ing dairy cow, for example, secreting 3 kg of milk solids per day, makes comparably wide demands on her physiology.

Eckhardt *et al.* argue that genetic variation for running ability in horses may have been depleted by a long evolutionary history during which this was an important survival trait. Again, it could be argued that the evolutionary imperative was to outdistance predators, whereas the modern racing goal is to outdistance other horses. The first may have an intermediate optimum; the latter clearly is unbounded. Our estimate of the heritability of TIMEFORM rating, about 35 per cent, is similar to other estimates for different measures of racing ability, and all indicate substantial additive genetic variance.

How can the different question of static (or nearly static) winning times in classic races be resolved? One answer may be that tracks are now watered in dry years. Another is discussed above by Beatson, who suggests that selection on a subjective criterion like TIMEFORM rating produces a negligible correlated response in racing speed because of the very low variance in the latter trait. The low estimate of variability of racing time which he provides (CV=1.5 per cent) is supported by a similar value (CV=1.3 per cent) obtained by analysing many time records in greyhounds[6].

Another reason could be that winners in classic races are close to some physiological limit. Lactic-acid accumulation in blood rapidly reaches critical levels in horses undergoing continuous exertion[7]. This would impose limits in longer races but be less restrictive in shorter ones. There is a suggestion of a more pronounced plateau in performance in winning times in the St Leger (1¾ miles), than in the Oaks, Derby and Belmont (1½ miles), with even less evidence of a plateau in the Kentucky Derby (1¼ miles) and the Preakness (1$^{3}/_{16}$ miles).

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HLA and insulin-dependent diabetes mellitus

SIR—The contribution of the polymorphic residue at position 57 of the HLA-DQβ chain to autoimmune diabetes (insulin-dependent diabetes mellitus or IDDM) has been discussed recently[1-5]. Genetic susceptibility to IDDM is positively correlated with a neutral residue (Ala, Val, Ser) and negatively correlated with an Asp at this position. Position 57 is also revealed as a critical residue in the analysis of *Pemphigus vulgaris*[6] but susceptibility to *P. vulgaris* seems to be a property of the allelic β-chain structure rather than just residue 57. Similarly, for IDDM susceptibility, there are several haplotypes with a neutral residue at 57 that do not confer high susceptibility (for example, DR7) and some with Asp 57 that seem to be disease-associated (for example, DR4 and DRw9 in the Japanese). Another challenge for the simple residue-57 model is how to account for the increased risk of DR3/4 individuals relative to DR3/3 or DR4/4 individuals as they are all non-Asp 57 homozygotes. These observations are most simply explained by assuming that other HLA class II sequences can also confer susceptibility to IDDM. The DRβI allele, for example, seems to contribute to the DR4 association with IDDM[7,8]. In general, it is specific combinations of class II alleles (haplotypes and genotypes) that are most highly associated with disease.

Notwithstanding these and other exceptions[9], the data implicating residue 57 as critical in disease susceptibility are striking: this intriguing correlation demands an explanation. One possibility is that the region around position 57 of the DQβ chain encoded by a susceptible allele (for example DQβ3.2) presents an autoantigen to the T cell or determines the expression of a particular T-cell receptor during thymic maturation[1,4]. The notion, however, that all allelic DQβ chains that contain Asp 57 (or non-Asp 57) bind a common islet cell autoantigenic epitope or influence the T-cell receptor repertoire in a similar way seems unlikely given the diversity of Asp 57 (or non-Asp 57) alleles (Table 1). An alternative interpretation is that the residue at position 57 may simply influence the overall conformation of the β-chain and not necessarily interact directly with a putative autoantigen. The functional significance of position 57 is suggested by the conservation of this charge polymorphism in all human class II β-chains (DQβ, DRβI, DRβIII, and DPβ). In fact, position 57 polymorphism at these other β-chain loci may also be relevant to disease susceptibility[4,5]. Moreover, the same polymorphic residues are found at position 57 in chimpanzee, gorilla, baboon, rhesus and cebus β-chain alleles (Table 2; Gyllensten *et al.* unpublished observations). The evolutionary maintenance over 10–20 million years of a balanced polymorphism between Asp 57 and Val, Ala or Ser at this position in all class II β-chains examined so far suggests that β-chains containing Asp 57 and those with Ala, Val, or Ser at position 57 may be structurally and functionally different. Perhaps, selection for the presence of both types maintains this polymorphism[10]. Whatever the functional significance of residue 57 polymorphism, the general correlation observed between disease susceptibility and the nature of residue 57 may ultimately reveal more about the structure of class II β-chains than about the specific response to a putative diabetes autoantigen.

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Table 1 HLA-DQβ sequences from residues 52 to 57

DQβ allele	Sequence	Group
DQβ3.2	—PLGPPA—	
DQβ2	—LLGLPA—	Ala, Val, Ser 57
DQβ1.1, 1.7	—PQGRPV—	
DQβ1.2	—PQGRPS—	
DQβ3.1, 3.3	—PLGPPD—	
DQβ4	—PLGRLD—	Asp 57
DQβ1.3, 1.4, 1.5, 1.6	—PQGRPD—	

Table 2 Residue at position 57 in class II β-chains

	DQβ	DRβI	DRβIII	DPβ
Human	Asp	Asp	Asp	Asp
	Val, Ala, Ser	Val, Ala, Ser	Val	Ala
Non-human	Asp	Asp	Asp	—
Primates	Ala, Val, Ser	Val, Ser		

Primate species examined include chimpanzee, pygmy chimpanzee, gorilla, rhesus, baboon and cebus.

Single-strand RNA

SIR—In their News and Views article, Lamb and Dreyfuss[1] state "All RNA viruses have to go through a ds RNA intermediate in their life cycle". If "ds RNA" designates double-helical RNA, this statement is incorrect, for the replication intermediate of RNA phage Qβ is a single-stranded minus strand, and not double-stranded RNA[2]. The same is thought to be true of many of the animal positive-strand RNA viruses, including picornaviruses, togaviruses and coronaviruses[3], although