

LONG LIVE THE QUEEN



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In insect societies, a queen can live for years, whereas workers expire in months. What can hives and anthills reveal about aging? *By Yao-Hua Law*

A small room in the University of Regensburg is home to more than 50 boxes of black, strikingly slender ants. Native to Central America, the clonal ant *Platythyrea punctata* has evolved a trait rare among ants: It can produce daughters from unfertilized eggs. A *P. punctata* colony can consist

entirely of clones, produced by one or two dominant females. That uniformity underscores a mystery.

“What is really fascinating is that they are the same” genetically, says evolutionary biologist Abel Bernadou, pointing to the 30 or so ants in a box, “but depending on their jobs, they will have totally different life spans.” Members of the colony’s working caste,

which nurse the brood, hunt for food, and defend the nest, die within 7 months, even when well-fed and protected in the lab. But ants in the reproductive caste, whose sole job is to lay eggs, can live 10 to 16 months.

To Bernadou, the questions raised by those disparities are irresistible. What causes some ants to live twice as long as nest mates that have exactly the same ge-

PHOTO: ALEX WILD

At almost 2 centimeters, the queen of the Texas leafcutter ant (*Atta texana*) is far bigger than her workers. She also has a longer life span.



Many who study those species have yet to be convinced that social insects have something important to contribute. “They think it’s fun and worthwhile to know the diversity of aging,” says biologist Gro Amdam, who studies aging in bees at the Norwegian University of Life Sciences and Arizona State University, Tempe. “But they don’t think we will make major discoveries in social insects that are relevant to their work.”

But Amdam and other social insect researchers—who this month published a big batch of findings in a thematic issue on aging and sociality in the *Philosophical Transactions of the Royal Society B*—say they promise new ways to understand aging. One reason is that many social insects live far longer than the more popular model organisms. Honey bee queens live up to 5 years, and termite and ant queens more than 20. *Drosophila*, by contrast, has a life span of 13 weeks at most, and *C. elegans* a mere 18 days. “If you want to know how to die quickly, then work on *Drosophila*,” quips evolutionary biologist Laurent Keller, who studies aging in ants at the University of Lausanne.

Even more intriguing is the fact that aging in social insects is plastic, changing with social context. Few social insects are as homogeneous as clonal ants, but in most, queens and workers have very similar genomes, because all colony members are offspring of one or several queens. Yet whereas queens seem to stay youthful through their long lives, workers age quickly and die fast. And within a colony, a worker’s job determines its life span, even though by and large all workers are siblings. Scientists can rush, slow, or even reverse aging in ants and bees simply by having them mate or changing their tasks.

Revealing the molecular mechanisms behind these strange phenomena may ultimately shed more light on aging in general, including in humans, says molecular biologist Roberto Bonasio at the University of Pennsylvania, who studies epigenetics in mammals, flies, and ants: “That’s the idea.”

AGING, OR SENESCENCE, is a progressive loss of function and performance with time. It saps the individual’s capacity to withstand stress, fight diseases, heal wounds, or learn new skills. But must we age? Why did organisms not evolve to maintain their youthful vigor until they’re about to die?

Rather counterintuitively, scientists argue aging is the outcome of natural selection, which favors genes that help an organism survive to reproductive age. Once the individual has produced offspring, selection for survival weakens, which opens the door for injurious genetic effects to accumulate. Aging sets in.

The strong selection to survive until reproduction may favor so-called pleiotropic genes, which are helpful in early life but harmful later on. An example is the *clk1* gene in *C. elegans*, which is known to boost the nematode’s metabolism. The gene promotes early reproduction and gives individuals a fitness edge over competitors, but shortens their life span by 40%, in part because it speeds the buildup of harmful metabolic byproducts.

Scientists have suggested organisms living in more precarious environments—for instance ones thick with predators or competitors—experience higher selection for survival and reproduction early in life, at the cost of faster aging later on. This so-called “extrinsic mortality hypothesis” is often used to explain why animals that fly, live underground, or are venomous—and as a result face fewer threats—also seem to live longer and presumably age less rapidly. Think of bats,

which live far longer than other mammals of similar size.

Back in the 1990s, Keller realized social insects offered “an interesting way” to test the extrinsic mortality hypothesis, he says. Safely ensconced in their nests and guarded by a legion of workers, ant queens are assumed to face a much lower risk of predation and disease, and thus of dying, than insects living a solitary life.

Keller and his Lausanne colleague Michel Genoud collected life span records of queens in 61 species of ants, termites, and the honey bee, and compared these with adults of 81 solitary insect species. On average, queens live 5 to 11 years, whereas solitary insects live only months, they reported in a 1997 paper. Everything was as the hypothesis predicted—and the paper kick-started aging research in social insects.

THE FIELD FACES plenty of challenges. Insect queens and kings are rare, which limits studies’ sample sizes. And keeping colonies of social insects alive can be laborious. At Regensburg, evolutionary biologist Jan



In the western honey bee (*Apis mellifera*), queens (middle) live longer than workers (top) and drones (bottom).

nome? And how can reproduction, a taxing effort that speeds up aging in most animals, make these ants live longer instead?

Bernadou and his myrmecologist colleagues at Regensburg are part of a small cadre of researchers who have turned to social insects—ants, bees, and termites—to help unravel the mysteries of aging. It’s a developing field that rarely features in conferences on aging biology, where the spotlight is on mice, *Drosophila* fruit flies, and the minuscule nematode *Caenorhabditis elegans*—three species researchers have probed and tweaked for well over half a century to learn what controls their life spans.

Oettler and graduate student Luisa Jaimes maintain 200 *Cardiocondyla obscurior* ant colonies that they need to feed and clean several times weekly over the 6 months or more that their queens live. By contrast, to grow hundreds of *Drosophila* maggots into adults, you only need a bottle, premade fly food, and 10 days. “One nasty reviewer asked why, since we can’t get the numbers, do we still use *Cardiocondyla*”—a tiny tropical ant—“instead of *Drosophila*,” says myrmecologist Jürgen Heinze, who has been studying the ants for 30 years at Regensburg. “They can’t see the benefits.”

Lagging experimental techniques are a problem as well. In mice, scientists can

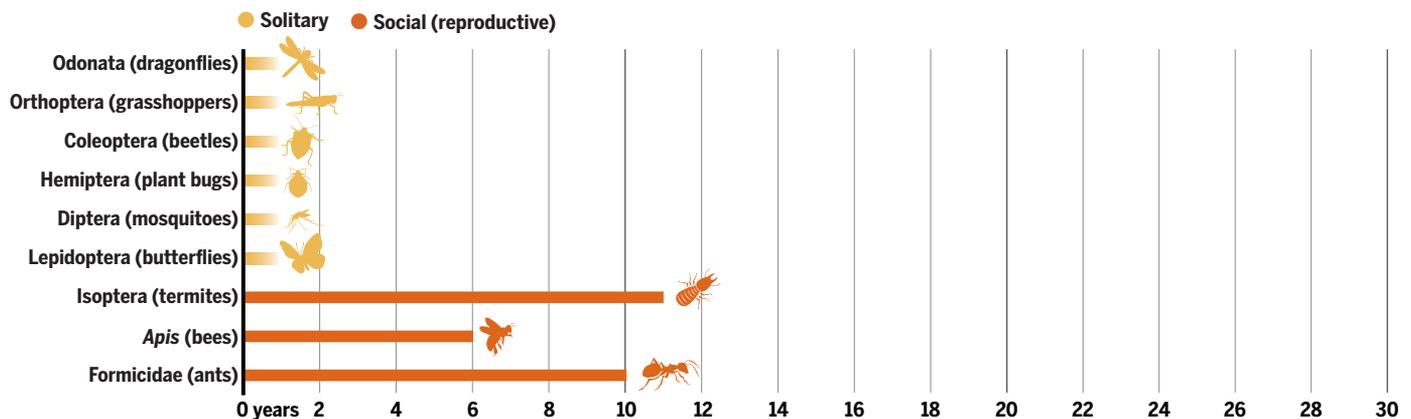
document physiological aging in urine and blood samples; in *Drosophila* and *C. elegans*, they can insert molecular tags into cells that show gene expression in real time. Such molecular clocks don’t exist yet for ants and termites. That’s a problem because aging isn’t always a linear process: Queen ants often churn out eggs for months or years without visible aging, only to drop dead abruptly. Without reliable and nonlethal ways to trace aging or physiological changes at the molecular level, comparisons between “old” and “young” individuals are questionable. “If you have a 10-day-old worker, to what do you compare it? A 10-day-old queen? Or a

queen that has lived the same proportion of its average life span?” Keller asks. “This is difficult.”

Gene editing would be a “game changer” for these studies, Oettler says, enabling scientists to disable specific genes and watch for effects on aging. But it has barely started to be used in social insects. Scientists only created the first genetically modified honey bees in 2014, and two species of transgenic ants in 2017. Amdam would love to see transgenic technology developed for free-flying honey bees, allowing real-world experiments on aging. But beekeepers staunchly oppose genetic modification, which they worry could affect their colo-

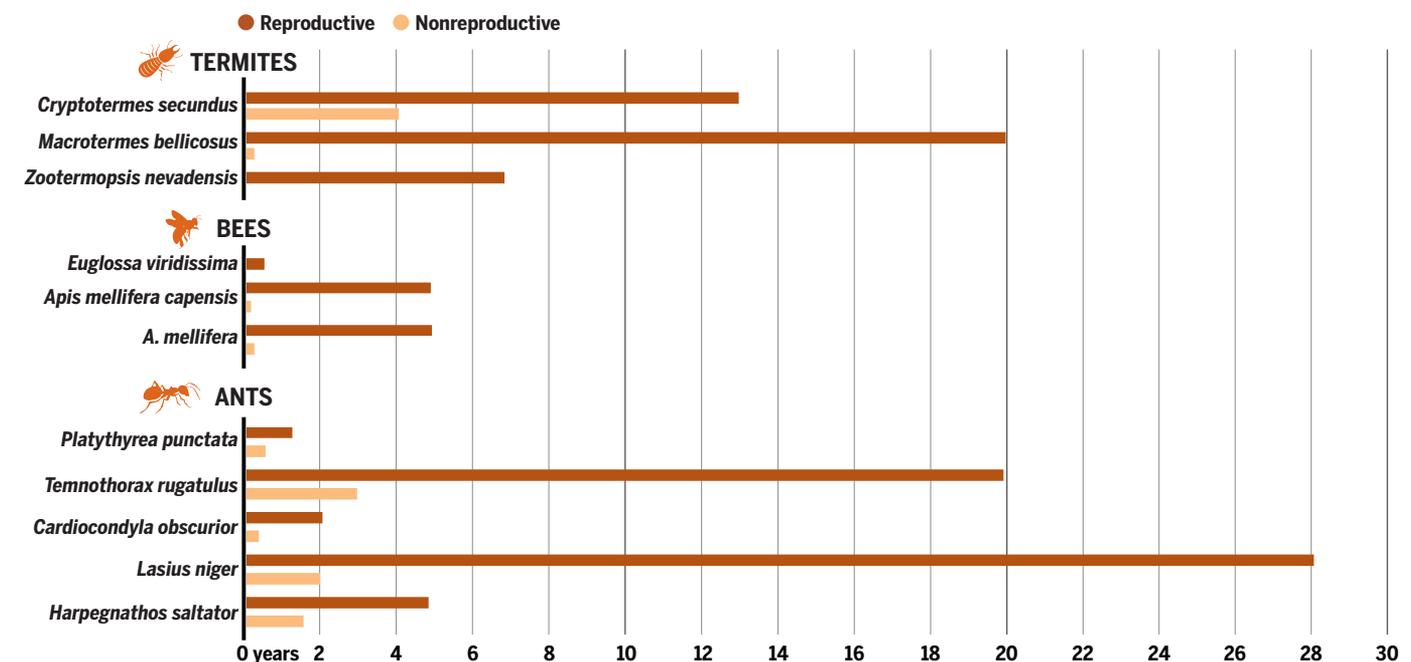
For some insects, living socially means living long

The average maximum life span for solitary insects is much less than for reproductive individuals—queens, kings, and some workers—among social insects.



A fountain of youth—for the happy few

Within social insect species, the life span of reproductive individuals far exceeds that of those that do not produce offspring.



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nies, and regulators are wary. “The moment you say ‘free-flying transgenic bee,’ it’s no-no,” Amdam says.

One way to speed progress, Bonasio says, is to “consolidate our efforts on one or two species so that more [molecular] tools are available to everybody.” But Heinze says researchers should embrace the bewildering variety of life histories and aging patterns seen in social insects. “There is no standard ant,” he says; for understanding the diverse causes and effects of aging, “plurality is best.”

DESPITE THE CHALLENGES, scientists are starting to link aging patterns in social insects to the underlying molecules. One oddity they’re probing is the link between reproduction and longevity.

In most animals, high fecundity almost universally comes with a quick burn-out; red deer, for example, age faster if they reproduce early. But social insect queens buck the trend: Reproduction stretches their life span rather than snipping it. For example, a 2005 study by Heinze’s team found that *C. obscurior* queens that mated had life spans 44% longer than virgin queens (26 weeks versus 18). And that’s despite these mated queens’ hectic lifestyles: They laid up to five times more eggs, and at faster rates, than queens that did not mate or were mated with sterile males.

Other scientists have discovered that procreation also extends the life spans of queens of other ant species, honey bee queens, and termite queens and kings. In species where a limited number of workers in a colony can also reproduce, such as the *P. punctata* ants that Bernadou studies, those that reproduce live longer, too.

In termites, reproduction may blunt the impact of transposons, bits of DNA that jump through the genome, disrupting genes and, at least in humans and *C. elegans*, promoting aging. Judith Korb, who studies aging in termites at the Albert Ludwig University of Freiburg, compared transposon activity in two termite species. In the species with sterile workers, older workers have higher transposon activity; in the species where older workers can reproduce, they show better defense against damage from transposons.

Social insects’ brains appear to benefit from sex as well. When *Harpegnathos saltator*

ants, also known as Indian jumping ants, lay eggs, their brain develops 40% more of a type of protective cell called ensheathing glia, Lihong Sheng, a postdoc in Bonasio’s lab, reported in August 2020. A decline of these cell types is associated with aging in flies and cognition loss in mice. “If we know what the ants themselves use to control the number of [ensheathing glia] in the brains,” Bonasio says, it could point to similar mechanisms in flies, mice, and “maybe in humans.” (Bonasio is now studying the phenomenon in *Drosophila* flies; the ants “showed us the way but once I know what the pathway is, I prefer to do the experiment in *Drosophila* ... because it is easier,” he says.)



Workers of the Japanese termite (*Reticulitermes speratus*) can’t repair oxidative damage as well as queens (not shown) and live shorter lives.

A worker’s job can also slow or speed up its aging. Honey bee workers, for instance, start out as nurse bees that stay in the hive and tend to the brood and the queen. About 3 weeks into their lives, they become foragers that fly out to collect food. Various studies show that nurse bees do not age, but foragers do so rapidly, declining in flight performance, immunity, and learning.

Amazingly, that process can be reversed. When a hive needs more nurse bees, foragers can switch back to their former roles. When Amdam removed nurse bees from hives, foragers were forced to revert to their former roles—and they also recovered their youthful traits. Such reverted nurse bees produce more cells that “mop up pathogens,” Amdam says. They also regain high levels of vitellogenin, “a multipurpose, Swiss knife sort of protein” that regulates a bee’s changing roles across its lifetime and declines as the insects age. She has found that reverted nurse bees learn faster than foragers of the same age and that their brains have more proteins associated with cellular stress resilience and repair.

These job switches in bees don’t only mean a new line of work; they also bring a different set of interactions with other members of the colony. Amdam thinks a bee’s social life plays an important role in its longevity. Social contact is also known to affect human physiological and mental health, and loneliness has been identified as a risk factor for cognitive decline—a provocative similarity. Although scientists have yet to determine how sociality can affect insects’ life span at the molecular level, “it certainly has people’s attention,” Amdam says.

SEVERAL PAPERS in this month’s theme issue of the *Philosophical Transactions* delve deeper into the molecular control of aging in social insects. One compared gene-expression patterns between young and old individuals of six species of ants, bees, and termites, for example. The study measured the activity of two biochemical pathways, both ubiquitous in animals, that detect nutrients and regulate cell development. Scientists had previously found strong links between these pathways and life spans in flies and other solitary insects—but not in social insects.

In the new study, however, they scrutinized parts and products of the same pathways that had been largely neglected in aging research, and found genes and proteins—including vitellogenin—that strongly associate with aging in social insects. These results reinforce the need to cast a wide net and study aging in many species, says Korb, lead author of the new paper.

Thomas Flatt, who studies the genetics of aging in *Drosophila* at the University of Fribourg, is one of the researchers who has been won over by the promise of social insects. Flatt has been working with Korb, Heinze, and other researchers in a €6.2 million project funded by the German Research Foundation to study the unusual relationship between fecundity and aging in social insects. The genomic revolution will eventually help the field take flight, Flatt predicts, and give scientists a much better understanding of how aging works across the animal kingdom. “My dream is that we will discover stuff in ants that ... is universally important,” he says—things “we don’t even know existed in *Drosophila*.” ■

Yao-Hua Law is a science journalist in Kuala Lumpur, Malaysia.

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Long live the queen

Yao-Hua Law

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