but who cannot communicate to summon it will also be incontinent—perhaps despite awareness of a full bladder and reasonable sphincter control.

Urinary incontinence after stroke, an unglamorous complication of a mundane disease, does not routinely attract much attention from doctors. Management may often be left to nursing staff prepared to tackle sympathetically the component problems of communication, dependency, and intimate personal care. Doctors should probably be more interested, and a recent prospective study from a group of geriatricians in New Zealand gives grounds for optimism.1 Of 151 stroke patients who required admission to hospital 17% had been previously incontinent, and incontinence rates among survivors were 60%, 42%, and 29% at one, four, and 12 weeks respectively. In patients with moderate or severe persistent incontinence the commonest cystometric finding was detrusor instability.

Urinary incontinence at four weeks was associated with mental impairment, earlier moderate or severe motor deficit, and current dependency in mobility. Early dysphasia in those with right hemiparesis was associated with incontinence, but sensory impairment in those with left hemiparesis did not appear to make incontinence more likely. At no time were more than a quarter of the patients catheterised (and those mainly in the early weeks), and only 9% required catheters 12 weeks after their strokes. Continence might be expected to go on improving after three months. Brocklehurst et al reported 85% urinary continence in 92 patients one year after a stroke. At two and three years’ follow up incontinence rates had increased again, but at four years they had fallen once more to 14%—a figure comparable to that for the elderly population at large.

Continence is a complex feat of awareness, control, mobility, and dexterity and is vulnerable at many points to the direct or indirect effects of cerebrovascular disease. In patients with strokes, as in others, faecal impaction, urinary retention, and urinary infection may contribute to urinary incontinence. Managing urinary incontinence after stroke is therefore complex, demanding awareness not only of the possibility of constipation and urinary tract infection, but also of how it might feel to be unable to move or speak.

If confusion can be minimised and mobility restored continence too will often return. Regular toileting and charting of continence is essential because progress is thereby both encouraged and recorded. The doctor looking after a patient with stroke should not ask simply “Is she continent?” but, if she is, go on to ask himself which of several predictable factors may be contributing. Some will be specifically and easily remediable. Others will diminish only as orientation, mobility, and self care improve. A few survivors of stroke, but only a few (mainly the very demented and dependent), have permanently lost normal continence and may need to be considered for permanent carers.

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Regular Review

Markers for insulin dependent diabetes: towards early detection

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Type I insulin dependent diabetes mellitus is probably due to autoimmune disease of the pancreatic β cells.1 The insulitis leads to insulin secreting cells being gradually destroyed and islet cell failure and clinical diabetes.2 The prediabetic phase, which is thought to last for many years, is symptomless.

Whether this account is correct is important for two reasons. Firstly, if clinical diabetes reflects the complete and irreversible destruction of the functioning islet cell mass, only replacement treatment—that is, insulin—can be offered. Secondly, treatment in the lengthy prediabetic phase might be able to halt immune destruction. Such a possibility would require not only a suitable treatment but also a way of identifying those who needed the treatment—and the markers that might be used are the subject of this review.

Islet cell antibodies

Islet cells have many antigens distributed on their surface and in their cytoplasm, but these antigens have not been purified, isolated, or even identified—so that whole tissue must be used for islet cell antibody assays. The variants of islet cell antibodies—known as cytoplasmic2 complement fixing1 and surface antibody4—mostly reflect differences in methods of preparing the substrate and detecting the signal.

Understanding these differences in assay technique is important for interpreting the data they provide. Only the β cells are destroyed in the insulitis of diabetes, yet the cytoplasmic islet cell antibodies react with all the islet cells. Complement fixing islet cell antibodies and islet cell surface antibodies10 11 may be selective for β cells, but this is not
always the case. What appears to be specific staining of β cells on pancreas fixed in Bouin’s preparation is probably due to insulin antibodies rather than to islet cell antibodies, and fresh frozen pancreas is now preferred to fixed material. Insulin antibodies are common in insulin treated diabetics but may be “removed” by adding excess insulin if fixed pancreas is used to avoid confusion with islet cell antibodies. Much of the work with cytoplasmic islet cell antibodies was done, however, before reports were published of autoantibodies to insulin yet they occur in many insulin dependent diabetics at diagnosis and often long before, and previous observations purporting to measure islet cell antibodies on human pancreas may have confused islet cell antibodies with insulin autoantibodies.

The same problem appears with islet cell surface antibodies because many of the living cell preparations used for their assay actively secrete insulin. Complement fixed islet cell antibodies were originally thought to be a separate variant of cytoplasmic islet cell antibodies, but more recent studies suggest that complement fixing antibodies represent high titre cytoplasmic islet cell antibodies measured in a less sensitive assay. About half of cytoplasmic islet cell antibody sera are positive for complement fixing islet cell antibody, but complement fixation does not occur without cytoplasmic islet cell antibodies.

Early clinical studies were primarily concerned with the frequency of islet cell antibodies, and most of the work was carried out on cytoplasmic islet cell antibodies. Islet cell antibodies were found in 0.5% of “normal” primary relatives of subjects with islet cell antibodies, and in 6% of patients with other organ specific autoimmune diseases. Their frequency in newly diagnosed type I diabetics varied between 65% and 85%. Islet cell antibodies are also present in type II diabetics but most probably relate to a less aggressive form of autoimmune insulin dependent diabetes that develops slowly and masquerades for a while as type II diabetes—so called “pseudo-type II” diabetes.

The presence of specific antibodies long before clinical onset of the disease is characteristic of all organ specific autoimmune disorders and is central to the concept that diabetes results from long term rather than acute immune damage. Long term studies attempting to relate islet cell antibodies to diabetic outcome are, however, few because the subjects are hard to find and follow up. The best known of such studies is the Barts/Windsor study that started in 1978, and at the time of writing (Spring 1986) 475 siblings and 510 parents of insulin dependent diabetics have been followed up. Fifty eight of these relatives have had cytoplasmic islet cell antibodies at some stage: 24 of these have complement fixing islet cell antibodies, of whom 13 have become diabetic, and another two have abnormal insulin release on metabolic testing. Of the 34 with only cytoplasmic islet cell antibodies only one has become diabetic. None of the relatives without islet cell antibodies has become diabetic (E Gale, personal communication). Thus the false positive rate is apparently high for cytoplasmic islet cell antibodies, although 46% of those selective for complement fixing islet cell antibodies have developed symptoms. An Italian study reported on 13 subjects with polyautoimmune disease and cytoplasmic islet cell antibodies; nine also had complement fixing islet cell antibodies, of whom four became diabetic and five remained normoglycaemic after five years. In a further study from the USA 38 of 135 subjects at high risk of developing insulin dependent diabetes had islet cell antibodies, and 14 progressed to diabetes after one month to several years.

In summary, islet cell antibodies appear to be associated only with autoimmune diabetes, whether or not it is acute in onset, and may well be a marker for active insulitis. Only high titre cytoplasmic islet cell antibodies, which incorporate complement fixing islet cell antibodies, offer any accuracy in predicting clinical diabetes; and patients who never have islet cell antibodies but who go on to develop insulin dependent diabetes are well described. People at risk of developing insulin dependency are, in order of risk: diabetics treated with oral hypoglycaemic agents who have islet cell antibodies; those with islet cell antibodies and glucose intolerance; and, finally, those with islet cell antibodies but normal glucose tolerance. From the start islet cell antibodies have suffered from practical and conceptual problems: they are difficult to measure reproducibly, depending as they do on the subjective interpretation of immunofluorescence patterns on cryostat group 0 human pancreas that is hard to come by; and they are directed against an unknown antigen.

**Insulin autoantibodies**

Insulin autoantibodies were first described in 1974 in a patient with reactive hypoglycaemia (insulin autoimmune syndrome), and over 100 cases of this syndrome have now been described. The antibodies have only recently been described in relation to insulin dependent diabetes and polyimmunity. Insulin autoantibodies that occur spontaneously in people who have never received insulin must be distinguished from insulin antibodies that result from injection of exogenous insulin and are common in insulin treated diabetes.

Studies of insulin autoantibodies in both children and untreated type I diabetics of mixed age groups quote a prevalence near to 40%. Some report a close correlation between insulin autoantibodies and islet cell antibodies but others do not. Similarly, some find an association between insulin autoantibodies and HLA-DR3 or DR4 haplotype, but others have been unable to. The reason for these differences is not clear, but assay systems for both islet cell antibodies and insulin autoantibodies differ widely in design and sensitivity from laboratory to laboratory. Consensus over the clinical correlates of insulin autoantibodies is unlikely to be reached until their measurement is standardised.

Insulin autoantibodies were reported in nearly half of identical twins discordant for type I diabetes. Failure of the insulin autoantibodies to diminish with time while the frequency of islet cell antibodies and the risk of diabetes fell led to the conjecture that insulin autoantibodies are a marker for susceptibility to diabetes that may or may not become clinically expressed within the lifetime of the individual. Others, however, have not found insulin autoantibodies in discordant twins.

Research into insulin autoantibodies is still in its infancy, but unlike cell antibodies—they are potentially simple to measure by objective methods and are directed against a known antigen that can be highly purified.

**Activated lymphocytes**

If a resting T lymphocyte encounters an antigen that it recognises in the context of major histocompatibility complex (HLA-DR) proteins the cell will quickly express a new receptor on its surface, the interleukin 2 receptor. Stimulation
of this receptor by interleukin 2 results in T cell maturation and clonal expansion—that is, activation. Activated T cells develop surface major histocompatibility complex antigens as well as interleukin 2 receptors and may be measured by labelling them with fluorescence tagged monoclonal antibodies specific for the major histocompatibility complex proteins or interleukin 2 receptors and counting them in a cell sorter. 17

Nine of the 11 patients with insulin dependent diabetes of short duration were found to have high counts of HLA-DR positive T cells, and in one the high count (>9%) was present before the onset of symptomatic diabetes. 19 Activated T cells may not be increased in diabetics without islet cell antibodies 20 and may occur only in association with high titre (complement fixing). 15 Like islet cell antibodies, activated T cells decrease rapidly after the onset of clinical disease 21 and are also reported to fall with the period of discordance in the unaffected homozygous twins of insulin dependent diabetes. 38

Genetic markers—polymorphism and linkage

Polymorphisms (literally multiple forms) are variations of a physical characteristic. The phenotypic polymorphisms of hair texture, skin colour, and blood group, etc, are the products of corresponding genotypic polymorphisms. Genotypic polymorphism is not always, however, expressed in the phenotype, and by implication genotypic polymorphisms are potentially more discriminating of the individual than phenotypic polymorphisms.

Genotypic polymorphisms are important because they may be linked and inherited together, and if one of the linked polymorphisms is the cause of a disease the presence of the other may provide a marker of susceptibility to the disease. Much of the impetus given to HLA typing and gene analysis during the past 10 years has derived from the hope of identifying susceptibility markers for disease in this way.

HLA phenotypes

Linkage associations between diseases and HLA have been shown by serological HLA phenotyping and expressed as relative risks. One of the best known associations is between HLA-B27 and ankylosing spondylitis, with a relative risk of 87.4. An important disturbance in the expected HLA haplotype distribution was first shown for type I diabetes in 17 Europid families with two or more affected siblings. 22 Associations between type I diabetes and class I antigens (HLA-A, B, and C) are weak but those with class II antigens (HLA-D) much stronger. The inheritance of DR3 in any member of the population confers a relative risk of about 5, similar to that of DR4. 23 The presence of the DR3/DR4 phenotype confers a relative risk for type I diabetes of up to 20%, considerably higher than the sum of the risk values of DR3/3 and DR4/4 homozygotes.

The strong association of insulin dependent diabetes with certain HLA-DR haplotypes suggests that the gene (or one of the genes) causing insulin is in linkage with HLA-DR3 and DR4. DR3 is present, however, in 32% of normal Europids and DR4 in 34%, 24 so that, although a statistically significant correlation exists between insulin dependent diabetes and DR3 or DR4, their genes are clearly not the cause of diabetes and they are of little value in identifying individuals with susceptibility to type I diabetes.

Though how HLA genes influence disease susceptibility is not known, the diseases, especially ones associated with class II products may reflect defective recognition or response to a causative agent by the host immune response. 25 An immense amount has been learnt from studying the HLA-D region phenotypes, and geneticists must now refine linkage analysis and ultimately identify the insulin genes. One approach is through allogenotypes.

HLA allogenotypes

Molecular biology now allows a direct approach to genes, with a more precise definition of the associations between polymorphisms and disease susceptibility. 26 Analysis of DNA fragments extracted from patients’ lymphocytes (restriction fragment length polymorphism analysis) using cDNA probes has already shown high risk associations for disease that had gone unrecognised. 27 The polymorphisms studied by the molecular geneticist are called allogenotypes, sequences of DNA that distinguish one group of individuals from another. An individual’s profile of allogenotypes represent his allogenotype. The diabetologist is interested in the allogenotype incorporating the putative “insulin gene,” but we do not know where on the genome it (or they) lie. Thus current studies aim at identifying allogenotypes showing linkage with clinical diabetes. A particularly striking example of allogenotype linkage with insulin dependent diabetes was the finding of 14·5 Kb and 1·8 Kb restriction fragments but absence of a 12·7 Kb fragment in 11 out of 12 HLA-DR3/DR4 diabetics. 28 These insertions and deletion were absent from all 12 HLA identical healthy controls, giving a relative risk to the marker of 400—some 20 times greater than the risk calculated using only serologically defined markers. Such studies show the greater discrimination between diabetics and normal subjects obtained by DNA analysis of the class II region compared with HLA class II phenotypic markers alone.

The results of investigating the DNA polymorphisms in the locus flanking the insulin gene on chromosome 11 have been less spectacular but do point to some minor linkage between particular polymorphisms and islin dependent diabetes. 29

Conclusions

There are many problems in interpreting markers for diabetes. Type I diabetes may represent the end stage of insulitis lasting many years, but the evidence for this is circumstantial and anecdotal. The immunological markers such as islet cell antibodies, insulin autoantibodies, and activated lymphocytes probably indicate clonal expansion and possibly active insulitis (again circumstantial), but we do not know how often insulitis develops into clinical diabetes and how often it remits spontaneously.

Studies in homozygous twins suggest that fewer than half those with known genetic susceptibility eventually develop clinical diabetes—so inheritance accounts for less than half the susceptibility to type I diabetes.

Only 12-15% of type I diabetes occurs within diabetic families, yet most studies on the predictive value of markers in diabetes have been carried out on the relatives of diabetics. About 85% of type I diabetes is thus unaccounted for in such studies, and the possibility of familial and non-familial types of type I diabetes has to be considered. There is almost
certainly heterogeneity within type 1 diabetes, so that current groupings may confuse rather than clarify the issue. Like all autoantibodies, islet cell antibodies and insulin autoantibodies may fluctuate and become transiently negative, so cross sectional studies in a population may not identify accurately those with insulitis. Although genetic markers are entirely stable and reproducibly identifiable, the genes responsible for diabetes have not been identified. The art currently rests on imperfect linkage with allelotypes.

If insulitis is a long term prelude to type 1 diabetes many cases of insulitis must never reach the clinical stage. Further, some of those with the genetic susceptibility will never develop insulitis. This implies the need for two different markers: one to identify those genetically susceptible to insulitis; and one to identify those with active insulitis. Only then can the susceptible be followed up regularly and those