unanswered. What exactly, for example, is the crystal structure of the superconducting phase? Also, although that material and the new one appear clearly to be electron doped, there seem to be some positively charged current carriers in the materials which make physical property measurements ambiguous. One can, of course, hope that the study of the new electron-doped superconductor $Sr_{1-y}Nd_yCuO_2$ (and also $(Ba,Sr)CuO_2$) will help to clear up some of the difficulties. Nature, however, never puts all her eggs in one basket: the possible simplicity of all-layer electron-doped copper-oxide superconductors will no doubt be partly offset by the fact that their relatively exotic synthesis will limit their availability for study. □

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GENETICS

Sweet mice, sugar daddies

Philip Avner

THE hunt for the genetic mechanism underlying diabetes will take on a fresh intensity with the observations by Todd and colleagues announced on page 542 of this issue[1]. The authors have pinned down the chromosomal location of two separate genes, *Idd-3* and *Idd-4*, which confer susceptibility to type 1 (insulin-dependent) diabetes in mice; notably, both genes lie outside the major histocompatibility complex, whose role in autoimmune disease has already been established. But the significance of the work goes further, in that the technique employed by Todd *et al.* is one which could well be applied successfully to other complex diseases.

Type 1 diabetes (see box) belongs to a group of complex disease conditions that includes atherosclerosis, hypertension, certain types of cancer and schizophrenia. We have only limited knowledge of the genetic basis of susceptibility to these diseases[2], but all of them are thought to be multifactorial — that is, to have both genetic and environmental components. All, moreover, are probably under polygenic control, with disease susceptibility resulting from the cumulative and interactive effect of several distinct genes.

The difficulty of studying such diseases in humans is in part due to their clinical and genetic heterogeneity, in part to the availability and informativeness of suitable cases. For some research groups the answer has been to develop animal models, the unspoken hope being that, at least in part, the same genes will control disease susceptibility in the animal model and in humans. In the long run, then, such an approach could enable targeted genetic studies to be undertaken in humans, based on our knowledge of the homologies between the genetic maps of humans and the animal species in question. Given the proven role of the major histocompatibility complex (MHC) in both human and murine type 1 diabetes, there are grounds for thinking this approach is not purely wishful thinking. Animal models for polygenic multifactorial diseases include mouse models for certain types of spontaneous cancer[3], a rat model for spontaneous hypertension, and the well-characterized BB rat and nonobese diabetic (NOD) mouse which provide productive analogues for probing the genetic and immunological basis of human type 1 diabetes (NOD mice spontaneously develop type 1 diabetes).

Studies on crosses involving mouse inbred strains, such as the NOD mice used in the study of Todd *et al.*, have in the past been severely hampered by the lack of informative genetic markers. Indeed, the main innovation of Todd and his colleagues has been to identify and map systematically a large number of simple repeat sequence microsatellite polymorphisms which provide the framework for subsequent exclusion mapping.

If the 1980s were the decade of *Mus spretus* — whose use in conjunction with restriction fragment length polymorphisms revolutionized mouse linkage analysis, and made the mouse a formidably efficient sys-

The immunology of diabetes mellitus

DIABETES mellitus is a common pathological state defined by hyperglycaemla (high levels of blood glucose); it affects 2–4 per cent of the population in industrialized countries and may arise through various mechanisms. The two most frequent types of diabetes are insulin-dependent diabetes mellitus (type 1) and the non-insulin-dependent form (type 2). Both are chronic diseases. Type 1 usually appears abruptly as a hyperglycaemic syndrome in young people; type 2 is seen in older, frequently overweight, people. It has a more progressive onset and a strong genetic basis, and is associated both with dysfunction of the insulin-secreting cells and peripheral resistance to insulin.

Type 1 diabetes, by contrast, is the direct consequence of destruction of insulin-secreting (β) cells within the islets of Langerhans in the pancreas. Its incidence shows a north–south geographical gradient reaching 40 cases per 100,000 people in Scandinavia. Development of the disease is a multifactorial process in which it seems that environmental factors may trigger an autoimmune reaction against β cells in genetically predisposed people (the genetic element is estimated at 30–40 per cent). The only available treatment is replacement therapy involving daily injections of insulin.

The frequent occurrence of type 1 diabetes in association with other immune disorders, the presence of insulitis (infiltration of the islets of Langerhans by lymphocytes) and the detection of islet cell antibodies at clinical onset of diabetes were all factors that first suggested that an immune process is involved. Type 1 diabetes is moreover associated with genetic markers that directly point to the immune system, genes in the HLA-D region on the short arm of chromosome 6 being associated with susceptibility to the disease. Studies of animal models, and therapeutic trials in humans, strongly implicate the involvement of T cells in particular. For instance, in humans islet β-cell destruction is transiently blocked by immunosuppressive drugs which target T cells. Other evidence for autoreactive T cells has come from the experimental transfer of diabetes, immunointervention using anti-T cell or anti-class II monoclonal antibodies in animals and, most importantly, the cloning of islet-cell-specific T cells.

A primary defect of autoantigen expression by β cells, defective autoantigen presentation, abnormal T-cell regulation of autoreactive T-cell clones and biased selection of the T-cell repertoire during ontogeny have all been invoked as allowing the development of anti-islet autoimmunity. Diabetes susceptibility genes, such as those mapped by Todd (see main article), could intervene in any one of these events. But it will be difficult to understand the breakdown of self-tolerance, and the triggering role of environmental factors, before getting a clear picture of the mechanisms involved in tolerance to peripheral self-antigens. Studies of tolerance in transgenic animals should help in understanding how tolerance breakdown develops.

Knowledge of the interaction between autoreactive T cells and antigen-presenting cells, which is central to the activation of the anti-islet immune process, stems almost entirely from experiments in the BB rat and the nonobese diabetic mouse (see main article). This key interaction needs to be defined at the molecular level. The first hint in this direction was the characterization of class II MHC antigens associated with susceptibility haplotypes. If antigen-presenting molecules actually explain part of diabetes susceptibility due to the MHC, one may infer that a unique peptide initiates the activation of autoreactive T cells. Of course, T-cell clones will have to be extensively studied to define T-cell receptor usage by autoreactive cells and to characterize autoantigenic peptides and their role in initiating autoimmunity.

Characterization of non-MHC genes, such as those mapped by Todd *et al.*, and of their products and their effects either on the target cell or the immune system, are among the next steps to be taken.

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