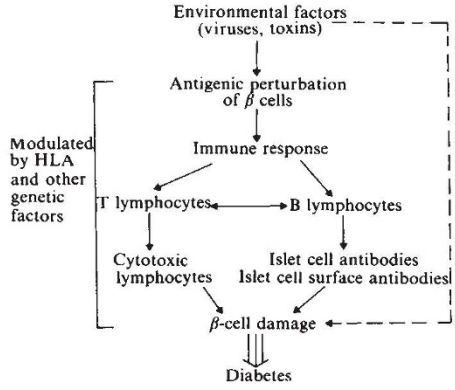
pancreas was provided in 1971 when it was found that the migration of leukocytes from patients with IDDM was inhibited by exposure to antigens prepared from endocrine pancreas[2]. Diabetic lymphocytes also have increased adherence and cytotoxicity against cultured insulinoma cells (tumour cells of the insulin-producing β cells in the islets of Langerhans — usually benign)[3]. The changes in function are accompanied by alterations in the circulating lymphocyte populations in acute IDDM in both man and the BB rat, which develops an IDDM-like syndrome[4]. The passive transfer of diabetes from man to mouse and mouse to mouse using affected lymphocytes has also been reported[5], but has been challenged as a number of groups have not been able to confirm the finding.

Despite the strong suspicion that autoantibodies might be important in IDDM, it was not until 1974 that autoantibodies against some component in the islet cell cytoplasm were detected in patients with diabetes mellitus and other autoimmune endocrinopathies[6]. Similar autoantibodies were soon confirmed in other patients and have now been found in over 2,000 diabetic patients who do not have polyendocrine failure (see review in ref.7).

As with other autoimmune features of IDDM, the exact prevalence of these autoantibodies depends on the duration of disease. Within the first one to two weeks of onset, they will be detectable in up to 85 per cent of diabetic children. This percentage rapidly declines, reaching 25 per cent by two to five years after diagnosis. The autoantibodies are present in 1–2 per cent of normal controls but their prevalence is increased in first-degree relatives of patients with IDDM and in patients with NIDDM. They are invariably of the IgG class, and, in most cases, react with the cytoplasm of all four major types of islet cells — the insulin-secreting β cells, glucagon-secreting α cells, somatostatin-secreting δ cells and pancreatic polypeptide-secreting PP cells. These autoantibodies may not be pathogenic in IDDM as only β cells are destroyed.

More recently, a complement-fixing immunofluorescence assay for detection of anti-islet cell cytoplasm autoantibodies has been used[8]. These complement-fixing antibodies seem to correlate more closely with disease. In addition, in a study currently underway, these antibodies appear to be a predictive marker of impending development of IDDM in the non-diabetic siblings of affected children.

In 1976, using a culture of insulinoma, a new class of islet cell antibodies that reacted with the surface membranes of islet cells was found[9] and later those observations were extended using dispersed rat islet cells[10]. Like the islet cell cytoplasm autoantibodies, the membrane autoantibodies are most prevalent in the early-onset diabetic. In the presence of complement, cell surface autoantibodies, but not cell cytoplasm autoantibodies, stimulate chromium release from radiolabelled islets and inhibit insulin release, suggesting direct cytotoxicity to islet cells[11]. Cell surface autoantibodies, however, are also found in the sera of non-diabetic first-degree relatives of patients with IDDM.



Possible pathogenesis of insulin-dependent *diabetes mellitus*.

The antigens at which the autoantibodies are directed remain to be identified. An immunoprecipitation technique[12] shows that most of the sera which contain them react with a protein of molecular weight 64,000 in ^{35}S-methionine-labelled human islet cell lysates. Hopefully, the determination of the nature of the antigen will provide a clue as to the earliest lesion in IDDM.

Circulating immune complexes have also been identified in patients with IDDM[13]. They are present not only in those patients with recent onset of disease, but also in the late phase, and in patients with NIDDM. Some of these may be immune complexes involving anti-insulin antibodies, but the widespread nature of their occurrence suggests that other antigens must be involved also.

Several animal studies suggest that virus or toxin may be the triggering factor in a genetically susceptible individual. Diabetes-like syndromes can be produced in mice by infection with encephalomyocarditis virus or reovirus[14,15]. Reovirus also triggers production of autoantibodies that react with antigens on the surface of islet and pituitary cells, as well as antibodies that react with the hormones secreted by these cells. Likewise, insulitis and diabetes-like syndromes can be produced by injection of low doses of β-cell toxins, such as streptozotocin[14]. In a series of elegant studies, Notkins and co-workers have shown that the effect of these environmental factors may be additive, and clearly varies with the genetic background of the animal[15].

In humans, the precise nature of the genetic influence in the pathogenesis of diabetes mellitus remains unclear as IDDM occurs concordantly in only about 50 per cent of identical twin pairs[16]. Alleles of the major histocompatibility system (the HLA system) are clearly associated with the occurrence of IDDM. Both HLA DR3 and DR4 are associated with a three- to fivefold increase in risk for IDDM[17]. Although there is no difference in risk between heterozygotes and homozygotes, the risk of disease to the double heterozygote — the individual with DR3/DR4 — increases almost 10-fold, suggesting that the effect of these antigens is dominant but involves independent mechanisms. HLA antigens in linkage disequilibrium with DR3 and DR4, such as B8 and B15, show similar associations. HLA B8/DR3 are associated with a persistence of islet cell surface autoantibodies in patients with IDDM[7,8] and also appear associated with antibodies to a specific 38,000 molecular weight antigen[12]. By contrast, NIDDM is not associated with any specific HLA alloantigens, but is clearly genetically influenced since it occurs in identical twins with almost total concordance[16].

The recognition of the possible important role for autoimmunity in IDDM has led to attempts to suppress immune response. In mouse and rat models of IDDM, immune suppression by irradiation, neonatal thymectomy, anti-lymphocyte serum or bone marrow transplant decreases the incidence of clinical disease[18]. At present it is too soon to know whether these techniques will alter the course of the human disease, but they certainly present hope for the first new approach to the therapy of IDDM since the introduction of insulin over 60 years ago. □

ERRATUM

In *The NK cell: a phagocyte in lymphocyte's clothing?* (**298**, 511) an error in our labelling of a graph led to the statement that O_2^- production by NK cells exceeds that of neutrophils by two orders of magnitude: the actual production rate is about one-tenth that of neutrophils.

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