in cloned mammals, this is a valid concern. Finally, the number of live cloned offspring produced per number of nuclear transfers was pitifully small — approaching one in a thousand. So we are still left wondering whether the nuclei of differentiated cells can only be reprogrammed under exceptional circumstances.

Why do nuclei from different adult tissues vary in the efficiency with which they can be reprogrammed? Could it be due to whether or not the tissues contain stem cells? That remains to be seen. The idea that stem-cell nuclei may be more easily reprogrammed came from using ES cells — which are even more developmentally versatile than adult stem cells — as a source of nuclei for nuclear transfer[7,8]. These studies showed that more cloned blastocysts developed to the point of live birth when the source of nuclei was ES cells rather than adult cells.

But fewer embryos produced from ES-cell nuclei reached the blastocyst stage, meaning that the overall percentages of live offspring per nuclear transfer were not very different. One problem with ES-cell-derived clones is that their expression of 'imprinted' genes — genes that are specifically expressed from either the maternally derived or the paternally derived chromosome, but not from both — is often abnormal. By contrast, a study[9] of cloned mice derived from adult cell nuclei showed that several imprinted genes were expressed normally. So stem cells from fetal or adult tissues (see, for example, refs 10, 11) might be a better choice than ES cells for testing the reprogramming potential of stem-cell nuclei.

These questions are of fundamental interest, but of course have practical implications. One of the potential uses of cloning is in treating human diseases; the idea is to use some of a patient's nuclei to produce genetically identical early embryos, from which ES cells would be generated and used to grow healthy replacement tissues *in vitro*. But unless there is a real breakthrough in finding a source of adult nuclei that can be efficiently reprogrammed, all the talk about this 'therapeutic cloning' will come to nothing. In the largest study in mice to date[12], only 35 ES-cell lines were generated from over a thousand nuclear transfers (an efficiency of just 3.4%). This will not be acceptable in humans, where eggs will be hard to come by. Reprogramming adult cells directly, without an oocyte intermediate, would seem a more viable alternative. Surely the time has come for the cloners to turn their attention to the molecular mechanisms of nuclear reprogramming in the egg, and to use the information to enhance the potential of adult cells for use in cell-based therapies. ■

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High-energy physics

The mass question

Edward Witten

Do the elementary particles known as neutrinos have mass? Yes, according to recent experiments. But how much? A surprising — and controversial — result suggests that the answer is not what we thought.

Neutrinos were long believed to be, like photons, massless particles that always travel at the speed of light. In the past few years, by studying neutrinos emitted by the Sun or created by cosmic rays in the Earth's atmosphere, physicists have learned that neutrinos actually have tiny but non-zero masses, roughly ten million times smaller than the mass of an electron. These masses are believed to result from physical processes occurring at energies well beyond those of known particle interactions. In *Modern Physics Letters A*, Klapdor-Kleingrothaus and colleagues[1] now claim to have observed a new type of nuclear decay process. If this somewhat controversial finding holds up, it implies that the three types of neutrino have almost the same mass, and gives us a window on physics that goes far beyond our present knowledge.

To put the mass of the neutrino in context, consider the mass of other elementary particles. The electron, for example, is about 1,800 times lighter than the proton or neutron, and about 200,000 times lighter than the heaviest known elementary particles, which are the W and Z bosons and the top quark (Fig. 1). Why these masses vary

100 YEARS AGO

In reviewing my child's book, "Beautiful Birds", F. E. B., writing in your columns, says, "Why should he select the 'beautiful birds' only, and, by implication, condone the massacre of birds that have not that advantage?" The question is a misstatement of fact, which I hope you will allow me to show, though I can only do so by quoting myself. On the last page — which I daresay F. E. B. did not get to — there is this: " 'Mother, promise not to wear *any* feathers except the beautiful ostrich feathers that you look so *lovely* in?' As soon as she promised, then all the beautiful birds in the world (and that means all the birds, for all birds are beautiful) will be saved," &c. (The italics are mine). This is the final promise and the goal to which I have been leading. May I ask F. E. B. whether, if he wished to arouse a child's interest and sympathies in any subject, he would choose the more or less salient material to do it with? Edmund Selous

I would commend to Mr. Selous Dr. Samuel Johnson's sound remark concerning a quite analogous statement. An orchard, observed the Doctor, would be properly described as barren of fruit, even if subsequent research discovered a dozen apples and pears upon two or three trees. Now Mr. Selous' book is called "Beautiful Birds." It is not called "Birds." It is clear, too, what Mr. Selous means by "beautiful." His plates and the greater part of his descriptions deal with the Paradiseidæ, Humming Birds, and other birds which everyone calls beautiful. I do not find chapter after chapter relating to partridges, quails, sparrows, and other "plain" birds. F. E. B.

From *Nature* 27 February 1902.

50 YEARS AGO

In *Nature* of January 19, p. 92, a translation was published of resolutions passed at a conference held in Moscow last June on the theory of chemical structure in organic chemistry. It was stated there that "The Conference has clearly demonstrated the soundness of the theory of the structure of organic compounds due to the great Russian scientist, A. M. Butlerov; this theory lies at the basis of the whole of modern organic chemistry". The theory of resonance or mesomerism was said to be "directly opposed to the basic thesis of Butlerov's theory", and it was condemned as physically untenable and sterile. Such sweeping claims require examination.

From *Nature* 1 March 1952.

Matter				Force	
Leptons		Quarks		Bosons	
Electron 0.0005	Electron neutrino < 2 x 10^{-9}	Up 0.003	Down 0.006	Photon 0	(Electromagnetic force)
Muon 0.106	Muon neutrino < 2 x 10^{-9}	Charm 1.3	Strange 0.1	W, Z 80.4/91.2	(Weak force)
Tau 1.777	Tau neutrino < 2 x 10^{-9}	Top 175	Bottom 4.3	Gluon 0	(Strong force)

Figure 1 **The standard model of high-energy physics: fundamental particles and their masses (in GeV $c^{1\,2}$, where *c* is the speed of light). Leptons and quarks interact through exchange of the particles associated with three forces (weak, strong and electromagnetic) to form the matter we see around us. The fourth fundamental force, gravity, cannot yet be described within the framework of the standard model. Although we do not yet understand why, the matter particles form three 'families' in order of increasing mass. The observation of a rare nuclear decay by Klapdor-Kleingrothaus *et al.*[1] suggests that neutrino masses may not follow this trend, but are in fact similar in value.**

so much is a mystery, even in the modern standard model of elementary particles. By contrast, until recently, neutrinos seemed to be massless, and in the 1950s physicists thought they had worked out why.

The key is chirality. In biochemistry, chirality describes the 'handedness' of a molecule, which may look different from its mirror image. A simple molecule such as H_2O looks the same as its mirror image, but a more complex molecule such as dextrose may not. That certain chiral molecules are important in biology, and their mirror-image molecules are not, is believed to reflect accidents in the evolution of life, rather than any inherent difference between the molecules.

Neutrinos have a similar kind of chirality. Elementary particles have an intrinsic quantum-mechanical 'spin'. Most particles can spin in a right-handed or left-handed sense around their direction of motion, but neutrinos always spin in a left-handed sense (Fig. 2). Like chirality in biology, this property may conceivably have its origins in a chance event, in this case an accident of the Big Bang. Such an intrinsic chirality is impossible for particles with mass (because the direction of spin of a massive particle can be changed by rotating the particle in its rest frame), so physicists concluded that neutrinos must have zero mass.

But there is a problem with this argument, and it has to do with antimatter. Every particle of elementary matter has a corresponding antiparticle, with the same mass but opposite electric charge. For example, the antiparticle of the electron, e^{1}, is the positron, denoted $e^{\&}$. Similarly, the neutrino has an antiparticle: the antineutrino. The antineutrino has the opposite chirality to the neutrino — it always spins in a right-handed sense around its direction of motion (Fig. 2).

Apart from their chirality, how can you tell a neutrino from an antineutrino? They are both electrically neutral, so we cannot distinguish them by their electric charge. But there is another apparently conserved charge in interactions between elementary particles: the lepton number. The electron and the neutrino are leptons, and the positron and the antineutrino are antileptons. The number of leptons minus the number of antileptons in an interaction is called the lepton number. Leptons and antileptons can be created by many processes, such as the decay of a neutron to a proton, an electron and an antineutrino. In this example, there are no leptons at the outset (the neutron is a 'baryon'), then one lepton (the electron) and one antilepton (the antineutrino) are created, so the lepton number does not change. Indeed, it is conserved in all the usual elementary particle processes.

The concept of lepton-number conservation was derived from experiment, and originally had no theoretical explanation behind it. In the 1970s, the newly developed standard model of high-energy physics offered some insight: given the particles assumed to exist in the standard model and the rules by which it is constructed, it is actually impossible to violate lepton-number conservation.

The standard model was barely in place

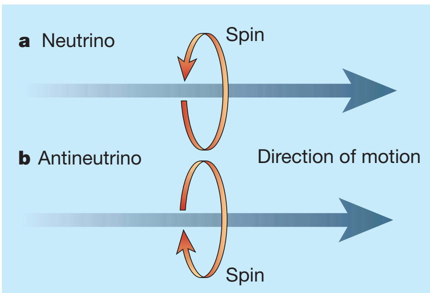

Figure 2 **Chirality is the spice of life.** a, **The neutrino spins in a left-handed sense around its direction of motion;** b, **the antineutrino spins in a right-handed sense.**

before physicists started trying to go beyond it. They wanted to build a unified theory that would motivate the existence of elementary particles and forces, rather than just describing them, as the standard model does[2,3]. In this more ambitious framework — optimistically dubbed 'grand unification' — lepton-number conservation is not automatic. Thus, a new perspective emerged[4–6]: lepton number should be very nearly conserved in nature because it is exactly conserved in the well-tested standard model; but it should be very slightly violated by the effects of grand unification.

If lepton number is not conserved, it no longer provides a way of distinguishing a neutrino from an antineutrino. They could, in fact, be two forms of the same particle. This particle has one state that spins one way and another state that spins the other way (Fig. 2), just like a particle with mass, such as the electron. So if lepton number is not conserved, neutrinos could have mass. But this mass can only be very small, because it arises from effects that are absent in the standard model. Direct measurement of such a small mass is difficult, but studies of the decay of the tritium nucleus have demonstrated[7] that one type of neutrino is lighter than about 2 electron volts.

A more subtle way of looking for neutrino mass depends on the fact that there are three kinds of neutrino: the electron neutrino, the muon neutrino and the tau neutrino (which are typically produced alongside electrons, muons and tau leptons, respectively). This leads to the possibility of an interesting quantum-mechanical effect: while travelling through a vacuum, one type of neutrino can convert spontaneously into another. This is known as neutrino oscillation, and can only happen if neutrinos have mass.

There is now extensive evidence for neutrino oscillations, both from neutrinos produced by cosmic rays in the Earth's atmosphere[8,9] and from neutrinos produced by the Sun[10]. (The interpretation in terms of neutrino oscillations has resolved a long-standing discrepancy[11] between the number of neutrinos expected from the Sun and the number we actually detect.) In this fast-moving area, experiment is well ahead of theory, and many important measurements are expected in the next few years. The results so far support the rough range of possible neutrino masses that arises from grand-unification theory. The experiments have also turned up a surprise: the measured 'mixing angles' (which determine the probability that neutrinos oscillate from one type to another) are much larger than theorists generally expected.

It seems logical to suspect that neutrino mass results from the non-conservation of lepton number. But the neutrino-oscillation measurements alone do not show that lepton number is not conserved. So can we do this in some other way? This is what Klapdor-Kleingrothaus *et al.*[1] claim to have done, by observing the nuclear decay $^{76}Ge \rightarrow {}^{76}Se + 2e^-$. This reaction is called neutrinoless double-β-decay, as the final state contains two electrons (historically known as β-particles) and no antineutrinos — so the reaction violates the conservation of lepton number by two units. Taken together with the oscillation measurements, and assuming that the only relevant particles are the three known types of neutrino, the new result implies that the three neutrinos have approximately equal masses, probably a few tenths of an electron volt. This is a surprising result because other particle families, such as quarks and the charged leptons, do not have approximately equal masses (Fig. 1), and it will put a severe constraint on theories of the origin of neutrino masses.

Some caution is called for, however, because of the exceptionally difficult nature of the experiment. Criticisms of the assumptions made by the authors in analysing the background and extracting an extremely small signal have already been offered[12,13]. At any rate, planned future experiments using much larger quantities of ^{76}Ge (or similar nuclei) will achieve much greater sensitivity. By extrapolating from the oscillation measurements, many physicists have guessed, prior to this claim, that a sensitivity 10^3 or 10^4 times greater than that of this experiment may be needed to conclusively observe the violation of lepton-number conservation. Such sensitivity suggests how difficult, as well as how potentially rewarding, future experiments are likely to be. ■

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Biomechanics

Walking with tyrannosaurs

Andrew A. Biewener

Tyrannosaurus terrorized the Earth — at least in the Hollywood version of history. But an estimate of the muscle volume in its hind legs suggests that the mighty giant could only walk, not run.

Over the course of history, vertebrates have evolved an enormous range of sizes, spanning well over six orders of magnitude in body mass. The largest and most captivating terrestrial giants were the dinosaurs, and *Tyrannosaurus* — although not the largest at around 6,000 kg — is perhaps the most famous and terrifying representative of this group. Some workers[1,2] have argued that bipedal tyrannosaurs and other huge dinosaurs could not move fast because their size would have imposed severe constraints on physiological and mechanical functions. But others claim that these creatures were much more athletic[3,4].

An obvious difficulty in resolving this argument is that dinosaurs have been extinct for a long time, so reconstructing how they moved is a challenge. But on page 1018 of this issue[5], Hutchinson and Garcia introduce a new biomechanical approach to the problem, applying an analysis of living animals to their ancient dinosaur relative. They show that *Tyrannosaurus* simply did not have large enough leg muscles to produce the forces required for an animal of such size to run.

The skeletal muscles in all animals are made of the same contractile proteins, so their intrinsic capacity for generating force is very nearly the same. The force that can be produced depends on the cross-sectional area of a muscle's fibres. But as body size increases, the geometrical effects of scale mean that muscle capability does not increase proportionately. The force that a muscle can generate increases less rapidly than body weight, so, despite their greater volume, the muscles of larger animals generate less force per unit weight.

In addition, the ability of an animal's skeleton to support mechanical loads decreases with size because bone area does not increase nearly as fast as an animal's weight. Living terrestrial mammals can accommodate these problems of scale by altering their limb posture when they run: larger animals run on more erect limbs than much smaller animals, which gives their muscles greater mechanical advantage[6] and allows them to maintain similar capacities of force generation and bone loading. But this only applies to animals as large as 300 kg or so. Above this weight, further changes in muscle mechanical advantage are probably limited[7], and sustaining force capacity for movement at greater speeds becomes a problem.

So how fast might a 6,000-kg dinosaur have moved? Previous estimates of the speed and locomotive capacity of dinosaurs and other extinct animals have been purely qualitative. Some models are based on the limb motion deduced from the step length and stride frequency derived from fossilized tracks[1,2,4,8]. However, such estimates depend on assumptions about body mass distribution, limb posture and limb length, and about kinematic similarities between species. The data[8] from fossilized tracks uncovered so far suggest that large bipedal dinosaurs moved at speeds of less than $5\ m\ s^{-1}$. But it may be that tracks left by faster-moving dinosaurs just haven't been discovered yet.

In their analysis of *Tyrannosaurus*, Hutchinson and Garcia[5] introduce an approach based on estimates of the minimum muscle mass needed for fast running. First they applied their analysis to alligators and chickens — two living relatives of bipedal dinosaurs. The results show that alligators have less than half the muscle mass that they would need to run fast (if, like bipedal dinosaurs, they used only their hind limbs), whereas chickens have nearly twice the necessary hind-limb muscle mass. This agrees with the observed fact that chickens and many other avian bipeds are good runners, but alligators must support themselves on four limbs and move at relatively modest speeds.

Hutchinson and Garcia then extended their analysis to estimate the limb muscle mass of extinct animals and quantify their locomotive performance. From fossil specimens of *Tyrannosaurus*, the authors estimated body and segment mass, worked out areas of muscle attachment, and deduced the forces and moments that the creature's leg muscles could have generated. Their analysis rests on assumptions about the limb posture and the magnitude of reaction forces exerted by the ground on the limbs of *Tyrannosaurus*, and about the kinematic similarity between dinosaurs and living birds and mammals[9]. But their results show that, even if the creature used all its hind-limb muscle mass, it could not have generated the forces necessary for running. They show that for a chicken scaled up to 6,000 kg to run, it would need muscles in each leg equivalent to 99% of its body mass — which is obviously impossible. The results for smaller bipeds, however, show they probably could run quickly, in agreement with estimates of their speeds from fossil tracks[8].

A pleasing aspect of Hutchinson and