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Evolution: Bedbugs Evolved before Their Assumed Ancestral Host

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It has long been assumed that human-parasitic bedbugs evolved from the ectoparasites of bats. However, new fossil-calibrated phylogenetic analysis places their appearance at ~115 million years ago; before the Cretaceous–Paleogene mass extinction and ~30 million years prior to fossil records of the first bats.

For most people, when we hear the word 'bedbug' what comes to mind are the insects that have plagued humans on a near-global scale following their re-emergence over the past two decades (Figure 1), the insects that likely send chills down peoples' spines, given their cryptic, blood-sucking parasitic nature. However, *these* bedbugs represent only two species of a family of insects that is comprised of over one hundred members; a family known as the Cimicidae [1]. All are obligate blood-feeders; however, the range of hosts over which they feed is limited to four deeply divergent vertebrate lineages: namely water birds, other birds, bats, and humans. Of the six subfamilies that make up the Cimicidae, four are considered bat specialists and two have later transitioned at least in part to birds [1]. The most basal of these specialize on bats, and as such, it has long been assumed that bats represent the ancestral host lineage upon which the first cimicids fed [1]. Few are host-generalists, and fewer still include human blood in their diet. With recent recognition that bedbugs represent models with which to study a breadth of both basic and applied questions [2,3], interest in the Cimicidae has escalated. Until now, what has been lacking has been a time-calibrated phylogeny with representation of species across multiple sub-families. Here, in this issue of *Current Biology*, Steffen Roth and colleagues [4] present such a phylogeny, shedding light on the dynamics of host utilization and transition.

One of the intrinsic qualities of scientific exploration is that most studies will generate more questions than they can answer; if anything it is this quality that allows our fields to expand and evolve. This study is no exception, presenting a remarkable take-home message: it appears that the Cimicidae evolved long before their assumed ancestral hosts; and when I say long, I mean very long. In fact, these results would suggest that bedbugs evolved when dinosaurs still roamed the earth, but unlike the dinosaurs, the early cimicids somehow survived the Cretaceous–Paleogene mass extinction. The basal lineages within the Cimicidae are all bat specialists, with the stem-group species (extinct species more related to the extant species than to others) dating back to around ~115 million years ago. The origin of its crown group (all living species and the fossils that are embedded within them) is placed at ~94 million years ago. In contrast, the crown group of the bats did not appear until ~64 million years ago, and the oldest known lineage that hosted cimicid parasites evolved ~50–52 million years ago [5]. As such, it seems then that bedbugs arose ~30 million years before bats.

What, therefore, could have been the ancestral host that existed prior to the Cretaceous–Paleogene mass extinction? Is it possible that bedbugs parasitized the extinct, presumed arboreal, Enantiornithes (the most abundant group of 'birds' from the Mesozoic period, and one whose stem group appeared ~140 million years ago [6]), then later switched to the largely terrestrial avian lineages that survived the Cretaceous–Paleogene event [7]? This would require a subsequent transition to bats as their predominant host. Alternatively, an early Cretaceous mammal, of which only the stem group of the Placentalia crossed the Cretaceous–Paleogene boundary [8], might have facilitated the colonization of

Figure 1. A bedbug *Cimex lectularius*.
A female bedbug *C. lectularius* swollen after recently receiving a blood meal. New phylogenetic evidence suggests that bedbugs emerged ~115 million years ago, long before humans. Photo by Matthew Bertone.

bats more readily and explain why transitions to birds only appear in more recent lineages. The answer to this tantalizing question is simple… *the ancestral host remains an enigma*.

Although this uncertainty regarding the ancestral host complicates our understanding of the evolution of the family, the phylogeny represents a useful tool with which to investigate the dynamics of host utilization and transitions. Ancestral-state reconstruction depicts extinct species as bat specialists and extant species as comprising both specialists (bat or bird) and generalists, thus informing us that transitions have occurred. These transitions have been both specialist to specialist, and specialist to generalist. Considering this, two hypotheses may explain both the *how* and the *why* of such transitions. Resource efficiency assumes that transitions will result from a fitness advantage on a new host. Recent work regarding *C. lectularius* suggests that this is certainly possible. In Europe, two host lineages exist, an ancestral bat-associated lineage, and a derived human-associated lineage [9]. Contemporary gene flow between these lineages appears non-existent [10,11]. Furthermore, Kamila Wawrocka and Tomáš Bartonička investigated the mechanisms maintaining these divergent host-lineages though a comparison of survival rates when cimicids are fed on the blood of their native host versus their non-native host [12]; the results of this study clearly supported a fitness cost when fed on a non-native host, hence inadvertently supporting resource efficiency.

Alternatively, the oscillation hypothesis posits that a specialist might possess sufficient genetic variation at genes associated with host detection and/or selection or plasticity in host preference that would allow them to diverge onto additional hosts. Transition to a generalist lifestyle would depend upon the presentation of ecological conditions conducive for host-species expansions. Given the laboratory rearing of a variety of cimicids, this hypothesis seems justifiable. For example, many species, such as *C. lectularius*, *C. hemipterus*, *C. pipistrelli*, and *C. adjunctus*, readily accept rabbit blood, thrive, and reproduce. The latter two are putative host-specialists. In contrast, *C. vicarius*, a species nested within the primarily bird-associated clade [13], do not feed (or at least do not thrive and reproduce) when offered rabbit blood. Thus, some species may possess sufficient genetic variation or plasticity, whereas others may not. However, as the authors of the present study point out, when offered alternative hosts outside of the lab, reports are anecdotal, and relate only to putative generalist species [4]. As such, although lab experiments might suggest a specialist has the capacity to be a generalist, there is little evidence to support oscillation across the cimicid phylogeny presented here [4].

The stringency in host usage, and thus the lack of widespread generalists across the phylogeny, potentially results from the strict association cimicids have with their hosts. Tied to blood-feeding for survival and reproduction, and with limited potential for dispersal and thus gene flow, few opportunities for generalism may arise. If other cimicids are comparable to *C. lectularius*, whose infestations are characteristically highly inbred [10,14], this provides a platform upon which selection on genes essential for host detection and feeding can act [15], thus promoting the maintenance of specialism.

Two generalist species are the common bedbug, *C. lectularius*, and the tropical bedbug, *C. hemipterus*. In 2000 [16], parasitologist Richard Ashford wrote "*one of the most intriguing aspects of the parasites of any animal is the way they and their hosts may have evolved in parallel*…". If it is true that humans and their bedbug parasite evolved in parallel, then we might expect this to be evident in the phylogenies of these human-associated cimicids. Based on this new phylogeny, there is no support for this hypothesis. In fact, human-associated cimicid species had evolved 5 to 10 million years before any member of the genus *Homo* even existed.

As mentioned earlier, scientific study begets further scientific questions and this paper is a perfect example of that. For it not only addresses some fundamental questions regarding the phylogenetic relationships and evolutionary dynamics within the family, but also fuels the minds of the readers with more. This phylogeny will no doubt act as a springboard from which these and many others can be explored.

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Evolution: Environmental Dependence of the Mutational Process

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Environmental dependence of mutation in microbes is well-known, but most experiments have investigated contexts in which growth rate is greatly reduced below optimum. A new experiment shows mutational variability extends to contexts in which growth is near optimum.

Evolutionary biologists recognize that, of the five evolutionary forces — mutation, recombination, migration, natural selection, and random genetic drift — natural selection is somehow exalted. George Williams ([1], p.9) put his finger on it when he wrote:

> "…Evolutionary adaptation is a special and onerous concept that should not be used unnecessarily, and an effect should not be called a function unless it is clearly produced by design and *not by chance*."

In evolution, chance is represented by mutation, recombination, and drift. The epistemology of evolutionary biology can thus be roughly summarized: if some facet of evolution is calculated to be unlikely, given the expected contributions of mutation, recombination, and drift, the case for a causal role for selection is strengthened. However, evolution is a symphony that depends on the interplay between the individual forces in complex ways. This joint dependency means that the observable *output* of evolution — variation within a population, divergence among groups — cannot be unambiguously attributed to a particular evolutionary force. To break the impasse, it is necessary to quantify the effects of at least one variable in isolation from the others.

As it happens, mutation is the only evolutionary force that can be characterized (almost) independent of other evolutionary forces. That is because mutation can never be 'turned off': errors occur with every round of genome replication. For that reason, evolutionary biologists have expended great effort to quantify the rate, molecular spectrum, and phenotypic effects of new mutations. In a recent issue of *Current Biology*, Liu and Zhang [2] report that both the rate and spectrum of mutations in yeast differ significantly depending on the environmental context. That finding has important implications concerning the robustness of the experimental methodology by which mutational properties are typically measured.

The rate and spectrum of mutation can be estimated in two basic ways. First, theory predicts that the substitution rate of neutral alleles is equal to the neutral mutation rate, so the rate of divergence between taxa at *neutral* loci should equal the mutation rate, independent of the population size [3]. However, this method presents two difficulties. First, the natural unit of evolutionary time is the generation, but the number of generations separating taxa can only be approximated. Second, whether a mutation is 'neutral' depends on the effective population size, and variants with selective effects less than about the reciprocal of the effective population size are effectively neutral [3]. Thus, some mutations whose fates are governed by selection in a large population will be effectively neutral in a small enough population. That logic extends to the mutational spectrum; if different types of mutations have different average selective effects, the effectively neutral spectra may differ depending on the population size.

The second way in which mutation rate and spectrum can be inferred is to count mutations as they occur over a known time interval by means of a 'mutation accumulation' experiment. A mutation accumulation experiment is simply a pedigree in which descendants ('mutation accumulation lines') of a common ancestor are maintained for a known number of generations under conditions of minimal selection, such that all but the most strongly deleterious mutations accumulate at the neutral rate.

In addition to the rate and spectrum, the phenotypic effects of mutations are