that the lithic body contains the remains of some 300,000 eggs. This suggests that the area was a nesting ground, and that the dinosaurs may have returned to this same area during several reproductive seasons.

The Bastús egg site is the result of the nesting behaviour of a dinosaur population living very near the sea shore and may represent a local example of a widespread phenomenon in the Upper Cretaceous of the south-central Pyrenees.

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Codon bias targets mutation

SIR — Serine is encoded by two sets of triplets (AGC and AGT (grouped as AGY) and TCA, TCC, TCG and TCT (grouped as TCN)). We have analysed the usage of the two types of codon in human immunoglobulin variable region (V) gene segments and have found a preference for AGY codons in the complementarity-determining regions (CDRs; particularly CDR1) and for TCNs in the frameworks (Fig. 1). This bias is not a peculiarity of human immunoglobulin *V* genes, but also occurs in mice (not shown) and *Xenopus*[1].

Immunoglobulins undergo functional diversification by somatic mutation, with nucleotide substitutions being introduced throughout the *V*-gene segment. Diversification is greatest in CDRs, the portions most strongly implicated in contacting antigen. We propose that the biased serine codon usage in immunoglobulins has evolved to help the somatic hypermutation machinery target these parts of the antibody molecule. Thus, mutations are targeted to residues that could yield increased affinity for antigen and away from places where they are more likely to destroy the structural scaffold. Consistent with this, the *V* genes of the T-cell receptor (TCR), where there is no evidence for functional diversification by somatic mutation, do not show a bias in their CDRs (Fig. 2).

During maturation of the antibody response, the V regions in those B lymphocytes selected by the initial antigen challenge contain many nucleotide substitutions. Cells expressing antibodies with improved binding characteristics are then selected from the population of somatically mutated daughter cells. The nucleotide substitutions are not targeted randomly. In mouse variable-region κ-chains (V_κs), for example, there is intrinsic favouring[2] of CDR1, and hotspots of mutation have been identified that are intrinsic to the mutational process[2,3]. The consensus [$^{A}/_{G}$ G $^{C}/_{T}$ $^{A}/_{T}$] has been proposed[4] as a preferred target for mutation and, indeed, the most striking of the hotspots are often associated with AGY serine codons[2,3]. Thus, the preponderance of AGY over TCN serines in the CDRs of germline *V* genes (and the converse in frameworks) suggests that the DNA sequence of germline *V* genes has evolved in response to selection for appropriately targeted mutability.

There are some significant exceptions to this biased codon usage. In germline V_κs, a TCN serine (position 52) is conserved in CDR2 presumably because it contributes to the structural integrity of the CDR loop[5]. On the other hand, V_κ framework position 77, a conserved AGY in human and mouse germline V_κs, is one of the intrinsic mutational hotspots located outside a CDR[2]. There is also a preference for serine AGY codons in positions at the 3′ end of TCR V_β genes flanking the heptamer/nonamer recombination signals which may reflect a role in the gene rearrangement process.

It has been noted that serine AGY codons are more mutable than serine TCNs in protein coding sequences of humans and mice. This observation parallels the mutability of *V*-gene serine codons during somatic hypermutation and is consistent with them being common features of the molecular mechanism of evolutionary and somatic mutation.

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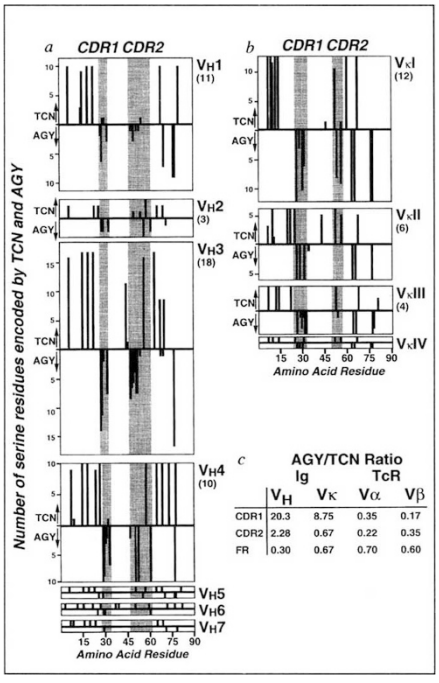

FIG. 1 Distribution of TCN and AGY serine in immunoglobulin V segments. *a*, *b*, Sequences of functional human V_H genes (kindly provided by G. Cook and I. Tomlinson[7]) and V_κ genes[8] have been grouped into families and, at each serine position, the number of family members containing a TCN codon is depicted above the line and an AGY codon below. The name of each family and the number of its members are given. CDRs are shaded. *c*, The ratio of serines encoded by AGY triplets to those encoded by TCN triplets is given for CDR1, CDR2 and the framework portions (in FR1, FR2 and FR3 are summed together) of human immunoglobulin (Ig) V_H and V_κ, and TCR V_α and V_β segments. This compilation has been made by combining all *V*-gene sequences for each locus. Using a large sample test for a binomial distribution, the AGY/TCN ratios in the V_H CDR1 and CDR2 and in the V_κ CDR1 are significantly skewed (p<0.03%) from the ratio (0.64) expected from the GenBank protein database[9]. There is slight inverted skewing of the AGY/TCN ratio in the case of the TCR CDRs, although this is of much less statistical significance.

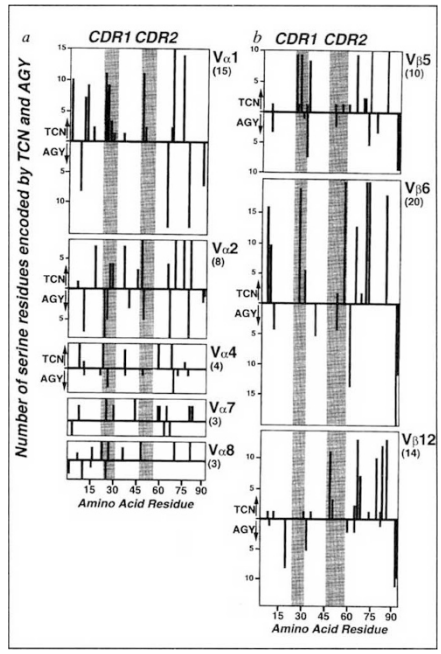

FIG. 2 Distribution of TCN and AGY serine in TCR V segments. Sequences of human TCR V_α and V_β genes (classified as in ref. 10) have been grouped into families and the serine codon usage displayed as in Fig. 1. Only the largest TCR *V*-gene families were used for the analysis.

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