. The International Conference on Primary Health Care, held in Alma-Ata,
USSR, in September 1978, laid major emphasis on preventive, promotive, diagnostic, curative and rehabilitative aspects of health (49). All health-directed efforts should emerge from within the community and be directed at the community. Enlightened and motivated individuals within the community should be the first-contact health care personnel. Primary health care should be central in the structure of a country’s health system (50, 51).

The health care of the diabetic forms an excellent example of a chronic disease where primary health care must play a key role. The personnel involved at local and referral levels are physicians, nurses, midwives, auxiliaries, and community workers, who should ideally work as a team, responding to local needs.

7.1.1 Self care

The importance of self care cannot be overstressed. Much hinges on the health education of the patient. The learning process should emphasize: (1) a basic knowledge of diabetes, including a knowledge of its common acute and chronic complications and their possible prevention, and the names of people from whom help can be obtained and the circumstances in which they should be called upon; (2) a few skills, such as urine testing, recording results of tests, and, where necessary, injection techniques; and (3) the right attitude to the illness. Health education must be constantly reinforced each time the patient meets the health care team, and the attainment of adequate knowledge and skill should be continually assessed.

7.1.2 Home as a health unit

The health education of the family is similarly important and should ensure: (1) the development of proper attitudes towards the patient and his disease, including the realization that diabetes is neither infectious nor contagious and is not transmitted through sexual contact; (2) a good knowledge of the management plan and of how to help compliance, including diet; (3) regular self-monitoring (urine and/or blood tests) by the patient; (4) the recognition of symptoms of hypoglycaemia and knowledge of corrective measures; and (5) the recognition of other potentially dangerous situations (e.g., infections) and where to go for advice.
7.1.3 *The community health worker*

After a period of training, community health workers have a valuable part to play in the health care team. Their training should enable them to detect new cases, test urine for glucose, ascertain specific problems, give advice, and know when and where to seek advice themselves. They should also be able to give prescribed follow-up care and provide accurate information to the patient and his family relevant to the patient's needs.

7.1.4 *Primary health centre*

The primary health centre should be staffed by a physician, a nurse, and some health auxiliaries. In addition to its health functions, it serves as an educational institution for both staff and patients, as a centre for the dissemination of printed information such as diet sheets, and as the place where patient records are kept.

7.2 *Diabetes care at the secondary level*

Secondary-level help for the diabetic is provided by a general physician trained in diabetes, assisted by nurses, a dietitian, a social worker, and a physical therapist. There should be access to inpatient facilities and day-care centres, and the staff of these places can contribute to the health education of the patient. Genetic counselling should be available. Investigative facilities should include:

1. routine radiography (chest X-rays etc.);
2. laboratories for bacteriological tests, haematological tests (e.g., haemoglobin, white blood cell count, and erythrocyte sedimentation rate), and biochemical tests (determination of blood glucose, electrolytes, and blood urea);
3. other special investigations such as electrocardiography.

In such units patients referred from primary health centres can undergo brief periods of more specialized care.

7.3 *Diabetes care at the tertiary level: specialized services*

Clinical units for the further investigation and treatment of diabetes should exist at the tertiary level. Staff will include experienced physicians, nurses with special training and experience in diabetic care, skilled nutritionists, and social workers and
therapists trained in rehabilitation. Special expertise in genetic
counselling in the conduct of diabetic pregnancy and in the
evaluation and treatment of retinopathy should be available.
Specialized renal units and arterial and orthopaedic surgical services
should also be found here. Research should be encouraged in these
centres.

7.4 The diabetic outpatient clinic

In both developed and developing countries there is a trend
toward the development of diabetes clinics. Some clinics assume
responsibility for the comprehensive health care of the patient while
others restrict their activities to the care of diabetes alone. Many
clinics occupy an intermediate position.

7.4.1 Advantages

Clinics may provide:
(1) skilled educational programmes for patients, their families,
and for health care workers who serve in other elements of the health
care system;
(2) consultative and specialized services to patients and
physicians concerning complex aspects of care such as treatment of
labile diabetes, difficult complications, and photocoagulation
(52);
(3) great expertise together with economies of scale because they
usually serve large numbers of patients;
(4) a base for certain types of clinical and epidemiological
research.

7.4.2 Disadvantages

These may include:
(1) removal of the patient from the care of the primary health
care team;
(2) non-availability of clinic or staff in diabetic emergencies
(though this can be met by special arrangements);
(3) discontinuities in patient-staff relationships;
(4) inadequate staffing with possible loss of individual care.

Despite its disadvantages, the diabetes clinic is uniquely placed to
bridge the gap between the diabetic in his home environment and the
unfamiliar environment of the hospital.
7.5 Major requirements of diabetics

There is a great need to define (and continuously review) the major requirements of the diabetic and to incorporate them, with flexibility, into the many existing systems of health care delivery. Some basic needs are as follows.

1. Access to insulin and the means of administering it to the insulin-dependent diabetic, who will die without it. Economic factors should not stand between the diabetic and this treatment.

2. The means of understanding the basic mechanisms of the disease and the various forms of treatment.

3. Relevant and locally appropriate nutritional advice and access to the foodstuffs recommended.


8. THE DIABETIC IN SOCIETY

Diabetes imposes financial and social burdens on the individual and the family. A stigma still surrounds the disease and may adversely affect acceptance in society. This will be influenced by the level of socioeconomic development and by the traditional and cultural backgrounds of different countries.

The diabetic often meets with discrimination or difficulty in matters affecting his way of life, his employment and career prospects, life insurance, car-driving, travel, and sport. Even the problems of eating away from home may create difficulties.

Ease of access to medical facilities, aid towards the cost of treatment, and the maintenance of good diabetic control will help to prevent complications and prevent loss of productivity. They are clearly features of government concern in respect of costs and benefits to the community.

8.1 Employment

Diabetics should not be discriminated against in employment or career prospects, provided the job is not one in which the insulin-dependent diabetic could endanger his own safety or that of others. Discrimination solely on the grounds of diabetes is unwarranted and should be actively resisted. Employment should depend upon ability
and qualification. In some countries, legislation protects the employment rights of the diabetic. Diabetics may themselves contribute to continued discrimination if their disease is poorly regulated, because this may lead to unpredictable behavioural patterns (53).

Although medical confidentiality is desirable, diabetics should disclose their condition to their employers and immediate working colleagues in order to ensure that they can take intelligent remedial action if the need arises and to maintain confidence in the working relationship.

Industrial medical and nursing staff should learn about diabetes so that they are able to protect the diabetic in the working environment.

8.2 Insurance and sickness benefit

Life assurance is generally available for well-controlled adult diabetics, but on payment of additional premiums. Improved health care should reduce morbidity and mortality rates for diabetics, and these should be reflected in a reduction in the excess premiums demanded.

Employed persons often qualify automatically for general health cover through company or state schemes. However, in some countries such cover is denied to diabetics and this is unjustifiable.

8.3 Other social problems

Travel, sport, and car-driving are additional areas in which the diabetic may encounter difficulty. Insulin-taking diabetics should not drive public service vehicles or heavy goods vehicles. Private car licences should be issued only when diabetic control is good and the level of understanding of diabetes management by the patient is adequate.

In case of emergencies, diabetics should always carry an identification card or bracelet.

8.4 Children with diabetes

There is no reason why diabetic children should not attend normal schools. The teaching staff must be informed and instructed in the essentials of diabetic management. The importance of camps
and holidays for diabetic children as an educational and support service cannot be stressed too strongly. All diabetic children should have the opportunity to attend such camps at least twice, the first visit being arranged soon after diagnosis. The social isolation of diabetes is a great burden for the young diabetic. To meet children with the same problems can cause an immense improvement in the child's acceptance of his condition and his capacity to make friends again.

Accommodation in special hostels for diabetic children when home conditions are unsatisfactory is occasionally unavoidable, but such separation from home life should be as brief as possible.

Adolescence is a period of new social adjustments, which may create special problems for the diabetic and his family, and will require sympathetic counselling from experienced advisers. To assist adaptation, treatment should be planned around the diabetic's life, not the other way around.

8.5 The elderly

The elderly diabetic is often neglected, especially when family structure is weak. Many suffer from chronic ill-health and are housebound. The provision of health care and social services in the home are of great importance for this group.

Those unable to continue living in their own homes may have to move into sheltered accommodation. Wardens and staff of institutions should learn about diabetes and its care.

The reduced mobility of old people and their dependence on simple routines make the imposition of the diabetes regimen particularly stressful. Many fail to comply with medical advice and they require sympathetic handling if effective therapy is to be maintained.

Simple measures, such as care of the feet, regular washing, and oral and perineal hygiene, may prevent damaging infections leading to serious disabilities. Adequate facilities, instruction, and supervision are necessary.

8.6 Nutrition

In diabetes, proper nutrition is the foundation of good metabolic control. Dietary advice should be based on local customs and availability of foodstuffs. Food taboos and misconceptions can interfere
with the achievement of adequate control but may be difficult to circumvent. Advice from people familiar to the diabetic is often more effective than professional instruction. Special food products made for diabetics are expensive and may not be necessary.

8.7 Drugs and equipment

The economic burden of being an insulin-dependent diabetic may seriously interfere with treatment. The free provision of insulin, syringes, and needles is highly desirable and should be high on the list of social priorities. In some countries tax concessions are granted to help meet the cost of such items.

9. EDUCATION

Education is the foundation of good therapy and of preventive medicine. Good therapy is aimed at both the short- and the long-term good health of the diabetic and has a directly related benefit in terms of hospital bed occupancy and health economics (54–56).

Health education is crucial if we are to improve the quality of life of the patient and enable him, to a large extent, to control his own destiny and to achieve a high level of independence. It is, moreover, an excellent investment and should be a standard part of total diabetic management. Its goals include the motivation of the patient to take better care of himself by developing the right attitude to the disease, the prevention of socioeconomic problems, and the alerting of the community, especially those persons most at risk, to the possibility of prevention. At present, diabetes is often not perceived by the diabetic or the community or the health services as a public health problem.

Evaluation of health education should be an integral part of health planning.

There are six interlinked target groups, forming two main divisions: the first concerned with the practical management of the diabetic and the high-risk individual, the second with overall awareness of the problem with particular emphasis on the economic and preventive aspects.
9.1 Patients

All those involved in patient education must take into account the socioeconomic, emotional, and cultural background of the individual patient, as well as his learning capacity.

Education needs to be directed to specific groups according to age and treatment. Insulin-dependent diabetics will require more detailed information.

Information must be repeated frequently to dispel misconceptions. It is important to emphasize the individual nature of the disease and its treatment and progression.

Once the patient and his family have been assured that his lifestyle need not be severely restricted he will more easily accept the discipline that diabetes imposes.

The patient taking insulin or oral hypoglycaemic agents needs to be taught:

1. the facts about diabetes,
2. the skills of self-management,
3. how to deal with changes in lifestyle,
4. how to cope with emergencies.

For the patient requiring dietary therapy only, particularly the obese, the emphasis will be on nutrition and prevention.

Those involved in educating the patient include: the physician, as team leader, allied health personnel, e.g., nurses, dietitians, primary health workers, and auxiliaries, family members, and carefully selected diabetic patients.

For the newly diagnosed diabetic who has no previous experience of the disease, the diagnosis is a door into an unknown world of complex medical terminology, the meaning of which is not clear. Education must be simple and relevant, must be given in the patient's own language, and should not attempt to cover too much too quickly.
The use of simple pictorial images should be encouraged in addition to straightforward literature. Teaching should be primarily on an individual basis, but much can be achieved through group teaching and also in the home, with the involvement of relatives. Education starts on diagnosis, and must be continuous.

Members of the community at high risk of developing diabetes, e.g., those with impaired glucose tolerance, require special attention, with particular emphasis on preventive measures.

9.2 The family

Family members need to be given a general understanding of the disease and its implications (57), including possible psychosocial problems and practical day-to-day management—e.g., the importance of diet and the care of the patient during illness and in emergency situations such as hypoglycaemia and ketoacidotic coma.

Instruction may be given individually or in groups by the physician, allied health personnel, and/or selected experienced patients. It should be supported by concise explanations in writing.

9.3 Health care personnel

The education of health care personnel should cover not only the practical needs of the patient but also the public health and economic implications of diabetes. It should emphasize the importance of reducing to a minimum the patient's dependence on the doctor.

There is a primary need for health care personnel to receive adequate training in educational methods and positive practical experience in teaching both during and after their training.

Health care personnel need to have a basic knowledge of the scientific background of diabetes, adapted to their professional level, and a clear understanding of the practical management of diabetes and its socioeconomic and psychological problems.

Those who may be involved in teaching health care personnel include: specially trained teachers, appropriate specialists, allied health personnel, and representatives of the government and of nongovernmental organizations.

Teaching should be effected during in-service training in hospitals and in the community, and through specially organized courses.
Education about diabetes must be incorporated into the basic training programmes for each cadre and continued at all levels.

9.4 The community

Better understanding of diabetes by the community will directly benefit the patient by improving his social acceptability and may also affect local and national government policy regarding the provision of health care services.

The community needs to be made aware of diabetes as a public health problem, particular emphasis being placed on obesity and preventive measures.

The use of mass media (press, radio, and television) is effective, but information should be provided on a continuous basis and according to well-thought-out guidelines by health care personnel in their interaction with national and local groups and community authorities. Local public meetings are also useful. Teaching can be done by health care personnel, representatives of diabetic associations, local community groups, and diabetics themselves.

9.5 Policy planners

If policy planners at national and local levels fully understood the socioeconomic implications of the disease and the resulting benefit of diabetes education they would be motivated to improve and extend the health services to include diabetes care.

It is therefore imperative that policy planners realize that diabetes, both of itself and through associated abnormalities, is a major and increasing public health problem. The long-term dividends from investment in preventive and promotive health care and health education need emphasis because they are less well recognized than are the short-term benefits of curative medicine.

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.

9.6 Resources

Learning is a fundamental part of diabetic management, and the resources needed for effective education must be made available.
These include trained personnel, literature, and equipment, as well as adequate facilities. Transport to and from the facilities must not be overlooked.

Certain groups of patients have special requirements. These include the elderly, the blind, the very young (and their parents), and the pregnant.

9.7 The role of the various organizations

There are four main groups of organizations that may be involved in diabetes education:
— patient-orientated associations, both local and national,
— medically orientated associations, both local and national,
— diabetes clinics and education centres,
— regional and international organizations.

It is essential that these groups work together and interact with each other. Being highly motivated, organizations can concentrate their resources and energies on areas of special concern to those with diabetes, such as the social acceptance of diabetics, welfare entitlement, the adequate distribution of essential drugs and equipment, the influencing of policy planning at governmental and local authority levels, the funding of research in all its aspects, and the protection of the rights of the individual.

10. RESEARCH AND FUTURE DEVELOPMENTS

The continuing health of the diabetic depends on both effective health care and related research. There is no natural division between basic research, clinical research, operational research, research in health economics, and population studies, but coordination between them is needed to protect the health of the diabetic. This needs effort and resources at local, national, and international levels.

There is a major need for: (1) community-based programmes with special opportunities in the developing nations, and (2) studies of the most cost-effective ways of delivering health care, including preventive services, in different socioeconomic environments.

The needs of both the developing and the developed world must be continuously reviewed. Diabetes research, even if carried out in developed countries, is usually applicable in developing countries also, if only in part.
This section will not detail individual advances but rather highlight areas in both health services and health sciences where more knowledge would be desirable or where important developments are occurring.

10.1 Population studies

10.1.1 Prevalence data

Much more information is required on the prevalence and incidence of the different forms of diabetes in developing countries and on the local associated factors. Accurate information is vital for the rational planning of health care delivery.

10.1.2 Mortality

Accurate mortality information is required in different countries, including age-specific information on diabetes both as an underlying and a contributory cause of death. Information on mortality from the acute metabolic complications is also needed for health care planning.

10.1.3 Cohort studies

Cohort studies to follow the course of diabetes and its complications in different societies should be initiated where practicable. Such information on the long-term problems of diabetes is scanty in general and totally lacking in most developing countries.

10.2 Studies on the prevention of diabetes

Prevention is the long-term goal of all those interested in diabetes. It has been brought measurably closer by recent research. To achieve the goal, more knowledge of the causes of the different forms of diabetes is needed.

10.2.1 Insulin-dependent diabetes

Investigation of the HLA system has shown that certain individuals have an increased risk of developing diabetes (21). Recently the properdin system has been used as a marker (24). These genetic characteristics of susceptibility need further definition so that
those at risk of developing diabetes can be identified. The factors responsible for precipitating diabetes in such individuals must be defined so that appropriate preventive measures can be taken. Possibilities include viruses (25), environmental factors, such as specific toxins, and immune phenomena (23). Diabetes secondary to malnutrition and/or pancreatic damage also needs further investigation.

10.2.2 Non-insulin-dependent diabetes

Obesity has long been recognized as one of the most important factors associated with non-insulin-dependent diabetes (38). Despite much work, further efforts are required to establish the cause of obesity, to find effective methods (physical, psychological, and social) for the treatment of obesity, and to prevent obesity. More work is also needed to see whether markers such as low insulin response to glucose challenge (22) and chlorpropamide-alcohol flushing (39) provide useful information either in selecting individuals at risk or as a guide to etiology or prevention.

10.2.3 The role of the community

The community can act as an effective preventive agency, particularly when the cause of a disease is known and reversible. In diabetes the main known preventable cause is obesity. Severe diabetes may also occur in people with a history of undernutrition. Possible ways in which community action and community education could correct these nutritional defects should be investigated.

10.3 Education

Education is a cornerstone of diabetic therapy and vital to the integration of the diabetic into society. Little effort has been expended to date on finding the best means of assisting learning in diabetics, whether individually or collectively, or of informing the community about diabetes. Developments are needed urgently in the following areas:
- methods of communicating ideas and information to individual diabetics,
- methods of group learning for diabetics and their families,
- means of improving public awareness,
- the use of diabetics themselves to assist the learning process, and
- the evaluation of learning materials.
10.4 Methods of treatment and assessment of diabetes

The suggestion that good control of blood glucose may prevent or retard the development of complications of diabetes (40, 60) has led to a more critical examination of the efficacy of therapy with diet, hypoglycaemic agents, and insulin.

10.4.1 Diet

Research into the effects of different diets on the metabolic status of the diabetic is in progress. The use of low-carbohydrate diets is being questioned and re-examined. Lowering the ratio of saturated to unsaturated fatty acids in the diet has been suggested. The influence of these dietary changes (and others, such as protein, and indeed energy, malnutrition) on the development of the long-term complications of diabetes remain unresolved, and adequate studies are badly needed in all these areas.

10.4.2 Dietary fibre

It has been suggested that deficiency of fibre in the diet may lead to non-insulin-dependent diabetes in susceptible individuals (61, 62). Conversely, increasing the dietary fibre content may improve blood glucose control in established diabetes. More specific are the data showing that the addition to the diet of certain viscous components of fibre ( guar, pectin) improves glycaemic control and decreases the requirements for insulin and oral antidiabetic agents (63). Field trials are urgently needed to test all these important hypotheses.

10.4.3 Insulin therapy

Many aspects of insulin therapy are changing as means are sought to improve glycaemic control of the diabetic. These include alterations in the conventional use of insulin as well as the development of entirely new means of insulin delivery.

Education. The Expert Committee felt that education of the diabetic and of those who deliver health care in the logical use of insulin and diet could effect widespread improvements in glycaemic control. Resources should be made available for this purpose.

Safety of insulin. No information is available on the efficacy and safety of different insulin regimens in countries where communi-
cations are difficult, access to health care facilities limited, and supplies of insulin intermittent. In such situations it is probably unwise to aim for "good" control. A field investigation is required to ascertain the problems precisely and devise a means of counteracting them.

Alternative methods of insulin delivery. Subcutaneous injection is still the standard method of insulin delivery, but possible alternatives are being investigated. Improved glycaemic and metabolic control has been reported with continuous subcutaneous insulin infusion (64) for periods of up to 4 months and with continuous intravenous infusion. Such systems are unlikely to be used widely but could be useful in patients with rapid development of microangiopathy or in pregnancy. Delivery of insulin by compressed air which obviates the need for injection has also been advocated.

The artificial pancreas. The long-term goal for many research workers has been the development of a system whereby insulin administration is controlled by the prevailing blood glucose level in such a way that normoglycaemia is maintained. Such systems—loosely called artificial pancreases—now exist (65). Not only do they use blood, however, but they are large, extracorporeal, expensive, and suitable only for short-term investigative studies. They have, as yet, little clinical value. Work is needed to develop much smaller, implantable, reliable systems that measure glucose without consuming blood. An intermediate stage could involve the development of portable feedback systems using extracorporeal glucose measurement.

Alternative routes for insulin delivery. Research into the administration of insulin by mouth, in the form of liposomes or other protected particles, has been relatively unsuccessful to date. The advantages of oral insulin administration are many, and research in this area should continue.

Pancreas transplants. A new boost to pancreas transplant research was given by the discovery that in animals this could lead to regression of long-term changes in blood capillaries. Whole-pancreas transplants have been uniformly unsuccessful in man (66), although more encouraging results have been obtained with transplants of pieces of pancreas (67). The possible benefits must, however, be weighed against the effects on the patient of the long-term treatment required to prevent rejection of the graft. This problem may be
circumvented by the implanting of pancreatic islets inside capillaries made from inert materials.

10.4.4 Oral antidiabetic agents

Although there has been much criticism of both sulfonylurea and biguanides (see section 5), it is of major advantage to have oral antidiabetic therapy available for use in less well controlled non-insulin-dependent diabetics. More emphasis should be placed on finding drugs that increase the insulin sensitivity of peripheral insulin receptors and that may be used to treat obesity.

10.4.5 Traditional methods

Little attention has been paid to the use of traditional medicines and methods in the treatment of diabetes (68). In many societies use has been made of plants and plant extracts and of methods such as yoga (69). A methodical investigation of these remedies is required to determine their possible role in the therapy of diabetes.

10.5 Improved assessment of treatment

If treatment of diabetes is to be improved then more accurate methods of assessment are required than those currently used—i.e., semi-quantitative estimation of urine glucose and acetone content, intermittent laboratory measurement of blood glucose levels. Some such methods are now available.

10.5.1 Glycosylated proteins

It has recently been established that a small fraction of circulating red cell haemoglobin exists in the glycosylated form. The amount of this fraction depends on the levels of blood glucose existing during the life-span of the red blood cell. Measurement of the percentage of haemoglobin present in the glycosylated form gives an indication of the integrated blood glucose level over a period of several weeks (70). This is proving useful as an objective means of assessing control. It is probable that many other body proteins are similarly glycosylated. Investigation of the utility of measuring these proteins in different populations is required, and much simpler measurement methods are urgently needed so that this type of assessment can be used in primary health care.
10.5.2 Self-monitoring of blood glucose

Recent reports have appeared that glycaemic control can be improved if diabetics monitor their own blood glucose levels several times per day on one or two days per week (77). Glucose test strips are used with battery-operated portable meters. Self-monitoring is unlikely to have wide application in most countries at present but could be of major use in special situations (pregnancy, particularly unstable diabetes). The meters themselves would be useful in primary health care, and the practicability of such use requires investigation.

10.6 Prevention and treatment of diabetic complications

10.6.1 Prevention

Information is urgently needed to confirm that the development of microangiopathic complications can be prevented by good therapeutic control of diabetes. For example, recent work has shown that certain diabetics are more likely than others to develop retinopathy (43) so that a high-risk group could be examined. Trials of dietary therapy to prevent the early appearance of cardiovascular disease are also needed.

10.6.2 Treatment

So long as prevention is not achieved, improved methods of treatment must be developed. The treatment of retinopathy has been revolutionized in the last decade, while the results of renal transplantation and dialysis in diabetics have improved greatly in the same period. However, few diabetics are able to benefit from such therapy, and cheaper methods are desperately needed, together with greater availability of existing methods.

10.7 Insulin production and distribution

10.7.1 Supply

The possibility of a future shortage of insulin has recently caused considerable disquiet. This concern arose from the move away from oral hypoglycaemic agents following the publication of the results of the University Group Diabetes Program (32), and from the reali-
zation that there was an increasing prevalence of diabetes in developing countries. However, it is a moot point whether such a shortage will ever develop.

10.7.2 Estimates of available resources and needs

The only large-scale formal study of supply and demand so far published was that by the National Diabetic Advisory Board of the US Department of Health, Education and Welfare (72). It was estimated that insulin supplies in the USA would be adequate only for the next 20 years. Others have advised that insulin supplies will meet demands for the foreseeable future and that, with the use of all available pancreases, supply will easily exceed demand. Distribution is more of a problem than supply, and efforts must be made to improve distribution in, and to rationalize types of insulin supplied to, developing countries.

10.7.3 Bacterial synthesis of human insulin

It has recently been proved possible to effect the bacterial synthesis of human insulin using recombinant DNA (73). Supplies for human use should be available in the near future, and this will probably resolve any question that demands cannot be met.

10.8 Basic research

Basic research should not be ignored in the hunt for immediate improvements of worldwide health care for diabetics. Particular areas where further knowledge could lead to improvements in diabetic care include mechanisms of insulin secretion, mechanisms of insulin action and resistance, mechanisms of glucose homeostasis, and mechanisms of insulin-receptor interactions and their modification by drugs. Perhaps more urgent is the need to know the precise biochemical lesions that lead to the characteristic complications of diabetes.

11. CONCLUSIONS

1. Diabetes mellitus is a major public health problem known to affect more than 30 million people. In many it remains undiagnosed. It contributes significantly to premature death and prolonged ill-health.

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2. Diabetes is widespread throughout the world. The known prevalence of diabetes is rising sharply in the developing countries in which it has been studied.

3. The causes of diabetes are manifold and often unknown. In most cases it probably results from the interaction of environmental factors in genetically susceptible individuals. In some this susceptibility can be determined, thus opening the way to identification of high-risk individuals and the possibility of protection from the environmental factors.

4. Diabetes may be divided clinically into two major types: insulin-dependent and non-insulin-dependent. These clinical types differ in genetic background and environmental determinants. There is heterogeneity within clinical groups. Present methods of classification are unsatisfactory and need to be reviewed.

5. Obesity is a major association of non-insulin-dependent diabetes. Its nature and causes are poorly understood, its treatment unsatisfactory. Further research on the relationship of obesity to diabetes, on its causes, and on simple methods of treatment and prevention are all relevant to the problems of diabetes. The role of malnutrition also requires careful investigation.

6. The diagnosis of diabetes is ordinarily made on the basis of obvious signs and symptoms, confirmed by blood glucose measurement. The oral glucose tolerance test is not usually considered necessary, but it is nevertheless useful in some situations and has application to population studies and as an adjunct to screening. Epidemiological and other studies suggest that criteria for the oral glucose tolerance test were set too low in the past. New criteria, with a standardized glucose load, are suggested. They incorporate a new intermediate state of "impaired glucose tolerance", and subjects in this category usually require surveillance.

7. Diabetes is a major cause of disability through its complications of retinopathy, nephropathy, neuropathy, and large blood vessel disease. These complications may lead to blindness, kidney failure, coronary thrombosis, gangrene of the lower extremities, and sometimes amputation. Present evidence suggests that some of these complications may be lessened or prevented by improved metabolic control of the diabetic, as well as by general health measures. Major efforts should be directed towards achieving this.
8. Care for the diabetic varies considerably in quality and availability. The major health services for the diabetic should be provided at community level. The community itself should be actively involved in the health care and support system for the diabetic. Preventive, promotive, curative, educational and research activities should be carried out at the primary health care level.

9. The provision of basic equipment, insulin, and drugs for all diabetics in all countries should be given the highest priority, and economic barriers to treatment removed.

12. RECOMMENDATIONS

1. Health care for the diabetic should be incorporated into community-based health care systems with appropriate additional facilities available at all levels of care. Models should be carefully evaluated in respect of both health care and cost-effectiveness. Such experience might serve as a prototype for other chronic disorders.

2. The adequate and continued availability of insulin must be assured to diabetics everywhere by national guarantee.

3. The establishment of special centres in developing countries to promote and integrate care, learning, and research in diabetes is desirable. These centres would constitute the focal points in the national network of diabetes health care.

4. An organizational structure for educational activities aimed at the patient as well as at health care personnel should be established.

5. International standardization should be increased and directed towards: diagnostic tests for diabetes and revised criteria for diagnosis; a more rational classification of diabetes; identification, labelling, types, and strengths of insulin; and learning aids and materials for global use.

6. The concept of primary prevention should be vigorously explored with particular attention to high-risk people and to environmental factors including undernutrition and overnutrition.

7. Intensive efforts should be made to reduce the burden of complications and premature death by improving the quality of diabetic care and metabolic control. Special measures should include: better
education; improved treatment regimens and self-monitoring; and the provision, as regionally appropriate, of facilities for early diagnosis and treatment of diabetic eye disease.

8. Traditional methods of treatment of diabetes should be further investigated.

9. The establishment of national and local registries of diabetics should be encouraged to facilitate health care, research, and education.

10. The World Health Organization should make every effort to promote the implementation of these recommendations.

ACKNOWLEDGEMENT

The Committee acknowledged the special contribution to its deliberations by Dr B. Tomic, Consultant, Health Education Unit, Division of Family Health, World Health Organization, Geneva, Switzerland.

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Annex 1

CHEMICAL METHODS OF MEASURING SUBSTANCES IN BLOOD AND URINE

Measurement of glucose in blood

The o-toluidine method is frequently used for the measurement of blood glucose, with glucose oxidase methods as alternatives. Hexokinase measurement is generally used as a reference method, but it is likely that the glucose dehydrogenase method will shortly replace it. Although these are recommended, it should be noted that equivalent results may be obtained with the Somogyi-Nelson, the autoanalyser ferricyanide, and the autoanalyser neocuproine methods (1).

Whole blood or plasma can be used. Whole-blood values are approximately 15% lower than plasma values (except in anaemia). Note must also be taken of whether samples are capillary or venous. In normal subjects capillary values are on average 7% higher than venous values in specimens from fasting patients and 8% higher 2 hours after a glucose load.

The "bedside" estimation of blood glucose is now possible using various glucose oxidase methods, which may, however, give false values if the chemicals are not stored dry in airtight containers. The contact time of blood is critical with some versions of the glucose oxidase method. These methods are semi-quantitative but can be used with meters to give results with a coefficient of variation of less than 12% with careful use. The meters require a power supply, but battery-operated meters have now been marketed. With all strip tests and meters, careful attention must be paid to technique. The use of such methods has been validated under tropical field conditions (2).

Oral glucose tolerance tests

Formal dietary preparation is not recommended by most authorities unless the diet prescribes less than 125 g of carbohydrate per day. In such subjects at least 3 days' preparation is advisable during which the intake of carbohydrate is limited to 150 g per day.

The test should be performed after overnight fasting for 10-14 hours, although water is permitted. The first step is to take a
fasting blood sample, after which the patient is given 75 g of glucose in 250–350 ml water in 5–15 min. Special testing solutions are available for use instead of glucose. They consist of partial hydrolysates of corn starch and are less likely to cause nausea, but they are more expensive than glucose. Further blood samples are then taken 2 hours after administering the glucose, and some physicians also draw a one-hour sample. Smoking must not be allowed during the test. It should be borne in mind that many factors (including drugs) can affect glucose tolerance (3).

Measurement of glucose in urine

In insulin-dependent diabetics, urine testing before breakfast, lunch, and the evening meal and at bedtime are helpful. In stable patients, this can be done on two days per week, while fasting urine specimens are tested on the other days. In non-insulin-dependent patients, morning and evening testing is probably adequate, with once-a-day testing in well-controlled subjects. Some authorities advise that the first urine specimen of the day be discarded or tested in addition to a second specimen taken for testing 15–30 min later—so-called “double voiding”. If frequent testing is required, compliance is improved by the use of test strips.

Ketone bodies in urine

The tests commonly used measure acetone and aceto-acetate, not the major ketone body 3-hydroxybutyrate.

Regular testing for ketone bodies is necessary only in “unstable” or “brittle” diabetics. Otherwise it should be carried out in insulin-dependent diabetics when ill or in any diabetic showing persistent 2% glycosuria.

Albumin in urine

Urine should be screened regularly (once or twice per year) for the presence of albumin, using either a strip test or sulfosalicylic acid. Failing the availability of such reagents, the urine may simply be boiled.

### Annex 2

**SUMMARY OF REPORTS OF HIGH AND LOW RATES OF DIABETES**

<table>
<thead>
<tr>
<th>Low rates</th>
<th>High rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nineteenth-century sugar-cane cutters of West Indies</td>
<td>Many tribes of American Indians</td>
</tr>
<tr>
<td>Poor of London and Berlin before 1900</td>
<td>Rich Indian men of Bengal</td>
</tr>
<tr>
<td>Eskimos</td>
<td>Many populations of immigrants from India living in</td>
</tr>
<tr>
<td>North American Indians before 1940 and in some present tribes</td>
<td>various parts of the world</td>
</tr>
<tr>
<td>Jewish Yemenites and Kurds</td>
<td>Malta</td>
</tr>
<tr>
<td>Micronesians, Melanesians and Polynesians</td>
<td>Uruguayans of Montevideo</td>
</tr>
<tr>
<td>Algeria</td>
<td>Many groups of Polynesians and Micronesians</td>
</tr>
<tr>
<td>Morocco</td>
<td>Black women in USA</td>
</tr>
<tr>
<td>Rural blacks of Africa south of the Sahara</td>
<td>Malays of Cape Town</td>
</tr>
<tr>
<td>Poor whites, blacks, and Indians of Central America</td>
<td>Many groups of Jews, including Sephardic Jews of</td>
</tr>
<tr>
<td>Blkack of rural USA prior to 1924</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>Belize</td>
<td>Welsh</td>
</tr>
<tr>
<td>Bahamas</td>
<td>Luxembourg, Belgium, and Holland</td>
</tr>
<tr>
<td>Grenada</td>
<td>Urbanized Australian Aborigines</td>
</tr>
<tr>
<td>Haiti, Jamaica, British Guiana (Guyana), and Cuba before 1922</td>
<td>Mabuiag Islanders of Torres Straits</td>
</tr>
<tr>
<td>Rural poor of India</td>
<td>Chinese-American men</td>
</tr>
<tr>
<td>Brokass of the Sahara</td>
<td>High frequency “legendary” in certain groups, including</td>
</tr>
<tr>
<td>Chinese and Malays of Singapore</td>
<td>sumo wrestlers of Japan and royal families of Polynesia</td>
</tr>
<tr>
<td>Philippines</td>
<td>and Zululand</td>
</tr>
<tr>
<td>Thailand</td>
<td>Mauritius</td>
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<td>Burma</td>
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<td>Papua New Guinea</td>
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<td>Rural Fiji</td>
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<td>Bangladesh</td>
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<tr>
<td>Yemen</td>
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<tr>
<td>Jordan</td>
<td></td>
</tr>
<tr>
<td>Affluent societies during war-related famines</td>
<td></td>
</tr>
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</table>

### Annex 3. DIABETES MORTALITY BY COUNTRY OR AREA

**Mortality rate by age per 100,000**

<table>
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<tr>
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<th>All ages</th>
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<th>45–54</th>
<th>55–64</th>
<th>65–74</th>
<th>75+</th>
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<td></td>
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<td>28.1</td>
<td>146.4</td>
<td>461.9</td>
<td>1,243.9</td>
</tr>
<tr>
<td>Netherlands, 1976</td>
<td>14.4</td>
<td>1.7</td>
<td>7.2</td>
<td>30.2</td>
<td>54.6</td>
<td>165.3</td>
</tr>
<tr>
<td>Northern Ireland, 1975</td>
<td>6.3</td>
<td>0.6</td>
<td>2.4</td>
<td>11.0</td>
<td>30.5</td>
<td>67.9</td>
</tr>
<tr>
<td>Norway, 1976</td>
<td>7.2</td>
<td>2.0</td>
<td>3.6</td>
<td>6.8</td>
<td>23.3</td>
<td>70.3</td>
</tr>
<tr>
<td>Romania, 1976</td>
<td>3.6</td>
<td>1.1</td>
<td>3.1</td>
<td>9.7</td>
<td>20.2</td>
<td>23.9</td>
</tr>
<tr>
<td>Scotland, 1976</td>
<td>12.2</td>
<td>2.0</td>
<td>4.4</td>
<td>17.5</td>
<td>45.8</td>
<td>114.2</td>
</tr>
<tr>
<td>Sweden, 1976</td>
<td>19.2</td>
<td>6.1</td>
<td>8.2</td>
<td>17.6</td>
<td>53.8</td>
<td>214.4</td>
</tr>
<tr>
<td>Switzerland, 1976</td>
<td>17.6</td>
<td>2.4</td>
<td>3.7</td>
<td>15.2</td>
<td>73.3</td>
<td>190.0</td>
</tr>
</tbody>
</table>

**Oceania**

| Australia, 1975 | 12.7     | 2.6   | 5.8   | 23.9  | 70.4  | 175.8|
| New Zealand, 1975 | 15.3     | 2.8   | 13.0  | 32.8  | 78.3  | 204.1|


Traditional methods tend to underestimate the diabetes mortality rates. This is mainly because atherosclerosis caused by diabetes is assigned to atherosclerosis alone as the underlying cause of death. Only 10-20% of the death certificates of diabetics assign diabetes as the underlying cause of death, even though mortality rates are excessive by a factor of 2-3 in diabetics.

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Annex 4

SOME COUNTRIES AND AREAS IN WHICH MALNUTRITION-RELATED DIABETES HAS BEEN OBSERVED

<table>
<thead>
<tr>
<th>Pancreatic fibrosis-calcification syndrome</th>
<th>“Jamaica” diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Brunei</td>
</tr>
<tr>
<td>Ghana</td>
<td>Fiji</td>
</tr>
<tr>
<td>India</td>
<td>Ghana</td>
</tr>
<tr>
<td>Indonesia</td>
<td>India</td>
</tr>
<tr>
<td>Jamaica</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Madagascar</td>
<td>Jamaica</td>
</tr>
<tr>
<td>Malawi</td>
<td>Kenya</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Malawi</td>
</tr>
<tr>
<td>Singapore</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Thailand</td>
<td>Pakistan</td>
</tr>
<tr>
<td>Uganda</td>
<td>Papua New Guinea</td>
</tr>
<tr>
<td>Zaire</td>
<td>South Africa</td>
</tr>
<tr>
<td>Zambia</td>
<td>Uganda</td>
</tr>
<tr>
<td></td>
<td>United Republic of Tanzania</td>
</tr>
<tr>
<td></td>
<td>Zaire</td>
</tr>
</tbody>
</table>


The syndrome in the first column is that of youth-onset diabetes attended by fibrosis and calcification of the pancreas. These patients typically have a history of severe undernutrition and often of high levels of cassava (tapioca) consumption.

Several populations have been described in which Jamaica diabetes is common but pancreatic calcification rare or absent.
Annex 5

COSTS OF DIABETES

1. Mortality excessive by a factor of 2–3.
3. Blindness 10 times more common than in the general population.
4. Gangrene and amputation about 20 times more common than in the general population.
5. Second leading cause of fatal kidney disease.
6. Other chronic disabilities (e.g., neuropathy, infections, and sexual dysfunction).
7. As compared to age-matched elements of the general population, hospitalization increased about twofold.
8. Direct costs to medical care system include professional time, drugs, and rehabilitative services (e.g., the diabetic blind), other services and materials.
9. Other costs to society include costs of medical services, pensions, and loss in productivity and earnings due to both disability and premature death.
10. Lifetime risk of diabetes 2–12% (variation by country).
Annex 6

MAIN TYPES OF INSULIN AVAILABLE

<table>
<thead>
<tr>
<th>Type</th>
<th>Species of origin</th>
<th>Available in highly purified form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid action</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular, soluble, crystalline</td>
<td>beef</td>
<td>•</td>
</tr>
<tr>
<td>Neutral</td>
<td>beef</td>
<td>•</td>
</tr>
<tr>
<td>Pig</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate action</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin zinc suspension (amorphous) (semilente)</td>
<td>pig</td>
<td>•</td>
</tr>
<tr>
<td>Insulin zinc suspension (crystalline plus amorphous) (lente)</td>
<td>pig (beef/pig)</td>
<td>•</td>
</tr>
<tr>
<td>Isophane</td>
<td>beef/pig</td>
<td>•</td>
</tr>
<tr>
<td>Pig</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td><strong>Long action</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protamine zinc insulin</td>
<td>beef</td>
<td>•</td>
</tr>
<tr>
<td>Insulin zinc suspension (crystalline) (ultraente)</td>
<td>beef (pig)</td>
<td>•</td>
</tr>
</tbody>
</table>

No precise specifications have yet been agreed for purity. The description "highly purified" thus covers several levels of purity, including "single peak" insulins as well as those of higher purity.

Insulins are available at strengths of 10, 20, 40, 80, and 100 International Units per milliliter. If required they may also be supplied at strengths of 320 and 500 IU/ml.
Annex 7

BASIC EQUIPMENT FOR SELF-CARE BY DIABETICS

Items required for self-management by:

Non-insulin-dependent diabetics

1. Urine testing materials for:
   (a) sugar (glucose);
   (b) ketone bodies.

2. Book and pencil (or chart) for recording results of tests and body weight.

3. When applicable, oral hypoglycaemic agents.

4. Sugar lumps or other readily absorbed carbohydrate.

Insulin-dependent diabetes

1. Urine testing materials as above.

2. Book and pencil (or chart) 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 in primary health care post:

1. All the items required for self-management, as above.

2. Weighing machine.


4. Glucose for intravenous use—glucagon if available.

5. Simple printed educational materials.

6. Place for storing patient records.
**Annex 8**

**LARGE-VESSSEL DISEASE IN POOLED DATA FROM MULTINATIONAL STUDY**

<table>
<thead>
<tr>
<th></th>
<th>Men (3301)</th>
<th>Women (3394)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— &quot;coronary probable&quot;</td>
<td>4.7</td>
<td>4.5</td>
</tr>
<tr>
<td>— &quot;coronary possible&quot;</td>
<td>13.2</td>
<td>18.4</td>
</tr>
<tr>
<td>Possible infarction</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>7.4</td>
<td>12.4</td>
</tr>
<tr>
<td>Amputation (Ischaemia)</td>
<td>2.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Claudication</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Stroke (hemiplegic)</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Total with 1 or more of above</td>
<td>39.5</td>
<td>37.4</td>
</tr>
</tbody>
</table>

Prevalence of various indices of arterial disease in 6696 diabetics included in the WHO multinational study of vascular disease in diabetics (number of subjects shown in parentheses). ECG records were Minnesota coded (ECG "coronary probable" = 1.1.1.2. and 7.1, "coronary possible" = 1.3.4.1.4.2.4.3.5.1.5.2. and 5.3), and symptoms were ascertained by the use of the WHO questionnaire.

Annex 9

SMALL-VESEL DISEASE IN VARIOUS GROUPS
OF DIABETICS

<table>
<thead>
<tr>
<th>Code No.</th>
<th>Eye Men %</th>
<th>Eye Women %</th>
<th>Kidney Men %</th>
<th>Kidney Women %</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 London</td>
<td>7.0</td>
<td>6.2</td>
<td>3.5</td>
<td>4.4</td>
</tr>
<tr>
<td>03 Switzerland</td>
<td>10.0</td>
<td>7.5</td>
<td>12.3</td>
<td>11.5</td>
</tr>
<tr>
<td>04 Brussels</td>
<td>6.7</td>
<td>6.3</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>05 Moscow</td>
<td>5.6</td>
<td>4.9</td>
<td>14.4</td>
<td>12.1</td>
</tr>
<tr>
<td>06 Warsaw</td>
<td>3.2</td>
<td>3.7</td>
<td>13.4</td>
<td>12.5</td>
</tr>
<tr>
<td>07 Berlin (GDR)</td>
<td>7.6</td>
<td>4.9</td>
<td>12.9</td>
<td>9.2</td>
</tr>
<tr>
<td>08 Zagreb</td>
<td>11.3</td>
<td>12.1</td>
<td>6.5</td>
<td>17.4</td>
</tr>
<tr>
<td>09 New Delhi</td>
<td>6.3</td>
<td>3.7</td>
<td>14.2</td>
<td>7.8</td>
</tr>
<tr>
<td>10 Hong Kong</td>
<td>4.2</td>
<td>5.5</td>
<td>1.8</td>
<td>2.9</td>
</tr>
<tr>
<td>11 Tokyo</td>
<td>12.7</td>
<td>11.9</td>
<td>22.2</td>
<td>13.5</td>
</tr>
<tr>
<td>13 Havana</td>
<td>4.6</td>
<td>3.0</td>
<td>7.8</td>
<td>6.7</td>
</tr>
<tr>
<td>14 Oklahoma</td>
<td>8.2</td>
<td>9.6</td>
<td>19.1</td>
<td>11.5</td>
</tr>
<tr>
<td>15 Arizona</td>
<td>15.3</td>
<td>10.3</td>
<td>13.1</td>
<td>10.2</td>
</tr>
<tr>
<td>17 Bulgaria</td>
<td>14.5</td>
<td>8.7</td>
<td>7.0</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Frequency of severe microvascular disease of the eye and the kidney in the 14 groups of diabetics examined in the WHO multinational study of vascular disease in diabetics. Values have been corrected for duration of illness. Patients were 35-54 years old. For the criteria used to define the disease, see the original source.

## Annex 10

**LARGE-VEssel DISEASE IN VARIOUS GROUPS OF DIABETICS**

<table>
<thead>
<tr>
<th>Code No.</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>4.3</td>
<td>5.5</td>
</tr>
<tr>
<td>03</td>
<td>10.0</td>
<td>6.4</td>
</tr>
<tr>
<td>04</td>
<td>4.0</td>
<td>5.1</td>
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<tr>
<td>05</td>
<td>3.7</td>
<td>3.6</td>
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<td>08</td>
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<td>0.9</td>
</tr>
<tr>
<td>11</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>9.2</td>
<td>4.6</td>
</tr>
<tr>
<td>13</td>
<td>9.2</td>
<td>10.4</td>
</tr>
<tr>
<td>14</td>
<td>7.7</td>
<td>8.8</td>
</tr>
<tr>
<td>15</td>
<td>6.8</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Frequency of severe large-vessel disease in the groups of diabetic patients described in Annex 9. For the criteria used to define "large-vessel disease" see the original source.


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