DEFINITION

1. **Diabetes mellitus** is a chronic disease characterised by an abnormally high concentration of glucose in the blood and glucose excretion in the urine (glycosuria). The World Health Organisation (WHO) has suggested a random plasma glucose level of 11.1 mmol/l or more as appropriate for a diagnosis of diabetes.

2. **Impaired glucose tolerance**, as defined by WHO, is a state of raised blood sugar (hyperglycaemia) less than that which is diagnostic of diabetes. Persons with this condition have an increased risk of developing diabetes within 5-10 years.

3. **Renal glycosuria** indicates a low renal threshold for glucose, and is common during pregnancy and in young people. It is the most common cause of glycosuria, and is unrelated to diabetes.

CLASSIFICATION

4. The classification of diabetes and the criteria for its diagnosis are currently undergoing further consideration by WHO and other international groups. The 1980 WHO classification divides diabetes mellitus into two main categories, primary and secondary. Primary diabetes is much the most common and is the main subject of this Appendix. In the primary category there is associated disease process.

    4.1. **Primary** diabetes mellitus. This category consists of two main clinical types –

        4.1.1. **Type 1** diabetes mellitus, often referred to an **insulin-dependent** diabetes mellitus (**IDDM**). This condition may be subdivided into **Type 1a** and **Type 1b** depending on whether it is juvenile or older age at onset.

        4.1.2. **Type 2** diabetes mellitus, often referred to as **non-insulin-dependent** diabetes mellitus (**NIDDM**). This condition was formerly called **adult-onset**, **maturity-onset** or **non-ketotic** diabetes. It may also be subdivided into **obese** and **non-obese** categories.

    It has been customary to classify **primary** diabetes mellitus as being insulin-dependent (IDDM) or non-insulin-dependent (NIDDM), according to whether it requires treatment with insulin. However, some type 1 cases of adult onset may initially present as NIDDM, while some type 2 cases may eventually require insulin to control their diabetes.

5. **Secondary** diabetes mellitus. This category comprises a minority of cases which occur as a result of a recognisable pathological process or the treatment of some other condition. Diseases affecting the pancreas, hormonal disorders, genetic syndromes and therapeutic drugs such as corticosteroids fall within this category. Thiazide diuretics may provoke hyperglycaemia and glycosuria in diabetic patients, and may aggravate or unmask diabetes.

CLINICAL MANIFESTATIONS

6. **Type 1 diabetes** is predominantly a disease of children and young adults, though uncommonly it occurs in older adults. Recent studies from Finland and the United Kingdom show that the incidence in children under 5 is increasing. Clinical onset is rapid, with symptoms of tiredness, loss of weight, thirst and polyuria. If not treated with insulin, the disease progresses to ketoacidosis, coma and death. Treatment with insulin abates the symptoms but in later years complications affecting various systems of the body are liable to develop.

7. **Type 2 diabetes** is essentially a disease of older adult life. Patients may not complain of acute symptoms indicative of hyperglycaemia, and the disease is often detected only by routine screening. Non-specific symptoms, such as weight loss, pruritus, or recurrent skin or genital infections, may give rise to suspicion of diabetes and lead to urine testing. It is sometimes detected only when the patient presents with evidence of a diabetic complication, such as defective vision. Most cases will have been present for a considerable time before being diagnosed.

Complications

8. As their disease progresses, all diabetic patients are liable to develop long term effects on various body tissues especially **kidneys**, **eyes** and **peripheral nerves**. These effects are brought about by specific changes in small blood vessels resulting from the hyperglycaemic state of diabetes. They are related to the severity and duration of hyperglycaemia rather than to the type of diabetes, and are less liable to occur if the blood sugar level is well controlled by medical treatment.

8.1. **Microvascular disease**

8.1.1. **Nephropathy**. This may lead to renal failure, or may produce secondary effects on the cardiovascular system, with hypertension.

8.1.2. **Retinopathy**. This leads to impaired vision and is the commonest cause of blindness in middle age in the United Kingdom.

8.1.3. **Neuropathy**. This may be sensorimotor mainly affecting the feet. It may be autonomic, giving rise to features such as dizziness, nausea, diarrhoea and dry skin.

8.2. **Macrovascular disease**

This is not related to blood glucose control. Diabetics have an increased incidence of premature arterial disease, and the process of atherosclerosis is accelerated. The most serious effects are on the coronary arteries and those of the lower limbs.

8.3. **Other complications**

8.3.1. **Impotence** develops in about 30% of male diabetics. This is mainly due to diabetic microvascular disease affecting the penile vessels, but autonomic neuropathy also plays a part.

8.3.2. Certain **soft tissue rheumatic syndromes** are more frequent in diabetics. These include periarthritis of the shoulder, Dupuytren's contracture, Peyronie's disease, carpal tunnel syndrome and flexor tenosynovitis. They seem to be a direct effect of the diabetic process, but are not related to the quality of diabetic control.

8.3.3. **Osteoporosis**. The precise relationship – in particular whether it is causal – between diabetes and bone metabolism remains controversial. Several studies over the last 50 years have reported an association between diabetes and osteoporosis and it has been shown that there is a significant loss of bone mass (**osteopenia**), of the order of 10%, in both types of primary diabetes. Some studies have shown as increased incidence of hip fractures in diabetics; these occurred in younger patients and in the presence of minimal trauma. Recent studies have generally concluded that diabetics have an increased incidence of osteoporosis. The decrease in bone mass accompanies the clinical onset of diabetes; significant reduction continues for about 2 years, with a stable state reached within 5 years of diagnosis of diabetes.

8.3.4. **Neovascular glaucoma** may occur in patients with longstanding diabetes (10 years duration or more), particularly those with proliferative diabetic retinopathy.

8.3.5. **Senile cataracts** develop at an earlier age in diabetes mellitus. Such cataracts are, however, not true diabetic cataracts, the situation being that the diabetes has merely brought forward the development of a cataract which would have occurred eventually, or has accelerated its progress. True **diabetic cataract** is a rare condition, occurring typically in young people in whom the diabetes is so acute as to disturb grossly the water balance of the body.

AETIOLOGY

PRIMARY DIABETES MELLITUS

TYPE 1

9. This disease results from insulin lack due to damage to the B islet cells of the pancreas. The process seems to occur over many years and probably follows environmental insults in genetically susceptible individuals. Most Type 1 diabetics have circulating autoantibodies to B cell antigens and immune attack is thought to be important in pathogenesis.

Genetic factors

10. Susceptibility to Type 1 diabetes has a substantial genetic component; the disease runs in families, with sibling risk about 15 times greater than in the normal population. The primary site for the diabetes gene in humans is considered to be on the short arm of chromosome 6; there may be other sites as well. There are strong associations between type 1 diabetes and certain Human Leucocyte Antigens (HLA).

Environmental factors

Epidemiology

11. The world-wide incidence of Type 1 diabetes varies greatly. It is predominantly found in Caucasian populations, and is particularly common in Northern Europe. Migration studies point to a substantial role for environmental factors in the geographical variation, in that the incidence of Type 1 diabetes rises if individuals move from a region of low incidence to one with a relatively high incidence. The higher the level of socio-economic development in a community, the greater the incidence of diabetes.

Diet

12. It has been suggested that introducing cow's milk into the diet of babies before the age of 4 months increases the risk of subsequent Type 1 diabetes, whereas breast feeding appears protective. Recent studies have failed to give support to this view. Nitrates and nitroso compounds in the diet have been advanced as aetiological factors, but data supporting this idea are weak.

Viruses

13. A viral aetiology for Type 1 diabetes has been postulated, and the known seasonal incidence of the disease would support this. The season of birth has also been shown to affect the subsequent risk, suggesting that viral infections in utero might be relevant. Three viruses cause direct damage to B cells in humans, namely mumps, rubella and Coxsackie. Cytomegalovirus has recently been implicated in both types of diabetes. However, there is no hard evidence to confirm viral causation.

14. An increasing incidence of the disease in **small children** points to environmental factors in early life, for example viruses and nutrition. The putative agent could be a virus, a toxin or a food and could act in one of several ways.

TYPE 2

15. Constitutional and life-style factors are both implicated in the genesis of type 2 diabetes, the former being preponderant. There is no evidence that autoimmunity or viruses have anything to do with its development. The patterns of prevalence of Type 2 diabetes in developing, newly industrialised and migrant populations strongly suggests that factors inherent in a western life-style are involved; these include a diet high in saturated fat, lack of exercise and obesity. Type 2 diabetes is therefore a life-style disease that emerges in people who are genetically predisposed.

Genetic factors

16. A family history of Type 2 diabetes is the strongest risk factor for the disease. If both parents are diabetic, the risk is at least 50%, and identical twin studies have shown concordance rates from 60-85%. High prevalence rates in certain ethnic groups, such as Indo-Asians, supports a strong genetic basis.

17. The rare **maturity-onset diabetes of the young (MODY)** is caused by specific genetic inheritance.

18. In Type 2 cases the disease results from reduced insulin secretion and/or increased resistance to insulin. The relative importance of these two mechanisms varies between individuals. Genetic factors are involved in both mechanisms.

Environmental factors

Epidemiology

19. Type 2 diabetes is far more common than Type 1. In the United Kingdom prevalence is usually quoted as 8-12% of the population. The usual age of presentation is in the range 50-65 years. Type 2 diabetes has a markedly increased incidence in people of Japanese descent who have moved to the United States; this is attributed to an inability of their metabolism to adapt to a westernised life-style.

Diet

20. The consumption of excessive amounts of food is associated with an increasing prevalence of Type 2 diabetes in a population. Obesity, especially abdominal obesity, is a major risk factor for the disease, the critical link being insulin resistance. The mechanisms by which obesity causes insulin resistance are not clearly understood, but are probably multiple and include a genetic component.

21. Individuals with a **low birth weight** have a higher risk of eventually developing Type 2 diabetes, particularly if they become obese later in life. It is thought that foetal malnutrition, probably resulting from placental deficiencies, adversely affects pancreatic cell development and so limits B cell function in adult life.

22. Obesity alone cannot, account for all the insulin resistance in obese patients with Type 2 diabetes. Some non-obese patients are also insulin-resistant. Insulin resistance may be due to any of three causes – an abnormal insulin molecule, an excessive amount of circulating antagonists or target tissue defects. The last is the most common cause of insulin resistance in Type 2 diabetes.

Physical activity

23. Reduced physical activity is associated with insulin resistance, and a high level of physical activity is inversely proportional to the prevalence of Type 2 diabetes. Physical activity without weight loss helps to prevent diabetes, even in genetically susceptible individuals.

SECONDARY DIABETES MELLITUS

24. The aetiology of diabetes falling within this category is that of the condition leading to the diabetes, whether it be an underlying disease (for example, a genetic syndrome) or an effect of drugs.

OTHER POSTULATED CAUSES OF DIABETES

25. **Trauma**. Some authorities consider that trauma is never a cause of diabetes. Most agree that a relationship cannot be denied where there is a severe injury to the pancreas or base of the brain and where signs of the disease develop in close time relationship to such injury; it would not apply where clinical diabetes showed itself years later. It must be borne in mind that trauma may seem to have given rise to diabetes because, at the time of injury, latent disease is discovered which otherwise might have remained undetected for years.

26. **Stress**. Psychological stress is a normal and essential part of life. Emotional stress to one person is not stress to another. The concept is difficult to define and investigate, and good quality evidence on the association of stress with diseases is limited.

27. Recent studies do not produce reliable evidence of any causal link between stress and Type 1 diabetes. A recent extensive study has concluded that there is no direct evidence that stress plays a significant role in the expression or control of Type 2 diabetes. These studies have emphasised the need for further research before any link between stress and diabetes can be precisely determined.

28. **Infection** has not been shown to be a factor in the development of diabetes other than, as mentioned in Paragraph 13 above, in the case of viral infection in an individual predisposed to develop Type 1. Diabetes has never been transmitted by transfusions, inoculations, food, drink or other means. Experts are agreed that bacterial infection is not a cause of diabetes, though uncontrolled diabetes renders the individual more susceptible to intercurrent infections.

29. **Gestation**. Gestational diabetes occurs in about 3% of pregnancies in women of European descent. It may be defined as transient diabetes induced by pregnancy, and in most cases the woman reverts to normal post partum. There is, however, an increased risk of developing Type 2 diabetes in later life.

CONCLUSION

30. **Primary diabetes mellitus** is a condition in which the ability of the body to deal adequately with dietary sugar is defective. Much of the current theory regarding its cause lacks research-based empirical confirmation. **Type 1** is a variety which occurs in individuals who are genetically predisposed and are subject to some environmental insult, possibly viral. **Type 2** is a westernised life-style disease, occurring in individuals who are genetically predisposed. Obesity can serve to bring forward in time the onset of this form of the condition. Intercurrent infections may exacerbate diabetes mellitus, usually temporarily but occasionally permanently. Except as in Paragraph 28 above, infection does not cause diabetes. **Secondary diabetes mellitus** occurs as a part of another disease process.

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January 2000