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# DIABETES MELLITUS: CLASSIFICATION, CHARACTERISTICS AND DIAGNOSIS

On April 27-28, 1978, an international workshop was assembled in Bethesda, Maryland under the auspices of the National Institutes of Health. Sixteen participants made up what was subsequently called the National Diabetes Data Group. A working paper was put together and widely circulated for suggestions and criticisms by workers in the field. The final report, which has received the official imprimatur of the American Diabetes Association, will be published in the December issue of Diabetes. Since its recommendations will be of wide interest to practicing physicians, the report will serve as the basis for a discussion of recent advances pertaining to the etiology and diagnosis of diabetes mellitus.

## I. Classification

It was recognized from the start that a whole host of diseases may cause either hyperglycemia or impaired glucose tolerance (1). Indeed Zonana and Rimoin (2) have pointed out that there are over 30 genetic diseases alone that have glucose intolerance or frank diabetes as part of the clinical syndrome. Some of these syndromes are shown in Table 1 (next page). In attempting to bring some order to this mass of conditions, a six part classification was devised. The aim was to make the classes mutually exclusive (so that a person would be in only one classification at any one time), simple and clear (that is, based on routinely available clinical laboratory tests) and relatively precise (in order that patients in each category would be generally homogenous). Six categories were finally listed:

1. Idiopathic diabetes mellitus (DM)
   - I. Insulin-dependent (IDDM)
   - II. Non-insulin-dependent (NIDDM)
     - a. Non-obese
     - b. Obese
2. Gestational diabetes (GDM)
3. Impaired glucose tolerance (IGT)
4. Previous abnormality of glucose tolerance (Prev. AGT)
5. Potential abnormality of glucose tolerance (Pot. AGT)
6. Secondary diabetes

Groups 4 and 5 are extremely questionable from a clinical standpoint and were widely objected to. However, the study group left them in because they thought they would be helpful for epidemiological investigators. The criteria for inclusion are as follows:

TABLE 1

CONDITIONS AND SYNDROMES ASSOCIATED WITH DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

1. Hormonal
   a. Hypoinsulinemic
      1) Endocrine overactivity
         Catecholamines - e.g. pheochromocytoma
         Somatostatinoma
         Mineralcorticoids - e.g. aldosteronoma
      2) Underactivity
         Hypoparathyroidism - hypocalcemia
         Type I isolated growth hormone deficiency
         Multitropic pituitary deficiency
         Laron dwarfism
         Hypothalamic lesions - "Piqure" diabetes (of Claude Bernard)
   b. Hyperinsulinemic - states of insulin resistance
      1) Overactivity
         Glucocorticoids
         Progestins and estrogens
         Growth hormone - acromegaly
         Glucagon
      2) Underactivity
         Type II isolated growth hormone deficiency

2. Drugs
   See Tables 4A and 4B

3. Pancreatic Disease
   a. Neonatal
      1) Congenital absence of the pancreatic islets
      2) Transient diabetes of the newborn
         Functional immaturity of insulin secretion
         ? Converse of infants of diabetic mothers
   b. Postinfancy
      1) Acquired - traumatic, infections, toxic, neoplastic
      2) Hereditary
         a) Cystic fibrosis
         b) Hereditary relapsing pancreatitis
         c) Hemochromatosis

4. Insulin receptor abnormalities
   a. Defect in insulin receptor
      1) Congenital lipodystrophy
      2) Associated with virilization, acanthosis nigricans
   b. Antibody to insulin receptor - associated immune disorders

5. Other Genetic Syndromes
   a. Inborn errors of metabolism
      1) Glycogen storage disease type I
      2) Acute intermittent porphyria
      3) Hyperlipidemia
      4) Hyperglycerolemia
   b. Insulin resistant syndromes
      1) Ataxia telangiectasia
      2) Myotonic dystrophy
      3) Mendenhall's syndrome
      4) Lipoatrophic syndromes
   c. Hereditary neuromuscular disorders
      1) Optic atrophy - diabetes mellitus
         Diabetes insipidus, nerve deafness
      2) Muscular dystrophies
      3) Late onset proximal myopathy
      4) Huntington's chorea
      5) Machado's disease
      6) Herrman syndrome
      7) Friedreich's ataxia
      8) Alstrom syndrome
      9) Laurence-Moon-Biedl syndrome
      10) Retinopathy, hypogonadism, mental retardation, nerve deafne
      11) Pseudo-Refsum's syndrome
   d. Progeroid syndrome
      1) Cockayne syndrome
      2) Werner syndrome
   e. Syndromes with glucose intolerance secondary to obesity
      1) Prader-Willi syndrome
      2) Achondroplasia
   f. Miscellaneous
      1) Steroid induced ocular hypertension
      2) Epiphyseal dysplasia and infantile-onset diabetes
   g. Cytogenetic disorders
      Down
      Turner
      Klinefelter

Insulin-dependent diabetes mellitus

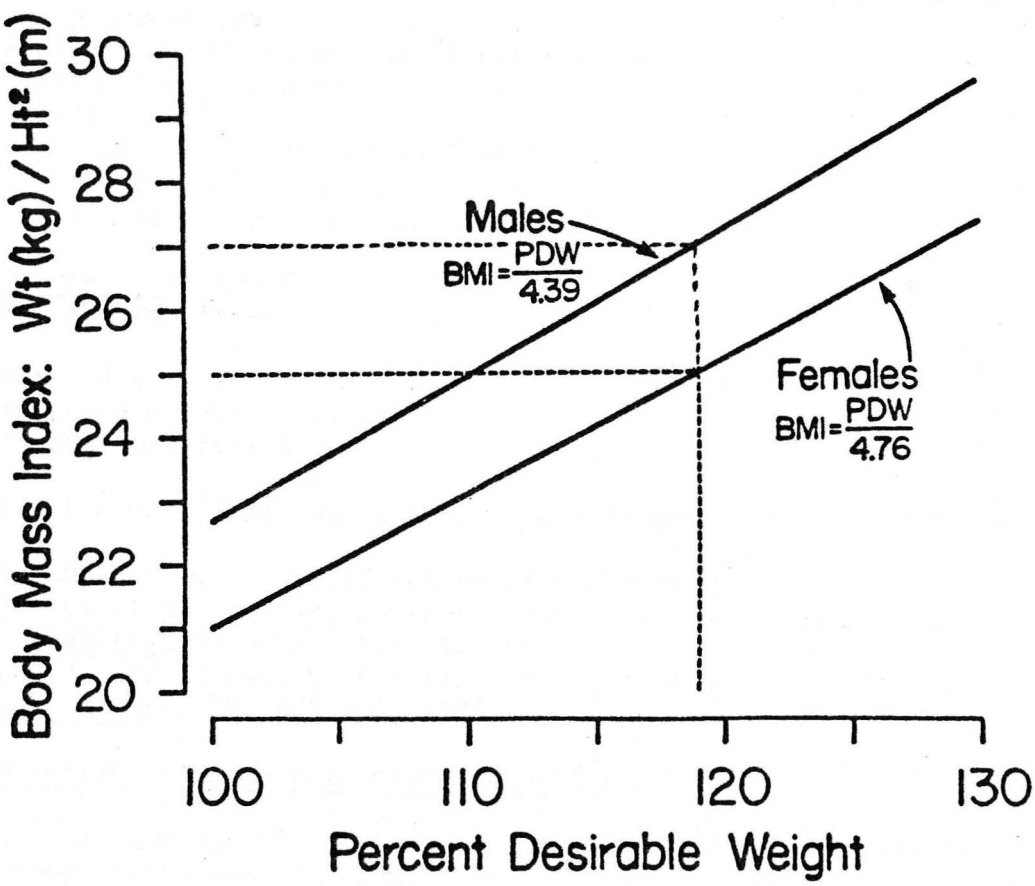
1. Dependent on insulin to prevent ketosis or to preserve life.
2. Onset usually in youth.
3. Low plasma insulin levels.
4. Associated with certain HLA types.
5. Associated with autoimmune phenomenon, especially islet cell antibodies.

Non-insulin-dependent diabetes mellitus

1. Non-insulin-dependent or ketosis prone (though insulin may be given for persistent hyperglycemia).
2. No HLA association.
3. No autoimmune phenomena.
4. Obesity defined by ideal body weight of greater than 120% or body mass index > 25 for women or > 27 for men.

The body mass index is defined as the weight in kilograms divided by the height (in meters) squared. The body mass index and percent desireable weight are closely related as shown in Fig. 1.

Figure 1 (Ref. 1)



Gestational diabetes mellitus

1. Glucose intolerance with onset or recognition during pregnancy.

Impaired glucose tolerance

1. Normal fasting plasma glucose.
2. Plasma glucose response after glucose challenge intermediate between normal and diabetes.
3. Replaces widely used terms (which should be abandoned) such as: "asymptomatic", "chemical" and "subclinical" diabetes. The term "prediabetes" should also not be used.

Previous abnormality of glucose tolerance

1. Patients currently have normal glucose tolerance.
2. At some previous time had fasting hyperglycemia or abnormal glucose tolerance occurring spontaneously or associated with stress such as myocardial infarction, infection, pregnancy, obesity, etc.

Potential abnormality of glucose tolerance

1. Normal glucose tolerance now and at all previous times.
2. Increased risk for diabetes because of:
   a. Identical twin with diabetes
   b. Both parents diabetic
   c. A diabetic parent and a diabetic sibling or a diabetic parent and grandparent.
   d. A diabetic sibling with a diabetic child
   e. Birth weight > 4.5 kg
   f. Obesity
   g. HLA haplotype identical to diabetic sibling
   h. Islet cell antibodies
   i. Certain ethnic groups (e.g. Pima Indians)

Secondary diabetes mellitus

1. Hormonal abnormalities
2. Drugs
3. Pancreatic disease
4. Insulin receptor abnormalities
5. Genetic abnormalities

The criteria for abnormal glucose tolerance and diabetes will be given below.

(1) Harris, M., et al. Classification of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group, NIH. Diabetes, December 1979, in press.
(2) Zonana, J. and Rimoin, D. L. Inheritance of diabetes mellitus. N. Engl. J. Med. 295:603-605, 1976.

II. Characteristics of idiopathic diabetes mellitus

A significant amount of new information has accumulated in the last several years regarding genetic, immunologic and infectious aspects of insulin-dependent diabetes mellitus. The advances with non-insulin-dependent diabetes have been far less impressive. A brief review of these three areas follows:

A. Genetics:

1. Mendelian aspects: The Mendelian aspects of the genetics of diabetes has been recently reviewed at this forum by Dr. Michael S. Brown (3) and will not be covered in detail here. Workers in the field still argue about whether a simple pattern of inheritance is present. Rubinstein and coworkers (4,5) argue for a recessive gene, linked to the HLA system, which exhibits a 50 percent penetrance. They explained discrepancies with theory (e.g., that siblings of the affected patient had distinct, non-identical HLA haplotypes) on the grounds by intra-HLA recombinations. I think it is fair to say that the majority of geneticists do not agree with their interpretation (6-9). Cudworth (9) states the argument of the latter succinctly as follows: "Several investigators favoured the idea of autosomal recessive inheritance, but found it necessary to postulate that penetrance is markedly reduced such that only about one-fifth of subjects with the genotype actually develop the disease. It has been pointed out that it is unlikely that a clinical entity as common as diabetes will be controlled by a single gene, and secondly by invoking incomplete penetrance of this magnitude it is possible to prove that almost everything has a genetic basis". Those sceptical of a recessive form of inheritance favor a polygenic or multifactorial inheritance pattern, especially for juvenile diabetes. One form of non-insulin-dependent diabetes, the so-called "Maturity-Onset Diabetes of Young People (MODY) is thought to be inherited in dominant fashion (10-12). This is a very mild type of hyperglycemia which has the following characteristics:

Maturity-onset diabetes of young people

(1) Dominant inheritance
(2) Onset in first two decades of life
(3) Disease tends not to be progressive
(4) Degenerative complications less common than in other forms
(5) Low plasma insulin levels (in contrast to ordinary non-insulin-dependent disease, where levels are normal or high)
(6) Glucagon levels only relatively elevated

(3) Brown, M. S. L'héredité du diabète sucré: Le cauchemar du genetician. Medical Grand Rounds, July 20, 1978.
(4) Rubinstein, P., Suciu-Foca, N. and Nicholson, J. F. Genetics of juvenile diabetes mellitus. A recessive gene closely linked to HLA D and with 50 per cent penetrance. N. Engl. J. Med. 297:1036-1040, 1977.
(5) Rubinstein, P., Suciu-Foca, N. and Nicholson, J. F. Letter. N. Engl. J. Med. 298:462, 1978.
(6) Barbosa, J., Kind, R., Noreen, H. and Yunis, E. J. The histocompatibility system in juvenile, insulin-dependent diabetic multiplex kindreds. J. Clin. Invest. 60:989-998, 1977.
(7) Barbosa, J., Noreen, H., King, R. and Yunis, E. J. Letter. New Engl. J. Med. 298:462, 1978.
(8) Neel, J. V. The genetics of juvenile-onset-type diabetes mellitus. N. Engl. J. Med. 297:1062-1063, 1977.

(9) Cudworth, A. G. Type I diabetes mellitus. Diabetologia 14:281-291, 1978.
(10) Tattersall, R. B. and Fajans, S. S. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes 24:44-53, 1975.
(11) Barbosa, J., Ramsay, R. and Goetz, F. C. Plasma glucose, insulin, glucagon, and growth hormone in kindreds with maturity-onset type of hyperglycemia in young people. Ann. Int. Med. 88:595-601, 1978.
(12) Fajans, S. S., Cloutier, M. C. and Crowther, R. L. Clinical and etiologic heterogeneity of idiopathic diabetes mellitus. Diabetes 27:1112-1125, 1978.

2. HLA associations: One of the exciting findings of recent years has been the observation that when one does population studies there is an increased risk of diabetes found in association with the HLA system of the sixth human chromosome in insulin-dependent diabetes which is not seen in non-insulin-dependent diabetes except for the Xhosa tribe of blacks in South Africa. (In this tribe both insulin-dependent and insulin-independent diabetic subjects show a significant increase in BW 35 and $A_2$ (13)). These associations are race related; i.e., orientals (Japanese) have different associations than do Caucasians and different Caucasian groups differ amongst themselves. The initial correlations were found with alleles at the A and B locus of the histocompatibility system (9,14). Representative percentages and risks for different antigens are shown in Tables 2 & 3.

Table 2 (Ref. 9)

Table 2. Spectra of relative risk for HLA A and B antigens in 323 'juvenile-onset' diabetics, age of onset below 30 years, compared with 451 healthy controls

| HLA | Relative risk | p value |
|---|---|---|
| A1 | 1.61 | 0.0017 |
| A2 | 1.38 | 0.0330 |
| A29 | 1.31 | 0.4260 |
| A9 | 1.16 | 0.4543 |
| A28 | 0.87 | 0.7728 |
| A3 | 0.69 | 0.0037 |
| AW30/31 | 0.66 | 0.3898 |
| A10 | 0.55 | 0.0533 |
| AW32 | 0.47 | 0.1057 |
| A11 | 0.31 | 0.0001 |
| | Total $X^2 = 42.40$ | |
| B8 | 2.63 | $2.2 \times 10^{-8}$ |
| B18 | 2.26 | 0.0028 |
| B15 | 1.85 | 0.0055 |
| B40 | 1.30 | 0.2690 |
| B14 | 0.84 | 0.6406 |
| B12 | 0.82 | 0.2569 |
| B27 | 0.67 | 0.2065 |
| B22 | 0.62 | 0.0055 |
| B13 | 0.61 | 0.2379 |
| BW35 | 0.60 | 0.2226 |
| B17 | 0.47 | 0.0222 |
| B5 | 0.43 | 0.0072 |
| B7 | 0.40 | $1.0 \times 10^{-4}$ |
| | Total $X^2 = 104.26$ | |

Table 3 (Ref. 14)

**Table 3. Association of Selected Histocompatibility Antigen Types with Insulin-Dependent Diabetes Mellitus in Population Surveys.***

| HLA | No. of Studies | Patients | | Controls | | Relative Risk |
|---|---|---|---|---|---|---|
| | | Total | % positive (range) | Total | % positive (range) | |
| A1 | 12 | 1,110 | 13–46 | 6,704 | 9–34 | 1.32 |
| A9 | 10 | 905 | 22–39 | 5,254 | 16–28 | 1.35 |
| Aw30 | 5 | 468 | 1–31 | 1,785 | 1–26 | 1.87† |
| B5 | 11 | 998 | 0–14 | 5,704 | 9–21 | 0.59 |
| B7 | 12 | 1,110 | 3–29 | 6,704 | 3–32 | 0.51 |
| B8 | 13 | 1,200 | 19–55 | 6,856 | 2–29 | 2.42† |
| B18 | 12 | 1,088 | 5–59 | 5,856 | 5–50 | 1.65† |
| B15 | 13 | 1,200 | 4–50 | 6,856 | 2–26 | 1.89† |
| Bw35 | 11 | 998 | 6–34 | 5,704 | 6–27 | 0.74 |

*Data compiled by the HLA and Disease Registry, Tissue Typing Laboratory, Rigshospitalet, DK 2100 Copenhagen, Denmark, courtesy of P Platz.

†$P<0.05$.

Thus far it is generally accepted that HLA $A_1$, $A_2$, $B_8$, $B_{15}$ and $B_{40}$ confer increased risk. The $A_1$ and $A_2$ antigens are thought to be involved by linkage disequilibrium with $B_8$ and $B_{15}$ respectively.[1] The latter are the most universally associated antigens at the B site. Interestingly, if $B_8$ and $B_{15}$ are inherited together, the risk of diabetes is additive (Table 4). It must be understood that antigens of the HLA system are not thought to be diabetes inducing genes themselves; rather they indicate proximity of the causal genes. It is now recognized that D locus alleles may be even more closely linked to a putative diabetic gene than B antigens and that $DW_3$, $DW_4$, $DRW_3$ and $DRW_4$ are specifically involved (D locus alleles are determined by mixed lymphocyte culture, while DR alleles are defined by serologic tests with isolated B lymphocytes or monocytes. W means an antigen provisionally accepted by the International Histocompatibility Workshop.) (9,14-17). In one study the relative risk imposed by $DW_3$ was 6.4 and by $DW_4$, 3.7.

Certain alleles are found in decreased frequency in insulin dependent

[1] If an allele X (an alternative gene) at locus A has a gene frequency of 0.2 and allele Y at locus B has a gene frequency of 0.3, then the combination of XY will occur with a frequency of 0.06. If the frequency of XY is not equal to the product of the frequencies of the respective alleles, then the two determinants are said to be in linkage disequilibrium. The association may be positive or negative depending on whether the frequency of XY is greater or less than expected.

Table 4 (Ref. 9)

Table 4. Analysis of HLA phenotypes in 51 probands of families with two or more Type I diabetic siblings

| HLA | Relative risk | p value |
|---|---|---|
| B5 | 0.27 | 0.042 |
| B7 | 0.52 | 0.043 |
| B8 | 2.08 | 0.012 |
| B15 | 3.45 | $9.1 \times 10^{-4}$ |
| B18 | 4.75 | $3.5 \times 10^{-4}$ |
| B35 | 0.37 | 0.057 |
| B40 | 2.21 | 0.036 |
| B8, B15 | 9.62 | $6.4 \times 10^{-4}$ |
| B8, B40 | 7.61 | 0.022 |
| B15, B18 | 7.42 | 0.225 |
| B8, B18 | 3.16 | 0.401 |

diabetes and therefore may be protective. Outstanding is $B_7$, but $DRW_2$, $DW_2$ and $A_4$ fall in the same category (Table 5) (9,15,18).

Table 5 (Ref. 18)

Table 5. Statistically Significant Decrease of HLA-B7 Frequency (Chi-Square = 27.88, P<0.0005) in Patients with Juvenile-Onset Diabetes (JOD) as Compared with Controls.*

| Source of Data | JOD | | Controls | |
|---|---|---|---|---|
| | B7-positive subjects | No. of patients studied | B7-positive subjects | No. of controls studied |
| Thomsen et al[1] | 9 (10.6%) | 85 | 527 (26.8%) | 1967 |
| Cudworth & Woodrow[2] | 8 (16.0%) | 50 | 75 (32.2%) | 233 |
| Bertrams et al[4] | 15 (13.4%) | 112 | 260 (26.0%) | 1000 |
| Our data & data of Schernthaner et al[3] | 9 (14.1%) | 64 | 117 (26.0%) | 450 |
| Data combined | 41 (13.2%) | 311 | 979 (26.8%) | 3650 |

*Combined data from various research centers.

A summary of the currently accepted relationships in Caucasians is shown in Figure 2.

Figure 2 (Ref. 9)

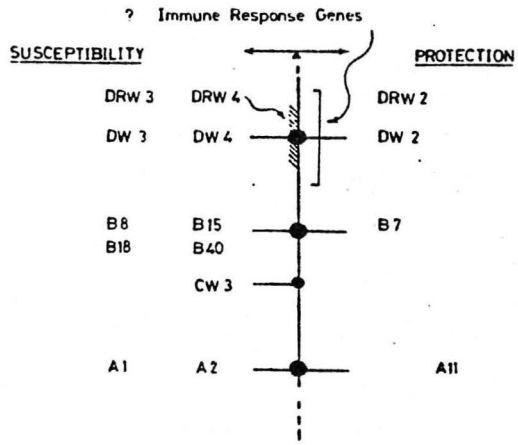



**Fig. 2.** Pattern of 'susceptibility' and 'protective' HLA factors in Type I diabetes

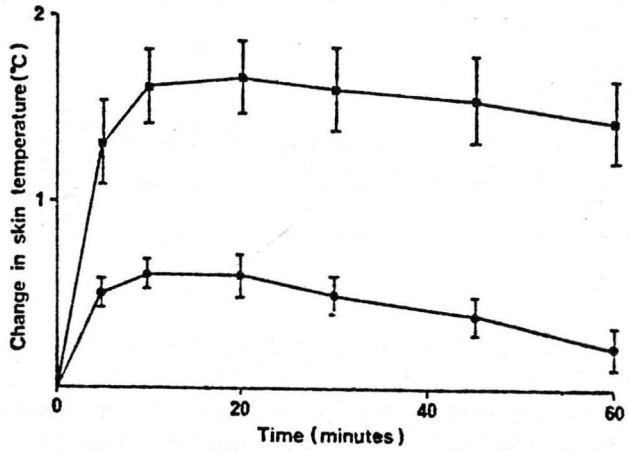
(13) Briggs, B. R., Jackson, W.P.U., du Toit, E. D. and Botha, M. C. The HLA antigen distribution in diabetes in Southern African blacks. Diabetes, in press.
(14) Craighead, J. E. Current views on the etiology of insulin-dependent diabetes mellitus. N. Engl. J. Med. 299:1439-1445, 1978.
(15) Cudworth, A. G. and Festenstein, H. HLA genetic heterogeneity in diabetes mellitus. Brit. Med. Bull. 34:285-289, 1978.
(16) Solow, H., Hidalgo, R. and Singal, D. P. Juvenile-onset diabetes: HLA-A, -B, -C, and -DR alloantigens. Diabetes 28:1-4, 1979.
(17) Garavoy, M. R., Barbosa, J., Reddish, M., Martin, S., Noreen, H., Yunis, E. J. and Carpenter, C. B. HLA-DR antigens and unique serologic reactions in juvenile-onset diabetes mellitus. Transplant. Proceed. 10:967-969, 1978.
(18) Ludwig, H., Schernthauer, G. and Mayr, W. R. Is HLA-$B_7$ a marker associated with a protective gene in juvenile-onset diabetes mellitus? N. Engl. J. Med. 294:1066, 1976.

3. Other markers: The $B_f$ locus codes for properdin factor B, a glycine rich β-glycoprotein present in serum which plays an important role in the alternate complement pathway. It is probably located to the left of the B locus. Alleles at this locus can be determined by isoelectric focusing in polyacrylamide gel. $Bf^S$ imparts a risk of 2.23, while a rare genetic type $Bf^{F1}$ increases the risk to 15 fold, by far the highest for any single allele in the HLA related system (19). This finding strongly suggests a close association with at least one powerful diabetic gene.

(19) Raum, D., Alper, C. A., Stein, R. and Gabbay, K. H. Genetic marker for insulin-dependent diabetes mellitus. Lancet 1:1208-1210, 1979.

Recently an interesting observation was made by chance in non-insulin dependent diabetic subjects (20). It has been observed that patients taking chlorpropamide exhibit an intense facial flush after drinking alcohol. This trait appears to be dominantly inherited and is infrequent in insulin-dependent diabetics and non-diabetics; the flush can be assessed by measuring skin temperature after drinking 40 ml of sherry. In the course of unrelated experiments on long-acting enkephalin analogues, one investigator (taking the drug) had an intense facial flush. Since his father was a diabetic, it was decided to test the analogue [D-Ala$^2$, MePhe$^4$, (0)-ol] enkephalin in control and diabetic subjects previously shown to have the chlorpropamide-alcohol flushing trait. The enkephalin analogue reproduced the phenomenon as shown in Figure 3.

Figure 3 (Ref. 20)




**Mean (S.E.M.) increase in facial temperature after intravenous DAMME (0·25 mg) in 9 C.P.A.F.-positive (■–■) and 8 C.P.A.F.-negative subjects (●–●).**

**All differences are significant ($P<0.01$).**

More interesting was the observation that naloxone, the opiate antagonist, blocked the alcohol-induced flush. While the authors vastly over-interpret their data, suggesting that sensitivity to enkephalin causes non-insulin-dependent diabetes, the observation is of interest since intraventricular injection of morphine causes hyperglycemia.

(20) Leslie, R. D. G., Pyke, D. A. and Stubbs, W. A. Sensitivity to enkephalin as a cause of non-insulin-dependent diabetes. Lancet 1:341-343, 1979.

B. Immunology:

1. Islet cell antibodies: The prevalence of plasma antibodies to thyroid

gland and gastric muscosa is three times higher in juvenile diabetic subjects than in age and sex matched controls. Similarly, antibodies to adrenal cortex occur 30 times more frequently in insulin-requiring diabetics than in non-diabetic subjects. Conversely, the prevalence of diabetes mellitus in idiopathic Addison's disease is 10 times that of the general population. Aware of this fact, in 1974 Bottazzo, Florin-Christensen and Doniach (21) tested the plasma of 171 subjects for the presence of circulating antibodies to pancreatic islet cells. 124 of these patients had organ-specific antibodies in the plasma and a number had multi-endocrine deficiency syndromes. As shown in Table 6, 13 of the 171 sera gave uniform cytoplasmic immunoflorescence when tested on unfixed human pancreas obtained at autopsy.

Table 6 (Ref. 21)

TABLE 6—IMMUNOFLUORESCENCE ON HUMAN PANCREAS

| Patients tested | Islet-cell antibody | |
|---|---|---|
| | Positive | Negative |
| Diabetes with negative autoantibodies .. | 0 | 39 |
| Diabetes with organ-specific autoimmunity .. | 10 | 20 |
| Non-diabetic with positive autoantibodies .. | 3 | 81 |
| Non-diabetic with negative autoantibodies .. | 0 | 18 |
| Total .. .. .. .. .. .. | 13 | 158 |

The antibody proved to be IgG in type and reaction was seen with $\alpha$, $\beta$ and $\Delta$ cells. Ten of the patients with positive antibodies had overt diabetes and 12 of the 13 positive patients had at least 1 (usually more) autoimmune disorder including thyrotoxicosis, myxedema, pernicious anemia, idiopathic Addison's disease, alopecia, and vitiligo. The antibodies were unrelated to insulin since at least 5 patients had never been treated with the hormone. Only 1 month later 5 additional patients with insulin-dependent diabetes mellitus and coexistent autoimmunity characterized by IgG antibodies to pancreatic islet cells were reported (22). In both series far more patients with diabetes were negative for antibodies than had them. The next important observation was that of Lendrum, Walker and Gamble (23) who found evidence of islet cell antibodies in 51 of 105 children when diabetes was of recent onset. Only 5 of 72 control sera gave positive results and the reactions were comparably very weak. The distribution of antibodies according to age and duration of symptoms is shown in Figure 4.

Two other extremely important points were made. First, of the 94 patients in whom a family history could be ascertained, only 6 of the children had a first degree relative known to have diabetes; 88 of the patients had no family history of diabetes. This is in

Figure 4 (Ref. 23)

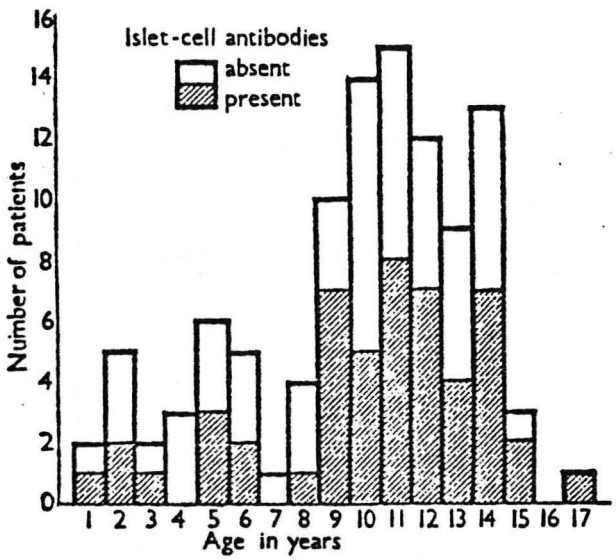



Fig. 1—Prevalence of islet-cell antibodies in relation to age in 105 diabetic children.

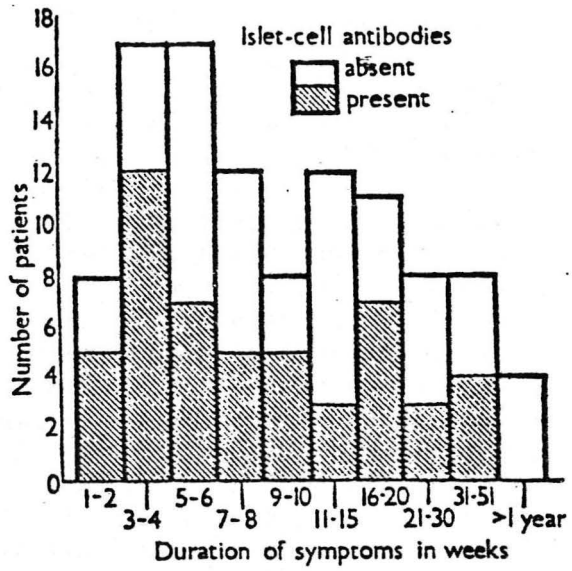
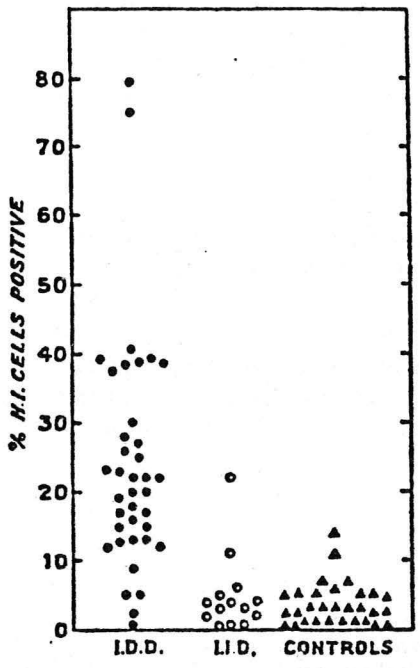



Fig. 2—Prevalence of islet-cell antibodies in relation to the duration of symptoms in 105 diabetic children.

marked contrast to non-insulin-dependent diabetes where a positive family history is obtained in some 80% or greater of cases. Second, thyroid or gastric antibodies were found in only about 20% of the patients with islet cell antibodies, a percentage which was no different from that seen in control plasmas. Thus, with early onset diabetes the prevalence of islet cell antibodies was much higher than in the first two cited studies (in which diabetes had been present for many years) and antibodies against other tissues were relatively less frequent with early disease. It was then found that when plasma was screened using cultured human insulinoma cells, 34 out of 39 insulin dependent diabetic patients had positive antibody responses (24). (Figure 5, next page). The authors postulated that lesser frequencies previously reported were due to insensitivity of assays using pancreatic slices obtained at autopsy because the number of islets in such preparations is small. On average about 27% of all cultured cells gave positive staining reactions when exposed to sera containing antibodies. A few non-insulin-dependent patients had positive antibody tests, but in this case the number of cells stained was only 4 to 5%. Interestingly, both IgG and IgM antibodies were found. (Some investigators have objected to the use of insulinoma cells for antibody screening feeling that malignancy itself might alter the response. This issue is unsettled).

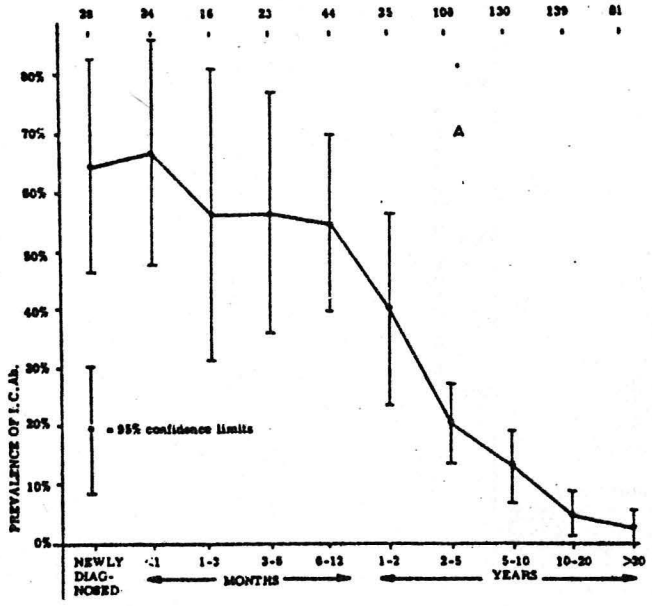
On the basis of studies in much larger numbers of patients a modified concept of the role of islet cell antibodies has now emerged. All investigators concur that the prevalence of islet antibodies is extremely high in newly diagnosed diabetics, in the range of

Figure 5 (Ref. 24)




Frequency of positive tests for antibody reacting to human insulinoma. H.I. = human-insulinoma cells.

Figure 6 (Ref. 25)



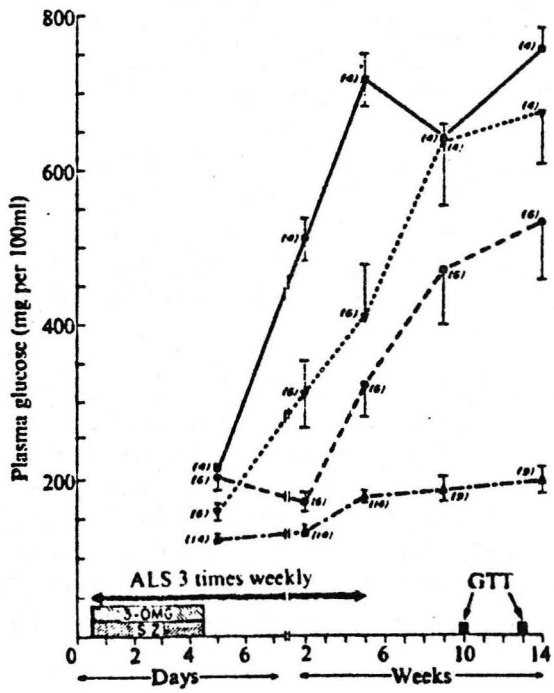

60-90%. (25-28). However, if one correlates the presence of antibodies with duration of disease the prevalence falls to about 20% by 5 years and after 10-20 years is only 5-10%. (Figure 6). Those patients with persistent islet cell antibodies have an increased association with HLA B8 and DW3 and a high incidence of concurrent polyendocrine disease. The bulk of patients with persistent antibodies are female and there is a tendency to develop diabetes later in life than is the case in patients with insulin-dependent diabetes who rapidly clear plasma antibodies to the islet cells. In the latter group there is a male predominance, the HLA associations include both B8 and B15 and antibodies to other endocrine glands are relatively rare. On the basis of these findings the British tend to divide insulin-dependent diabetes type I into 2 subcategories called type IA and type 1B. They believe that in type IA a virus interacts with receptors on beta cell membranes (see below for discussion of virology) causing leakage of tissue antigens with subsequent antibody formation which then further catalyzes pancreatic destruction. Onset of clinical diabetes is rapid and permanent. In type IB, on the other hand, it is considered that a true autoimmune phenomenon is operative; i.e., there is no initial precipitating damage. Whether this subgrouping will prove to be true remains to be seen, although the concept is extremely attractive (26,28).

It should be noted that the damaging agent in type IA need not be a virus. Experimentally diabetes may be induced in rodents by administration of the beta cell toxin streptozotocin. When given in large doses the poison rapidly induces diabetes with complete destruction of the pancreas and animals die (in a large percentage of the cases) in acute diabetic ketoacidosis. On the other

hand, if streptozotocin is administered in subdiabetogenic doses for 5 injections, immediate hyperglycemia does not appear. Rather there is evidence of insulitis with lymphocyte infiltration of the pancreas. Only subsequently does hyperglycemia supervene. The acute toxic effects of streptozotocin can be prevented by administration of 3-O-methyl-D-glucose (3-OMG) when the glucose analogue is given before or simultaneously with the large dose of streptozotocin. It has now been shown, however, that 3-OMG alone will not prevent hyperglycemia when given with subdiabetogenic doses of streptozotocin. By contrast if 3-OMG is combined with antilymphocyte serum (ALS), the disease is completely prevented provided ALS is administered for a long enough period of time (29). This experiment strongly suggests that the toxin is inducing diabetes both by direct action (prevented by 3-OMG) and lymphocyte-mediated inflammatory islet cell lesions (prevented by antilymphocyte serum). The observation raises the exciting possibility that toxic environmental chemicals may also play a role in initiation of idiopathic diabetes mellitus.

Figure 7 (Ref. 29)

**Fig. 7.** Plasma glucose levels (mean ± s.e.m.) for 14 weeks in CD-1 mice after: five daily i.p. injections of SZ (40 mg per kg) (■); ALS injections (0.25 ml) three times per week for 5 weeks plus SZ (▼); 3-OMG (1 g per kg) before each SZ dose (●); 3-OMG, plus SZ plus ALS regimen (▲). Numbers in parentheses indicate the number of mice in each group. The mice, histological examination, collection, and assaying glucose levels, preparation and administration of 3-OMG, SZ, and ALS, are as previously described[10] GTT, i.p. glucose tolerance test.



Further support for this conept comes from clinical observation of the effects of the rat poison called Vacor which produces insulin-dependent diabetes and ketoacidosis coupled with a severe peripheral neuropathy when ingested by humans provided the patient survives (30). Some 20 cases have now been reported. It turns out that surviving patients have circulating islet cell antibodies which, on the face, would seem to have to develop in response to chemical damage to the islets (31).

(21) Bottazzo, G. F., Florin-Christensen, A. and Doniach, D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 2:1279-1283, 1974.
(22) MacCuish, A. C., Barnes, E. W., Irvine, W. J. and Duncan, L. J. P. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. Lancet 2:1529-1531, 1974.
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(24) Maclaren, N. K., Huang, S-W. and Fogh, J. Antibody to cultured human insulinoma cells in insulin-dependent diabetes. Lancet 1:997-1000, 1975.
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(30) Prosser, P. R. and Karam, J. H. Diabetes mellitus following rodenticide ingestion in man. JAMA 239:1148-1150, 1978.
(31) Karam, J. H., Prosser, P. R., LeWitt, P. A. Islet-cell surface antibodies in a patient with diabetes mellitus after rodenticide ingestion. N. Engl. J. Med. 299:1191, 1978.

2. Lymphocyte abnormalities: Lymphocyte function appears to be abnormal in diabetes (32). Blastogenesis after exposure to insulin occurs much more frequently in diabetics than in controls (Figure 8). The antigenicity for lymphocyte transformation is provided by the B chain of insulin with little response to the A chain. In poorly controlled diabetes the number of T-cells (detected by E-rosettes) and B-cells (detected by erythrocyte antibody complement rosettes) is significantly decreased. Cells bearing receptors for the Fc fragment of

Figure 8 (Ref. 32)

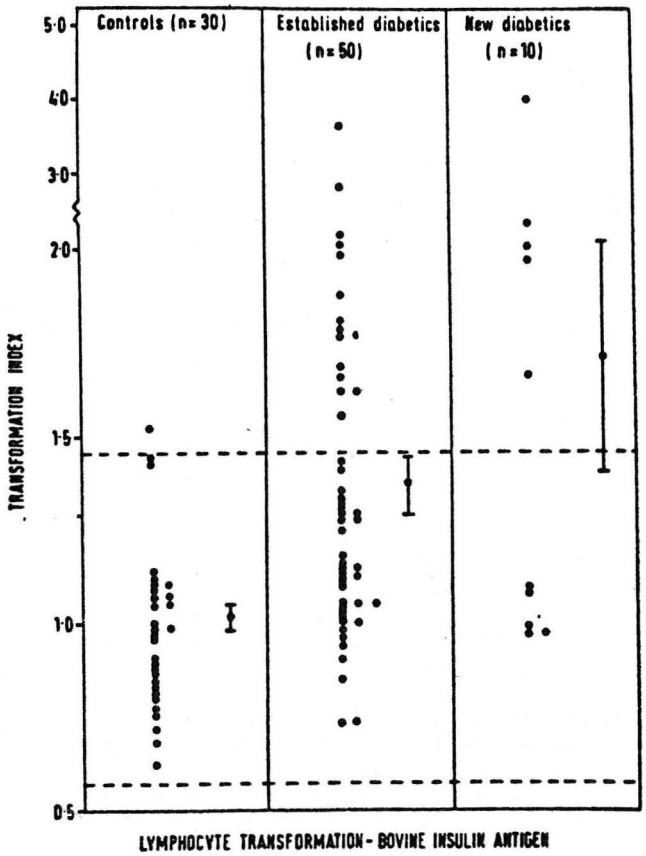


FIG. 8. Lymphocyte transformation in controls and diabetics induced by bovine insulin antigen. The mean transformation index ± S.E.M. is shown to the right of the individual results for each group. Dotted lines (- - - -) indicate the normal range (mean ± 2 S.D.) of transformation indices in control subjects. Significant transformation (index >1.45) is shown by fifteen established and five newly diagnosed diabetics as compared to one control. Both diabetic groups differ significantly ($p < 0.01$) from the control group.

immunoglobulins are diminished in all diabetics and not influenced by the degree of control. Finally, stimulation of lymphocytes by mitogens is defective in poorly controlled subjects. Of great interest was the observation that when plasma glucose was normalized through use of an artificial pancreas, the number of B-cells and T-cells was rapidly restored to control levels and mitogen stimulatory defects were repaired (33). (Table 7)

Huang and Maclaren (34) have reported a provocative observation, namely that lymphocytes from patients with insulin dependent diabetes bind to cultured human insulinoma cells and cause their destruction in a complement independent reaction. Lymphocytes from control subjects were only minimally capable of initiating cytotoxicity. Both antibody independent (T-cells) and dependent (B- or K-cells) lymphocytes from diabetic patients function in the cytotoxic process. The authors state: "Our study indicates that lymphocytes, and not antibodies, in IDD patients are the primary aggressors in the process of pancreatic β cell autoaggression. Thus, cell-mediated immunity against β cells may be an important

Table 7 (Ref. 33)

Table 7. Results of lymphocyte membrane markers and lymphocyte stimulation from patients studied before and immediately after optimal blood glucose control by an artificial pancreas

| | Mean blood glucose | | E-RFC | HTLA | "Active" SIg E-RFC | | EAγ RFC | $^3$H Thymidine incorporation of cells | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Unstimulated | Stimulated with | | |
| | (mmol/l) | | | | | | | | PHA | ConA | PWM |
| Before | 19.0 ± 0.7[a] | mean | 69.0 | 76.6 | 29.8 | 15.6 | 7.6 | 749 | 64,471 | 46,514 | 51,029 |
| (n = 8) | | SEM | 1.8 | 2.9 | 4.6 | 2.1 | 1.1 | 42 | 7,621 | 9,189 | 10,307 |
| After | 5.0 ± 0.1[b] | mean | 76.6 | 79.7 | 25.0 | 15.6 | 10.6 | 949 | 101,514 | 63,157 | 58,900 |
| (n = 8) | | SEM | 3.4 | 4.1 | 2.2 | 1.6 | 1.5 | 133 | 9,778 | 18,012 | 14,789 |
| | - | p | <0.05 | NS | NS | NS | NS | NS | <0.02 | NS | NS |

Means of individual blood glucose means recorded before (a) and during (b) the period of blood glucose control (5 ± 2 days)
Expression of results and abbreviations as in Tables 2 and 3

pathogenic mechanism in IDD. These findings would explain the pancreatic lesions of IDD that are characterized by marked infiltration of mononuclear cells, which are commonly seen in other autoimmune endocrine diseases."

In 1977, Buschard and Rygaard (35) published the sensational claim that they were able to transfer diabetes passively by injecting spleen cells from streptozotocin treated animals into non-diabetic recipients. They subsequently indicated that the disease was carried specifically by T-lymphocytes (36) (see Table 8).

Table 8 (Ref. 36)

Table 8. *Blood Glucose Values in Normal BALB/c Recipient Mice after Transfer of T-Lymphocytes*

| No. of cells in the transplants | S/B | Days after transfer | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 3 days | 6 days | 9 days | 13 days | 20 days | 39 days | 52 days | 66 days |
| $10^3$ | S | (8) 146 ± 34 | (8) 160 ± 38 | (8) 185 ± 37 | (7) 212 ± 45 | (7) 230 ± 41 | (7) 226 ± 25 | (7) 181 ± 24 | (7) 175 ± 18 |
| | B | (5) 79 ± 13 | (5) 90 ± 25 | (5) 90 ± 22 | (5) 103 ± 25 | (5) 108 ± 27 | (5) 112 ± 36 | (5) 103 ± 13 | (5) 103 ± 15 |
| $10^4$ | S | (8) 160 ± 43 | (8) 151 ± 46 | (8) 177 ± 47 | (8) 213 ± 58 | (8) 221 ± 60 | (8) 267 ± 40 | (8) 230 ± 27 | (8) 202 ± 17 |
| | B | (5) 112 ± 12 | (4) 109 ± 29 | (4) 104 ± 22 | (4) 101 ± 15 | (4) 96 ± 12 | (4) 101 ± 13 | (4) 90 ± 4 | (4) 99 ± 12 |
| $10^5$ | S | (8) 133 ± 21 | (8) 146 ± 19 | (8) 144 ± 20 | (8) 155 ± 18 | (8) 170 ± 27 | (8) 213 ± 48 | (8) 161 ± 24 | (8) 151 ± 17 |
| | B | (5) 95 ± 17 | (4) 86 ± 15 | (4) 92 ± 16 | (4) 96 ± 13 | (4) 100 ± 16 | (4) 113 ± 13 | (4) 96 ± 5 | (4) 101 ± 14 |
| $10^6$ | S | (8) 121 ± 15 | (8) 129 ± 13 | (8) 136 ± 21 | (8) 160 ± 27 | (8) 180 ± 39 | (8) 198 ± 36 | (8) 174 ± 26 | (8) 175 ± 22 |
| | B | (6) 102 ± 13 | (5) 110 ± 31 | (4) 107 ± 21 | (4) 107 ± 18 | (3) 105 ± 39 | (2) 126 | (2) 123 | (1) 126 |
| $10^7$ | S | (8) 132 ± 22 | (8) 143 ± 24 | (8) 151 ± 36 | (8) 176 ± 47 | (8) 183 ± 53 | (8) 180 ± 51 | (8) 175 ± 47 | (8) 175 ± 39 |
| | B | (6) 93 ± 18 | (5) 91 ± 17 | (5) 94 ± 13 | (5) 100 ± 7 | (5) 117 ± 26 | (4) 109 ± 25 | (4) 110 ± 14 | (4) 110 ± 15 |

S: Streptozotocin treatment of donor mice.
B: Buffer treatment of donor mice.
Average blood glucose values of mice in mg/100 ml ± 2 SEM. Number in brackets indicate number of mice in each group. Blood glucose values for day 0: 93 ± 9 mg/100 ml.

While tremendously exciting, it must now be reported that no other laboratory can reproduce the finding (37,38).

(32) MacCuish, A. C., Jordan, J., Campbell, C. J., Duncan, L. J. P. and Irvine, W. J. Cell-mediated immunity in diabetes mellitus. Lymphocyte transformation by insulin and insulin fragments in insulin-treated and newly-diagnosed diabetics. Diabetes 24:36-43, 1975.

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(36) Buschard, K. and Rygaard, J. T-lymphocytes transfer streptozotocin induced diabetes mellitus in mice. Acta Path. Microbiol. Scand., Sect. C, 86:277-282, 1978.
(37) Beattie, G., Lannom, R., Lipsick, J., Kaplan, N. O. and Osler, A. G. Streptozotocin-induced diabetes in athymic and conventional BALB/$_c$ mice. Diabetes (in press).
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III. Viruses and diabetes

It is quite remarkable that the incidence of diabetes in the United States increased by more than 50% between 1965 and 1973, with more than 5% of the population now having overt disease (39). The cause of this increase is not known but both environmental and genetic factors have been implicated. The fact that most young patients with insulin-dependent diabetes have no family history and that the concordance rate for diabetes in proven monozygotic twins with insulin-requiring disease is less than 50% spotlights the role of environment. The possibility that a virus might be involved was first mentioned in 1899 when a case of diabetic ketoacidosis was observed in a previously non-diabetic youth following mumps infection. It was subsequently noted that there was a seasonal variation in the onset of new cases of diabetes and that this appeared to parallel that time of the year when viruses were most prevalent. A high incidence of diabetes has also been noted in young adults with congenital rubella and there appears to be a more than chance occurrence of the disease in subjects infected with mumps, Coxsackie virus B, infectious mononucleosis and infectious hepatitis (39). Major emphasis has focused on the possibility that Coxsackie viruses are primary offenders. In Great Britain, Gamble, Taylor and Cumming (40) examined sera from 162 patients with insulin-dependent diabetes of recent onset and 319 control subjects. Antibody to Coxsackie virus B4 was found much more frequently in young diabetics than in controls. Nelson, Pyke and Gamble (41), on the other hand, failed to find evidence for a viral etiology for diabetes in a careful study of identical twins. Sera collected from 49 pairs of twins (27 discordant, 22 concordant) failed to show increased antibody titers to mumps, cytomegalovirus, rubella, Coxsackie virus types B1-5 or Mycoplasma pneumoniae in affected individuals; i.e., antibody titers in non-diabetic discordant twins were equivalent to those of the diabetic twin.

The brilliant work of Notkins and colleagues on experimentally induced viral diabetes has shed much additional light on the problem (42-44). It has been shown that there is a marked difference in susceptibility to development of diabetes for the same inoculum of virus in different strains of mice and rats. This differential (genetic) susceptibility to induction of diabetes by virus is not limited to one viral strain; i.e., mice or rats susceptible to Coxsackie B virus are also susceptible to induction by Encephalomyocarditis M-virus (42).

The predisposition to EMC-induced diabetes is inherited as an autosomal recessive trait (43). Interestingly, this susceptibility appears to be uninfluenced by the major histocompatibility complex (H-2) in mice (45). (The major histocompatibility complex does markedly influence susceptibility to pancreatic islet damage by islet cell antibodies.)

All of the viruses inducing diabetes in experimental animals infect the β cell but not the α cell in contrast to islet cell antibodies which do not discriminate, at least in humans (46,47). The recovery of viral antigens in pancreatic monolayers prepared from different strains of mice after infection with EMC-virus is shown in Table 9 and illustrates the genetic differences just described. The susceptibility gene for diabetes appears to act primarily

Table 9 (Ref. 44)

NUMBER OF CELLS CONTAINING VIRAL ANTIGENS IN PANCREATIC MONOLAYERS PREPARED FROM STRAINS OF MICE SUSCEPTIBLE AND RESISTANT TO EMC-INDUCED DIABETES*

| Hours after inoculation | Inoculum (PFU/cell) | Strain | Type of culture | Number of cells observed | Cells showing viral antigens (%) |
|---|---|---|---|---|---|
| Uninfected | – | C57BL/6J | β | 179 | 0 |
| Uninfected | – | SJL/J | β | 245 | 0 |
| 18 | 20 | C57BL/6J | β | 304 | 6 |
| 18 | 20 | SJL/J | β | 360 | 52 |
| 24 | 10 | C57BL/6J | β | 913 | 5 |
| 24 | 10 | NIH-Swiss | β | 531 | 46 |
| 24 | 10 | SJL/J | β | 301 | 54 |
| 24 | 100 | C57BL/6J | β | 314 | 19 |
| 24 | 100 | SJL/J | β | 71 | 91 |
| 18 | 20 | C57BL/6J | MEF† | 69 | 95 |
| 18 | 20 | SJL/J | MEF | 81 | 97 |

* Monolayers were inoculated with EMC virus and stained with FITC-labeled anti-EMC antibody, and the number of cells containing viral antigens was determined.

† Mouse embryo fibroblast.

by controlling the number of viral receptors on the surface of the β cell (44). Another factor influencing infection rate is the trophic effect of passing virus repeatedly through pancreatic β cell cultures. Following serial passage the virus shows a markedly increased capacity to cause diabetes in the same recipient strain (42).

On the basis of these studies it can be seen that susceptibility to diabetes as a consequence of viral infection can be influenced at several levels (i.e.,

in both host and virus). First, there may be genetically controlled differences in whole organism susceptibility to viral infection. Second, the same strain of virus may vary widely in pathogenetic capacity depending on whether it has passed through human pancreas one or several times. Third, the susceptibility of the pancreas to infection by virus (given equivalent inocula) will be determined via genetic control of the number of viral receptors on the β cell. Finally, the HLA makeup of the individual will influence the capacity to make antibodies released from damaged and leaking β cells.

The strongest evidence for virus-induced diabetes mellitus in humans comes from the recent report of Yoon et al (48) who isolated Coxsackie B virus from a 10 year old boy, previously healthy, who died from complications of ketoacidosis following a flu-like illness. The virus was shown to induce hyperglycemia when injected into mice and caused inflammatory changes and necrosis in the β cells of experimental animals. Thus, Koch's four postulates were met: (1) the virus was isolated from the pancreas, which showed lymphocytic infiltration and necrosis of β cells on histologic examination; (2) the virus was recovered after inoculation into mouse, monkey and human cell cultures; (3) inoculation of the human isolate into genetically susceptible mice resulted in both β cell damage and hyperglycemia; and (4) the virus was recovered from infected laboratory animals. Additionally, a rise in antibody titer to the virus was found both in the patient who died and in infected experimental animals. There thus appears to be no doubt that viruses can cause diabetes in humans in and of themselves if the genetic background is correct. (There was a strong family history of diabetes in the young man who died with the Coxsackie B4 induced diabetes.) A list of all the viruses known to cause diabetes either in experimental animals or man can be found in reference 49.

Figure 9 (Ref. 39)

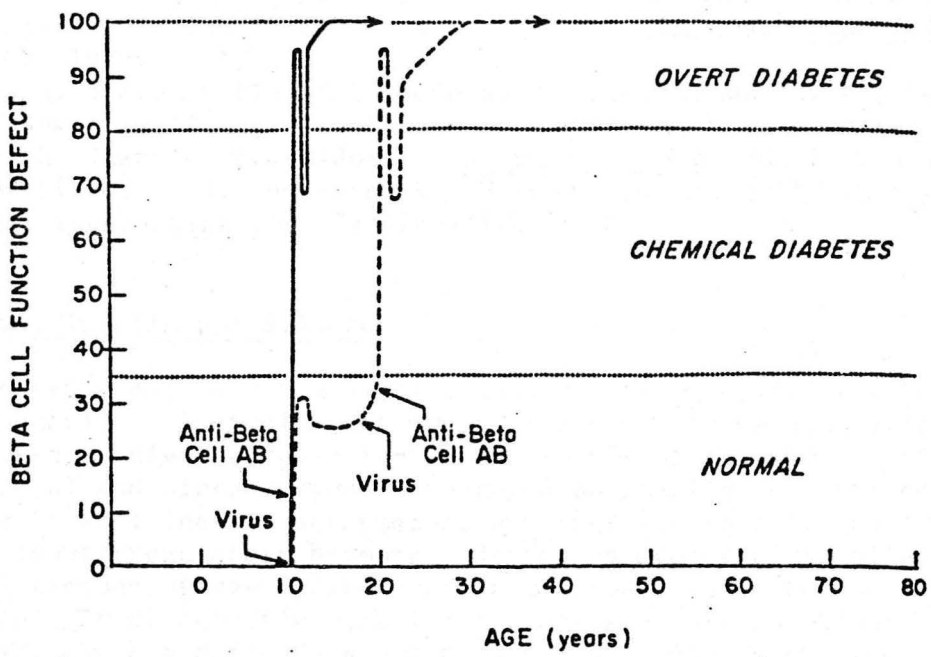


Fig 9.—A diagrammatic representation of the etiopathogenetic mechanism in severe, insulin-requiring diabetic syndrome, usually involving young individuals (AB signifies antibody).

It should be noted that a single viral infection might not be sufficient to cause the diabetic state. Rather, repeated infections with the same or different diabetogenic viruses might cause the clinical picture. This is shown schematically in Figure 9. (Previous page)

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(40) Gamble, D. R., Taylor, K. W. and Cumming, H. Coxsackie viruses and diabetes mellitus. Brit. Med. J. 4:260-262, 1973.
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(45) Kromann, H., Lernmark, Å., Vestergaard, B. F., Egeberg, J. and Nerup, J. The influence of the major histocompatibility complex (H-2) on experimental diabetes in mice. Diabetologia 16:107-114, 1979.
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(47) Stefan, Y., Malaisse-Lagae, F., Yoon, J-W., Notkins, A. L. and Orci, L. Virus induced diabetes in mice: a quantitative evaluation of islet cell population by immunofluorescence technique. Diabetologia 15:395-401, 1978.
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## IV. Abnormal insulin and diabetes

As noted previously (Table 1) a number of abnormalities induce hyperglycemia secondarily. A significant proportion can best be classified as insulin-resistant states since circulating plasma levels of insulin are high (despite hyperglycemia) and since response to exogenous insulin is impaired. Resistance may be due to anti-insulin antibodies, anti-insulin-receptor antibodies, high levels of counterregulatory hormones, decreased number of insulin receptors in peripheral tissues or even post-receptor abnormalities. For years, the theoretical possibility of defective insulin synthesis as a cause of diabetes has been entertained. Such a defect has now been specifically identified (50). The patient involved had diabetes coupled with hyperinsulinemia suggesting an insulin-resistant state; i.e., the fasting plasma glucose was consistently above

200 mg·dl$^{-1}$ while the fasting plasma insulin concentration was in the range of 70-120 μU·ml$^{-1}$. However, none of the conditions ordinarily associated with insulin resistance were found to be present. Specifically, the ratio of proinsulin:insulin in the patient's plasma was normal, anti-insulin or anti-insulin receptor antibodies could not be demonstrated, growth hormone, glucagon and cortisol levels were normal and the monocytes isolated from peripheral blood contained normal numbers of insulin receptors. Despite signs of resistance to endogenous insulin, when exogenous insulin was injected the patient showed normal hypoglycemic responses. This strongly suggested that an abnormal plasma insulin was being synthesized. When the patient's insulin was extracted from plasma it showed a decreased ability to bind to cultured IM-9 lymphocytes as well as rat adipocytes. Moreover, its capacity to stimulate glucose uptake and oxidation in fat cells was impaired. Careful chemical examination of the insulin indicated the presence of an abnormal variant which contained a leucine for phenylalanine substitution at either position 24 or 25 of the insulin B-chain. While this is the first case of a specific defect in insulin structure impairing its biological activity and causing a clinical disease, it seems certain that more will be discovered. Whether the defect described in this patient is congenital (genetic) or acquired has not yet been ascertained. Discovery of this abnormality expands to 5 the number of general causes of hyperinsulinemic diabetes: (1) a mutation in the structural gene for preproinsulin, (2) incomplete conversion of proinsulin to insulin, (3) circulating antagonists to insulin, (4) defects in the insulin receptor site and (5) defects in target cell responsiveness at a site distal to hormone receptor binding.

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## V. The diagnosis of diabetes

When a patient presents with symptoms of polyuria, polydipsia, polyphagia, weight loss and elevation of the fasting plasma glucose concentration, the diagnosis of diabetes is not in doubt. Even in the absence of these signs, the presence of fasting hyperglycemia would be accepted by most physicians as adequate evidence to sustain diagnosis. The problem comes from the widespread use of the oral glucose tolerance test for the diagnosis of the disease. The National Diabetes Data Group began with the assumption that present standards for abnormality in glucose tolerance testing vastly overdiagnosed the true incidence of diabetes. The initial scientific study showing this to be the case was that of Unger (51) but the evidence from many studies (documented in the report) is now so overwhelming as to be incontrovertible. The evidence will not be specifically reviewed here although one illustrative example is shown in Table 10 (next page). In this study O'Sullivan and Mahan followed 352 patients with a diagnosis of chemical diabetes for up to 12 years and analyzed rates of progression to overt diabetes depending on 3 separate sets of initial standards. The Mosenthal and Barry criteria were a 1 hour glucose greater than 150 mg·dl$^{-1}$ or a 2 hour value greater than 100 mg·dl$^{-1}$. Fajans and Conn criteria placed the upper limits of normality at 160 mg·dl$^{-1}$ at 1 hour and 120 mg·dl$^{-1}$ at 2 hours. The U. S. Public Health Service standards

Table 10 (Ref. 52)

listed upper limits as following: fasting - 110 $mg \cdot dl^{-1}$, 1 hour - 170 $mg \cdot dl^{-1}$, 2 hours - 120 $mg \cdot dl^{-1}$, and 3 hours - 110 $mg \cdot dl^{-1}$. Diabetes was diagnosed if any 3 values were abnormal or if the fasting and 3 hour combination averaged more than 110 $mg \cdot dl^{-1}$. (Note that these values are for true glucose in whole blood. Plasma values would be approximately 14% higher.) Using the 10 year life table technique it can be seen that decompensation to frank diabetes was low with the rigid Mosenthal and Barry criteria and high with the more stringent U. S. Public Health Service requirements. The widely used Fajans and Conn criteria resulted in a 10 year decompensation rate of 27%. Almost 3/4 of the patients were normal on retesting. This type of study has been reduplicated many times.

TABLE 10. *Progression and Remissions among Patients with Chemical Diabetes According to United States Public Health Service Criteria.*

| FINAL STATUS | ORIGINAL DIAGNOSTIC CRITERION | | |
|---|---|---|---|
| | MOSENTHAL & BARRY ONLY | FAJANS & CONN ONLY | U.S. PUBLIC HEALTH SERVICE |
| | % | % | % |
| Decompensation | 3.0 | 10.7 | 25.9 |
| Abnormal GTT | 21.3 | 18.7 | 29.5 |
| Normal | 75.6 | 70.6 | 44.6 |
| Decompensation (10-yr life table) | 8.9 | 27.3 | 52.5 |

The new criteria for diagnosis are as follows:

1. Criteria for diagnosis of diabetes based on fasting plasma glucose concentration:
   Fasting plasma glucose concentration $\geq$ 140 mg/dl on more than one occasion.
2. Criteria for diagnosis based on the oral glucose tolerance test (which should not be done if fasting plasma glucose concentration is elevated):
   a. Diabetes mellitus:
      Two-hour plasma glucose concentration $\geq$ 200 mg/dl and at least one value between zero time and 2 hours $\geq$ 200 mg/dl.
   b. Impaired glucose tolerance:
      Two-hour plasma glucose concentration $\geq$ 140 mg/dl but < 200 mg/dl and at least one value between zero time and 2 hours $\geq$ 200 mg/dl.
   c. Gestational diabetes:
      Gestational diabetes is diagnosed when two or more of the following plasma glucose values are met or exceeded (after 100 g glucose dose):

      fasting - 105 mg/dl
      1 hour - 190 mg/dl
      2 hour - 165 mg/dl
      3 hour - 145 mg/dl

The glucose tolerance test, if used, requires administration of 1.75 g of glucose/kg/body weight up to a maximum of 75 g of glucose. Normal glucose tolerance implies glucose values below 140 $mg \cdot dl^{-1}$ both fasting and 2 hours after the glucose tolerance test.

(51) Unger, R. The standard two hour glucose tolerance in diagnosis of diabetes in subjects without fasting hyperglycemia. Ann. Int. Med. 47:1138, 1957.

(52) O'Sullivan, J. B. and Mahan, C. M. Prospective study of 352 young patients with chemical diabetes. N. Engl. N. Med. 278:1038-1041, 1968.

## CONCLUSION

The studies briefly reviewed in this Grand Rounds indicate the tremendous advances that have been made in understanding what was once considered to be a single homogeneous disease, namely diabetes mellitus. Against this background the statement of Rotter and Rimoin (53) seems appropriate:

"The heterogeneity that has so far been discovered in typical diabetes mellitus probably represents the 'tip of the iceberg.' But even this currently demonstrable heterogeneity has immediate relevance to present research efforts into the pathogenesis and therapy of the diabetic state. Various agents - e.g., viruses - have been implicated as inciting or promoting diabetes in individuals with the appropriate genetic predisposition. The susceptibility to a given specific agent may well depend on the heterogeneity elucidated by these studies. The long-standing debate on the efficacy of tight vs. loose control in preventing vascular complications might well be resolved when this heterogeneity is taken into account in appropriately designed studies - i.e., there may be forms of diabetes in which control is vital and others in which it is less so; there may be subgroups with inexorable complications and others who are complication-free. Only when each of the many disorders resulting in diabetes mellitus and/or glucose intolerance are delineated will specific genetic counseling, prognostication and therapy be possible for all diabetic patients." That seems a fair judgment.

(53) Rotter, J. I. and Rimoin, D. L. Heterogeneity in diabetes mellitus - update, 1978. Evidence for further genetic heterogeneity within juvenile-onset insulin-dependent diabetes mellitus. Diabetes 27: 599-608, 1978.