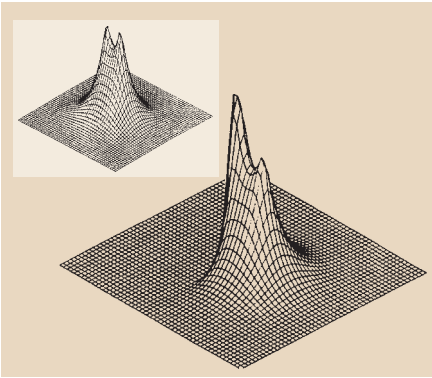

Figure 3 **The newly predicted ground state of molecular hydrogen at ultra-high pressure[3]. Here the electron (charge) cloud preferentially accumulates at just one of the two protons, producing an electric dipole. (The magnitude of this charge transfer has been exaggerated for clarity.) The inset shows molecular hydrogen under normal conditions; here the two protons are surrounded by a symmetrical charge cloud.**

gap of solid hydrogen closes continuously with pressure, there comes a point at which it may be energetically favourable to mix in a small proportion of these ionic states, resulting in a hybridized ground state. The pressure-induced electric dipole formed on any one of these hydrogen molecules will interact with, and be stabilized by, the other remaining molecules in the dense solid. The stabilization of this new dipolar state will be pressure dependent, and so above a critical density a spontaneous permanent electric polarization sets in on each molecule (Fig. 3).

Edwards and Ashcroft calculate the necessary conditions for the evolution of an induced molecular dipole in hydrogen. They predict the appearance of a spontaneous electronic polarization at a pressure where, experimentally, one sees the onset of the striking infrared activity in hydrogen. So dense hydrogen in phase III is composed of molecular, dipolar hydrogen. There may also be a reorientation and displacement of the dipolar molecules as the new, partly ionic state of hydrogen forms.

But what of the anticipated transition to metallic hydrogen at even higher densities? It has been suggested that molecular hydrogen may eventually become fully ionic, namely H^+H^-, with enough compression[6]. But from their calculations Edwards and Ashcroft find that the system does not seem to be progressing towards a fully ionic state.

What seems clear, however, is that the presence of even partially ionic character in the ground state of dense solid hydrogen will act to widen the previously narrowing band gap and hence frustrate the transition to the long-sought metallic state. Will solid hydrogen ever become a metal? A pessimistic prospect, contrary to Bernal's optimistic 1926 generalization, might be that solid hydrogen may never achieve metallic status. Only time — and pressure — will tell. □

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1. Wigner, E. & Huntington, H. B. *J. Chem. Phys.* **3,** 764–770 (1935).
2. Silvera, I. F. in *Metal–Insulator Transitions Revisited* (eds Edwards, P. P. & Rao, C. N. R.) 21–42 (Taylor & Francis, London, 1995).
3. Edwards, B. & Ashcroft, N. W. *Nature* **388,** 652–655 (1997).
4. Mao, H.-K. & Hemley, R. J. *Rev. Mod. Phys.* **66,** 671–692 (1994).
5. Ashcroft, N. W. *Phys. World* **8,** 43–47 (1995).

Evolutionary biology

Even-toed fingerprints on whale ancestry

Michel C. Milinkovitch and J. G. M. Thewissen

Both morphological[1] and molecular[2] studies indicate that cetaceans (whales, dolphins and porpoises) and artiodactyls (even-toed ungulates, which include pigs, hippos, camels and ruminants) form a clade or monophyletic group — that is, they have a common ancestor that is not shared by any other group of mammals. This is counter-intuitive, because it implies that a cow is more closely related to a dolphin or a whale than to a horse, yet it is one of the best examples of congruence between morphological and molecular estimates of mammalian phylogeny.

The molecular analyses of Shimamura *et al.*[3], reported on page 666 of this issue, further disrupt phylogenetic dogma. Indeed, not only do the authors confirm the close relationship between artiodactyls and cetaceans, but they propose that cetaceans are deeply nested within the phylogenetic tree of the artiodactyls. These results strikingly contradict the common interpretation of the available morphological data (supporting artiodactyl monophyly) and, if correct, would make a cow or a hippopotamus more closely related to a dolphin or a whale than to a pig or a camel (Fig. 1).

Although it is compatible with earlier molecular analyses (for example, refs 4, 5), the idea that cetaceans are highly derived artiodactyls was first suggested in 1994 on the basis of mitochondrial and nuclear DNA and amino-acid sequences[6]. The idea was corroborated by other phylogenetic analyses of DNA sequences[7]. But the issue is still controversial, because the exact means by which molecular sequence data should be analysed remains debated — although analytical settings that are particularly meaningful with respect to phylogenetic inferences can probably be identified in specific instances[8]. But, basically, many morphologists consider that molecular data are necessarily more noisy than morphological data.

The analyses by Shimamura and colleagues now provide a remarkable example of molecular markers, which should lead

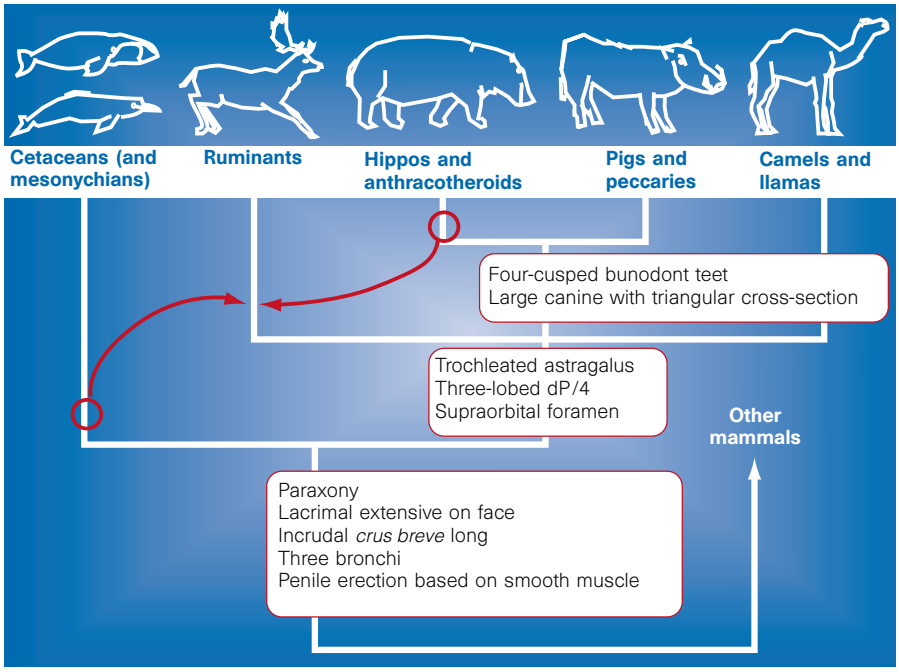

Figure 1 **Twisted or untied? Shimamura *et al.*[3] propose to attach the lineages of hippos and cetaceans (curved arrows, red) to the ruminant branch on this phylogenetic tree of artiodactyls — a marked diversion from the traditional view (white branching pattern). The two smaller boxes summarize some of the morphological evidence that disagrees with the new data.**

morphologists to re-examine what might have misled them for more than a century. The authors report phylogenetic interpretations of nine retropositional events that led to the insertion of so-called 'short interspersed elements' at particular loci in the nuclear genome of various artiodactyl and cetacean ancestors. Three of these events unambiguously support the grouping of cetaceans, hippos and ruminants in a clade, and the other six provide a partial resolution of the relationships within that clade. Because the likelihood of these elements being independently inserted at the same locus in different lineages (or precisely excised) seems virtually nil, these markers can reasonably be considered to be essentially noise-free.

So, these molecular results may prompt a serious revision of how we view morphological transformations in whales and artiodactyls. Three salient features of artiodactyls are: first, the axis of symmetry of hand and foot runs between the third and fourth digit (paraxony); second, the heel has developed an extremely mobile joint at a place where most mammals have a barely mobile joint[9]; and third, the last lower milk molar consists of three rows of cusps (three-lobed deciduous lower premolar 4, DP/4). Although paraxony is a striking feature, it also occurs in primitive whales[10], so it is uninformative for the issue at hand. But the remodelled heel is a different matter — because it is present in all artiodactyls and in no other mammal, this character is classically interpreted as derived and, therefore, as supporting artiodactyl monophyly.

The presence of the mobile joint in artiodactyls can be inferred from bones: there is a pulley (or trochlea) on the distal part of the astragalus (one of the heel bones) — a so-called trochleated astragalar head. This led to efficient and fast locomotion in the earliest artiodactyls. Although some features of the artiodactyl heel are present in other mammals such as rabbits, the astragalar head is never trochleated. In modern cetaceans, the hindlimb is so greatly reduced that the heel cannot be recognized, and no complete functional astragalus is known for a fossil whale. However, the mesonychians — a group of land mammals that is considered to be the closest extinct relative of cetaceans — also lack a trochleated astragalus. So if Shimamura and colleagues' hypothesis is correct, then either mesonychians are not closely related to cetaceans (and many dental characters are convergent), or the specialized heel morphology is not the exclusive character that many morphologists take it to be. It may have evolved several times independently in artiodactyls, or have been lost in the mesonychian/cetacean clade. The complete astragalus of an early cetacean would probably shed light on this issue.

The hypothesis put forward by Shimamura *et al.* also clashes with the DP/4 character — the tooth has three lobes in all artiodactyls, but not in early cetaceans or mesonychians. If the new molecular data are correct, the morphology of this tooth has, like the trochleated astragalus, a complicated phylogenetic history that includes reversals, convergences or both. Dental differences could reflect dietary differences, because both early cetaceans and mesonychians were probably carrion feeders or carnivores, whereas all early artiodactyls were omnivores or herbivores. But many morphological systematists are reluctant to let functional arguments influence their evaluation of characters.

What characters, besides the molecular ones described by Shimamura *et al.* and by Gatesy[7], do hippos, ruminants and cetaceans have in common that makes them different from pigs, peccaries and tylopods (camels and llamas)? Morphological studies have usually upheld close genealogical ties among pigs, peccaries and hippos (and the larger group that includes hippos: anthracotheroids), but the similarities are usually uninformative primitive characters that are also present in the ancestral artiodactyl, or features that are subject to rampant convergences (such as certain dental characters, see Fig. 1). Shimamura *et al.* also suggest that artiodactyls and cetaceans diverged in the Cretaceous — about 15 million years before they are found in the fossil record. However, if hippos are closely related to cetaceans, and if mesonychians are not, then the discrepancy in the times of origin is considerably less: it amounts to the difference between the origin of cetaceans (approximately 50 million years ago) and that of anthracotheroids (around 49 million years ago). But because of the rapid and unique specialization of cetacean morphology, few characters can be recruited to bolster the grouping of ruminants, hippos and cetaceans into a clade. Recovery and study of the earliest cetaceans would probably help to resolve this problem.

Few molecular studies rule out previously accepted morphological trees as convincingly as that of Shimamura *et al.* However, the face of phylogenetic science itself is changing rapidly — it is becoming more objective and less inductive. For example, phylogeneticists no longer need to ask whether molecular data are superior or inferior to morphological data, because the signal-to-noise ratio in morphological, molecular and combined data sets can now be measured directly, even before examining phylogenetic trees[11]. In any case, the new analyses indicate that the use of retropositional events as molecular markers may define a new power of resolution in estimating phylogenies. This method could even bring to a close some of the most intense controversies[2,12,13] in the field, such as whether the toothed whales[2,12] are monophyletic or paraphyletic, and likewise for the rodents[13]. □

100 YEARS AGO

'Cyclone sail' – I have sent to you, for publication, if you think desirable, a photograph of a type of an ideal sail – ideal, in that the wind acting on it has no tendency whatever to incline the boat. The wind pressure acts practically at right angles to the mean surface of the sail. When the wind is making a large angle with the sail, the centre of pressure is almost at the centre of the surface, but when the wind strikes the sail at an acute angle, as in all sails or kites, the centre of pressure moves towards the weather edge; but by suitably adjusting the sail, the desirable result of obliterating all heeling movement has been achieved.
Percy S. Pilcher
From *Nature* 12 August 1897.

50 YEARS AGO

On June 6, 1942, there was a second meeting in Berlin, when the results of the uranium project were reported to Speer, as Minister for War Production. The facts reported were as follows: definite proof had been obtained that the technical utilization of atomic energy in a uranium pile was possible. Moreover, it was to be expected on theoretical grounds that an explosive for atomic bombs could be produced in such a pile.... Following this meeting, which was decisive for the project, Speer ruled that the work was to go forward as before on a comparatively small scale. Thus the only goal attainable was the development of a uranium pile producing energy as a prime mover – in fact, future work was directed entirely towards this one aim.
Prof. W. Heisenberg
From *Nature* 16 August 1947.

Many more abstracts like these can be found in *A Bedside Nature: Genius and Eccentricity in Science, 1869–1953*, edited by Walter Gratzer. Contact David Plant. e-mail: subscriptions@nature.com

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1. Thewissen, J. G. M. & Hussain, S. T. *Nature* **361,** 444–445 (1993).
2. Milinkovitch, M. C. *Trends Ecol. Evol.* **10,** 328–334 (1995).
3. Shimamura, M. *et al. Nature* **388,** 666–670 (1997).
4. Irwin, D. M., Kocher, T. D. & Wilson, A. C. *J. Mol. Evol.* **32,** 128–144 (1991).
5. Czelusniak, J. *et al. Current Mammalogy* Vol. 2 (ed. Genoways, H. H.) 545–572 (Plenum, New York, 1990).
6. Graur, D. & Higgins, D. G. *Mol. Biol. Evol.* **11,** 357–364 (1994).
7. Gatesy, J. *Mol. Biol. Evol.* **14,** 537–543 (1997).
8. Milinkovitch, M. C. *et al. Genetics* **144,** 1817–1833 (1996).
9. Schaeffer, B. *Am. Mus. Novit.* **1356,** 1–24 (1947).
10. Thewissen, J. G. M., Madar, S. I. & Hussain, S. T. *Cour. Forschungsinst Senckenbg* **191,** 1–86 (1996).
11. Lyons-Weiler, J., Hoelzer, G. A. & Tausch, R. J. *Mol. Biol. Evol.* **13,** 749–757 (1996).
12. Milinkovitch, M. C., Ortí, G. & Meyer, A. *Nature* **361,** 346–348 (1993).
13. Hasegawa, M., Cao, Y., Adachi, J. & Taka-aki, Y. *Nature* **355,** 595 (1992).

Adenosine receptors

Knockouts anxious for new therapy

Solomon H. Snyder

Over the past two decades, putative neurotransmitters have proliferated, from biogenic amines to amino acids, neuropeptides and, most recently, gases such as nitric oxide and carbon monoxide. Amidst the ferment over recently discovered messengers, scant attention has been paid to an atypical neurotransmitter whose candidacy dates back almost 30 years — adenosine. But the field may now be rejuvenated, thanks to a report by Ledent *et al.*[1] (page 674 of this issue) showing that there are behavioural and physiological alterations in mice lacking one adenosine-receptor subtype, A_{2a}.

Neurotransmission by adenosine and ATP — designated 'purinergic' by Burnstock[2] — is difficult to study because both molecules are involved in many pathways of general cellular metabolism. Nonetheless, the evidence for adenosine as a neurotransmitter is as persuasive as for any other substance: immunohistochemical studies have shown that adenosine is found in discrete neuronal populations in which those cells that use it as a neurotransmitter have much higher localized densities[3]; an efficient, energy-requiring uptake system exists which could account for synaptic inactivation of adenosine; and adenosine has prominent functions outside the brain. Studies by Berne[4] have shown that oxygen starvation leads to a massive accumulation of adenosine, which causes vasodilation and increased blood flow.

The most compelling evidence for the specific actions of adenosine has come from the characterization of its receptors. The influences of adenosine on levels of cyclic AMP in brain slices provided the first molecular evidence for the function of receptors and differentiation of subtypes. At nanomolar concentrations, adenosine lowers the activity of adenylyl cyclase (which converts ATP to cAMP) through adenosine A_1 receptors, whereas micromolar levels augment adenylyl-cyclase activity at A_2 receptors[5].

Xanthines and caffeine both block adenosine receptors[6], and this ability could account for their effects as behavioural stimulants. Xanthine derivatives can block adenosine receptors in direct proportion to their potencies as behavioural stimulants, and at concentrations similar to blood levels of caffeine after a few cups of coffee[7,8]. The bronchodilating, antiasthmatic effects of theophylline and other xanthines may involve adenosine-receptor blockade, although the evidence is controversial.

Molecular-biological techniques have further discriminated receptor subtypes, specifically A_1, A_{2a}, A_{2b} and A_3 (ref. 9). The A_{2a} receptor (which stimulates adenylyl cyclase) is particularly abundant in the basal ganglia, blood vessels and platelets, so it was selected by Ledent *et al.*[1] for targeted deletion.

The A_{2a}-receptor knockout mice seem to be normal on a gross level, and they breed successfully. But whereas the A_2-agonist drug CGS-21680 reduces locomotor activity in wild-type mice, it has no behavioural effect in the knockouts. Strikingly, caffeine, which normally stimulates locomotor activity, substantially depresses activity in the knockout mice. These findings cement the conclusion that the stimulant effects of caffeine are derived from adenosine-receptor blockade. But why should caffeine depress behaviour in the knockouts? Adenosine analogues and caffeine can either stimulate or depress locomotor activity depending on the dose[7]. So, in the knockouts, a stimulatory action of adenosine — perhaps through A_1 receptors — may be unmasked.

Ledent *et al.* also found that the knockout mice seem to be more anxious and aggressive than wild-type animals. This fits with abundant clinical evidence that caffeine increases anxiety, and that stimulation of the adenosine receptor can relieve anxiety. Adenosine modulates pain pathways in complex ways. There is evidence that stimulation of A_{2a} receptors on sensory pain fibres increases pain perception. The knockout mice show reduced pain responses, suggesting that — at least at A_2 receptors — adenosine normally augments pain perception. This also fits with observations that caffeine can be analgesic.

Adenosine has many effects in the cardiovascular system; it inhibits platelet aggregation and dilates several vascular beds. The knockout mice show more efficient platelet aggregation than wild-type animals, and they are resistant to inhibition of platelet aggregation by adenosine analogues. Ledent *et al.* also found that the knockout mice have increased blood pressure, supporting a tonic vasodilatory role for adenosine.

Pinning down the diverse biological functions of A_{2a} receptors should provide a route for the pharmaceutical industry to develop related therapeutic agents (Table 1). One possibility might be new cognitive stimulants. Although the relative merits of caffeine's stimulant effects are a source for debate, its cognition-enhancing actions are well documented. Agents that elicit these beneficial influences, without side-effects such as tachycardia, increased urination and agitation, may treat cognitive impairment of the elderly. At present, despite the wealth of available analgesics, none is entirely satisfactory. Moreover, the complex effects of adenosine on pain perception have thwarted efforts to develop adenosine-based analgesics[10]. The findings by Ledent *et al.*[1] from the knockout mice favour selective A_{2a} antagonists as non-addictive analgesics. Finally, antagonists to the A_{2a} receptor might improve defects in blood clotting and vascular shock, whereas A_2 agonists should decrease clotting and guard against low blood pressure. □

Table 1 **Potential adenosine-receptor drug development based on the A_{2a} knockout phenotype**

Phenotype	*Drug*
Altered locomotor response to caffeine	A_2 antagonists as cognition enhancers
Apparent anxiety	A_2 agonists as anxiolytics
Lesser pain responses	A_2 antagonists as analgesics
Increased platelet aggregation	A_2 agonists as anticoagulants; A_2 antagonists for clotting defects
Hypertension	A_2 agonists as antihypertensives; A_2 antagonists for shock

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1. Ledent, C. *et al. Nature* **388,** 674–678 (1997).
2. Burnstock, G. *J. Physiol. (Lond.)* **313,** 1–35 (1981).
3. Braas, K. M., Newby, A. C., Wilson, V. S. & Snyder, S. H. *J. Neurosci.* **6,** 1952–1961 (1986).
4. Berne, R. M. *Circ. Res.* **46,** 807–813 (1980).
5. Daly, J. W. *Cyclic Nucleotides in the Nervous System* (Plenum, New York, 1977).
6. Satin, A. & Rall, T. W. *Mol. Pharmacol.* **6,** 13–23 (1970).
7. Katims, J. J., Annau, Z. & Snyder, S. H. *J. Pharmacol. Exp. Ther.* **227,** 167–173 (1983).
8. Fredholm, B. B. *Pharmacol. Toxicol.* **76,** 93–101 (1995).
9. Olah, M. E. & Stiles, G. L. *Annu. Rev. Pharmacol. Toxicol.* **35,** 581–606 (1995).
10. Sawynok, J. & Yaksh, T. L. *Pharmacol. Rev.* **45,** 43–85 (1993).