EDITORIALS

The 64 K question in diabetes

A large body of evidence assembled over the past two decades supports the hypothesis that insulin-dependent diabetes mellitus (IDDM, type I diabetes) is caused by autoimmune destruction of insulin secreting pancreatic β-cells.[1,2] A better understanding of the mechanisms underlying the autoimmune process is important for the prediction and early diagnosis of IDDM, and especially for the long-term goal of a rational immunotherapy to prevent the disease. The well-recognised genetic susceptibility to IDDM appears to be at least partly determined by certain alleles of genes in the major histocompatibility complex which are involved in the presentation of antigens to effector components of the immune system.[1,2] However, it is unclear what might trigger the initial "insult" to the β-cell. A plausible hypothesis is that of molecular mimicry, whereby a foreign antigen (bacterial or viral) provokes an immune response, which cross-reacts with a similar epitope on an endogenous antigen.[1,3] Whatever the mechanism, the β-cell autoantigens that are the targets for autoimmune attack have proved difficult to identify, and have been studied largely by investigating the specificity of antibodies which are present in the circulation of most IDDM patients.[4] There are two potential difficulties with this approach. First, it appears that a cell-mediated mechanism (probably involving T cells and/or macrophages), rather than antibody-mediated immunity, is of greatest importance in the initiation of β-cell destruction.[2,3] Second, at least some of the autoantibodies found in overt diabetics may arise as a response to antigens released from damaged cells—ie, as a consequence rather than a cause of the disease process.

Various components of β-cells have been shown to be autoantigens in IDDM. Insulin itself is the only fully characterised autoantigen,[5] but although insulin autoantibodies may have predictive value they are unlikely to be responsible for β-cell destruction. Antigens exposed on the cell surface, at least transiently, would seem to be the best candidates for involvement in the primary immune attack. A major fraction of human islet cell antibodies appears to be directed against membrane glycolipids.[6] However, specific protein antigens have also been implicated, including a 38 kD protein of the insulin secretory granule membrane which reacts with T-cell clones from an IDDM patient.[7] Another autoantigen that has aroused special interest is a 64 kD protein[8] revealed by immunoprecipitation or immunoblotting of β-cell lysates with diabetic sera. Circulating antibodies to 64 K protein are present not only in human diabetics[9] but also in two animal models of diabetes—the BB rat[10] and the NOD mouse.[11] Although 64 K protein appears to be membrane-associated by some criteria,[12] it may not be exposed at the cell surface.[13,14] Since the identity and function of 64 K protein have remained obscure, its importance in the pathophysiology of IDDM has been difficult to assess.

In this issue (p 583) Jones and Hunter present evidence that 64 K protein is related to the hsp 65 protein family. The term "heat shock protein" (hsp) denotes a growing number of proteins which are synthesised in response to moderately raised temperatures in all organisms studied, from bacteria to man.[15] The increased synthesis of these proteins can be provoked by various stimuli including ethanol, glucose deprivation, steroid hormones, and cytokines,[16,17] so it is more correct to call them stress proteins. That most of these proteins are constitutively expressed and some are among the most abundant cellular proteins suggests they have important functions in normal cells as well as in stress responses. These functions may include assembly and disassembly of protein complexes, and the translocation and degradation of proteins.[15,16] For the present, hsps are classified largely on the basis of size. Proteins of the hsp 65 family have been highly conserved during evolution: bacterial forms have several counterparts in mammals.[18] Bacterial hsp 65 is the major antigen of various infections including tuberculosis, leprosy, syphilis, legionnaire's disease, and also Lyme disease.[17] Moreover, hsp 65 immunoreactivity has been associated with rheumatoid arthritis in man and in rats,[19] which suggests that clinical effects of the disease may be a consequence of an autoimmune reaction to an antigen structurally related to mycobacterial hsp 65. A molecule cross-reactive with hsp 65 of *Mycobacterium tuberculosis* may also be a target antigen in autoimmune NOD mice.[20] It was shown that development of hsp-65-reactive T cells and circulating antibody to hsp 65 correlated with disease progression in diabetic mice. The importance of these responses in pathogenesis was emphasised by the demonstration that injection of bacterial hsp 65 could either induce or prevent development of diabetes depending on the form administered.[20]

Jones and Hunter present two lines of evidence that the endogenous β-cell antigen cross-reactive with