Review article

Juvenile diabetes mellitus

Possibility of prevention

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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 multiples in the pancreatic β-cells of mouse 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...
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 $\beta$-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 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.

Raeder 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 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

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<tr>
<td>Alström’s syndrome</td>
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<td>Ataxia telangiectasia</td>
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<td>Chromosome abnormalities:</td>
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<td>Down’s syndrome; Klinefelter’s syndrome; Turner’s syndrome and Turner’s mosaicism and relatives; 47,XX,21 + 46XX mosaic with liver cirrhosis</td>
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<td>Cockayne’s syndrome</td>
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<td>Cystic fibrosis</td>
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<td>Diabetes insipidus</td>
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<td>Friedreich’s ataxia</td>
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<td>Glucose-6-phosphate dehydrogenase deficiency</td>
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<td>Type I diabetes</td>
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<td>Haemochromatosis</td>
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<td>Huntington’s chorea</td>
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<td>Hyperlipaemia, diabetes, hypogonadism, and short stature syndrome</td>
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<td>Isolated growth hormone deficiency</td>
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<td>Laurence-Moon-Biedl syndrome</td>
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<td>Leucoderma</td>
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<td>Lipatrophic diabetes</td>
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<td>Muscular dystrophy</td>
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<td>Myotonic dystrophy</td>
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<td>Ocular hypertension induced by dexamethasone</td>
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<td>Optic atrophy and diabetes</td>
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<td>Hereditary relapsing pancreatitis</td>
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<td>Photomycelonous, diabetes, deafness, nephropathy, and cerebral dysfunction</td>
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<td>Pinal hyperplasia and diabetes</td>
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<td>Acute intermittent porphyria</td>
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<td>Phaeochromocytoma</td>
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<td>Prader-Willi syndrome</td>
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<td>Retinitis pigmentosa, neuropathy, ataxia, and diabetes</td>
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<td>Schmidt’s syndrome</td>
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<td>Werner’s syndrome</td>
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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 monzygous ‘identical’ twins.

The antigens associated with JOD are B₈, BW₂₅, B₁₈, BW₃₅, A₁, AW₃₅, DW₂₅, DW₄, CW₂₅, DRW₃₅ and DRW₄. 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 B₈ 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 B₈ 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; Viallettes 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 B₈ 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-B₈ is uncommon in the Alueitan people of the Pribilof Islands (Menser et al., 1974).

Cudworth and Woodrow (1974, 1975a,b, 1976) reported increased representation of BW₁₅ 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 B₈ and BW₁₅ may have a significant effect. Nerup et al. (1976) suggested an increased risk to siblings of the propositus, while Koivisto et al. (1977) found it at its greatest when JOD coexisted with coeliac disease. Barta and Simon (1977) found increased representation of B₈, but not of BW₁₅, in Hungary. When they looked at coexisting B₈ and BW₁₅, 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 B₈, and for B₈ and BW₁₅ at 2·027 and 18·25 respectively. Cudworth et al. (1977) however estimated the relative risk of B₈ and BW₁₅ at 5·59.

Cudworth and Woodrow (1976) reported increased representation of B₁₈ in patients with JOD and calculated the relative risk to be 2·56. According to Viallettes et al. (1976) B₁₈ occurs in 26·6% of those with JOD compared with 11·8% in the general population.

Contu et al. (1976) reported that BW₂₅ was present in 29·2% of patients with JOD compared with 12·5% of the non-diabetic 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 BW₂₅ was significantly decreased in those with JOD.

Morris et al. (1976) found A₁ 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). Vialettes 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).

AW69 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 B4 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 (Schernthaner 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-B27-positive patients with JOD reported by Rolles et al. (1975) 81% presented between October and the end of February, whereas those with HLA-B27-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 B4 and BW15, had higher neutralising antibody titres to Coxsackie B virus strains 1–4.

\( \beta \)-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 insulitis 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 \( \beta \)-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 \( \beta \)-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.

\( \beta \)-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 ß-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 ß-cell destruction? Intra-HLA recombination has been shown by Suciu-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 ß-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 ß-cell death. Alternatively the process of virus replication in ß-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 ß-cells, release of virus, antibody response, and either the end of the attack (if all virus is eliminated), or reinfecion of surviving ß-cells. T-cell 'helper-effect' may stimulate ß-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 ß-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 ß-cells

*Anti-Hbs and hepatitis were in fact found more commonly in diabetics than in nondiabetics by Hassacher et al. (1973) but, while more frequently seen in patients with JODs rather than those with MOD in a later study (Hassacher 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.
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 unfortunately 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, B2, B5, 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 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

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Juvenile diabetes mellitus


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