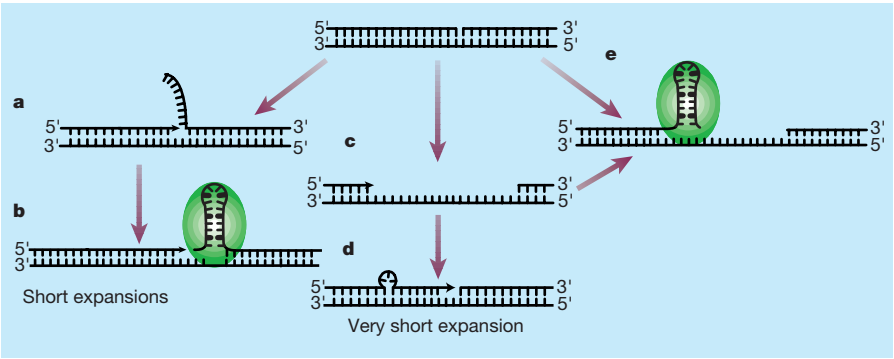

Figure 2 **A nick in DNA could promote the instability of tracts of nucleotide repeats.** a, **During the repair of the gap, too much of the lower strand might be copied, producing a flap. This is 'strand-displacement synthesis'.** b, **Continued copying will lead to the formation of a hairpin within the flap. The repair proteins MSH2 or MSH3 might bind to and stabilize the hairpin; sealing the nick will then lead to an expansion in the upper strand. The next time the cell duplicates its DNA, the expansion will be copied if unrepaired, and both strands will contain the expansion.** c, **A large gap might form as a result of the initial nick.** d, **The error-prone replication enzyme DNA polymerase-β (or another polymerase) fills in the gap; if it slips, it could cause addition or deletion of one or more repeats.** e, **DNA 'melting' at the nick could lead to hairpin formation, perhaps stabilized by MSH2/MSH3, creating a gap. DNA melting and hairpin formation could also occur at a gap, as well as a nick. The hairpin may form at either end of the gap. If the gap is filled without removing the hairpin, repeat expansion will occur.**

and recombination are thereby excluded as obligatory pathways to repeat variability.

What mechanism, then, can explain the age-dependent accumulation of mutations in non-dividing cells? A key revelation was that mice with Huntington's disease that lack the DNA-repair protein MSH2 do not show age-dependent repeat variability in different tissues[10]. Studies of animal models of myotonic dystrophy that lack the DNA-repair proteins MSH2 (G. Gourdon, Hôpital Necker-Enfants Malades, Paris), PMS2 (D. Monckton, Univ. Glasgow) or MSH3 (B. Wieringa, Univ. Nijmegen), as well as further studies of mice with Huntington's disease[9], have now confirmed that age-dependent repeat instability requires repair proteins. Moreover, MSH2 is required for repeat instability in developing sperm in mice with Huntington's disease[9]. However, instability still occurs in animals that lack the repair protein MSH6 (B. Wieringa) or the recombination proteins RAD52 and RAD54 (G. Gourdon).

There are several ways in which DNA can be altered that might lead eventually to DNA-repair-dependent repeat instability. First, alternative DNA structures, such as slipped-strand DNA, might form within repeat tracts after DNA replication. These structures could then bind to MSH2 or MSH3, which would try to mend the unusual structures, perhaps (in fairly complicated ways) resulting in errors such as repeat expansion (Fig. 1; C. Pearson). Second, DNA sustains continuous spontaneous damage, for example as a result of oxidation[8]. Repeat tracts or alternative structures might be particularly sensitive to damage — and so particularly dependent on effective DNA repair.

Third, single- or double-stranded breaks can occur in DNA, either *de novo* or as a result of incomplete DNA replication. Moreover, larger gaps could accumulate, with flaps, hairpins or other complex structures forming at their ends (C. McMurray, Mayo Foundation, Rochester, Minnesota). DNA-repair proteins might bind to and stabilize these unusual repeat structures, indirectly promoting expansion (Fig. 2). In the case of mice with Huntington's disease, the repeat tracts expand by just one to three repeats[9]; this may be too few to allow a stable repeat secondary structure to form. Here, instability might instead reflect the slippage of replicating enzymes during an error-prone repair process.

With this new knowledge in hand, it may one day prove possible to develop approaches that minimize the lengthening of repeat tracts that can occur throughout life. But another important part of the story — the molecular basis of the large-scale tract expansion that can occur between generations — remains a mystery. ■

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Daedalus

The tense road

A road, says Daedalus, is quite a clever mechanical invention. It takes the force applied by a driven wheel, and reacts to it by momentary deformation. The resulting reaction of the road on the vehicle drives it along. Fast or heavy vehicles, by the powerful reaction they impose on the road, soon damage it. Their powered wheels do far more damage than the merely passive load of the coasting wheels. Daedalus sees the force of the engine being applied first to the tyre, and only then to the road. The tyre is canted, at least at the bottom, and the angle of cant applies a force to the vehicle.

So Daedalus wonders what would happen if the tyre were made from his 'slow rubber' of last week. At a slow enough speed, nothing would happen, and the vehicle would proceed with normal engine efficiency along the road. But at some well-defined speed, the slow restitution of the rubber would hold the canting effect well beyond the time of contact. The tyre would become very lossy, and most of the car's energy would appear not in acceleration, but as heat in the tyres. (Carbon black is put into tyres specifically to dissipate heat.)

Thus a tyre of a properly compounded slow rubber would act as an automatic speed limit. On the principle 'never do by law what you can do by engineering', Daedalus advocates the sale of 'slow tyres' to prove to the police that a specific car could never have exceeded the speed limit.

But clearly the law would be better served by a 'slow road' with the equivalent property. Any car or lorry, no matter what its tyres, would then feel a dramatic slowing on passing onto such a road surface. The road would be deformed by the driven tyres, and this deformation would be restored too late to power them along. Instead, the road would get hot.

The slow road might need to be replaced at frequent intervals, as it absorbed the power of many roadhogs, but it could still be a sound investment. On roundabouts, junctions and sharp bends, and on motorways (with the exception of overtaking lanes), it would restrict motorists to the speed limit, without requiring any legal action. A driver would notice nothing, except that no amount of throttle could accelerate him above the legal limit on such stretches of road. Daedalus hopes that such stretches will hardly get warm from the few roadhogs who challenge them, and that their deterioration (thermal and mechanical) will be very slight. David Jones