

per megabase (compared with the 16.3 genes per megabase on chromosome 22, and 6.7 on chromosome 21).

Deloukas *et al.* analysed the sequence of chromosome 20 with methods similar to those used for the other chromosomes²⁻⁵. But they also introduced new approaches; for example, they compared the sequence with newly released genome data from species such as mice⁶ and puffer fish⁷. Comparing sequences between evolutionarily disparate species reveals genomic sites that have not been able to change much during evolution, because they have essential functions. Such sites are often genes or gene-regulatory elements, and most (even though they are often shorter than 50 bases) are found at similar positions in different genomes. So comparative analyses can be superior to more traditional methods such as computer predictions in allowing unknown genes and regulatory elements to be annotated. And comparative analyses also allow researchers to evaluate the results obtained by these traditional methods. All in all, Deloukas *et al.* suggest that they have annotated as many as 95% of the genes on chromosome 20.

The finished sequence and annotation¹ will be a boon to researchers interested in the diseases that have been linked to chromosome 20. The genes that cause Creutzfeldt-Jakob disease and severe-combined immunodeficiency (an autoimmune disease) were identified and mapped to chromosome 20 several years ago; the genes have since been well characterized.

But many other disorders caused by mutations in single genes or a variety of genes — including type 2 diabetes, obesity, cataracts and eczema — have also been linked to this chromosome. Although the exact genes have not yet been identified, the complete sequence will be invaluable, particularly as researchers have unlimited access to, and are able to freely use, the data. Even while the draft genome sequence was being generated, the discovery of several disease genes linked to chromosome 20 — including those that underlie Hallervorden-Spatz syndrome⁸ (a nerve-degeneration disorder) and Alagille syndrome⁹ (which is characterized by narrowing of the vein leading to the lungs) — was accelerated because the data were freely available. This was one of the goals of the public project from the beginning, and has meant that scientists have also been able to study several forms of cancer associated with chromosome 20. Of course it may take years, but identification of the disease-associated genes should lead, eventually, to a better understanding of the processes that lead to disease, and perhaps to treatments.

Another of the consortium's agreements¹⁰ was that the sequencing of each chromosome would be finished to the same high standards. These standards have been

met for all three completed chromosomes. Although draft data, even at low quality, are useful for initial gene identification and genomic studies, further sequencing and experiments are needed for more precise analyses. It took close to a year to convert the draft data of chromosome 20 to the finished sequence now published. The effort required to polish the last 5 megabases of draft data — and to close 38 of the 42 gaps in the sequence — is comparable to what was required to produce the entire draft. This highlights the fact that 'finishing' has many difficulties, both technically as well as in assessing whether the entire sequence has been covered and the data are of high enough quality.

Finishing includes a tedious process in which incorrect and ambiguous sites in the draft, even those as small as one base, are identified and corrected. Errors such as this have proven recalcitrant to automated sequencing processes, making it clear that the more laborious 'clone-by-clone' approach to finishing is a necessity (as opposed to the whole-genome shotgun approach used by Celera to obtain its draft data⁵). As a good example of this, the highest peak of G+C bases along chromosome 20 occurs at a different position in the finished chromosome 20 sequence¹ and in Celera's draft data⁵. (G+C-rich regions are often difficult to sequence and are of interest because they tend to contain more genes.) There are also major discrepancies between the public consortium's draft⁴ and finished¹ data for chromosome 20 (Fig. 1) — probably due to large duplications in the genome. As

pointed out by Deloukas *et al.*¹ (see Fig. 2 on page 868) and previously^{4,5}, the human genome contains many of these duplications, which might provide the raw material for the emergence of new genes during evolution in higher primates, including humans. Without clone-map information, it is hard to work out where duplicated segments fit in.

As with the Harry Potter series, we already know how long the complete works of the human genome will be — 24 instalments — and we can't wait to get our hands on them all. We have already had a few glimpses of what's to come, but there are many mysteries and secrets yet to be revealed. It's been a long wait between instalments two and three, but there should be a flurry of activity over the next year and a half; we expect the book of human genes to be wrapped up in spring 2003.

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Biomechanics

Damper for bad vibrations

R. McNeill Alexander

Some muscle fibres in the legs of horses seem to be evolutionary leftovers with no function. But in fact they may act to damp damaging vibrations generated in the leg as the horse runs.

Horses¹ and camels² have muscles in their legs with tendons more than 600 millimetres long connected to muscle fibres less than 6 millimetres long. Such short muscles can change length only by a few millimetres as the animal moves, and seem unlikely to be of much use to large mammals. The tendons function as passive springs, and it has been assumed that the short muscle fibres are redundant, the remnants of longer fibres that have lost their function over the course of evolution. But Wilson and colleagues argue, on page 895 of this issue³, that these fibres might protect bones and tendons from potentially damaging vibrations.

For mammals and birds with masses greater than a few kilograms, tendon elasticity substantially reduces the energetic cost of

running⁴. In humans, the Achilles' tendon is the principal tendon involved. In animals, other tendons in the lower leg are also important. Each time a foot hits the ground, these tendons are stretched. As the foot leaves the ground again, the tendons recoil elastically. Kinetic and gravitational potential energy are stored as elastic energy in the tendons and returned in the elastic recoil. Similarly, the kinetic energy lost by a bouncing ball when it hits the ground is also stored as elastic energy and returned in the recoil. So running animals effectively bounce along, using less energy than would be needed if their tendons were not elastic.

Compared with other tendons, such as those of the muscles that bend the joints of the leg, the energy-saving tendons have much

smaller cross-sectional areas, relative to the strengths of their muscles⁵. Consequently, in strenuous activities such as running and jumping, much larger stresses act in them than ever occur in more typical tendons. If these energy-saving tendons were thicker, the stresses in them would be lower — but then they would stretch less and store less elastic energy.

In fact, these tendons may stretch so much that the muscle fibres to which they are attached do not need to lengthen or shorten at all as the leg joints bend and re-extend during a step. Experiments on turkeys⁶ and kangaroos⁷ have shown that the bending and extension of the ankle, while the foot is on the ground in a running step, is almost entirely due to tendon stretching and recoil. The muscle fibres remain almost constant in length, doing hardly any work, which suggests that the muscle fibres are superfluous. If so, one would think that the animal could save energy by losing the muscles over the course of evolution: muscles require metabolic energy to develop tension, even when they do not change length and so do no work. In fact, good runners such as antelopes, camels and horses have remarkably short fibres in the muscles whose tendons serve as springs. Yet these muscle fibres have not disappeared.

In their studies of horses' limbs, Wilson *et al.*³ have found a possible explanation. Their experiments show that short muscle fibres can damp the damaging vibrations following the impact of a foot on the ground. When the foot of a running animal hits the ground, the impact sets the leg vibrating; the frequency of the vibrations is relatively high — for example, 30–40 Hz in horses — so many cycles of vibration would occur while the foot was on the ground if there were no damping.

The vibrations might cause damage, because bone and tendon are susceptible to fatigue failure⁸. Fatigue in bones and tendons is the accumulation of damage resulting from repeated application of stresses. Bone fatigue is responsible for the stress fractures suffered by both human athletes and racehorses, and tendon fatigue may explain at least some cases of tendonitis. Wilson *et al.*³ suggest that the very short muscle fibres protect both bones and tendons from fatigue damage by damping out vibrations, but I find the suggestion more convincing for tendon than for bone.

Damage accumulation in tendons is a function of both the total time for which stress is applied, and the number of applications of stress. However, damage accumulation in bones loaded under tension seems to depend only on the total duration of the stress, and not on the number of cycles⁹. Stress fluctuations due to vibrations, superimposed on the overall rise and fall of stress while a foot is on the ground, can be expected to shorten the life of a tendon, but I doubt whether they would have a similar effect on bone.

The findings of Wilson *et al.*³ are original and welcome, and lead one to consider why these tiny muscles might have taken on this role. There is no need to exploit the special properties of muscle to damp vibrations; any viscoelastic material could do the job. For example, if the properties of the tendons were a little different they could be effective as dampers — but then the tendons would not be effective as energy-saving springs. In their elastic recoil, tendons return 93% of the work previously done in stretching them¹⁰, so they have very little damping effect. The 7% of the work that is not returned is dissipated as heat, raising the temperature of the tendons. For galloping horses, the cores of their tendons can reach temperatures high enough to cause damage¹¹, and if tendon properties were modified to make the tendons effective as dampers, the problem of overheating would be worse.

Wilson *et al.*³ have found an important role for a muscle that seemed to be the relic of a structure that had lost its function in

the course of evolution. Their work makes us wonder whether other vestiges (such as the human appendix) are as useless as they seem.

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Meteoritics

Life's sweet beginnings?

Mark A. Sephton

Sugars are common components of organisms on Earth. So their discovery in a meteorite from a lifeless part of the asteroid belt has implications for theories of the origin of life.

There are reasons to believe that some of the building blocks needed to start life on Earth may have come from outer space. Meteorites can be particularly useful vehicles in this regard, especially a type called carbonaceous chondrites, which, as their name suggests, are rich in carbon. Cooper *et al.*¹ have been studying two such carbonaceous chondrites, and on page 879 identify the first extraterrestrial sugar-related compounds found in meteorites.

The Murchison and Murray meteorites studied by Cooper and colleagues (Fig. 1, overleaf), like all carbonaceous chondrites, are derived from ancient asteroids that can be considered as a sort of builder's rubble left over from the construction of the planets. As a result, they have avoided being recycled by planetary processes, and are a valuable record of the state of matter shortly after the Solar System was formed. The diverse types of organic matter present within carbonaceous chondrites constitute evidence that as the Solar System formed it was accompanied by a great deal of organic chemistry. 'Organic' in this sense does not refer to matter created by biological processes, but simply to the chemistry of carbon compounds.

In their paper¹, Cooper *et al.* discuss the significance of the organic matter in meteorites for the origin of life, but in a different

context. In 1961, Oro² first suggested that the early Earth inherited substantial amounts of organic matter from the influx of extra-terrestrial organic-rich objects. There has since been a growing acceptance that extra-terrestrial organic matter, similar to that found in the Murchison and Murray meteorites, provided the raw materials to help kick-start life on Earth. Until now, though, the organic mixtures in carbonaceous chondrites were missing one obvious ingredient from the recipe of life: sugars.

Collectively, sugars and their related compounds are called polyols. Chemically speaking these are compounds that have a number of hydroxyl (OH) groups attached to their carbon skeleton. Sugars are important biologically because they provide the carbon skeletons for many other molecules. They are also a source of energy for organisms and, when combined to form larger molecules, they can act as food stores and give structural support.

Where did the sugar-related compounds in the meteorites come from? Cooper *et al.* discuss the possibility that they were first formed in interstellar space where there are vast and relatively dense clumps of dust and gas called molecular clouds. Starlight could have irradiated icy mixtures of water, ammonia and carbon monoxide that coated the