information at the level of single neurons (see [5] for an elegant review of this work). These quantity-sensitive neurons tend to have a 'preferred numerosity', firing most strongly when presented with a specific number of visual objects. Unfortunately, the level at which these cells represent numerical information is at present unclear. While it is possible that number-sensitive cells reflect abstract numerical processing, it is also possible that such cells process only visual numerical content, and thus may be tied to a single sensory modality.

The findings of Jordan *et al.* [13], however, suggest that the macaque brain is capable of integrating multi-sensory information about quantity, and thus raise the possibility that previously identified prefrontal number-sensitive cells may underlie this processing. Future work could therefore profit from developing cross-modal tasks that can be used in conjunction with neurophysiological recordings. In this way, the results of Jordan *et al.* [13] pave the way for a broader comparative investigation of modality-independent number representations; their approach will undoubtedly lead to new insight into both the nature of and mechanisms underlying numerical representations.

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Evolution: Revenge of the Clones!

Recent work on ants shows both extraordinary patterns of reproduction and a new type of sexual conflict, leading to the remarkable scenario where females have no father and males have no mother.

Edward M. Sykes and Stuart A. West

Why do we have sex, and why so often, when many species do without it? This question still poses a major problem for biologists [1,2] and is raised once again with the recent discovery [3,4] that two species of ant produce workers sexually but queens and sons (reproductives) asexually.

If the main aim of reproduction is to create copies of our genes, then why don't we simply produce clones of ourselves, as asexual organisms do? Our gene combinations have been selected over time as successful, yet we pass on only half of them and mix these up with our partner's during meiosis — twisting fully working gene combinations into ones that may not function as well; this is the so-called 'recombination load'. This cost alone may seem bad enough, but in species such as humans with separate sexes, there is the added cost of producing males to fertilise the females, effectively cutting the number of reproducing individuals by half. This is known as the two-fold cost of sex. A variety of theories have been put forward to explain why, despite these costs, sexual reproduction is widespread in animals and plants [1,2].

The two most favored hypotheses explaining sex and recombination are, first, that they provide an advantage in coevolutionary arms races, especially with parasites; and second, that they facilitate the purging of deleterious mutations [1,2]. The parasite hypothesis relies on the idea that parasites will evolve to infect common genotypes in a population, providing an advantage to the production of rare genotypes by sex [5]. This explanation has been termed the Red Queen theory, because it suggests that, just like Alice, one has to run just to stay in the same place — mixing the successful genes from the last generation to stop the parasites infecting the offspring in the next. The mutation hypothesis relies on the idea that sex allows you to lose deleterious mutations in a few low quality offspring. This can make up for a two-fold cost of sex, as long as there are at least one or two mutations per genome per generation, and the fitness cost of each additional deleterious mutation is greater than the last, a phenomenon termed synergistic epistasis [6].

A common theme with most theories that provide an advantage

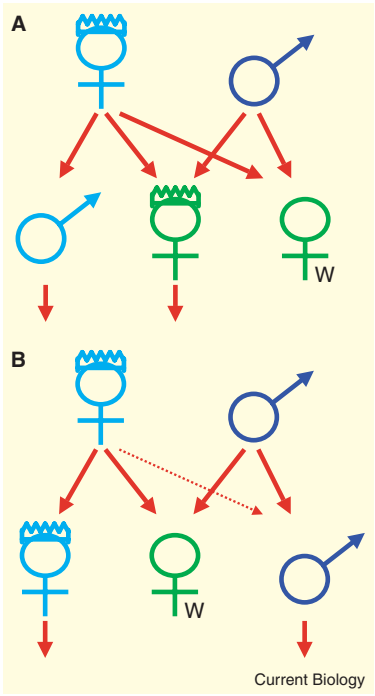

Figure 1. Reproduction in eusocial insects.
(A) Typical haplodiploid reproduction: unfertilised eggs become haploid males, while fertilised eggs develop into diploid females, either future queens or workers, (W). (B) A unique form of reproduction has been found in the ant *Wasmannia auropunctata*. Queens and males form reproductives through asexual reproduction, while sterile workers are the product of sexual reproduction. The dotted line shows how sons are induced as haploids containing only the father's genes, despite initially being produced sexually. In this way the gene pools of the two sexes are effectively separate except when they meet in sterile workers (W).

to sex is that nearly as much benefit can be obtained from only occasional sex [1,2]. Recent studies [3,4] have shown that two species of ant seem to get the best of both worlds, by switching between sexual and asexual reproduction, depending on what kind of offspring they are producing. In both species, the queens of the colonies produce future queens (gynes) asexually with all the benefits of cloning, but they produce workers sexually.

Why do they do this, and can this tell us anything about the benefit of sex? One possibility could relate to the desirability of variation to increase resistance against parasites [7,8]. If a single queen produced gynes and workers asexually, the entire colony would have the same genotype, which could make them extremely vulnerable to parasite infection. Producing workers sexually increases the number of genotypes in the colony. As workers are more numerous than reproductives, gynes are always of the less common genotype. making them safer from parasites even when produced asexually.

Does this mean that these ants provide unambiguous support for the parasite driven Red Queen explanation of sex? Sadly not, as an explanation can also be given that depends upon deleterious mutations. The colonies expand through a process known as 'budding', whereby new queens and workers simply pick up and move to a new location, taking larvae with them. At no point are the queens exposed to life 'outside' the colony without the aid of a fully developed workforce [3,4]. This may have reduced the selection pressure on the queens so that fewer mutations reduce fitness, enabling the queens to produce gynes asexually.

This illustrates the general problem that observational data on the pattern of reproduction within or across species can always be potentially explained by competing theories [2].

There is, of course, another problem with the queens producing asexually — the males don't get to pass on any genes to future reproductives. In one of the species, *Cataglyphis cursor*, the workers can reproduce, so there is still some opportunity for males to sire grandoffspring [3]. In the little fire ant *Wasmannia auropunctata*, however, the workers are sterile [4]. Somehow the males have got round this, as in some fertilised eggs the female's genes are ignored (how is not known) leaving haploid males instead of diploid workers (Figure 1). In this species we therefore have ended up with the remarkable scenario that females have no father and males have no mother!

This leads to another question: why do the males not make sure more eggs become sons? As there are multiple queens to a colony, there would always be other daughters for their sons to mate with, potentially even leading to a dichotomy of females, some producing only females and others producing only males. This evidently does not happen, and it seems male control only occurs rarely as there are a great many more workers than sons.

Perhaps the most exceptional aspect of this biology is that each sex is almost its own species, as the two gene pools only interact in the non-reproductive workers. This means that the two sexes are unfettered from the possibility of sexually antagonistic alleles, where selection acts in different directions in the two sexes [9]. Selection can still act on the alleles present in the workers though as, if they fail, the colony will not be able to support the production of reproductives. However, selection could be pushing the workers in a third direction, and so they don't necessarily reduce the antagonism. The importance of this antagonism is likely to vary across traits — for example, in some traits such as mandible size the separate groups could all have their own optimum, whereas in other traits, such as hormone production, the workers may have no optimum and could exist in an androgenous form.

Whether the two sexes no longer have to compromise or if this male control of reproduction is just a snapshot in an arms race, it seems that relaxed natural selection has allowed females to reproduce without sex, while sexual conflict has forced the males to follow suit. A major question is whether the workers are maintained sexually because of parasite load, mutation accumulation or a mixture or both?

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Neurotransmission: Emerging Roles of Endocannabinoids

Postsynaptic release of endocannabinoids can inhibit presynaptic neurotransmitter release on short and long timescales. This retrograde inhibition occurs at both excitatory and inhibitory synapses and may provide a mechanism for synaptic gain control, short-term associative plasticity, reduction of synaptic crosstalk, and metaplasticity.

Anatol C. Kreitlzer

Endocannabinoids are a class of lipophilic signaling molecules that are synthesized and released by postsynaptic neurons in response to increases in intracellular calcium levels or activation of metabotropic receptors. As their name implies, endocannabinoids activate the same G protein-coupled receptors as the active compounds in *Cannabis sativa* (marijuana). The primary neuronal subtype of this receptor, known as CB1, is widely distributed in the mammalian brain and is expressed in presynaptic terminals, where it can inhibit neurotransmitter release. The endocannabinoid system is thus well suited for rapid retrograde signaling across activated synapses. Recent studies are beginning to elucidate the physiological roles of this signalling.

Retrograde signaling by endocannabinoids was first observed in the cerebellum and hippocampus as a phenomenon termed depolarization-induced suppression of inhibition (DSI) [1,2]. DSI is a short-term depression of neurotransmitter release that can be elicited by postsynaptic depolarization sufficient to activate voltage-sensitive calcium channels. Increases in intracellular calcium levels stimulate the production of endocannabinoids, perhaps via phospholipase D (PLD) [3], which can then diffuse to adjacent presynaptic terminals and suppress neurotransmitter release for tens of seconds [4,5]. A similar phenomenon has been observed at excitatory synapses and is known as depolarization-induced suppression of excitation (DSE) [6].

In addition to depolarization-mediated calcium entry, activation of metabotropic glutamate and acetylcholine receptors can drive endocannabinoid release through a separate biosynthetic pathway [7,8]. Receptor-mediated endocannabinoid production requires phospholipase Cβ (PLCβ) [9], an enzyme which is activated by G protein signaling and modulated by calcium. Thus, increases in intracellular calcium can directly stimulate endocannabinoid production via PLD, while at the same time increasing the efficacy of receptor-driven PLCβ-mediated biosynthesis. This receptor-driven release is critical for endocannabinoid-mediated long-term depression (LTD) of neurotransmitter release at both excitatory and inhibitory synapses [10–12]. Although LTD can be elicited by short (1 second) presynaptic bursts sufficient to activate postsynaptic metabotropic glutamate receptors, the subsequent receptor-driven endocannabinoid release may feature slower kinetics since LTD induction requires a sustained (5–10 minute) activation of presynaptic CB1 receptors [12,13].

Modulation of synaptic transmission by endocannabinoids was initially studied using non-physiological methods, such as seconds-long depolarization or application of high-affinity metabotropic receptor agonists, to evoke endocannabinoid release. But the modulatory role of endocannabinoids during normal synaptic activity was not known. Brenowitz and Regehr [14] found that depolarization-evoked endocannabinoid release from cerebellar Purkinje cells requires high levels of intracellular calcium, suggesting that depolarization alone may not play a prominent role in the release of endocannabinoids under normal physiological conditions.

Another study, in the cerebellum, by Maejima *et al*. [7] found that 50–100 Hz activation of excitatory parallel fiber synapses onto a Purkinje cell could yield a transient 10–15% heterosynaptic inhibition of neurotransmitter release at excitatory climbing fiber synapses on the same Purkinje cell. This synaptically evoked inhibition was mediated by endocannabinoids and required activation of postsynaptic metabotropic glutamate receptors, an early indication that receptor-driven endocannabinoid release is critical under more physiological conditions.

The first systematic study of synaptically evoked endocannabinoid release was that of Brown *et al*. [15], again in the cerebellum. Following brief trains of parallel fiber stimulation, they observed a transient ~50% inhibition of neurotransmitter release from parallel fibers, which