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Diabetes' sweet little mystery

As the new Republican-controlled United States Congress settles down to business amid a heavy atmosphere of budget-cutting and renewed fiscal responsibility, it is probably not the time to be seeking a substantial increase in biomedical research funding. But that is exactly what the American diabetes community is doing, as it has watched with envy bordering on despair as one worthy cause after another has secured significant increases in funding, leaving diabetes funding almost at a standstill (see Table overleaf).

Concerned that only 15% of diabetes-related grant applications to the National Institutes of Health (NIH) receive funding, 14 of the leading United States diabetes research and support organizations have banded together to form the National Diabetes Research Coalition (NDRC). Last month, in a briefing on Capitol Hill packed with celebrities from the world of entertainment, politics and science, the NDRC, in conjunction with the Juvenile Diabetes Foundation, drew attention to the plight of diabetes research, which it says has been 'decimated by inadequate funding'. It asked for an additional $315 million a year to bolster the NIH's research into the causes, treatment and prevention of the disease and its many life-threatening complications. The fact that this is American Diabetes Alert month should drive home the need for a new commitment to understanding and treating the seventh leading cause of death in the United States.

"The human cost and the economic cost of diabetes is simply too high." — Representative Elizabeth Furse (D-Oregon)

Diabetes exists in two forms. Type 1, or insulin-dependent diabetes mellitus (IDDM)[1], results from the autoimmune destruction of the insulin-producing pancreatic β cells. Type 2 — the adult-onset, non-insulin-dependent form (NIDDM) — is far more common and is preceded by the development of insulin resistance. IDDM carries about a 0.4% lifetime risk, affecting about a million people in the United States. However, about 90% of diabetes is the type 2 form. More than 14 million Americans suffer from diabetes, although only half of them are aware of it, and more than 650,000 new cases are diagnosed each year. According to the NDRC's white paper, the consequences each year of diabetes in the United States alone include:

- 15–39,000 new cases of blindness.
- 13,000 cases of end-stage renal disease.
- 54,000 amputations, mostly of lower extremities.
- 162,000 deaths from heart attacks, strokes, and so on.

These figures are bad enough, but they carry a powerful economic argument as well. In 1992, the direct costs of treating diabetes in the United States was $85 billion. If one factors in lost productivity due to death and disability, that figure

Table Increase in NIH funding for various diseases, 1991-1994

Disease	Percentage increase
Breast cancer	200
Ovarian cancer	157
Cervical cancer	87
Alzheimer's disease	32
AIDS	30
Diabetes	15

Source: NDRC white paper

rises to a staggering $130 billion.

There is steady progress to report in diabetes research, particularly in the field of genetics. Recent advances in NIDDM research include the discovery of mutations in the glucokinase gene (accounting for as many as 5% of NIDDM cases), mitochondrial DNA, and now the glucagon receptor (see pages 223 and 299 of this issue). Further advances are on the horizon, especially as the resources come into play of gene companies such as Millennium Pharmaceuticals, Sequana Therapeutics and Myriad Genetics, which are targeting NIDDM and related diseases such as syndrome X.

Research into IDDM received a welcome boost late last year, when the genome search of John Todd's group at Oxford[2] and similar studies by other groups[3,4] added at least five susceptibility loci to those already known to reside on chromosomes 6 (the HLA region; *IDDM1*) and 11 (*IDDM2*). The identity of these new loci remains to be solved, but a bigger challenge is perhaps to determine the role and interaction of those that have already been incriminated. Many people have long regarded the polymorphisms in the HLA class II region tied to *IDDM1* as the dominant factor in inherited susceptibility, but two papers in this issue[5,6] shift the spotlight onto the nature of *IDDM2* and its possible relevance to the disease.

The *IDDM2* locus was mapped to the short arm of chromosome 11 several years ago, and subsequently narrowed to a stretch of just 4.1 kilobases spanning the insulin gene[7]. The most likely candidate for *IDDM2* within this segment was a highly polymorphic stretch of DNA lying a few hundred basepairs (bp) upstream of the start of the insulin gene; it consists of a variable number of tandem repeats (VNTR) of a 14 bp sequence, which exists in a dozen or more different forms. In humans, this VNTR is divided into three size classes: class I (~40 repeats), class II (~85 repeats) and class III (~150 repeats). Type 1 diabetes is associated with homozygosity for the class I repeat.

On page 284, Todd, Bennett and colleagues show convincingly that it is indeed this minisatellite sequence at the *IDDM2* locus, and not one of the other polymorphic markers in the region, that contributes to protection from and susceptibility to diabetes[5]. Bennett *et al.* discerned 21 different class I VNTR alleles which, with just a couple of exceptions (including an allele which in their terminology migrates at '698 mobility units'; see below), are significantly associated with susceptibility to IDDM.

But if the VNTR is in fact *IDDM2*, how does it render individuals more susceptible or more resistant to diabetes? Although studies are still in their infancy, the answer may lie in a direct effect on transcription of the insulin gene. On page 293, Kennedy and co-workers examine the long-suspected role of the insulin VNTR on transcription[6]. They took the first class I allele ever cloned[8], λHI-1, and compared its effect on the transcription of reporter genes to that of a class III allele. Both VNTR elements stimulated transcription, but the longer class III allele was more than twice as effective as the λHI-1 allele. They also found that the VNTR is able to bind the transcription factor, Pur-1, with some of the individual 14 bp repeats, notably the most common 'a' repeat, binding significantly better than others.

A number of other groups[5,9] have also begun to examine the role of the VNTR on insulin mRNA levels, and find instead that it is the class I allele that is associated with higher amounts of transcription. A way out of this possible dilemma is suggested by Bennett *et al.*[5], who note that the λHI-1 class I allele used by Kennedy *et al.*[6] in fact corresponds by size to the '698' allele which, unlike most class I VNTRs, is not associated with IDDM susceptibility. Perhaps the specific repeat composition of this allele, rather than its unique length, is the key factor[6]. Tempting though it is to speculate that IDDM susceptibility is linked to the inheritance of a class I VNTR which, in most cases, is linked with higher levels of insulin transcription, the true answer may not be quite so simple. Clearly the money requested by the NDRC could be put to good use.

1. Atkinson, M.A. & MacLaren, N.K. *New Engl. J. Med.* **331**, 1428–1436 (1994).
2. Davies, J.L. *et al. Nature* **371**, 130–136 (1994).
3. Field, L.L. *et al. Nature Genet.* **8**, 189–194 (1994).
4. Hashimoto, L. *et al. Nature* **371**, 161–164 (1994).
5. Bennett, S.T. *et al. Nature Genet.* **9**, 284–292 (1995).
6. Kennedy, G.C., German, M.S. & Rutter, W.J. *Nature Genet.* **9**, 293–298 (1995).
7. Lucassen, A.M. *et al. Nature Genet.* **4**, 305–310 (1993).
8. Bell, G.I., Selby, M. & Rutter, W.J. *Nature* **295**, 31–35 (1982).
9. Lucassen, A.M. *et al. Hum. molec. Genet.* (in the press).

Correction

In the editorial appearing in the November 1994 issue ('Anastasia and the tools of justice', vol. 8, 205-206; 1994), reference was made to the wife of Mr. Richard Schweitzer, whom, it was stated, '... claimed to be a descendant of the Tsar's private physician ...' We did not intend to imply that there was any doubt about Mrs Schweitzer's ancestry, and regret any distress this statement may have caused.