Review article**Juvenile diabetes mellitus****Possibility of prevention****J. W. FARQUHAR***Department of Child Life and Health, University of Edinburgh*

Knowledge of insulin-dependent juvenile-onset diabetes (JOD) has grown quickly during the last 5 years, particularly in three areas. (1) A small number of viruses may be associated with the development of JOD. (2) Certain genetic markers (HLA types) provide a means of identifying who is vulnerable. (3) Autoimmunity may cause more or less rapid pancreatic islet cell destruction and may be initiated in those who are vulnerable by specific virus action. The gene responsible for diabetic vulnerability may be identified in the next decade. It may then be possible to prevent JOD. Such research could be as profitable as the development of new treatment techniques.

Children form one-tenth of the recognised diabetic population in Europe and North America. The disease affects about one child in 800 under 16 years (Bloom *et al.*, 1975; Calnan and Peckham, 1977) and one young person in 300 under age 26 (Wadsworth and Jarrett, 1974). Many physicians share the impression that it is becoming more prevalent (Calnan and Peckham, 1977; Craig *et al.*, 1977).

JOD is generally insulin-dependent from the time of diagnosis or soon afterwards. The child's daily insulin injections, spaced meals, and monitoring tests may be simplified to an acceptable routine (Farquhar, 1972, 1976; Craig, 1977) but even the lightest impositions can exaggerate such behavioural flaws as already exist in him or in his family. This can cause unhappiness and tragedy (MacGregor, 1977). Mothers of diabetic children can suffer nervous strain (Olatawura, 1972) and need generous support and treatment.

For the diabetic child lies the possibility of a major disability—such as retinopathy, nephropathy, and neuropathy. Thus in the UK almost

1000 diabetics are added annually to the register of blind persons; diabetes is, at the least, the third most common cause of blindness in the age group 30–49 years (Sorsby, 1966). From the Joslin Clinic, White (1960) reported some degree of retinopathy in 93% of diabetics after 20 to 40 years. While optimal control may limit the risk (Farquhar, 1977), these statistics carry the disturbing implication that many diabetic children will have some visual handicap by the time they are between 30 and 50 years, and likely to have dependent families. The other results of microangiopathy and ischaemic heart disease are just as crippling and more life-threatening, life expectancy being about two-thirds that for normal children (Bloom *et al.*, 1975).

To the possible unhappiness and anxiety of patients and relatives must be added the cumulative economic burden to the community—hospital admissions for restabilisation, medical supplies for home control, related educational and social needs, extra care in pregnancy, and (when diabetic disability arises) long-term support for the individual and his dependants. Such massive annual cost makes attractive the direction of financial resources towards research into cure or, better still, prevention. 'Cure' may be possible when effective human pancreatic islet transplantation (Lancet, 1975; Turtle, 1977) or the implantation of an 'artificial pancreas' or of crossed-species islets in a micropore chamber (Gates and Lazarus, 1977) can be offered to all. The warning of Gajdusek (1979) about the possible transmission of slow virus in transplant tissue may be less relevant when fetal islets are used. Advances in prevention will cost much money but is there any hope? The evidence is now reviewed.

Clinical characteristics

JOD is characterised by three phases.

Phase 1. The acute and largely permanent process in

which hyperglycaemia, ketoacidosis, and coma develop and kill in the absence of insulin treatment. Overt infection coexists or closely precedes this phase in at least one patient in 3. Less noticeable infection may be common.

Phase 2. A phase of partial recovery commonly known as the 'honeymoon' lasting a few weeks or months when only small doses of insulin are needed or, more rarely, when it may be replaced by reducing the carbohydrate intake and adding an oral hypoglycaemic agent.

Phase 3. A subacute or chronic phase of progressive intrinsic insulin inadequacy within which diabetic control has a variable cycle of ups and downs (variable energy intake and output, variable dose of insulin, and variation in the diabetic process).

The pathological process should satisfactorily explain these phases.

Epidemiology

Physicians closely concerned with diabetes have for decades noted a tendency for new patients with JOD to cluster in time and space. They experience quiet and busy years in registering new patients, obvious variation within a year, little outbreaks within small communities, and unusual prevalence in cohort analysis of older patients. Adams (1926) recorded seasonal variations, while Gunderson (1927) was so impressed by this that he asked the question 'Is diabetes of infectious origin?'

The register of newly diabetic children (age group 0–15 years) sponsored by the British Diabetic Association gave much epidemiological information (Bloom *et al.*, 1975; Gamble and Taylor, 1976). It recorded a seasonal variation in incidence in children aged 5–15 years with peaks in the autumn and winter, although little relationship to environmental temperature was noted (Gamble, 1974). A seasonal incidence in children was also recorded by Rolles *et al.* (1975), but denied by Barbosa *et al.* (1976). Preschool children, on the other hand, showed less variation and no seasonal pattern. Age incidence in the register seems to be bimodal with peaks at about 5 and 11 years when children are joining primary and secondary schools. There is no consistent relationship to growth or puberty. During the years 1973–74 the incidence varied from 4.78 to 10.61 per 100 000 children each year geographically. In spite of a financial incentive to notify new cases to the national register, it seems that staff in some parts of the country (for example London) were less likely to do so than in other parts. Thus the register probably underestimated the number of children with JOD.

Lastly there were some surprising outbreaks

within families—diabetes developing almost simultaneously in 5 cases in two years. In one family there were 3 siblings. Does JOD result from infection? If so how often, and is it preventable?

An environmental factor

The possibility of an infective cause was raised by Harris (1899) when he described the rapid development of diabetes after mumps. The same association was described by others—such as Cole (1934), Melin and Ursing (1958), Hinden (1962), and McCrae (1963). Since then there have been many reports on animals and man. Indeed Brown (1956) stated 'the most common cause of diabetes in children is a systemic infection which injures the islets of Langerhans'.

Animal diabetes. The virus of foot-and-mouth disease was linked with the development of diabetes mellitus in some cattle by Barboni and Manocchio (1962). In 1965 Craighead reported an association between encephalomyocarditis (EMC) virus and pancreatitis in mice. Subsequently he showed that EMC virus multiplies in the pancreatic β -cells of mice to produce diabetes mellitus and pancreatic islet histology which closely resembled that in JOD (Craighead, 1975, 1976, 1978). He showed that the islet insulin increased 3-fold before falling to very low values. These and further studies by Ross *et al.* (1975) and Boucher *et al.* (1975) established that diabetes mellitus was produced only when a particular breed of mouse was used and only when the infection was caused by the M variant of EMC virus. Five very similar strains failed to invade the pancreatic β -cells. This work was reviewed by Notkins (1977) and indicated the need for a genetic factor both in the host and in the infecting agent. Another interesting observation was the failure, even of M strain EMC virus, to induce diabetes in athymic (nude) mice although it did so in suitable controls (Buschard *et al.*, 1976).

Similarly, Coleman *et al.* (1973, 1974), Gamble (1975), and Smith and Deibel (1975) showed that a specified breed of mouse could be made diabetic by infecting it with Coxsackie virus B4, the pancreatic islet histology again resembling the findings in JOD. This is particularly interesting in view of observations in man.

Child diabetes. The association with mumps seems clear but it may contribute very little to the annual incidence of JOD. Notkins (1977) stated the obvious—that mumps is common but complicating diabetes is rare. It should be remembered however that months (Melin and Ursing, 1958), or years

(Sultz *et al.*, 1975), may separate the infection from the recognition of diabetes. The report of a patient with JOD after inoculation with a live-attenuated mumps vaccine (Sinaniotis *et al.*, 1975) will be discussed later.

Rubella virus

The development of diabetes was described in a patient after congenital rubella (Menser *et al.*, 1967) and was followed by a series of well substantiated reports on other patients (Menser *et al.*, 1978), many of whom had insulin-dependent JOD. Experimental work with rubella virus on pregnant rabbits produced histological changes in the fetal pancreatic β -cells similar to those produced in mice by EMC virus.

Coxsackie B virus

British research focused attention on the possible role of Coxsackie B virus. This began (Gamble *et al.*, 1973) with the observation that Coxsackie B4 (CB4) virus was more often found in new patients with JOD aged 10 to 19 years than in control subjects, although the significance of this may now be uncertain. A matching seasonal incidence was also noted. This hypothesis is being developed and applied to HLA typing (Cudworth *et al.*, 1977).

Acute JOD has been described in a boy of 18 months who had a high titre of CB2 and of CB-specific IgM (Wilson *et al.*, 1977). Three unrelated young adults developed acute diabetes in association with symptoms suggesting a virus illness (Gibbs, 1974). All 3 had ECG changes suggesting a myocarditis which was assumed viral.

Nine of a cluster (in time and space) of 12 patients with JOD were investigated by Huff *et al.* (1974); 8 of the 9 had suffered a recent 'viral illness', mainly respiratory. No single virus test in a panel of 26 common viral agents was positive in all, but CB3 was proved in 33%, compared with 6% of the controls.

In one family reported by Nelson *et al.* (1977) in which both parents were diabetic, 3 of their 5 children developed classical JOD within 4 months. One had an attack of Bornholm disease one month before developing diabetes and was found to have high antibody titres to CB1 and CB5. Another had a low antibody titre to CB2.

Baum *et al.* (1974) tested 11 new patients with JOD for evidence of recent infection by a wider range of viruses including CB1-5, but none was found.

A population was studied in the Pribilof Islands (Behring Sea) 5 years after an epidemic of CB4 infection. Those with serological evidence of previous infection were given glucose tolerance tests, but

there was no evidence of increased prevalence (Dippe *et al.*, 1975). Subsequent appreciation of the susceptibility to diabetes of persons sharing the same HLA type (described later), and the possible protection of others, robbed the Pribilof study of some of its value. The indigenous Alaskan in these islands is not Caucasian and might not have been vulnerable to CB4 infection (Cudworth *et al.*, 1975). This point was agreed by Dippe *et al.* (1975).

So the case remains unproved but may be partly true. Kono (1976) stated that CB3 and CB4 can be isolated from the human infant's pancreas. Further work on this association is justified in the light of the reports on fetal rubella (Menser *et al.*, 1978).

Other infections

A major epidemic of infective hepatitis in West Africa was reported to have caused diabetes mellitus (Adi, 1974; Osuntokun, 1974) and, in Australia, a young man became acutely diabetic during an attack of infectious mononucleosis (Burgess *et al.*, 1974).

An inherited factor

Diabetes in relatives. The experiments already described with viruses and mice established that, for the mouse model, the genetic complement of the host is essential to the production of diabetes mellitus. This will now be examined by looking closely at diabetes mellitus occurring in relatives.

Children of diabetic mothers

Long-term follow-up studies on large populations of such children are difficult but information (Farquhar, 1969) strongly suggests that the incidence of diabetes should be high. White (1959) reported that 9% of such offspring were diabetic by age 14 and that a further 14% had chemical diabetes (see below). It is important to remember that most of the mothers in the Edinburgh study (Farquhar, 1969) had type 1 diabetes—that is, they were insulin-dependent young diabetics.

Children of conjugal diabetics

One study of such children (Cooke *et al.*, 1966) gave an incidence of 4.4%, and there were earlier studies by West (1960), Post (1962), and Simpson (1964). In the light of later knowledge it is interesting to find that diabetes was found more often among children whose parents had become diabetic early in life. The facts that earlier workers did not discriminate between JOD and MOD (maturity-onset diabetes), and that chemical testing for diabetes was

too often more a matter of opinion than of science, lead to difficulties of interpretation. Thus the study by Rojas *et al.* (1969) noted the ages of the young people but not of the parents at the time of their becoming diabetic. The parents cannot therefore be assigned to the JOD or MOD group. It was concluded that the only revealing test was a poor initial insulin response to glucose in those whom it had been decided were 'prediabetic', postulated as a defective glucose-responsive mechanism for insulin secretion. In another paper Kahn *et al.* (1969) estimated from such tests that 40% of those born to conjugal diabetics had evidence of chemical diabetes.

Radder and Terpstra (1975) studied the children of patients with conjugal MOD, mean age at diagnosis 61 years. About 45% of these children were chemically diabetic on oral glucose tolerance tests but fewer than one child in 4 had previously been diagnosed. The diagnosis related to the offspring being overweight. Similarly in the study by Tattersall and Fajans (1975a) most of the parents had MOD, with a mean age at diagnosis of 54.5 years. The 'children' had a mean age of 32.6 years and 28% had impaired glucose tolerance, 2% had JOD. It was estimated that 60% would give positive results to tests by age 60 years and it was rightly concluded that results based on the offspring of 2 patients with MOD cannot be assumed to be relevant to children of 2 patients with JOD.

Siblings of diabetics

Investigators in the 1950s and 1960s half-expected to find 'heterozygotes' with abnormal glucose tolerance (chemical diabetes) among the siblings of patients with JOD. Indeed, Fajans and Conn (1954) found 19% of young adults with diabetic glucose tolerance tests. When such siblings develop insulin-dependent diabetes the diagnosis is not in doubt, but when they do not, their subjection to batteries of tests and the correlation of results widen the range of possible interpretation (Kahn *et al.*, 1969).

Thus 16% of siblings were classified as being chemically diabetic by Jackson *et al.* (1968) and 11% were so classified by Rosenbloom *et al.* (1972). Rosenbloom (1975) subsequently investigated glucose tolerance in a large group serially and found that 0.5% had overt JOD and that fewer than 5% had chemical diabetes by his standards. Adult siblings were studied by Kobberling *et al.* (1969) who estimated that 39% had chemical diabetes. It now seems less likely that their diabetes was that of the propositi.

Identical twins

A selected series of identical twins was studied and reported (Pyke and Taylor, 1967; Pyke *et al.*, 1970;

Nelson *et al.*, 1975). More than half the pairs have proved to be discordant for diabetes but Rosenthal *et al.* (1976) argued that there would be concordance in at least 80% if the series were followed up. Certainly concordance for MOD is almost 100% in identical twins after age 40 (Gottlieb and Root, 1968; Tattersall and Pyke, 1972). The latter study is nevertheless interesting in that the older the discordant twins become the more likely they are to develop insulin-dependent JOD. The results of extensive virus studies are given by Nelson *et al.* (1975). While it is disappointing that there was little difference in antibody levels between the diabetic and unaffected twins, it was acknowledged that only a few were examined within 2 years of diagnosing diabetes. It was suggested that the non-diabetic twins may have had too low a dose to cause pancreatic damage.

Triplets, claimed to be monozygotic, discordant for diabetes were described by Ganda *et al.* (1977). The first developed JOD at age 13 years. The second had normal glucose tolerance tests until she became diabetic at age 21. The third remains normal on testing.

Parents and ancestors

The clearer separation of diabetes mellitus into two main groups—type 1 or JOD, and type 2 or MOD—has made family studies more meaningful. Thus MacDonald (1974) compared the ancestors of patients with type 1 with a control group and found an equal incidence of diabetes mellitus, surprising as this may be for several reasons. Separate groups of JOD and MOD (of the young) were studied by Tattersall and Fajans (1975b). Only 11% of those with JOD had a diabetic parent compared with 85% of those with MOD. In only 6% of those with JOD had the disease been present in three generations compared with 46% of those with MOD. These studies give further evidence of genetic heterogeneity in diabetes mellitus.

Disease associations

Insulin-dependent JOD can be associated with disorders ranging remarkably from Down's syndrome (and other chromosomal abnormalities) to coeliac disease, and from autoimmune endocrinopathies to nerve deafness and optic atrophy. The nature of the diabetes may differ in the disorders listed in the Table but there is doubtless a message in these associations for him who finds the cypher.

HLA antigens

It may soon be understood why a specific virus strain, sweeping through a community and through

Table Syndromes associated with glucose intolerance

Alstrom's syndrome
Ataxia telangiectasia
Chromosome abnormalities:
Down's syndrome; Klinefelter's syndrome; Turner's syndrome and
Turner's mosaicism and relatives; 47,XX,21 + 46XX mosaic with
liver cirrhosis
Cockayne's syndrome
Cystic fibrosis
Diabetes insipidus
Friedreich's ataxia
Glucose-6-phosphate dehydrogenase deficiency
Type I glycogen storage disease
Haemochromatosis
Huntington's chorea
Hyperlipaemia, diabetes, hypogonadism, and short stature syndrome
Hyperlipoproteinaemia III
Hyperlipoproteinaemia IV
Hyperlipoproteinaemia V
Isolated growth hormone deficiency
Laurence-Moon-Biedl syndrome
Leucoderma
Lipoatrophic diabetes
Muscular dystrophy
Myotonic dystrophy
Ocular hypertension induced by dexamethasone
Optic atrophy and diabetes
Hereditary relapsing pancreatitis
Photomycloclonus, diabetes, deafness, nephropathy, and cerebral
dysfunction
Pineal hyperplasia and diabetes
Acute intermittent porphyria
Phaeochromocytoma
Prader-Willi syndrome
Retinitis pigmentosa, neuropathy, ataxia, and diabetes
Schmidt's syndrome
Werner's syndrome

a family possessing diabetic relatives, picks out this or that child's pancreatic β -cells for destruction. As in the selectively bred mice, an unknown number (perhaps all) of these individuals are genetically vulnerable. Those at greater than normal risk can now be identified by HLA tissue-typing because they possess in greater than normal degree a number of identifiable antigens. Minor differences, caused perhaps by inherent instability, in relevant alleles may even explain the surprising discordancy for diabetes between monozygous 'identical' twins.

The antigens associated with JOD are B_8 , BW_{15} , B_{18} , BW_{35} , A_1 , AW_{30} , DW_3 , DW_4 , CW_3 , DRW_3 , and DRW_4 . Reports on individual antigens are briefly reviewed. Changes in nomenclature are common and can be confusing.

Individual associations. Cudworth and Woodrow (1974) and Nerup *et al.* (1974) noted that B_8 was more common in patients with JOD—54% compared with 31.8% in controls. Others found it to be even more common. The relative risk for developing JOD was given as 2.12 but was later increased in those under 30 years to 2.5 (Cudworth and Woodrow, 1976; Nerup *et al.*, 1976). It was found to be increased also in congenital rubella (Menser *et al.*, 1974). The significantly higher representation

of B_8 in differing degree in JOD has been reported in many papers from different communities (Löw *et al.*, 1975; Rolles *et al.*, 1975; Barbosa *et al.*, 1976; Landgraf *et al.*, 1976; Morris *et al.*, 1976; Pointel *et al.*, 1976; Savi *et al.*, 1976; Vialettes *et al.*, 1976; Barta and Simon, 1977; Illeni *et al.*, 1977; Koivisto *et al.*, 1977; Ludwig *et al.*, 1977). Illeni *et al.* (1977) found the increase in B_8 to be significant in the 0–5-year age group. This antigen was found not to be increased beyond the expected normal in Sardinia despite a high prevalence of diabetes (Contu *et al.*, 1976). It should be noted that HLA- B_8 is uncommon in the Aleutian people of the Pribilof Islands (Menser *et al.*, 1974).

Cudworth and Woodrow (1974, 1975a,b, 1976) reported increased representation of BW_{15} and a relative risk of 1.85. Similar experience was recorded by Nerup *et al.* (1974, 1976), Löw *et al.* (1975), Morris *et al.* (1976), and Solow *et al.* (1977), but not in rubella by Menser *et al.* (1974, 1978). In Sardinia, Contu *et al.* (1976) found it in 11.4% of patients with JOD but in only 2% of the rest. It was not increased however in studies made in France (Pointel *et al.*, 1976) or Finland (Koivisto *et al.*, 1977).

The coexistent increased representation of B_8 and BW_{15} may have a significant effect. Nerup *et al.* (1976) suggested an increased risk to siblings of the proband, while Koivisto *et al.* (1977) found it at its greatest when JOD coexisted with coeliac disease. Barta and Simon (1977) found increased representation of B_8 , but not of BW_{15} , in Hungary. When they looked at coexisting B_8 and BW_{15} , however, it was present in 15–16% of patients with JOD but in only 0.9% of controls. From this they calculated relative risks for B_8 , and for B_8 and BW_{15} at 2.027 and 18.25 respectively. Cudworth *et al.* (1977) however estimated the relative risk of B_8 and BW_{15} at 5.59.

Cudworth and Woodrow (1976) reported increased representation of B_{18} in patients with JOD and calculated the relative risk to be 2.56. According to Vialettes *et al.* (1976) B_{18} occurs in 26.6% of those with JOD compared with 11.8% in the general population.

Contu *et al.* (1976) reported that BW_{35} was present in 29.2% of patients with JOD compared with 12.5% of the nondiabetic population. In Italy Savi *et al.* (1976) found it was present in 38% of those with JOD compared with 23% in controls in Parma, while Illeni *et al.* (1977) reported from Milan that BW_{35} was significantly decreased in those with JOD.

Morris *et al.* (1976) found A_1 to be over-represented in insulin-dependent diabetics, the proportion being greater in those with thyrogastric antibodies and persistence of pancreatic islet cell antibodies for

more than 5 years (see later). Viallettes *et al.* (1976) found the antigen was almost twice as common in diabetics described as 'low-insulin responders' to glucose, likelier perhaps to be MOD or MODID (maturity-onset diabetes insulin-dependent).

AW₃₀ antigen is increased (Illeni *et al.*, 1977) in JOD patients diagnosed between October and January and this could be related to a specific seasonal infection.

DW₃ and DW₄ are associated even more strongly than B₈ and BW₁₅ with JOD (Nerup *et al.* 1976). DW₃ and DW₄ were found in 80% compared with 24% in controls, as stated also by Hsu *et al.* (1977); its importance was also noted by Bottazzo and Doniach (1976) and Irvine *et al.* (1977a).

The increased representation of CW₃ in JOD is described by Ludwig *et al.* (1977).

DRW₃ and DRW₄, the alloantigens found on B-lymphocytes, are believed to carry a relative risk of 4.5 and 2.5 respectively (Schernthaler *et al.*, 1977).

The importance of B₇ (Ludwig *et al.*, 1977) lies in its significantly low representation in JOD (13.2% v. 26.8% in the normal population).

The technique of HLA-typing now makes possible the recognition of an individual who is likely to develop JOD when appropriately challenged. The exact locus and nature of the fault is likely to be found as HLA mapping continues.

Viral association. Of HLA-B₈-positive patients with JOD reported by Rolles *et al.* (1975) 81% presented between October and the end of February, whereas those with HLA-B₈-negative JOD presented throughout the year. The late autumn and winter period coincides with the highest incidence of Coxsackie B virus infections. This was not the experience of Barbosa (1977). Cudworth *et al.* (1977) recorded twice as many new patients with JOD in autumn/winter as in spring/summer. They reported BW₁₅ clustering in winter but not in the previous autumn. They also reported that new patients with JOD with BW₁₅, and especially with B₈ and BW₁₅, had higher neutralising antibody titres to Coxsackie B virus strains 1-4.

β-Cell destruction and autoimmunity

Histology. Death is rare in diabetic children and adolescents who attend good clinics. Pathologists therefore have little chance to examine the pancreas from recently diagnosed young diabetics. Gepts (1965, 1976) has attracted material from other centres and has acquired great experience. He described a characteristic lymphocytic insulinitis in the pancreas of young people dying within 6

months of diagnosis. This looked like a response to direct viral aggression or an immune reaction and it is seldom seen in patients who die after being diabetic for one year. It may well indicate the process by which β-cell function is more or less suddenly interrupted, recovers briefly, and is then lost steadily. Similar histology was described in a child who died from congenital rubella (Bunnell and Monif, 1972), and the virus may persist in human pancreas for months or years (Cooper *et al.*, 1965). Gepts *et al.* (1977), using new immunocytochemical methods, found that β-cells could be identified in JOD of recent onset. In chronic JOD the atrophic islets are composed mainly of glucagon, and of somatostatin cells. In addition the JOD pancreas contains ribbon-like cells considered to secrete pancreatic polypeptide. Hyperplasia of such 'HPP cells' in JOD is thought to represent atypical islet regeneration induced by severe and prolonged injury to pancreatic endocrine tissue.

β-Cell changes, similar to those found in mice made diabetic by EMC virus, were consistently found in the offspring of rabbits infected with rubella during pregnancy (Menser *et al.*, 1978).

Association with autoimmune diseases. A clinical association between diabetes mellitus and diseases characterised by organ-specific autoimmunity is well recognised and documented (Carpenter *et al.*, 1964; Irvine *et al.*, 1967) and its familial character has been reported by Bottazzo *et al.* (1978). Antibody evidence of thyroid and gastric autoimmunity was given by Irvine *et al.* (1970) who concluded that there seemed to be 'a disorder of the immunological system related to insulin-dependent diabetes'. The subject was reviewed by MacCuish and Irvine (1975).

Pancreatic islet-cell antibodies (PICA). These were reported by Bottazzo *et al.* (1974) and have attracted much attention and caused some controversy, but their existence is not in doubt. Debate continues on whether they result from pancreatic islet cell damage or represent the attacking process. They are certainly associated more with insulin-dependent JOD than with MOD, although the latter may be divisible into those with and those without PICA. Those patients with MOD and PICA may be controlled by oral hypoglycaemic agents, and Irvine *et al.* (1977a, b) suggested that they represented a less severe form of JOD in those who will eventually require insulin. PICA are classified as IgG (MacCuish *et al.*, 1974a; Lendrum *et al.*, 1975). According to Lendrum *et al.* (1976) they are found in fewer than 2% of non-diabetics, in 5% of insulin-independent diabetics, and in 38% of those who are insulin-dependent. They are

detectable however in 85% of JOD immediately after diagnosis and decrease with time. Irvine (1977) suggested that in some there is such sudden islet cell death that PICA are not found at any stage. If they represent only the response to attack, then their usefulness in prevention or restriction of damage is limited; but Irvine *et al.* (1976) gave some evidence of their presence in nondiabetic patients with other autoimmune problems.

Tests of immune response. Cellular sensitivity to an extract of human pancreas assessed by MacCuish *et al.* (1974b), using the leucocyte migration test, gave abnormal results only in young JOD. Patients with JOD and controls were tested by Richens *et al.* (1976) for cellular sensitivity to pancreatic preparation, liver mitochondrial, and CB4 virus. The JOD response was again increased to pancreas and to mitochondria but it did not differ from controls when tested with CB4. There was a suggestion of CB4 hypersensitivity 3 months after diagnosis.

Huang and Maclaren (1976) demonstrated significant cytoadherence and cytotoxicity to human insulinoma cells *in vitro* when compared with controls. They favoured the hypothesis that JOD is a 'disease of autoaggression' and that lymphocytes and not antibodies deliver the attack on pancreatic β -cells. The role of T-cell suppressor function was studied by Horowitz *et al.* (1977). It was successfully demonstrated in all controls but was deficient in 6 of 9 patients with JOD.

The destructive device. What changes an apparently healthy child into one with JOD within days or weeks? Rubella and mumps certainly seem to trigger a genetic time-bomb with a delayed action system. While it is impossible to disregard the negative virus study from Oxford (Baum *et al.*, 1974), it only excluded appropriate antibody responses to that panel of viruses about which evidence was sought. Recent history confirms that previously unrecognised micro-organisms are responsible for serious diseases of which the aetiology was unknown (Gajdusek, 1979). Reports strongly suggest the involvement of Coxsackie B viruses and there may be others. Alternatively a failure to raise antibody may be a meaningful observation, but this would then be out of step with the fact that CB4 antibody was more common in patients with JOD than in controls (Gamble *et al.*, 1973). Perhaps a time factor, as in rubella, or fatigue or stress, as in paralytic poliomyelitis, also operate. Certainly a small but varied group of infective triggers to the device would explain the epidemiological facts.

Only a small minority of the population carries the next stage of the destructive device. Alternatively it

is made safe by age. Thus either all potential patients with JOD are triggered in their early years or some escape the initial attack (virus) when the device is sensitive. Age certainly has some influence as it would seem, for example, that rubella is only insulopathic when prenatally acquired although this has still to be proved. Few people escape rubella and mumps in their first 20 years and scarcely any become quickly diabetic in association with it.

The usefulness of HLA-typing in the identification of those who are vulnerable is apparent, but why do these particular types carry an increased risk of β -cell destruction? Intra-HLA recombination has been shown by Suci-Foca and Rubinstein (1976) to be less than 1% in offspring of apparently normal parents (6 crossovers in 2000 babies in 600 families). They claim it to be 15% however in families containing one or more person with JOD. They suggest the existence of a gene which increases the rate of recombination (that is chromosomal instability) in at least a segment of human chromosome 6. In cases where the individual is homozygous it may be associated with the appearance of JOD. Others share this view that the specific antigens already reviewed closely adjoin an immunoreactive gene concerned somehow with the autoaggressive reaction. The β -cell receptor may favour the attachment of specific viruses. A series of possible effects follow, analogous perhaps to those in response to hepatitis B virus* (HBV) shown in the Figure, taken from Eddleston and Williams (1974). A direct attack may cause β -cell death. Alternatively the process of virus replication in β -cells is sublethal to them and the damage is mediated by a host immune response. Virus-associated antigen on the cell surface provokes a T-cell response with destruction of infected β -cells, release of virus, antibody response, and either the end of the attack (if all virus is eliminated), or reinfection of surviving β -cells. T-cell 'helper-effect' may stimulate β -cells to produce antibody which attaches to virus antigen or virus-associated antigen on the cell surface.

K-cells would then kill the antibody-coated β -cells. This reaction should be time-limited by suppressor T-cells and failure would lead to a sustained attack. Lastly there is the possibility of a delayed immune response in which T-cells, alerted to seek and kill minor deviations from normality, sustain an autoaggressive action on surviving β -cells

*Anti-HBs and hepatitis were in fact found more commonly in diabetics than in nondiabetics by Hasslacher *et al.* (1973) but, while more frequently seen in patients with JODs rather than those with MOD in a later study (Hasslacher *et al.*, 1977), the prevalence had fallen to that in the nondiabetics. Previous patient-to-patient transmission and subsequent improvement in disposable syringes, needles, etc. are thought to explain the change.

Figure Hypothesis for pancreatic β -cell damage and JOD.

so that the child's own virus-modified cells maintain the process. Such a hypothesis could explain the clinical variations in JOD. Overwhelming infection could produce those cases in which symptoms of diabetes are virtually simultaneous with those of acute infection. Indeed, certain virus infections may be associated with pancreatic β -cells more often than is realised. The rare case of apparent complete recovery may represent the rare defensive success; or perhaps it is common and diabetes fails to develop.

Case report

In 1972 I admitted a 4.7-year-old girl who had suffered for a day or two from diarrhoea and vomiting. She was found to have diabetic ketoacidosis. Within hours of her admission her 20-month-old sister was admitted with identical symptoms but without diabetes. The elder child responded well to insulin and intravenous fluid. She was discharged within a week and has remained completely well for over 5 years. Her oral glucose tolerance test in 1978 and July 1979, when the blood glucose 2 hours after a glucose load was 5.2 mmol/l (93.7 mg/100 ml), was absolutely normal. The younger sister was also discharged within a week and remains well. From neither case was a virus recovered on culture. In July 1979 her blood glucose 2 hours after a glucose load was 4.6 mmol/l (82.9 mg/100 ml). The initial blood specimen from the elder child was un-

fortunately inadequate for a Coxsackie B neutralising antibody test. The second specimen however had a titre of 1024 for CB2. The younger (nondiabetic) child had a CB2 titre of 64 in the first and second specimens. In both sisters the titres for B₁, 3, 4, 5, and 6 were less than 16. There was local scepticism about the significance of these results in 1972 and no further samples were taken. The stability of the younger sister's titre in 1972 may suggest a previous infection, rather than a response to the infection which led to the admission. The elder sister's titre exceeded the younger's by a factor of 16. Does this imply that the infection was more severe or that the response was exaggerated? And why, if the infection was an old one, did the diabetes develop severely at the time it did and as a brief phenomenon?

Between these two extremes may lie a range of diabetic progress reflecting the autoimmune response, the acute episode, the 'honeymoon', β -cell atrophy, the development of ribbon-like cells, secretion of polypeptide, and the downward drift of insulin secretion, with oscillations, especially during re-encounters with the virus, until a steady diabetic state is achieved. The contention (Irvine *et al.*, 1977a) that some young diabetics controlled on oral hypoglycaemic agents for varying periods until insulin injections are obligatory are JOD in the making (MODY) rather than MOD is consistent with this. PICA in blood would then be expected for a much longer period.

The observation by Block *et al.* (1973) that C-peptide may be detected for several years after diagnosing JOD signifies continuing but failing insulin secretion. It has been repeated recently by Werther *et al.* (1978).

Speculation

It is now possible to screen by HLA-typing the offspring and the siblings of patients with JOD for vulnerability. It is costly as an individual test but, if there were a means of protection, such an initial outlay would be miniscule compared with the cost and the suffering involved in a life-time of diabetic care. Rubella vaccine should eliminate the presumably small problem of future JOD being produced by prenatal rubella infection. Mumps vaccine is available but more information is needed about JOD arising after vaccination. Such protection however is unlikely to contribute much to a programme designed to eliminate JOD.

A polyvalent CB virus vaccine is presumably possible and could prevent much morbidity other than diabetes. As with mumps vaccines, clinical trials on people likely to be vulnerable would need to be conducted with care. Once pronounced safe, it might be better to immunise all offspring and all siblings of patients with JOD, rather than to categorise them by HLA-type for vulnerability. In either, the obstetric history of birthweight for gestational age and for fetal malformations would be of great interest. A study of vaccinated and unvaccinated siblings might help to establish the aetiological role of CB virus strains.

Whether the use of highly-purified porcine insulins for maternal control or fastidious blood glucose control during diabetic pregnancy will prevent pancreatic islet fibrosis in the fetus and future JOD is still a matter for speculation, and a source of fetal lymphocytes for HLA-testing in early pregnancy remains unavailable. It is desirable however that such pathological material be pooled and expertly examined, as provided by the diabetic pregnancy study group in Europe. Perhaps the attachment of iatrogenic maternal insulin antibody or the overstimulation of fetal β -cells causes structural change capable of initiating an autoaggressive response. The answer may come when the gene defect, to which investigators now seem so close, is identified. The absent or abnormal response may prove correctable or the vulnerable child may be protected from its attack. Cahill (1976) optimistically says, 'New cases of juvenile diabetes may be prevented if our present rate of knowledge about the disease continues to grow over the next 2 or 3 years at the rate that it has for the past 5 years'.

References

- Adams, S. F. (1926). The seasonal variation in the onset of acute diabetes; the age and sex factors in 1000 diabetic patients. *Archives of Internal Medicine*, **37**, 861–864.
- Adi, F. C. (1974). Diabetes mellitus associated with infectious hepatitis in Nigeria. *British Medical Journal*, **1**, 183–185.
- Barboni, E., and Manocchio, J. (1962). Alterazioni pancreatiche in bovini con diabete mellito post-afoso. *Archivio veterinario italiano*, **13**, 477–489.
- Barbosa, J. (1977). Letter: HLA and diabetes mellitus. *Lancet*, **1**, 906–907.
- Barbosa, J., Noreen, H., Goetz, F., Simmons, R., Najarian, J., and Young, E. J. (1976). Letter: Juvenile diabetes and viruses. *Lancet*, **1**, 371.
- Barta, L., and Simon, S. N. (1977). Letter: Role of HLA-B8 and BW15 antigens in diabetic children. *New England Journal of Medicine*, **296**, 397.
- Baum, J. D., Aynsley-Green, A., and MacCallum, F. O. (1974). Letter: Coxsackie viruses and diabetes mellitus. *British Medical Journal*, **3**, 172.
- Block, M. B., Rosenfield, R. L., Mako, M. E., Steiner, D. F., and Rubenstein, A. H. (1973). Sequential changes in beta-cell function in insulin-treated diabetic patients assessed by C-peptide immunoreactivity. *New England Journal of Medicine*, **288**, 1144–1148.
- Bloom, A., Hayes, T. M., and Gamble, D. R. (1975). Register of newly diagnosed diabetic children. *British Medical Journal*, **3**, 580–583.
- Bottazzo, G. F., Florin-Christensen, A., and Doniach, D. (1974). Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet*, **2**, 1279–1283.
- Bottazzo, G. F., and Doniach, D. (1976). Letter: Pancreatic autoimmunity and HLA antigens. *Lancet*, **2**, 800.
- Bottazzo, G. F., Mann, J. I., Thorogood, M., Baum, J. D., and Doniach, D. (1978). Autoimmunity in juvenile diabetics and their families. *British Medical Journal*, **2**, 165–168.
- Boucher, D. W., Hayashi, K., Rosenthal, J., and Notkins, A. L. (1975). Virus-induced diabetes mellitus. III. Influence of the sex and strain of the host. *Journal of Infectious Diseases*, **131**, 462–466.
- Brown, E. E. (1956). Infectious origin of juvenile diabetes. *Archives of Pediatrics*, **73**, 191–198.
- Bunnell, C. E., and Monif, G. R. G. (1972). Interstitial pancreatitis in the rubella syndrome. *Journal of Pediatrics*, **80**, 465–469.
- Burgess, J. A., Kirkpatrick, K. L., and Menser, M. A. (1974). Fulminant onset of diabetes mellitus during an attack of infectious mononucleosis. *Medical Journal of Australia*, **2**, 706–707.
- Buschard, K., Rygaard, J., and Lung, E. (1976). The inability of a diabetogenic virus to induce diabetes mellitus in athymic (nude) mice. *Acta pathologica et microbiologica Scandinavica, Section C*, **84**, 299–303.
- Cahill, G. F., Jr (1976). Diabetes mellitus—progress report. *Progress in Clinical and Biological Research*, **10**, 69–81.
- Calnan, M., and Peckham, C. S. (1977). Incidence of insulin-dependent diabetes in the first sixteen years of life. *Lancet*, **1**, 589–590.
- Carpenter, C. C. J., Solomon, N., Silverberg, S. G., Bledsoe, T., Northcut, R. C., Klinenberg, J. R., Bennet, I. L., and Harvey, A. McG. (1964). Schmidt's syndrome (thyroid and adrenal insufficiency). A review of the literature and a report of fifteen cases, including ten instances of co-existent diabetes mellitus. *Medicine*, **43**, 153–180.
- Cole, L. (1934). Diabetes mellitus in children. *Lancet*, **1**, 947–950.

- Coleman, T. J., Gamble, D. R., and Taylor, K. W. (1973). Diabetes in mice after Coxsackie B4 virus infection. *British Medical Journal*, **3**, 25-27.
- Coleman, T. J., Taylor, K. W., and Gamble, D. R. (1974). The development of diabetes following Coxsackie B virus infection in mice. *Diabetologia*, **10**, 755-759.
- Contu, L., Puligheddu, A., Mura, C., and Gabbas, A. (1976). HLA antigens in Sardinian patients with diabetes mellitus (abstract). *Diabete et Metabolisme*, **2**, 158-159.
- Cooke, A. M., Fitzgerald, M. G., Malins, J. M., and Pyke, D. A. (1966). Diabetes in children of diabetic couples. *British Medical Journal*, **2**, 674-676.
- Cooper, L. Z., Green, R. H., Krugman, S., Giles, J. P., and Mirick, G. S. (1965). Neonatal thrombocytopenic purpura and other manifestations of rubella contracted *in utero*. *American Journal of Diseases of Children*, **110**, 416-427.
- Craig, J. O. (1977). *Childhood Diabetes and Its Management*. Postgraduate Paediatric Series. Butterworth: London.
- Craig, J. O., Ford, J. A., and McCuish, A. C. (1977). Letter: Rising incidence of childhood diabetes. *British Medical Journal*, **1**, 639.
- Craighead, J. E. (1965). Necrosis of the pancreas and parotid and lachrymal glands associated encephalomyocarditis virus infection. *Nature*, **207**, 1268-1269.
- Craighead, J. E. (1975). The role of viruses in the pathogenesis of pancreatic disease and diabetes mellitus. *Progress in Medical Virology*, **19**, 161-214.
- Craighead, J. E. (1976). Virus-induced insulinitis in experimental animal models. *Acta endocrinologica*, **83**, Supplement 205, 123-128.
- Craighead, J. E. (1978). Current views on the aetiology of insulin-dependent diabetes mellitus. *New England Journal of Medicine*, **299**, 1439-1445.
- Cudworth, A. G., and Woodrow, J. C. (1974). Letter: HLA antigen and diabetes mellitus. *Lancet*, **2**, 1153.
- Cudworth, A. G., and Woodrow, J. C. (1975a). HLA system and diabetes mellitus. *Diabetes*, **24**, 345-349.
- Cudworth, A. G., and Woodrow, J. C. (1975b). Evidence for HLA-linked genes in 'juvenile' diabetes mellitus. *British Medical Journal*, **3**, 133-135.
- Cudworth, A. G., Woodrow, J. C., and Gamble, D. R. (1975). Letter: Coxsackie B4 virus infection and diabetes. *Lancet*, **2**, 129.
- Cudworth, A. G., and Woodrow, J. C. (1976). The HLA system and diabetes mellitus (abstract). *Diabete et Metabolisme*, **2**, 159.
- Cudworth, A. G., White, G. B. B., Woodrow, J. C., Gamble, D. R., Lendrum, R., and Bloom, A. (1977). Aetiology of juvenile-onset diabetes. *Lancet*, **1**, 385-388.
- Dippe, S. E., Bennett, P. H., Miller, M., Maynard, J. E., and Berquist, K. R. (1975). Lack of causal association between Coxsackie B4 virus infection and diabetes. *Lancet*, **1**, 1314-1317.
- Eddleston, A. L. W. F., and Williams, R. (1974). Inadequate antibody response to HBsAg or suppressor T-cell defect in development of chronic active hepatitis. *Lancet*, **2**, 1543-1545.
- Fajans, S. S., and Conn, J. W. (1954). An approach to the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisone. *Diabetes*, **3**, 296-304.
- Farquhar, J. W. (1969). Prognosis of babies born to diabetic mothers in Edinburgh. *Archives of Disease in Childhood*, **44**, 36-47.
- Farquhar, J. W. (1972). Care of the diabetic child. *British Journal of Hospital Medicine*, **7**, 208-216.
- Farquhar, J. W. (1976). Diabetic adolescence. *International Diabetes Federation Bulletin*, **21**, No. 3, 6-12.
- Farquhar, J. W. (1977). Letter: Diet and the diabetic child. *British Medical Journal*, **1**, 285-286.
- Gajdusek, D. C. (1979). In *Proceedings of the Working Conference on Preventable Aspects of Genetic Morbidity, Cairo, 30 March-4 April 1978*. In press.
- Gamble, D. R. (1974). Epidemiological and viral observations on juvenile diabetes. *Postgraduate Medical Journal*, **50**, Supplement 3, 538-543.
- Gamble, D. R. (1975). Viral and epidemiological studies (abstract). *Proceedings of the Royal Society of Medicine*, **68**, 256-258.
- Gamble, D. R., Taylor, K. W., and Cumming, H. (1973). Coxsackie viruses and diabetes mellitus. *British Medical Journal*, **4**, 260-262.
- Gamble, D. R., and Taylor, K. W. (1976). Epidemiological background to diabetes. *Acta endocrinologica*, Supplement 205, 161-166.
- Ganda, O. P., Soeldner, J. S., Gleason, R. E., Smith, T. M., Kilo, C., and Williamson, J. R. (1977). Monozygotic triplets with discordance for diabetes mellitus and diabetic microangiopathy. *Diabetes*, **26**, 469-479.
- Gates, R. J., and Lazarus, N. R. (1977). Reversal of streptozotocin-induced diabetes in rats by intraperitoneal implantation of encapsulated neonatal rabbit pancreatic tissue. *Lancet*, **2**, 1257-1259.
- Gepts, W. (1965). Pathologic anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes*, **14**, 619-633.
- Gepts, W. (1976). Islet changes suggesting a possible immune aetiology of human diabetes mellitus. *Acta endocrinologica*, Supplement 205, 95-106.
- Gepts, W., De Mey, J., and Marichal-Pipeleers, M. (1977). Hyperplasia of pancreatic polypeptide-cells in the pancreas of juvenile diabetics. *Diabetologia*, **13**, 27-34.
- Gibbs, P. (1974). Three cases of acute ketotic diabetes mellitus with myocarditis: a common viral origin? *British Medical Journal*, **3**, 781-783.
- Gottlieb, M. S., and Root, H. F. (1968). Diabetes mellitus in twins. *Diabetes*, **17**, 693-704.
- Gunderson, E. (1927). Is diabetes of infectious origin? *Journal of Infectious Diseases*, **41**, 197-202.
- Harris, H. F. (1899). A case of diabetes insipidus quickly following mumps. *Boston Medical and Surgical Journal*, **140**, 465-469.
- Hasslacher, Ch., Wahl, P., and Sanwald, R. (1973). Australia-Antigen bei Diabetikern. *Deutsche medizinische Wochenschrift*, **98**, 301-304.
- Hasslacher, Ch., Thamer, G., Wahl, P., and Kommerell, B. (1977). Antibodies against the hepatitis B surface antigen in diabetics. *Diabete et Metabolisme*, **3**, 19-21.
- Hinden, E. (1962). Mumps followed by diabetes. *Lancet*, **1**, 1381.
- Horowitz, S. D., Borchering, W., and Bargman, G. J. (1977). Letter: Suppressor T-cell function in diabetes mellitus. *Lancet*, **2**, 1291.
- Hsu, S. H., Hsu, T. H., Chase, G. A., and Dias, W. B. (1977). Further data on HLA recombination in juvenile onset diabetes. *Transplantation Proceedings*, **9**, 1855-1858.
- Huang, S. W., and Maclaren, N. K. (1976). Insulin-dependent diabetes: a disease of autoaggression. *Science*, **192**, 64-66.
- Huff, J. C., Hierholzer, J. C., and Farris, W. A. (1974). An 'outbreak' of juvenile diabetes mellitus: consideration of a viral etiology. *American Journal of Epidemiology*, **100**, 277-287.
- Illeni, M. T., Pellegris, G., Guercio, M. J. D., Tarantino, A., Busetto, F., di Pietro, C., Clerici, E., Garotta, G., and Chiumello, G. (1977). HLA antigens in diabetic children. *Diabetes*, **26**, 870-873.
- Irvine, W. J. (1977). Letter: Autoimmunity in diabetes. *Lancet*, **1**, 189-190.

- Irvine, W. J., Stewart, A. G., and Scarth, L. (1967). A clinical and immunological study of adrenocortical insufficiency (Addison's disease). *Clinical and Experimental Immunology*, **2**, 31-69.
- Irvine, W. J., Scarth, L., Clarke, B. F., Cullen, D. R., and Duncan, L. J. P. (1970). Thyroid and gastric autoimmunity in patients with diabetes mellitus. *Lancet*, **2**, 163-168.
- Irvine, W. J., Gray, R. S., and McCallum, C. J. (1976). Pancreatic islet-cell antibody as a marker for asymptomatic and latent diabetes and prediabetes. *Lancet*, **2**, 1097-1102.
- Irvine, W. J., Toft, A. D., Holton, D. E., Prescott, R. J., Clarke, B. F., and Duncan, L. J. P. (1977a). Familial studies of type-1 and type-2 idiopathic diabetes mellitus. *Lancet*, **2**, 325-328.
- Irvine, W. J., McCallum, C. J., Gray, R. S., and Duncan, L. J. P. (1977b). Clinical and pathogenic significance of pancreatic islet-cell antibodies in diabetes treated with oral hypoglycaemic agents. *Lancet*, **1**, 1025-1027.
- Jackson, R. L., Murthy, D. Y. N., Guthrie, R. A., Burkeholder, J. N., Womack, W. H., and England, J. D. (1968). Endogenous insulin reserve in adolescent children with chemical and overt diabetes mellitus. In *Memoirs of the Twelfth International Congress of Pediatrics, Mexico, 1968*, volume 3, p. 612. Impresiones Modernas: Mexico.
- Kahn, C. B., Soeldner, J. S., Gleason, R. E., Rojas, L., Camerini-Davalos, H. A., and Marble, A. (1969). Clinical and chemical diabetes in offspring of diabetic couples. *New England Journal of Medicine*, **281**, 343-347.
- Kobberling, J., Appels, A., Kobberling, G., and Creutzfeldt, W. (1969). Glucose tolerance tests in 727 first-degree relatives of maturity-onset diabetics. *German Medical Monthly*, **14**, 290-294.
- Koivisto, V. A., Kuitunen, P., Tiilikainen, A., and Akerblom, H. K. (1977). HLA antigens especially B8 and BW15, in patients with juvenile diabetes mellitus, coeliac disease, and both of these diseases (abstract). *Diabete et Metabolisme*, **2**, 161.
- Kono, R. (1976). Enteroviruses other than poliovirus. *Bulletin of the Pan American Health Organisation*, **10**, 337-340.
- Lancet (1975). Editorial: Islet-cell transplantation. *Lancet*, **2**, 909-910.
- Landgraf, R., Landgraf-Leurs, M. M. C., Lander, T., Scholtz, S., Kuntz, B., and Albert, E. D. (1976). Letter: HLA haplotypes and glucose tolerance in families of patients with juvenile-onset diabetes mellitus. *Lancet*, **2**, 1084-1085.
- Lendrum, R., Walker, G., and Gamble, D. R. (1975). Islet-cell antibodies in juvenile diabetes mellitus of recent onset. *Lancet*, **1**, 880-883.
- Lendrum, R., Walker, G., Cudworth, A. G., Theophanides, C., Pyke, D. A., Bloom, A., and Gamble, D. R. (1976). Islet-cell antibodies in diabetes mellitus. *Lancet*, **2**, 1273-1276.
- Löw, B., Schersten, B., Sartor, G., Thulin, T., and Mitelman, F. (1975). Letter: HLA8 and W15 in diabetes mellitus and essential hypertension. *Lancet*, **1**, 695.
- Ludwig, H., Scherthaner, G., and Mayr, W. R. (1977). The importance of HLA genes to susceptibility in the development of juvenile diabetes mellitus. A study of 93 patients and 68 first degree relations. *Diabete et Metabolisme*, **3**, 43-48.
- McCrae, W. M. (1963). Diabetes mellitus following mumps. *Lancet*, **1**, 1300-1301.
- MacCuish, A. C., Barnes, E. W., Irvine, W. J., and Duncan, L. J. P. (1974a). Antibodies to pancreatic islet-cell in insulin-dependent diabetes with co-existent autoimmune disease. *Lancet*, **2**, 1529-1531.
- MacCuish, A. C., Jordan, J., Campbell, C. J., Duncan, L. J. P., and Irvine, W. J. (1974b). Cell-mediated immunity to human pancreas in diabetes mellitus. *Diabetes*, **23**, 693-697.
- MacCuish, A. C., and Irvine, W. J. (1975). Autoimmunological aspects of diabetes mellitus. *Clinics in Endocrinology and Metabolism*, **4**, 435-471.
- MacDonald, M. J. (1974). Equal incidence of adult-onset diabetes among ancestors of juvenile diabetics and nondiabetics. *Diabetologia*, **10**, 767-773.
- MacGregor, M. (1977). Juvenile diabetics growing up. *Lancet*, **1**, 944-945.
- Melin, K., and Ursing, B. (1958). Diabetes mellitus som komplikation till parotitis epidemica. *Nordisk Medicin*, **60**, 1715-1717.
- Menser, M. A., Dods, L., and Harley, J. D. (1967). A twenty-five year follow-up of congenital rubella. *Lancet*, **2**, 1347-1350.
- Menser, M. A., Forrest, J. M., Honeyman, M. C., and Burgess, J. A. (1974). Letter: Diabetes, HLA antigens, and congenital rubella. *Lancet*, **2**, 1508-1509.
- Menser, M. A., Forrest, J. M., and Bransby, R. D. (1978). Rubella infection and diabetes mellitus. *Lancet*, **1**, 57-60.
- Morris, P. J., Vaughan, H., McCallum, C. J., Gray, R. S., Irvine, W. J., Campbell, C. J., Duncan, L. J. P., and Farquhar, J. W. (1976). HLA and pancreatic islet-cell antibodies in diabetes (abstract). *Diabete et Metabolisme*, **2**, 158.
- Nelson, P. G., Pyke, D. A., and Gamble, D. R. (1975). Viruses and the aetiology of diabetes: a study in identical twins. *British Medical Journal*, **4**, 249-251.
- Nelson, P. G., Arthur, L. J. H., Gurling, K. J., Gamble, D. R., and Taylor, K. W. (1977). Letter: Familial juvenile-onset diabetes. *British Medical Journal*, **2**, 1126.
- Nerup, J., Platz, P., Andersen, O. O., Christy, M., Lyngsøe, J., Poulsen, J. E., Ryder, L. P., Nielsen, L. S., Thomsen, M., and Svejgaard, A. (1974). HLA antigens and diabetes mellitus. *Lancet*, **2**, 864-866.
- Nerup, J., Andersen, O. O., Christy, M., Platz, P., Ryder, L. P., Thomsen, M., and Svejgaard, A. (1976). HLA, autoimmunity, irus, and the pathogenesis of juvenile diabetes mellitus. *Acta endocrinologica*, **83**, Supplement 205, 167-175.
- Notkins, A. L. (1977). Virus-induced diabetes mellitus. *Archives of Virology*, **54**, 1-17.
- Olatawura, M. (1972). The psychiatric complications of diabetes mellitus in children. *African Journal of Medical Sciences*, **3**, 231-240.
- Osuntokun, B. O. (1974). Letter: Diabetes mellitus and infectious hepatitis. *British Medical Journal*, **1**, 639.
- Pointel, J. P., Raffoux, C., Janot, C., Sauvanet, J. P., Drouin, P., Strieff, F., and Derby, G. (1976). HLA-antigens and insulin dependent diabetes mellitus (abstract). *Diabete et Metabolisme*, **2**, 162.
- Post, R. H. (1962). An approach to the question does all diabetes depend upon a single genetic locus? *Diabetes*, **11**, 56-65.
- Pyke, D. A., and Taylor, K. W. (1967). Glucose tolerance and serum insulin in unaffected identical twins of diabetics. *British Medical Journal*, **4**, 21-22.
- Pyke, D. A., Cassar, J., Todd, J., and Taylor, K. W. (1970). Glucose tolerance and serum insulin in identical twins of diabetics. *British Medical Journal*, **4**, 649-651.
- Radder, J. K., and Terpstra, J. (1975). The incidence of diabetes mellitus in the offspring of diabetic couples. *Diabetologia*, **11**, 135-138.
- Richens, E. R., Ancil, R. J., and Hartog, M. (1976). Autoimmunity and viral infection in diabetes mellitus. *Clinical and Experimental Immunology*, **23**, 40-46.

- Rojas, L., Soeldner, J. S., Gleason, R. E., Kahn, C. B., and Marble, A. (1969). Offspring of two diabetic parents: differential serum insulin responses to intravenous glucose and tolbutamide. *Journal of Clinical Endocrinology and Metabolism*, **29**, 1569–1579.
- Rolles, C. J., Rayner, P. H., and Mackintosh, P. (1975). Letter: Aetiology of juvenile diabetes. *Lancet*, **2**, 230.
- Rosenbloom, A. L. (1975). Chemical diabetes in children with idiopathic hypoglycemia of infancy and idiopathic glucogen unresponsive (ketotic) hypoglycaemia. In *Diabetes in Juveniles: Medical and Rehabilitation Aspects*, pp. 94–96. Edited by Z. Laron and M. Karp. Karger: Basel.
- Rosenbloom, A. L., Bianchi, R., and Chin, F. T. (1972). Chemical diabetes mellitus in siblings of children with overt diabetes. *Israel Journal of Medical Science*, **8**, 841–847.
- Rosenthal, M. B., Goldfine, I. D., and Siperstein, M. D. (1976). Letter: Genetic origin of diabetes. *Lancet*, **2**, 908–909.
- Ross, M. E., Onodera, T., Hayashi, K., and Notkins, A. L. (1975). Virus-induced diabetes mellitus. V. Biological differences between the M-variant and other strains of encephalomyocarditis virus. *Infection and Immunity*, **12**, 1224–1226.
- Savi, M., Neri, T. M., Zavaroni, I., and Coscelli, C. (1976). HLA antigens and insulin dependent diabetes mellitus. A family study (abstract). *Diabete et Metabolisme*, **2**, 159.
- Scherthaner, G., Ludwig, H., and Mayr, W. R. (1977). Letter: B-lymphocyte alloantigens and insulin-dependent diabetes mellitus. *Lancet*, **2**, 1128.
- Simpson, N. E. (1964). Multifactorial inheritance; a possible hypothesis for diabetes. *Diabetes*, **13**, 462–471.
- Sinaniotis, C. A., Daskalopoulou, E., Lapatsanis, P., and Doxiadis, S. (1975). Letter: Diabetes mellitus after mumps vaccination. *Archives of Disease in Childhood*, **50**, 749.
- Smith, R., and Deibel, R. (1975). Coxsackie virus infection in mice. *Archives of Internal Medicine*, **135**, 238–239.
- Solow, H., Hidalgo, R., Biajchman, M., and Singal, D. P. (1977). HLA-A, B, C, and B-lymphocyte alloantigens in insulin-dependent diabetes. *Transplantation Proceedings*, **9**, 1859–1861.
- Sorsby, A. (1966). *The Incidence and Causes of Blindness in England and Wales, 1948–1962*. Ministry of Health Reports on Public Health and Medical Subjects, No. 114, pp. 15, 39, 48, 61. HMSO: London.
- Suciu-Foca, N., and Rubinstein, P. (1976). Letter: Intra-HLA recombinations in juvenile diabetes mellitus. *Lancet*, **1**, 371–372.
- Sultz, H. A., Hart, B. A., Zielezny, M., and Schlesinger, E. R. (1975). Is mumps virus an aetiological factor in juvenile diabetes mellitus? *Journal of Pediatrics*, **86**, 654–656.
- Tattersall, R. B., and Pyke, D. A. (1972). Diabetes in identical twins. *Lancet*, **2**, 1120–1125.
- Tattersall, R. B., and Fajans, S. S. (1975a). Prevalence of diabetes and glucose intolerance in 199 offspring of thirty-seven conjugal diabetic parents. *Diabetes*, **24**, 452–462.
- Tattersall, R. B., and Fajans, S. S. (1975b). A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes*, **24**, 44–53.
- Turtle, J. R. (1977). Ability and stability in diabetes in providing a rational basis for pancreatic transplantation. In *Proceedings of the Pancreatic Islet Workshop, Cardiff, March 1977*. British Diabetic Association: London.
- Vialettes, B., Vague, Ph., and Mercier, P. (1976). HLA differences between insulin dependent diabetics and non-diabetic low insulin responders (abstract). *Diabete et Metabolisme*, **2**, 162.
- Wadsworth, M. E. J., and Jarrett, R. J. (1974). Incidence of diabetes in the first 26 years of life. *Lancet*, **2**, 1172–1174.
- Werther, G. A., Baum, J. D., Jenkins, P. A., and Turner, R. C. (1978). Once or twice daily insulin injections for diabetic children? (abstract). *Archives of Disease in Childhood*, **53**, 835.
- West, K. M. (1960). Response to cortisone in prediabetes. *Diabetes*, **9**, 379–385.
- White, P. (1959). Pregnancy complicating diabetes. In *Joslin's Diabetes Mellitus*, tenth edition, pp. 690–716. Lea and Febiger: Philadelphia.
- White, P. (1960). Childhood diabetes. Its course and influence on the second and third generations. *Diabetes*, **9**, 345–355.
- Wilson, C., Connolly, J. H., and Thomson, D. (1977). Coxsackie B2 virus infection and acute-onset diabetes in a child. *British Medical Journal*, **1**, 1008.

Correspondence to Professor J. W. Farquhar, Department of Child Life and Health, University of Edinburgh, 17 Hatton Place, Edinburgh EH9 1UW.