Entomology

The alkaloid defence

W. E. CONNER

M. EISNER

The moth *Cosmosoma myrodora*, pictured left, is visually striking. And, as revealed by William E. Conner and colleagues in the *Proceedings of the National Academy of Sciences USA* (**97,** 14406–14411; 2000), its behaviour is also rather unusual. The male moths seem to have developed a chemical system to protect themselves, their female mates and their offspring from predation by spiders.

Conner *et al.* provide evidence that male — but few female — *C. myrodora* feed on the fluid secreted from certain plants (perhaps *Eupatorium capillifolium*). The alkaloid compounds thus ingested become particularly concentrated in a mass of filaments (pictured right) in the abdomen of the moths. The authors assume that this protects the males from spiders such as *Nephila clavipes* — when the moths were fed a similar alkaloid in the lab, the spider cut the moths free from its web rather than eat them.

Before mating, male *C. myrodora* release some of their filaments, covering their chosen female. This seems to protect the female from spiders, too. The females may also receive alkaloids from the males' sperm, and in turn pass on some of these protective chemicals to their eggs.

But questions remain. Do the females use receipt of alkaloids as a measure of a male's 'worth'? Females did seem to prefer males that had released filaments, but it is not certain if females could discern whether the filaments were laden with alkaloids. It is also not clear which plants the moths feed on in the wild, because the moths are rare and hard to spot. **Amanda Tromans**

These fluctuations are an expression of the Heisenberg uncertainty principle, and they set a quantum noise limit on the accuracy of any precision measurement. In a squeezed state, this quantum noise is 'squeezed', or redistributed in the system, so that some measurable properties become 'quieter', whereas other properties become 'noisier'.

The states studied by Sørensen *et al.*[1] are 'spin squeezed'[11,12]. In the quantum world we often represent an atomic spin by an arrow (Fig. 1a). For the simplest spins, like those of electrons, these arrows can point either up or down. Now, applying the uncertainty principle, we find that the transverse part of the spin (the part not exactly in the up–down direction) is uncertain by an amount represented by a small disc. In other words, if we try to find out whether the spin is angled left or right, or in or out of the page, we find that we cannot specify both the amount of left–rightness and in–outness at the same time. In the language of quantum noise, the transverse spin is 'noisy' in the left–right and in–out directions.

For a gas made up of many atoms, each with their own spin, the collective atomic spin is represented by one big arrow and one big uncertainty disc (Fig. 1b). A key idea exploited by Sørensen *et al.* is that if we entangle the individual atomic spin states, by introducing carefully tailored correlations between the individual atomic spins, then the collective spin state of the vapour can be squeezed. In Fig. 1c the transverse components of the individual atomic spins preferentially add up in the left–right direction, as opposed to the in–out direction, changing the uncertainty disc of the total spin from a circle into an ellipse — it is now squeezed.

One consequence of this spin-squeezing is that the quantum noise involved in measuring in–outness can be made smaller than that for measuring left–rightness. This entangled squeezed state provides a way to break what is known as the standard quantum limit for the measurement of one component of the collective spin (the standard quantum limit is the diameter of the unsqueezed uncertainty circle in Fig. 1b). The essence of Sørensen *et al.*'s idea is that by shining a judiciously tailored microwave field on a BEC and letting atoms in the condensate collide with each other, it is possible to achieve entanglement-induced squeezing.

This route to entanglement not only demonstrates the sort of large-scale quantum engineering needed for quantum-information applications, but also has potentially important consequences in other areas, such as precision atomic clocks[12,13]. The performance of sophisticated laser-cooled atomic clocks is already close to the limits set by quantum noise[14], a limitation that could be overcome if a spin-squeezed atomic BEC is used to run the clock.

Although recent experiments in our group and elsewhere have shown that a BEC is not absolutely required to create a spin-squeezed atomic vapour[15,16], the idea of marrying the power of entanglement with the remarkable properties of a BEC offers outstanding possibilities for creating a new generation of non-classical atomic states[1,4–6]. One day, we may even hear about entanglement of another macroscopic form of matter — the bulk sample of metal found in a simple pair of coins. ■

Nick Bigelow is in the Department of Physics and Astronomy and the Laboratory for Laser Energetics, PO Box 270171, University of Rochester, Rochester, New York 14627, USA.
e-mail: nbig@lle.rochester.edu

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Mammalian evolution

Relationships to chew over

Anne Weil

Did advanced mammals evolve on the southern continents and then move north? Not according to a new study, which concludes that such mammals evolved in both the south and the north.

There are three groups of living mammals — placentals, marsupials and the monotremes. The first two, along with some mammalian fossil relatives, have so-called 'tribosphenic' teeth, which provide a highly efficient way of chopping and grinding food. Monotreme ancestors are also thought to have possessed such teeth.

On page 53 of this issue, Luo *et al.*[1] argue that mammals with tribosphenic teeth evolved not once but twice, after the supercontinent of Pangaea pulled apart more than 160 million years ago. According to their hypothesis, one lineage radiated across the southern landmass of Gondwana but is represented today by only the platypus and

echidnas, which together constitute the monotremes. The other lineage, isolated on northern Laurasia, gave rise to living marsupial and placental mammals (Fig. 1a). Luo and colleagues' taxonomy is based on an extensive analysis of teeth and skeletal remains. But it is radically at odds with other interpretations of fossil data[2,3], and also with an evolutionary history reconstructed from sequences of mitochondrial DNA[4] (Fig. 1b,c).

In the past three years, there have been reports[2,3] of two significant discoveries of early Gondwanan mammals. In both cases, the fossil animals are surprisingly advanced, given their antiquity. Rich *et al.*[2] placed the 120-million-year-old *Ausktribosphenos* firmly within the Tribosphenida, a clade of mammals that includes marsupials and placentals, and that is diagnosed by the presence of tribosphenic teeth. Indeed, they suggested that *Ausktribosphenos* might be an early representative of the placental lineage. This seems arguable, however — *Ausktribosphenos* has peculiar teeth, and a jaw structure that is in some respects primitive[2,5].

The other fossil, *Ambondro*, known from a 167-million-year-old jaw from Madagascar, was described by Flynn *et al.*[3]. They placed *Ambondro* within the Tribosphenida, too, fuelling speculation that the break-up of Pangaea had not been much of a barrier to mammalian dispersal, or even that Tribosphenida originated in the south. In placing *Ausktribosphenos* and *Ambondro* in the Tribosphenida, Rich *et al.* and Flynn *et al.* upheld a long-standing view that the tribosphenic dentition evolved once. Their findings contradicted previous fossil evidence for a Laurasian origin of the Tribosphenida.

The extant platypus and echidnas are specialized for feeding on invertebrates and have no teeth. But a toothed monotreme, *Steropodon*, is known from a partial jaw, which was discovered in an Australian opal mine and dates to between 113 million and 97.5 million years ago[6]. Analyses that included *Steropodon* indicated that monotremes were more primitive than mammals with tribosphenic teeth; they have been considered to possess a precursor morphology to the more advanced condition. Now Luo *et al.*[1] have included *Ausktribosphenos*, *Ambondro* and *Steropodon* with other Mesozoic mammals in three phylogenetic analyses that include characters from the teeth and jaws, and also from the rest of the skeleton. Each analysis produces the same elegant result: the Gondwanan animals, including monotremes, are closely bound together in a clade that is widely separated from that of the marsupial and placental mammals. In this new model, mammals evolved tribosphenic teeth in parallel, on either side of a vast and widening gulf — the Tethys Sea that divided Gondwana and Laurasia.

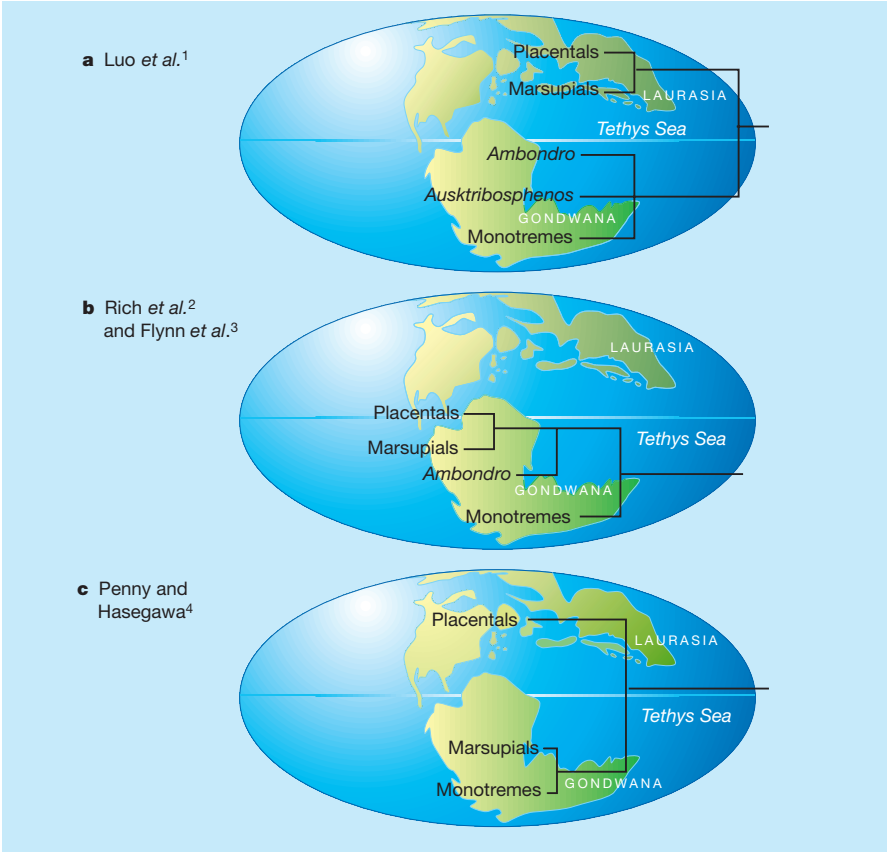

Figure 1 **Proposed evolutionary relationships and origins of living mammals — placentals, marsupials and monotremes — and some fossil relatives.** a, **Luo *et al.*[1] retain a widely accepted theory of early mammalian biogeography, but propose that complex tribosphenic teeth evolved twice.** b, **This contrasts with a composite phylogenetic tree inferred from relationships favoured by Rich *et al.*[2] and Flynn *et al.*[3], in which the fossil *Ausktribosphenos* is included among placentals. In this scheme, tribosphenidans would have dispersed northwards from a southern point of origin. Both** a **and** b **are based on fossil data.** c, **Both views conflict with that of Penny and Hasegawa[4], who considered molecular data without discussing biogeographical or fossil evidence. The geographical distribution of origins shown in** c **is that favoured by Gregory for Marsupionta[9].**

This view of events does not require as unlikely a convergence as it might seem. Early mammals were small and endothermic (loosely speaking, warm-blooded), with high surface-to-volume ratios. They probably had high metabolic rates and correspondingly high nutritional requirements. Living shrews, which face the same constraints, have prodigious appetites. So survival probably depended on efficient food processing, and the tribosphenic dentition provides just that.

As a tribosphenic mammal bites down, a large cusp on the upper molar settles, mortar-like, into a pestle-like basin of the lower molar. Simultaneously, notched shearing crests on the sides of the triangular upper molar scissor against those of the lower molars. This combination of shearing and grinding has long been considered a key innovation in the clade containing marsupial and placental mammals — indeed, as the innovation that was possibly most significant in the spread and diversification of mammals. So advantageous is it that a third, entirely extinct, mammalian lineage, represented by the fossil *Shuotherium*, seems independently to have evolved a 'pseudo-tribosphenic' system that functioned identically, although the positions of the lower molar basin and shearing crests were reversed[7].

Nor is the hypothesis that marsupials and placentals originated on the northern continents startling. Although most living marsupials are restricted to the Southern Hemisphere, the fossil record of the early marsupial lineage (Metatheria) is all Laurasian: the earliest metatherians are Asian, and the most diverse are North American. Marsupials are thought to have spread into Gondwana sometime between 84 and 64 million years ago, moving between Australia and South America by way of Antarctica[8].

This view superseded an earlier hypothesis of mammalian relationships, espoused by W. K. Gregory before the acceptance of plate tectonics and before the discovery of toothed monotremes, *Ambondro*, *Ausktribosphenos* or many fossil metatherians. Gregory's hypothesis was that monotremes and marsupials are more closely related to each other than they are to placentals, forming a clade

dubbed Marsupionta[9]. Ironically, as new fossil evidence makes the Marsupionta hypothesis ever more obsolete, some[4], although not all[10], phylogenies based on gene sequencing appear to support it.

With three competing hypotheses on the table, we can only be sure that more genes will be sequenced and more fossils will be found. What Luo *et al.*[1] offer is a well-supported theoretical framework in which everything seems to make sense: unusual morphological features of the early southern mammals are explained in a phylogenetic context, and biogeographical considerations do not require mouse-sized animals to cross the Tethys Sea. This framework is certain to be useful, but it will also engender controversy. And, like Gregory's Marsupionta, it may eventually turn out to be wrong. The Mesozoic of Gondwana is not well known — surprises are no doubt still in store. ■

Anne Weil is in the Department of Biological Anthropology and Anatomy, Duke University, 08 Biological Sciences Building, Science Drive, Box 90383, Durham, North Carolina 27708-0383, USA.
e-mail: annew@duke.edu

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Immunology

It takes more than two to tango

Ronald H. Schwartz

In vivo studies of a pair of co-stimulatory molecules in the immune system of mice may further our understanding of allergic reactions and inflammatory immune responses in humans.

Most T cells of the immune system recognize antigens — substances that stimulate an immune response — as protein fragments. These fragments must be presented to T cells by molecules on the surface of another type of cell, an antigen-presenting cell (APC). But this recognition event alone is not enough to fully activate the T cell. Simultaneous 'co-stimulatory' signals from the APC are needed before the T cell can proliferate and become specialized to perform a particular function, such as secreting intercellular signalling molecules called cytokines. On pages 97–109 of this issue[1–3], three groups investigate a receptor protein called ICOS, which occurs on T cells and recognizes a co-stimulatory signal on APCs. All three groups agree that experimentally inactivating the ICOS gene in mice profoundly impairs the animals' ability to produce certain types of cytokines and antibody molecules.

The first co-stimulatory pair of molecules to be identified were the receptor protein CD28 — expressed continuously on all mouse and many human T cells — and its two binding partners, CD80 and CD86. The expression of these binding partners, or ligands, is not continuous but rather can be induced on all APCs[4] (Fig. 1). Together with signalling through the T cell's antigen receptors, this co-stimulatory set enhances the production of the cytokine interleukin-2, which encourages the growth and differentiation of T cells. Subsequent work uncovered a second molecule on the T-cell surface that recognizes CD80 and CD86. The expression of this molecule, called CTLA-4, is inducible and imposes negative feedback on the process of T-cell activation.

A completely different molecular pair was then also found to be essential for co-stimulation[5]. In this case, the co-stimulatory signal (CD40) is continuously expressed on the APC, and the expression of its receptor (CD154) can be induced on the T cell (Fig. 1). Signalling through this co-stimulatory pair creates a strong positive-feedback loop, augmenting the expression of CD80 and CD86 on the APC. Many other co-stimulatory molecules have since been described. One of the most recently discovered pairs — consisting of ICOS and its binding partner, B7RP-1 — is another positive regulatory set.

Why is co-stimulation so complex? Presumably, each molecular pair has some important, unique function and so needs to be regulated independently of the other sets. A major clue to the function of ICOS and its partner lies in where and how these molecules are expressed. ICOS is expressed on the T cell in response to signalling through CD28 and the T-cell antigen receptor[6]. More important, its binding partner has a unique expression pattern. B7RP-1 is found only on the types of APCs called B cells and macrophages, and not on the major category

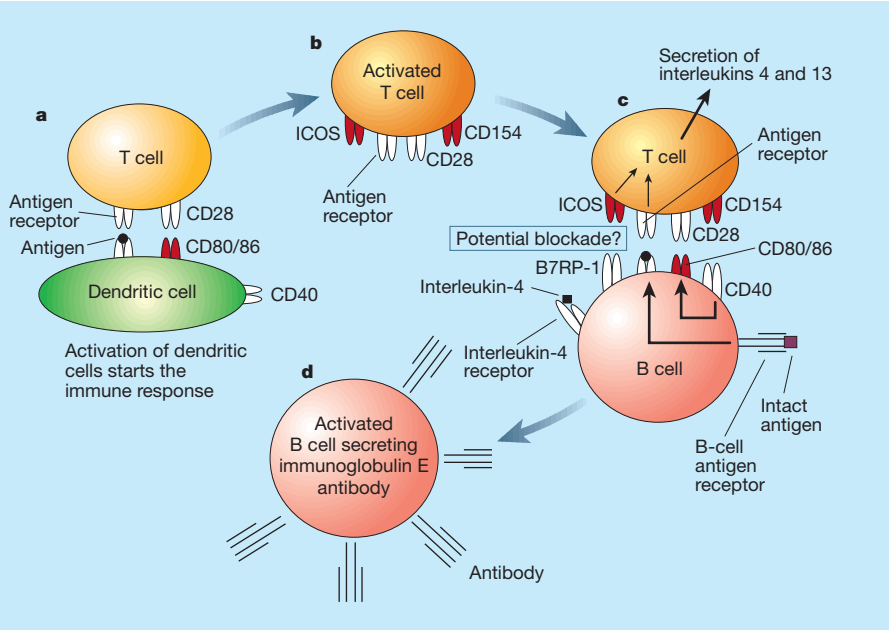

Figure 1 **Co-stimulatory signals and immune responses.** a, **A dendritic cell (a type of antigen-presenting cell) is activated to express the co-stimulatory molecules CD80 and CD86. It can then present antigen to a T cell, which is activated by signalling through its antigen receptor and through CD28, the receptor for CD80/86.** b, **The activated T cell expresses all of its inducible co-stimulatory-signal receptors, such as ICOS.** c, **When the T cell next encounters a B cell that has become an antigen-presenting cell, the interactions of the co-stimulatory sets of molecules augment the production of cytokines (interleukins 4 and 13) by the T cell and of antibodies by the B cell** (d). **The interaction between ICOS and B7RP-1 is particularly potent in stimulating immunoglobulin E production, important in allergic reactions. Blocking this might be useful in treating asthma. Three new papers[1–3] show that inactivating the ICOS gene in mice inhibits production of these cytokines and antibody, among other effects. Molecules in red are expressed only after cell activation.**