neopeptide in the thymus provides a new approach for exploring the role of peptide in the positive selection of T cells. This strategy inverts the traditional one of starting with a T cell displaying a particular TCR and then attempting to define the requirements for its selection; rather, it begins with expression of a new peptide and permits one to study the T cells naturally selected on it. Our data show that the peptide sequence influences the sequence of the TCRs on selected cells, significant and systematic variations resulting from single-residue changes at putative TCR-contact points. The relation between selecting peptide and selected TCR shows significant, but not complete, two-way degeneracy, analogous to what is seen with the responses of mature T cells. Taken together, these observations support the hypothesis that positive selection involves direct recognition of peptide features, but they do not entirely rule out the possibility that peptide plays primarily a structural role, its precise sequence impinging on the process when it leads to steric hindrance of the TCR (12).

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14. T. Miyazaki et al., ibid., p. 531.
17. R. N. German, Cell 267, 284 (1994).
18. S. Vville et al., ibid.72, 635 (1993). If “immature” mice came from a backcross of the il null mutation onto the B10.BR background for three to five generations. Heterozygote controls were littermates or from parallel crosses to B10.BR.
(1); however, the problem is particularly critical in figure 4, which provides the primary data to suggest a relation between the growth of the brain and the detachment of the ossicles. In this figure, Rowe superimposes his data on the growth of the ectotympanic and dentary bones and the date of the detachment of the auditory ossicles in *Monodelphis* on data on brain growth in *Didelphis* presented by Ulinski (5). He does not correct for the differing rates of development; instead, the two data sets are combined. This is equivalent to taking one set of measurements on a domestic cat and another on a tiger and, without correction for size or rates of development, summarizing the "felid" pattern. The auditory ossicles do not detach from Meckel’s cartilage at day 21 in *Didelphis* because at this time there is no jaw condyle nor is there ossification of any ossicle (4). Further, all evidence suggests that at 20 days after birth the brain is far more advanced in *Monodelphis* than in a 20-day *Didelphis* pouch young (6). If Rowe is to argue a relation between the timing of events in development, he must either compare data derived from a single species or, at the least, correct for the differing rates of development in two very different species.

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**REFERENCES AND NOTES**

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Response: Do *Didelphis* and *Monodelphis* really have differing rates of growth? In answering this question, care must be taken to distinguish between rates of growth and rates of maturation because the two are broadly correlated but are not strictly coupled throughout ontogeny (1). *Didelphis* and *Monodelphis* undoubtedly have different growth rates. These closely related didelphid marsupials (2) have similar life-spans of 2 to 3 years in the wild, yet *Didelphis* reaches two to three times the adult size of *Monodelphis* (3). This accords with the observation that *Didelphis* young remain attached to the teat longer and are weaned much later than *Monodelphis* young.

Do rates of maturation also differ? My observations on skeletal maturation in *Monodelphis* (4–5) agree closely with those of Smith (6) and van Nievelt, but we disagree on the timing of maturation events in *Didelphis*. Their statements about *Didelphis* are based on a study by Nesslinger (7), who examined only whole specimens that were cleared and stained for bone (alizarin). As histology shows, clearing and staining does not allow one to detect bone at its earliest stages in ontogeny. Nesslinger’s specimens consisted of only road-killed and wild-caught *Didelphis*, so that chronological ages could only be approximated. More thorough studies on the embryology of *Didelphis* (8–11) were based on a collection of several hundred specimens raised by the Wistar Institute in the 1930s. Histological sectioning of individuals of known ages indicates that, insofar as the skeletons of *Monodelphis* (4–6, 12) and *Didelphis* (8–11) can be compared, they are virtually identical in timing of maturation.

For example, a synovial joint is present between the incus and malleus at birth in both *Didelphis* (10) and *Monodelphis* (12). Ossification of the ectotympanic has begun by the middle of the second day in both species. In *Didelphis* (10, p. 235) at 7 days the mandible has a definite temporomandibular articulation ... the mandibular condyle contains a larger condylar cartilage which has developed between the seventh and fifteenth day. It is rather large and is already undergoing some ossification ... just as in *Monodelphis* (5, 6, 12). Ossification of the malleus has begun in both *Monodelphis* (5) and *Didelphis* (10) by the end of the second week. By the third week the incudo-malleolar joint is well formed and enclosed in a fibrous joint capsule in both species. In the fourth week, about the time of detachment, the incudo-stapedial joint becomes well formed and also enclosed in a fibrous joint capsule in both species. Over the remainder of ontogeny, the bones of the auditory chain in the two didelphids share similar chronologies. My examination of the surviving materials from the Wistar collection and other large North American skeletal collections of *Didelphis* substantiates these observations (5); I can find no support for the statement that “any given event will occur 2 to 4 weeks later in *Didelphis* than in *Monodelphis*.” Although didelphid species have different growth rates, their chronologies of maturation are closely comparable.

Last, the relation that I described between the brain and middle ear (4, 5) is one of relative growth, not timing of maturation. The relative size of the adult brain varies over more than an order of magnitude among different mammalian species, hence mammals must have widely varying rates of brain growth (13). But the small middle ear ossicles are far less variable in size, their growth ceasing early in ontogeny as a constraint of their function in high-frequency audition. Repositioning of the auditory chain occurs in the wake of continued cerebral growth. Didelphids are among the least encephalized mammals and offer the most generalized examples of this relationship. The patterns of variability among other species are invariably superimposed upon a more general pattern of differential growth of the brain and middle ear bones that is common to all mammals.

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Editor's Summary

Comparative Rates of Development in *Monodelphis* and *Didelphis*
Kathleen K. Smith and Alexander F.H. van Nievelt (January 31, 1997)

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